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Christopher R. Chapple
William D. Steers
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Urologic Principles and Practice

Second Edition

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Urologic Principles and Practice

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This edition of Urologic Principles and Practice is dedicated to William D. Steers, co-author of the first edition. Dr. Steers, a man of many diverse interests and talents, had a dominant presence in International urology until his untimely passing on April 10, 2015. He was the Paul Mellon professor and Chair of the Department of Urology at the University of Virginia School of Medicine. He was a past President of the American Board of Urology from 2010 to 2011 and Editor of the Journal of Urology from 2007 until his passing. With a strong interest in female and pelvic medicine and sexual medicine, Dr. Steers served as chair of the joint ABU/ABOG fellowship in female pelvic medicine and Director on the American Board of Obstetrics and Gynecology. Steers was a member of the U.S. Food and Drug Administration's Reproductive Medicine Advisory Panel and chaired the National Institutes of Health's urinary incontinence and interstitial cystitis clinical trial groups. In 2011, Steers was appointed to the advisory council at National Institutes of Health by Kathleen Sebelius and Francis Collins. Steers was President of the University of Virginia physician's practice plan from 2002 to 2009 and was a member of the Health System Strategic Planning and Executive

Committees. In 1998, he described the efficacy of Viagra in a highly cited New England Journal of Medicine publication.

In 2003, the University of Virginia awarded Dr. Steers the Hovey Dabney Professorship. Dr. Steers was named by Men's Health magazine as one of the top 15 doctors for men in the USA. He was awarded the American Urological Association's Hugh Hampton Young Award, Gold Cystoscope Award, Dornier's Innovation prize, Gineste Award for research in erectile dysfunction, and the Zimskind Award in Neurourology.

Dr. Steers had many interests. He was a viticulturist aficionado and with his wife Amy co-owned Well Hung Vineyard in Charlottesville, VA. He also authored YOURometer an iPhone App. used to record urological-related symptoms. Steers' entrepreneurial activities include the development of a cell phone application to record patient symptoms and using the internet Crowdcasting to fund medical research. He was an active runner and outdoorsman.

Bill is survived by his wife, Amy; sons, Colin and Ryan; daughter-in-law, Ali; and grandchildren, Rex and Reese. His vibrant personality, incredible knowledge, and medical skills and thoughtful and generous nature is sorely missed by many. We honor him with this second edition.

Christopher R. Chapple and Christopher P. Evans

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Part I

Basic Sciences in Urology

1 Gross and Laparoscopic Anatomy of the Upper Tract and Retroperitoneum

Paras H. Shah and Bradley C. Leibovich

Introduction

It is of paramount importance that the Urologic surgeon possess a comprehensive anatomic understanding of the retroperitoneal compartment given that in this space, and the contiguous extravesical domain below the peritoneal reflection, reside all the major urologic organs. Moreover, traversing the retroperitoneum are the body's primary blood vessels—the aorta and inferior vena cava (IVC)—from which emerge the vascular supply to the urologic organs. As control of arterial and venous structures is often a critical component to surgery, particularly when performed for an oncologic indication, familiarity with both the conventional and variant anatomic course of these vessels as they approach their target organ is essential. Within the retroperitoneal space is also a rich lymphatic network intimately associated with the aorta and IVC. Secondary infiltration of these lymphatics by kidney, upper tract urothelial, and primary testicular germ cell tumors may necessitate surgical resection of the peri-caval and peri-aortic lymph nodes, emphasizing the importance of understanding principles by which the retroperitoneal compartment is accessed.

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Herein, we review the structural organization of the retroperitoneal space, highlighting how the anatomy of this compartment is maneuvered during major urologic procedures, performed via either an open or laparoscopic approach.

Anatomy

The retroperitoneum is bounded anteriorly by the parietal peritoneal layer and posterolaterally by the transversalis fascia. The compartment itself rests upon the belly of the psoas and paraspinal (specifically the quadratus lumborum) muscles, over which lies the lumbodorsal fascia—a connective tissue layer that is itself continuous more laterally with the transversalis fascia (Fig. 1.1).

The retroperitoneum can be divided further into four compartments, which from a surgeon's perspective aids in the understanding of access to the urologic organs and major blood vessels situated within this space. These compartments include the Perirenal Space, the Anterior Pararenal Space, the Posterior Pararenal Space, and the Central Vascular Compartment (Figs. 1.2a, b).

Perirenal Space

The perirenal space contains within it the adrenal gland, kidney, and ureter—organs that are all supported by a body of perinephric fat. The volume

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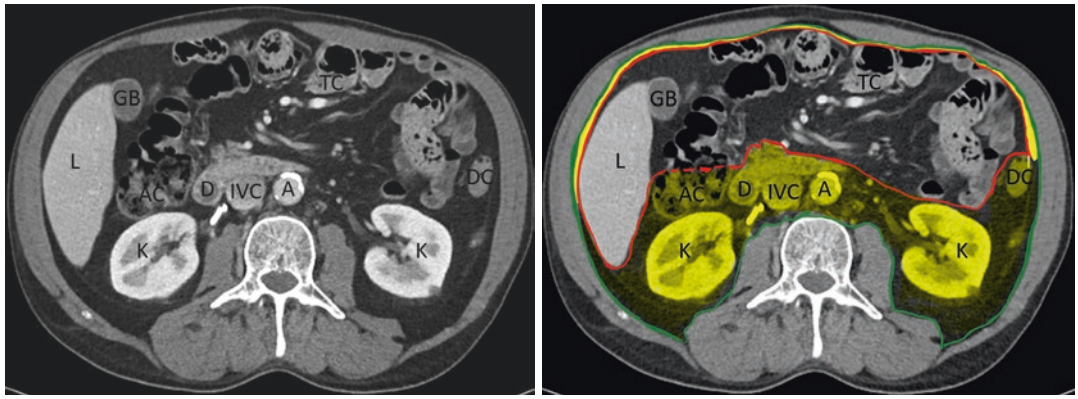

Fig. 1.1 Retroperitoneum vs. peritoneal cavity: the boundaries of the retroperitoneal space, which is highlighted in yellow, are formed by the parietal peritoneum (red) and the transversalis fascia (green). The retroperitoneal compartment is continuous anteriorly with the preperitoneal space (dense yellow shade). Within the retroperitoneum are bilateral Kidneys (*K*), the 2nd and transverse segments of the Duodenum (*D*), Ascending Colon at the level of the hepatic flexure (*AC*), Descending Colon below the splenic flexure (*DC*), Aorta (*A*) and Inferior Vena Cava (*IVC*). Additionally, the Liver (*L*), Gallbladder (*GB*), Transverse Colon (*TC*) and Jejunal loops of small intestine are appreciated within the intraperitoneal space

of fat within this compartment varies widely and is based partly on age, gender, and body mass (Fig. 1.3). The perirenal space is delineated anteriorly by Gerota's fascia (anterior perirenal fascia) and posteriorly by Zuckerkandl's fascia (posterior perirenal fascia), which fuse laterally to essentially envelop these organs and overlying fat layer (Fig. 1.2c). The point of fusion along the lateral contour of the kidney is of clinical relevance as it offers a nice cleavage plane through the perinephric fat by which the capsular kidney surface can be accessed, as is necessary during partial nephrectomy.

The posterior perirenal fascia is in fact comprised of two layers, the deep and superficial lamina, which explains its prominence on cross-sectional imaging. Whereas the deep layer is continuous with the anterior renal fascia, the superficial layer of the perirenal fascia deviates anteriorly off the lateral contour of the perirenal space, and is referred to here as the lateral conal fascia. The lateral conal fascia runs along the lateral edge of the anterior pararenal space as it fuses here with the parietal peritoneum (Fig. 1.2c).

The perirenal space is shaped as an inverted pyramid, with the diaphragm serving as the base of this space and the apex of the space directed towards the pelvis. Although the superior border of the perirenal space is solely the diaphragm on the left (Fig. 1.4), the superior border of the perirenal compartment on the right is formed anteriorly by the bare segment of the liver, which is devoid of a peritoneal lining, and posteriorly by the diaphragm (Fig. 1.5). The perirenal space rests on top of the psoas and quadratus lumborum muscles; this interface is formed by close apposition of the Zuckerkandl fascia with the psoas fascia and thoracodorsal fascia, which overlie the psoas and quadratus lumborum muscles, respectively (Figs. 1.2c and 1.6).

Piercing the perirenal fascia medially are renal hilar vessels, which are derived from the great vessels situated within the central vascular compartment (Fig. 1.7). Although the right and left perirenal spaces are separated by this central vascular compartment, cross-talk is thought to exist between them, particularly given the anatomic configuration of Gerota's fascia whereby it crosses the midline to drape over the great vessels at the level of the L3 to L5 vertebrae to fuse with the Gerota's fascia of the contralateral side (Fig. 1.2c). Indeed, it is proposed that trabeculae within the anterior perirenal fascia connective tissue crossing the midline forms the Kneeland channels, allowing for communication between both perirenal spaces [1].

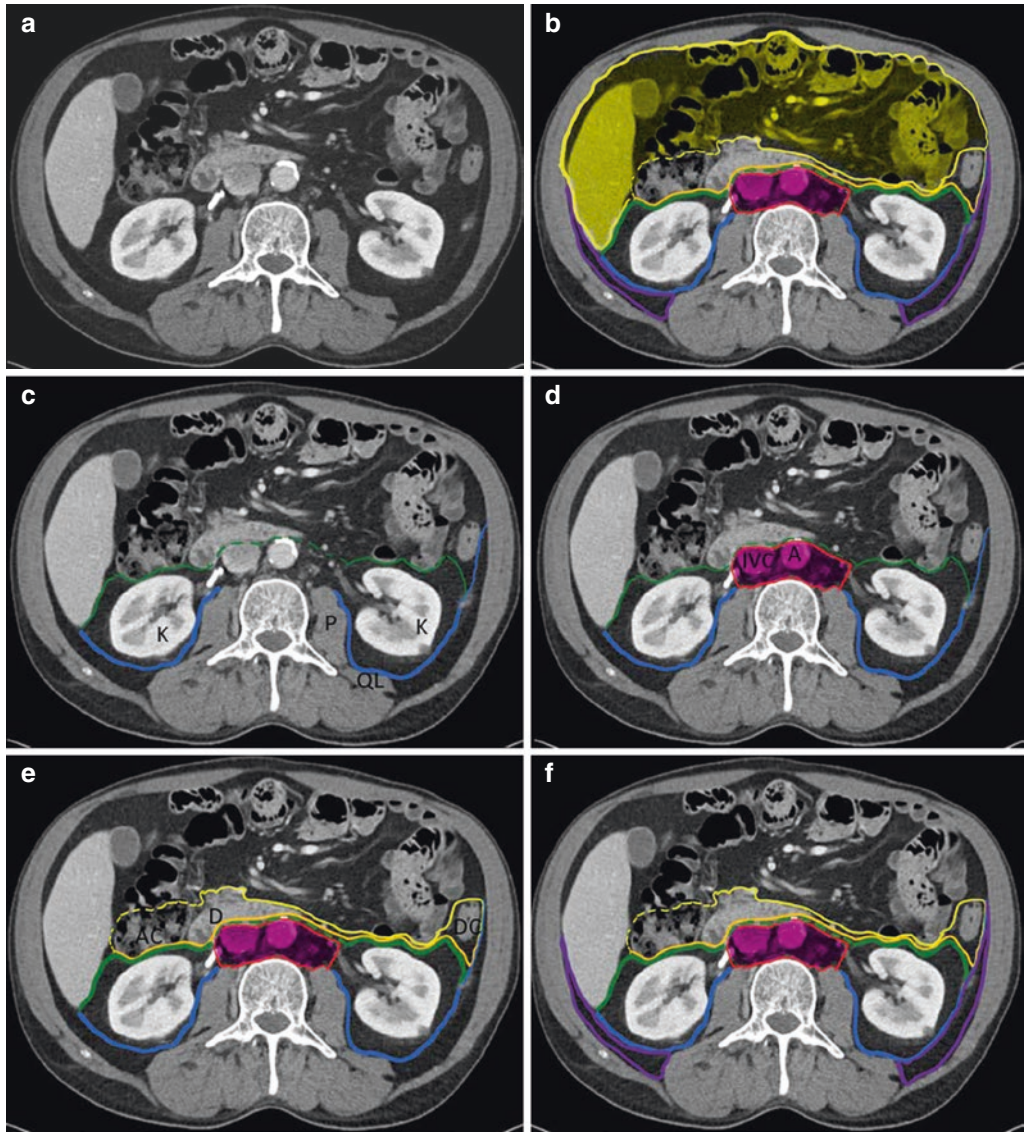

Fig. 1.2 Cross-sectional image of CT abdomen. (**a**) Cross-section image of CT abdomen. (**b**) Divisions of the Retroperitoneum: The peritoneal cavity is lined by a layer of mesothelial tissue referred to as the parietal peritoneum (yellow). The retroperitoneum can be subdivided into four compartments: the perirenal space (blue/green), the central vascular compartment (red), the anterior pararenal space (yellow/orange lines), and the posterior pararenal space (purple). (**c**) Perirenal Space: The Kidneys (*K*) are situated within the perirenal space, which is bordered by the Gerota's fascia anteriorly (green) and the Zuckerkandl's fascia posteriorly (blue). Additionally, the Gerota's fascia crosses over the midline (dashed green) as it drapes over the central vascular compartment to connect to the contralateral perirenal space; within this are the Kneeland's channels, which may allow for communication between the spaces. The Zuckerkandl's fascia continues anteriorly (blue) off the lateral contour of the kidney, forming the lateral border of the anterior pararenal space and connecting to the parietal peritoneum. The perirenal space rests on top of the psoas (*P*) and Quadratus Lumborum (*QL*) muscles. (**d**) Central Vascular Compartment: The Aorta (*A*) and Inferior Vena Cava (*IVC*) are located within the central vascular compartment, outlined in red and shaded in purple. Peri-aortic and peri-caval lymph nodes are within the surrounding fibroadipose tissue. The Gerota's fascia can be seen crossing the midline and draping over the central vascular compartment (dashed green lines). (**e**) Anterior Pararenal Space: Seen here within the Anterior Pararenal Space, which is outlined in yellow anteriorly and orange posteriorly, is the Ascending Colon (*AC*), the Duodenum (*D*), and the Descending Colon (*DC*). The anterior connective tissue border of this space is formed anteriorly by the parietal peritoneum (yellow), which serves as the posterior abdominal wall of the peritoneal compartment, and posteriorly by the Toldt's fascia (orange). (**f**) Posterior Pararenal Space: This compartment, outlined in purple, contains only adipose tissue

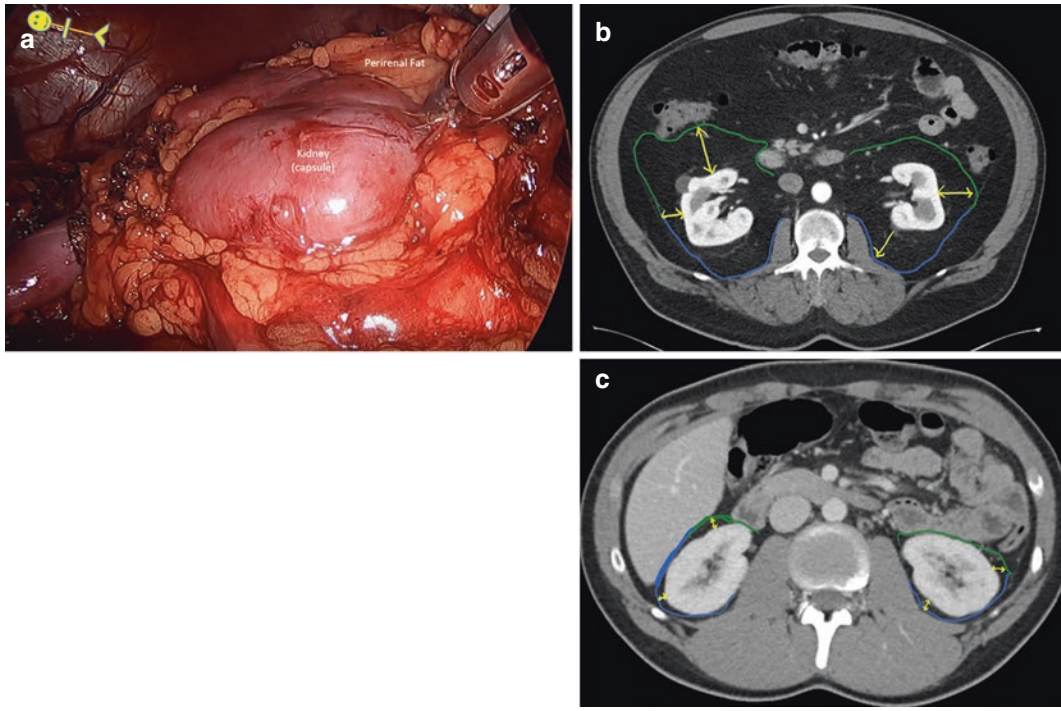

Fig. 1.3 Perinephric fat. (**a**) Intraoperative view of the Kidney with the surrounding Perinephric fat removed off its capsular surface. (**b**) A large volume of perinephric fat, as delineated by yellow arrows, is appreciated around both kidneys. The anterior and posterior perirenal fascia are delineated in green and blue, respectively. (**c**) Minimal perinephric fat volume, as delineated by yellow arrows, is appreciated around both kidneys. The anterior and posterior perirenal fascia are delineated in green and blue, respectively

The ureter is the most posterior structure within the renal hilum, resting behind the renal vessels. It descends within the perirenal space on the anterior surface of the psoas muscle and associated fascia (Fig. 1.8). It courses lateral to the gonadal vein—an important anatomic consideration during urologic procedures in the retroperitoneum. When performing laparoscopic nephrectomy or nephroureterectomy, the gonadal vein should be kept medial (particularly for right-sided procedures) and the ureter displaced anterolateral off the psoas muscle to facilitate dissection towards to renal hilum; this maneuver helps separate the perirenal space (via Zuckerkandl's fascia) off the psoas muscle and is critical in preventing violation of the perirenal fat (Fig. 1.8). Similarly, during retroperitoneal lymph node dissection, the ureter is identified and swept laterally and the gonadal vein kept medially so as to create a space between the perirenal space and central vascular compartment (Fig. 1.9) as well as facilitate ligation of the gonadal vein.

The ureter in its descent will subsequently course medially and travel underneath the gonadal vein and artery—an anatomic relationship that is often referred to by the aphorism "water under the bridge." It will eventually cross over the common iliac artery just proximal to its bifurcation and dive medially to enter the bladder under the shade of the superior vesical artery.

Anterior Pararenal Space

The anterior pararenal space is situated directly in front of the perirenal spaces laterally and the central vascular compartment medially. It is bounded anteriorly by the parietal peritoneum and posteriorly by the Toldt's fascia, which directly overlies and is opposed to the anterior leaf of the perirenal fascia (Gerota's fascia) (Fig. 1.2e). The anterior pararenal space contains the ascending colon, its mesocolon, and

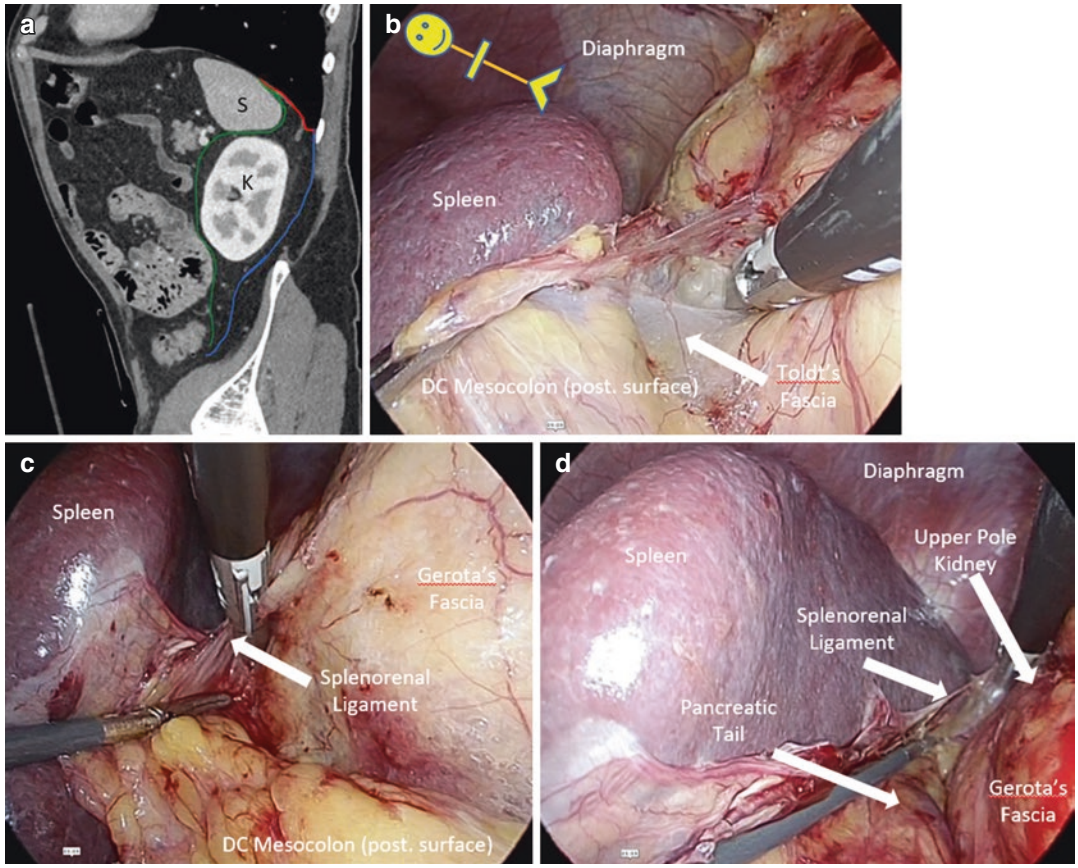

Fig. 1.4 Left perirenal space. (**a**) The superior border of the left perirenal space is the diaphragm (red). The anterior and posterior perirenal fascia are delineated in green and blue, respectively. (**b**) Medial reflection of the left mesocolon permits access to the left perirenal space. (**c, d**) Division of the splenorenal ligament permits medial reflection of the spleen (intraperitoneal location) off the superior aspect of the left perirenal space. *DC* descending colon, *K* kidney, *S* spleen

the duodenum on the right and the descending colon along with its mesocolon on the left. The pancreas also resides here with the head oriented towards the right, the tail towards the left, and the pancreatic body in the midline anterior to the central vascular compartment.

Transperitoneal access to the kidney and ureter (perirenal space) as well as the major vessels (central vascular compartment) requires sufficient reflection of structures not only within the peritoneal cavity (intraperitoneal location), but also within the anterior pararenal space. In this regard, it is helpful to understand the relationship of the anterior pararenal space to the intraperitoneal contents.

As aforementioned, the anterior pararenal space is limited anteriorly by the posterior wall of the peritoneal cavity, which is formed by a sheet of mesothelial tissue referred to as the parietal peritoneum (Figs. 1.2 and 1.10) [2]. The perpendicular projection of this mesothelial layer into the peritoneal space is referred to as the visceral peritoneum as it lines the mesentery of the small intestine, which is in an intraperitoneal location. At the level of this small bowel peritoneal reflection, the small bowel mesentery has a broad base that obliquely runs from the duodeno-jejunal flexure (left upper quadrant) towards the cecum (right lower quadrant), essentially mounting the small bowel to the posterior abdominal wall via

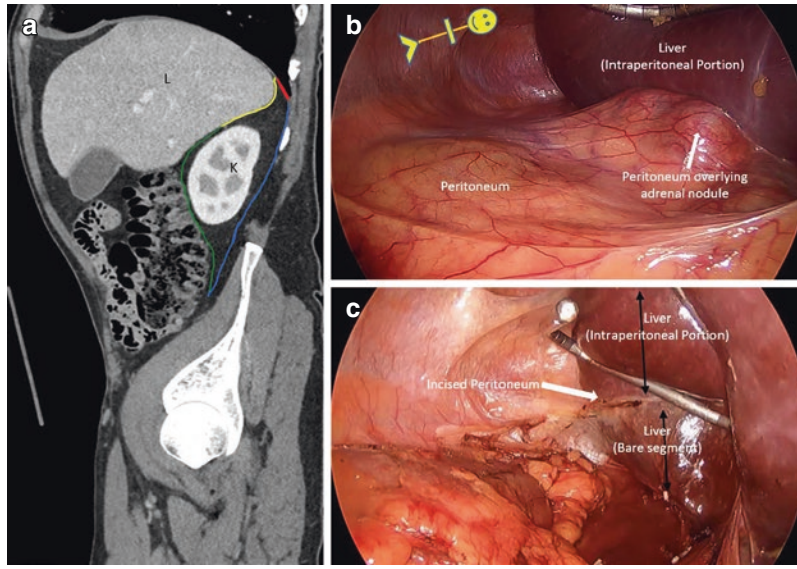

Fig. 1.5 Right perirenal space. (**a**) The superior border of the right perirenal space is formed by both the bare segment of liver (anteriorly; yellow) and the diaphragm (posteriorly; red). The anterior and posterior perirenal fascia are delineated in green and blue, respectively. (**b**) Intraoperative view of the intraperitoneal portion of liver. (**c**) The bare segment of the liver, serving as the superior border of the right perirenal space, can be visualized upon accessing the upper region of the right perirenal space. Of note, the adrenal gland and surrounding perirenal fat have been removed. *K* Kidney, *L* liver

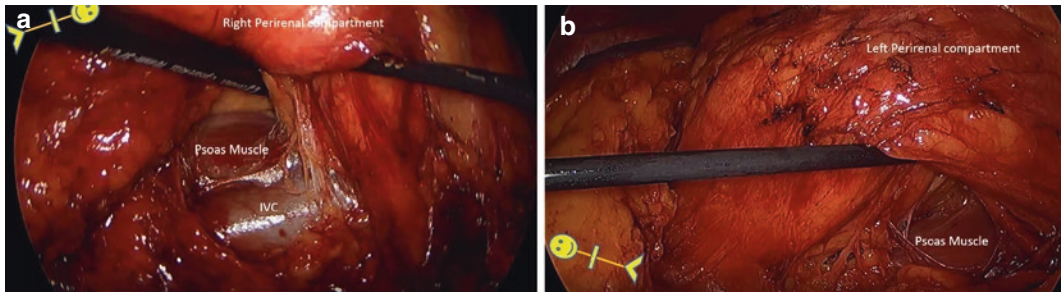

Fig. 1.6 The posterior perirenal fascia of the right (**a**) and left (**b**) perirenal spaces is lifted anteriorly off the Psoas muscle/fascia

its mesentery (Fig. 1.10). Invested within the thin fibroadipose layer of the small bowel mesentery are blood vessels derived from the superior mesenteric artery and vein accompanied by lymphatics. In fact, although the small bowel mesentery is attached to the posterior abdominal wall by a broad base, the root of this mesentery is situated primarily around the takeoff of the superior mesenteric artery such that if the small bowel mesentery were detached from its broad-based attachment, it would remain suspended by the SMA, which would essentially serve as a point of pivot (Fig. 1.10).

The fatty fibrovascular sheet comprising the small bowel mesentery, which is oriented perpendicular to the posterior abdominal wall and enveloped by visceral peritoneum, is continuous with a similar broad-based adipose-rich fibrovascular sheet that lays horizontally within the anterior pararenal compartment of the retroperitoneum.

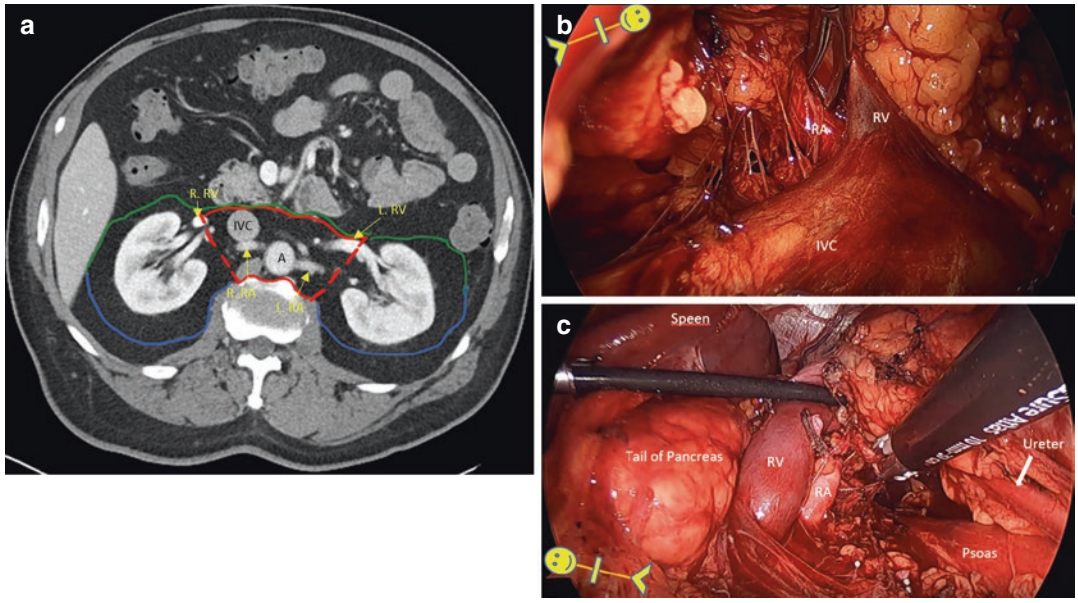

Fig. 1.7 Renal hilum. (**a**) The major renal vessels (RA and RV) pierce the perirenal fascia medially, exiting the central vascular compartment (encircled in red) to enter the hilum of the perirenal space (green and blue). The RA is generally situated posterior to the RV, with the right RA assuming a retrocaval location. (**b**, **c**) The renal vessels can be visualized within the hilum of the right (**b**) and left (**c**) kidney. *A* aorta, *IVC* inferior vena cava, *RA* renal artery, *RV* renal vein

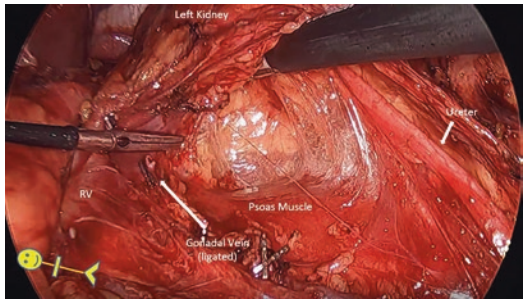

Fig. 1.8 The ureter is situated within the posterior-medial aspect of the perirenal compartment. As the perirenal compartment is lifted anteriorly off the psoas muscle, the ureter can be seen on the posterior-medial aspect of the plane that is created. *RV* renal vein

This structure is referred to as the ascending mesocolon given its insertion into the mesenteric border of the ascending colon (Fig. 1.10), and is comprised of a vast arcade of blood vessels also derived from the SMA, specifically the right colic arterial branch (Fig. 1.11).

Embryologically, however, the ascending colon is initially in an intraperitoneal location and attached to the true parietal peritoneal layer of the posterior abdominal wall by its broad-based mesentery that projects into the peritoneal space; as such, the mesentery of the ascending colon is initially lined by a visceral peritoneal layer of mesothelium [2]. It is in later stages of development that the ascending colon, along with its mesentery, assumes a more horizontal position flush up against the original parietal peritoneal layer (which originally had been directly overlying the Gerota's fascia of the perirenal compartment). In doing so, the visceral peritoneal layer lining the mesentery of the ascending colon fuses with the parietal peritoneum of the original posterior abdominal wall, eliminating the potential space in between. This fusion of these visceral and parietal mesothelial layers gives rise to the Toldt's fascia, which now rests on top of the Gerota's fascia and lines the posterior surface of the ascending mesocolon (Fig. 1.12) [2]. Moreover, it is based on this positional shift that the ascending colon and its mesocolon transition from the intraperitoneal to

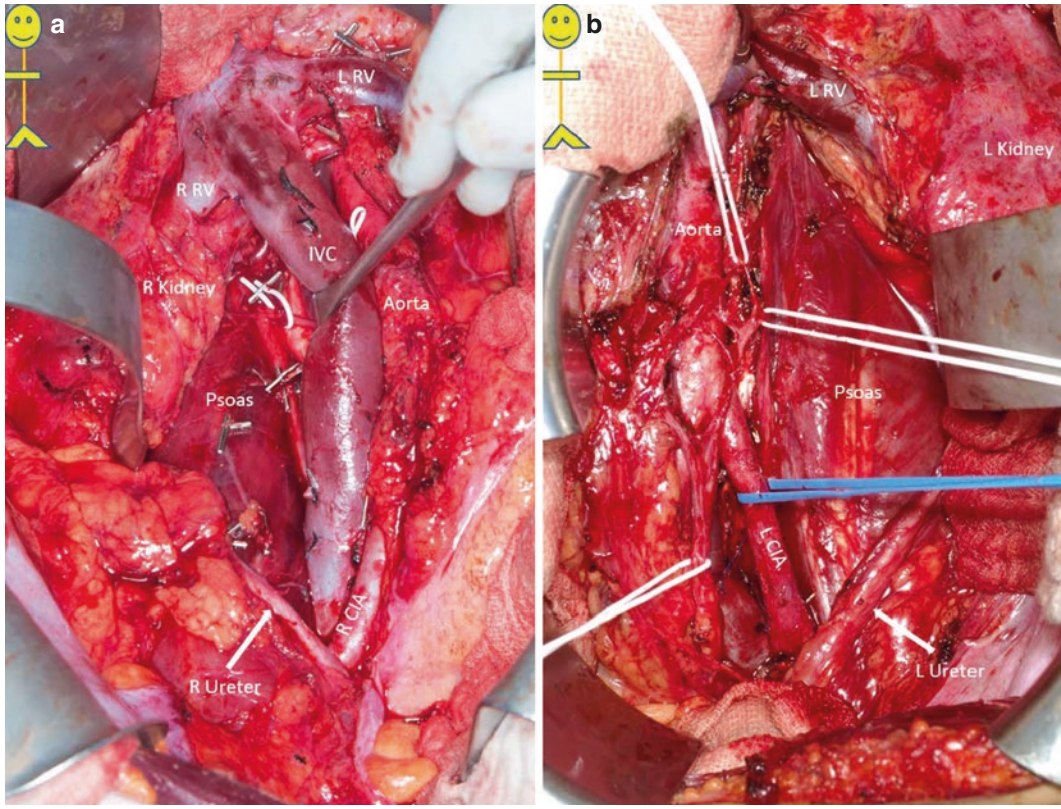

Fig. 1.9 Separation of the perirenal space and the central vascular compartment is facilitated by identification and lateralization of the ureter so as to separate it off from the lateral border of the IVC on the right (**a**) and the from the lateral border of the Aorta on the left (**b**). White vessel loops are used to isolate postganglionic sympathetic fibers. *CIA* common iliac artery, *IVC* inferior vena cava, *RV* renal vein

retroperitoneal compartment and become situated immediately anterior to the right perirenal space.

The descending colon develops in a manner similar to the ascending colon. Although initially suspended within the peritoneal compartment by a broad fibrovascular mesenteric sheet, it subsequently assumes a more parallel orientation and opposes the posterior abdominal wall so as to overlie the left perirenal space. In doing so, the visceral peritoneal tissue originally lining the back surface of the descending colon mesentery fuses with the parietal peritoneal layer of the posterior abdominal wall, forming Toldt's fascia (Fig. 1.12) [2]. Moreover, the descending colon effectively assumes a retroperitoneal position whereby the mesentery of the descending colon is referred to as the mesocolon and the visceral peritoneal layer that had been lining it forms the new parietal peritoneal surface of the posterior abdominal wall.

Transperitoneal access to the right kidney and hilar vessels is gained primarily through medial reflection of both the ascending colon and mesocolon. This involves first incising the white line of Toldt, which occurs where peritoneal mesothelium reflects over the lateral contour (antimesenteric border) of the ascending colon. The surgeon is now able to access the delicate fibroconnective tissue of Toldt's fascia such that dissection here will allow the right colon and it's mesocolon to detach from the underly-

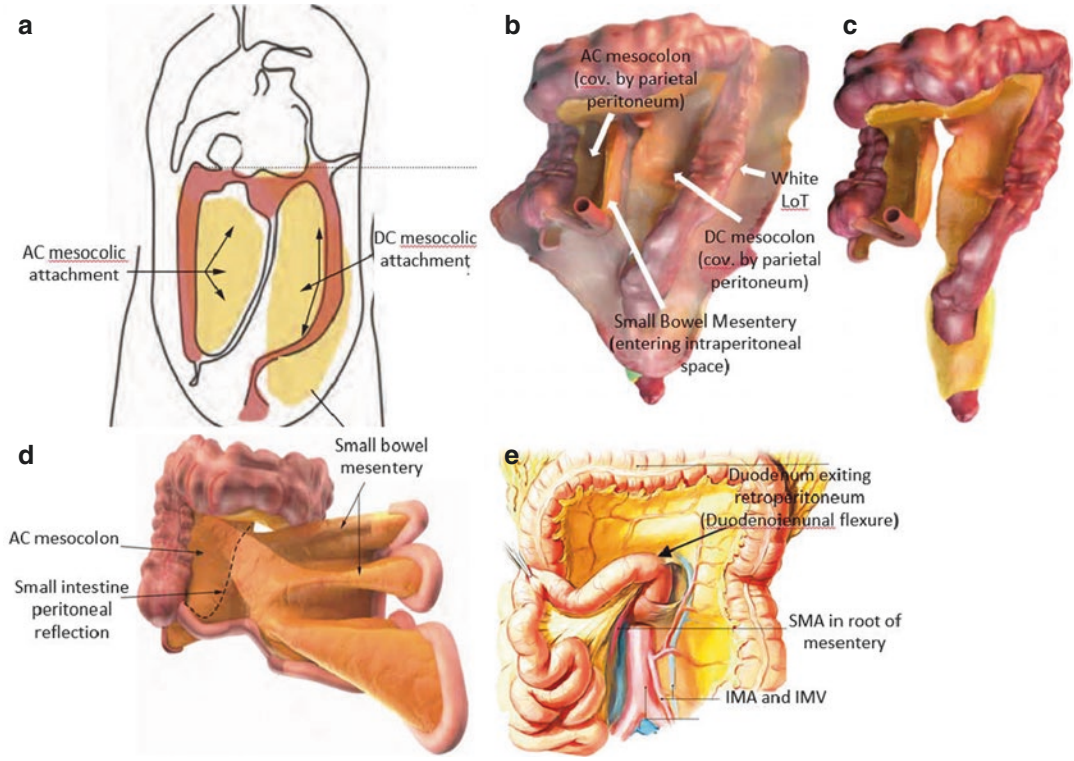

Fig. 1.10 AC mesocolon, DC mesocolon, and small bowel mesentery. (**a**) The AC mesocolon and DC mesocolon lie flat within the anterior pararenal space parallel to the posterior abdominal wall. (**b**) The posterior wall of the peritoneal cavity is formed by a sheet of mesothelial tissue referred to as the parietal peritoneum. This layer drapes over the AC, DC and their respective mesocolons, which are situated within the anterior pararenal space of the retroperitoneum. The lateral edge (antimesenteric border) of the AC and DC where the peritoneal layer drapes over the AC and DC is referred to as the white LoT. (**c**) The AC, DC and their respective mesocolons shown here without the overlying parietal peritoneal covering. (**d**) The small bowel mesentery is covered by the peritoneal reflection and projects into the peritoneal cavity perpendicular to the posterior abdominal wall. (**e**) The root of the small bowel mesentery is formed by the SMA. *AC* ascending colon, *DC* descending colon, *IMA* inferior mesenteric artery, *IMV* inferior mesenteric vein, *LoT* line of toldt, *SMA* superior mesenteric artery [3, 7]

ing Gerota's fascia overlying the right perirenal space (Fig. 1.13). Of note, the second portion of the duodenum, which also lies within the anterior pararenal space, will subsequently be encountered as the ascending colon mesocolon is lifted off the right perirenal space. Division of duodenal connective tissue attachments to the Gerota's fascia (preferably with non-thermal dissection) enables medial reflection (Kocher maneuver) [4] so as to expose the right renal vein and inferior vena cava (Fig. 1.14).

Similar to the right perirenal space, transperitoneal access to the left perirenal space involves medial reflection of the descending colon and its mesocolon along with the tail of the pancreas (more superiorly) (Fig. 1.15). This has historically been referred to as the Mattox maneuver. In addition, the splenorenal ligament is often divided to allow medial reflection of the spleen and improve exposure of the upper pole of the kidney (Fig. 1.4).

The Cattel-Braasch maneuver [5] (right medial visceral rotation) is commonly employed during open surgery to gain access to the central vascular compartment. The parietal peritoneum is incised lateral to the ascending colon,

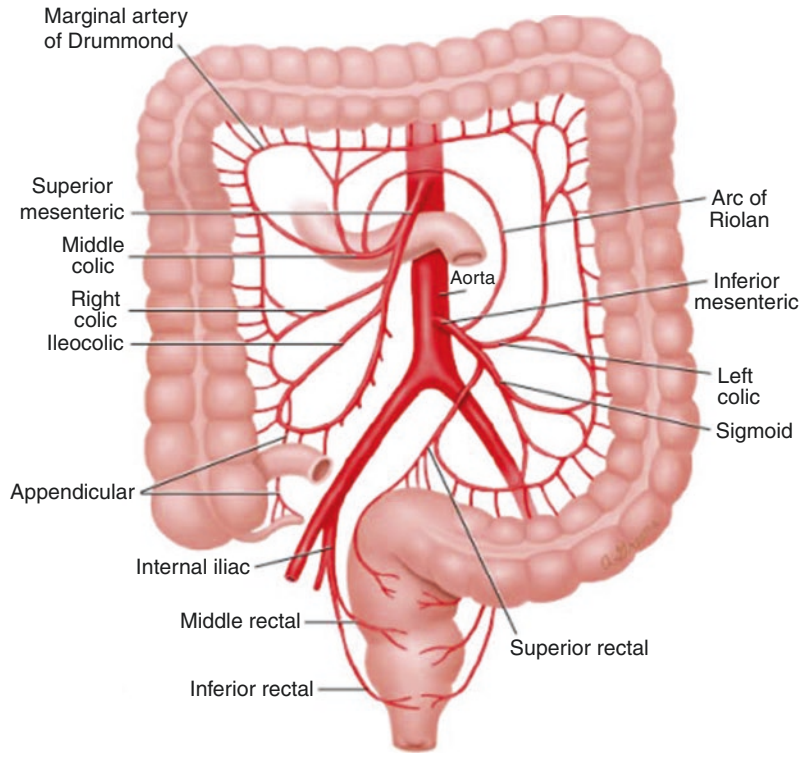

Fig. 1.11 Shown here are the arterial branches of the SMA and IMA. The primary blood supply within the AC mesocolon is derived from the right colic artery whereas the blood supply within the DC mesocolon is primarily from the left colic artery. The Marginal Artery of Drummond and Arc of Riolan permits extensive communication between the SMA, IMA, and hemorrhoidal/rectal arteries, thus allowing for collateral blood supply to the left colon and rectum. *AC* ascending colon, *DC* descending colon, *IMA* inferior mesenteric artery, *SMA* superior mesenteric artery [8]

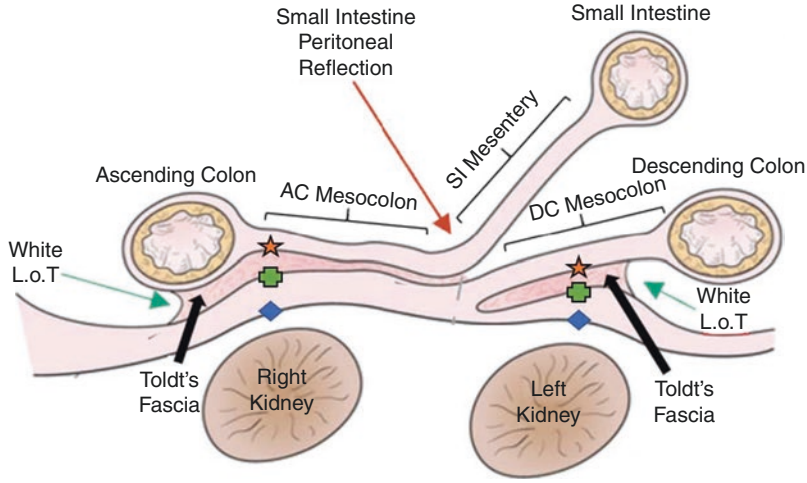

Fig. 1.12 The Toldt's fascia is formed by fusion of the visceral peritoneum layer, which had previously lined the under-surface of the AC mesocolon and DC mesocolon (orange star), and the parietal peritoneum layer (green cross), which had previously formed the posterior wall of the peritoneal cavity as it draped over Gerota's fascia (blue diamond). *AC* ascending colon, *DC* descending colon, *IMA* inferior mesenteric artery, *LoT* line of toldt, *SI* small intestine, *SMA* superior mesenteric artery [9]

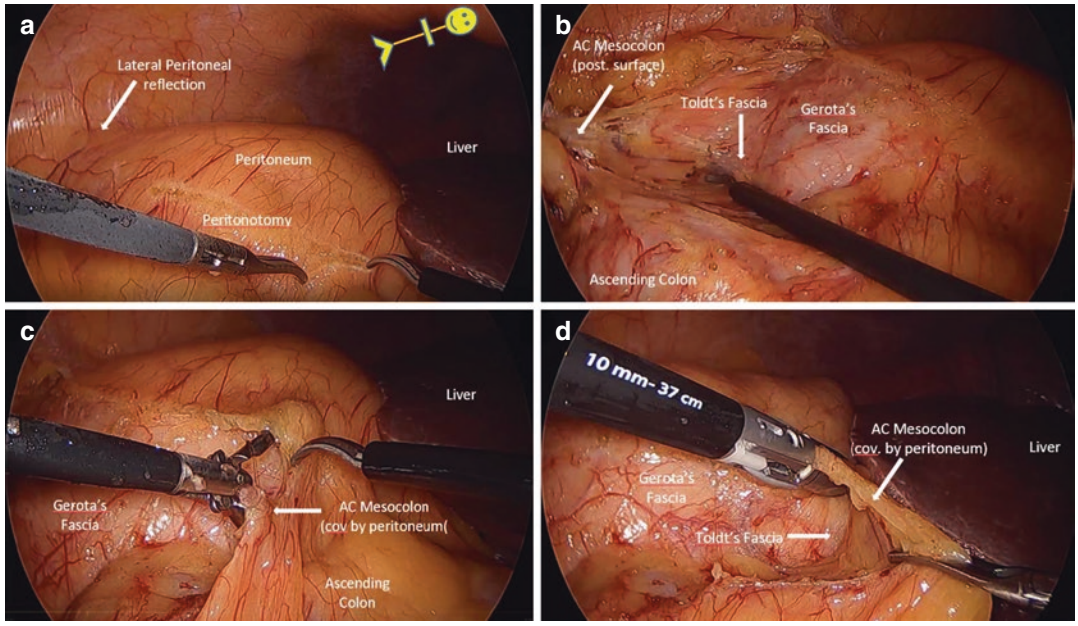

Fig. 1.13 Transperitoneal access to the right perirenal space. (**a**) An incision is made in the peritoneum at the proximity of the white line of Toldt (which occurs at the lateral/antimesenteric border of the AC). (**b**–**d**) The AC along with its mesocolon are medially reflected to permit continued dissection and division of Toldt's fascia. This permits further medial reflection of the AC mesocolon and exposes the underlying Gerota's fascia overlying the right perirenal space. *AC* ascending colon

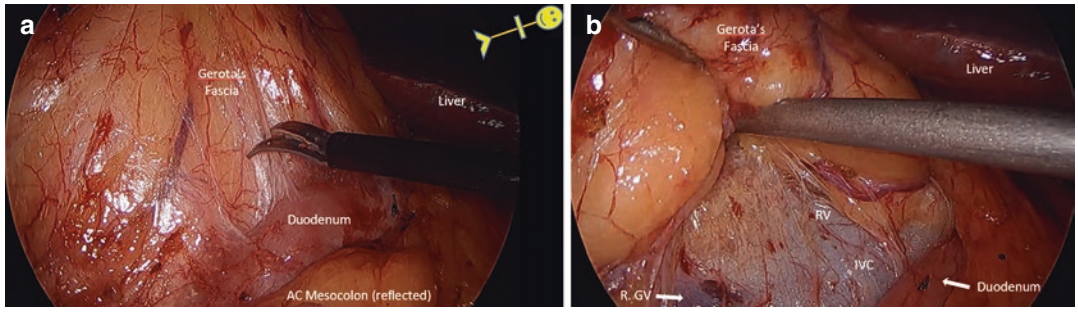

Fig. 1.14 Kocherization of the duodenum. (**a**) Connective tissue attachments of the duodenum to the Gerota's fascia are divided sharple with athermal dissection. (**b**) Medial reflection of the duodenum (Kocherization) exposes the underlying IVC and right RV. The right GV is also sees as it drains directly into the IVC. *AC* ascending colon, *GV* gonadal vein, *IVC* inferior vena cava, *RV* renal vein

around the cecum, and then superiorly along the parietal peritoneum of the posterior abdominal wall at where the peritoneum reflect to line the small bowel mesentery towards the ligament of Treitz/root of the small bowel mesentery, allowing for medial and cephalad displacement of the ascending colon and its mesocolon, the second through fourth portions of the duodenum, and the jejunum and ileum (Fig. 1.16). Landmarks used during this maneuver include the left renal vein, which can be adequately should be exposed as the transverse segments of the duodenum are lifted anteriorly, and/or the inferior mesenteric vein.

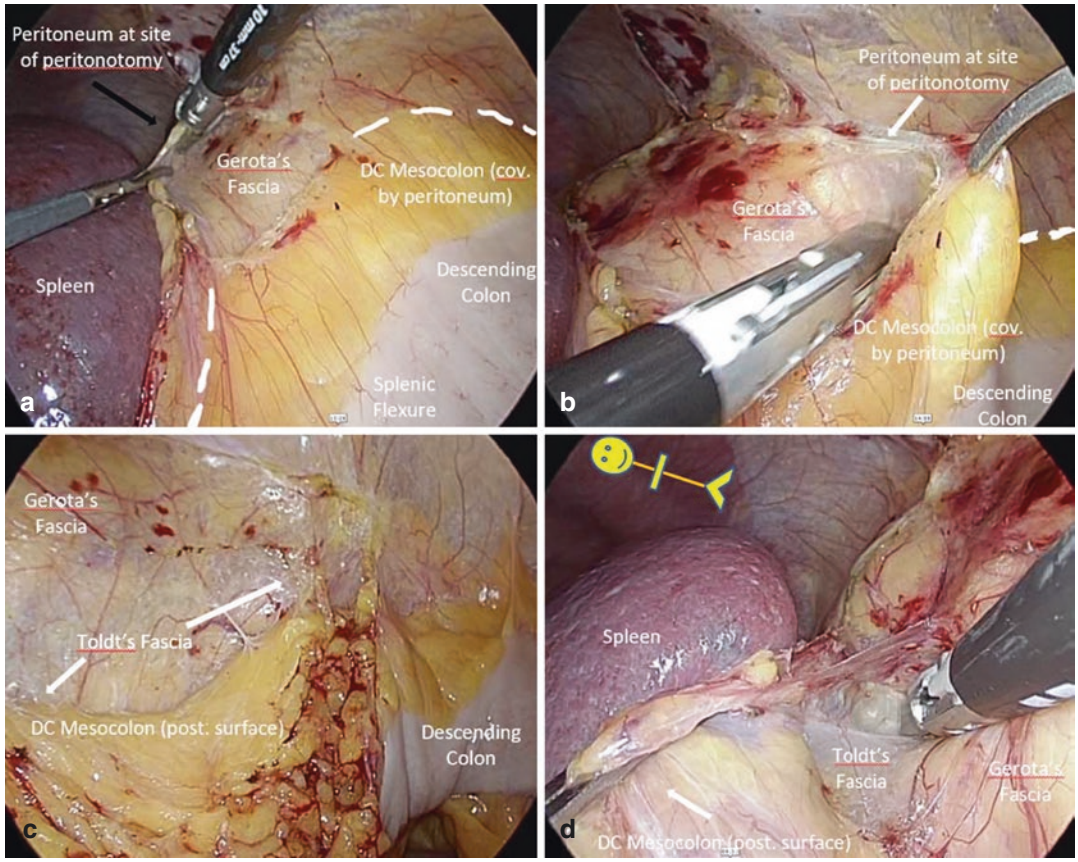

Fig. 1.15 Transperitoneal access to the left perirenal space. (**a**) An incision is made in the peritoneum at the proximity of the white LoT (which occurs at the lateral/antimesenteric border of the descending colon). (**b–d**) The DC along with its mesocolon are medially reflected to permit continued dissection and division of Toldt's fascia. This permits further medial reflection of the DC mesocolon and exposes the underlying Gerota's fascia overlying the left perirenal space. *DC* descending colon, *LoT* line of toldt

Posterior Pararenal Space

The posterior pararenal space consists entirely of adipose tissue (Fig. 1.2f). It is situated immediately behind the posterior perirenal fascia and its anterior fascial extension, the lateral conal fascia. The posterior pararenal space is bounded posteriorly by the transversalis fascia. Given that the lateral conal fascia fuses with the parietal peritoneum, the posterior pararenal space is contiguous with the preperitoneal fatty layer (Fig. 1.1).

Central Vascular Compartment

The central vascular compartment of the retroperitoneum extends from the T12 vertebrae, where the aorta passes through the aortic hiatus of the diaphragm and emerges from the thoracic space, down to the level of the L4 vertebrae, where the aorta bifurcates into the common iliac arteries. Within this space reside the abdominal aorta and its efferent branches, the vena cava and its afferent tributaries, an elaborate network of lymphatics that invest the aorta

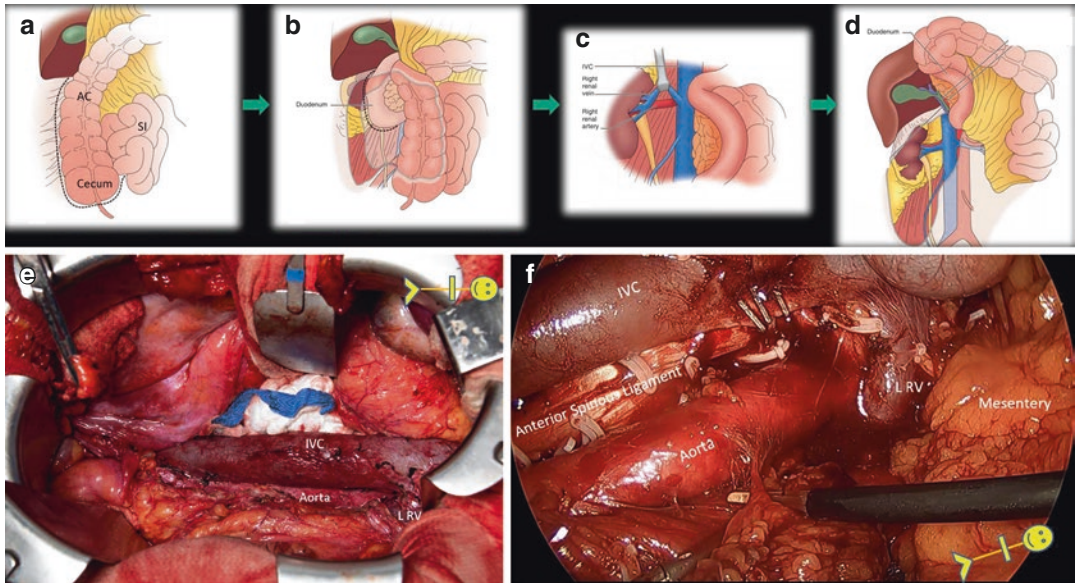

Fig. 1.16 Cattel-Braasch maneuver. (**a**) The parietal peritoneum is incised lateral to the AC (at the white LoT) and around the cecum. (**b**) The AC and its mesocolon are then reflected medially exposing the duodenum. (**c**) The connective tissue attachments of the duodenum to the underlying Gerota's fascia and central vascular compartment are divided, permitting medial reflection of the duodenum—a maneuver referred to as Kocherization. (**d**) The parietal peritoneum of the posterior abdominal wall at the peritoneal reflection of the small bowel mesentery is then incised from the right lower quadrant to the left upper quadrant towards the root of the small bowel mesentery. This incision is continued until visualization of the L RV. This maneuver allows for medial and cephalad displacement of the AC and its mesocolon, the 2nd through 4th portions of the duodenum, and the jejunum and ileum. (**e**) Exposure of the central vascular compartment after Cattel Braasch maneuver during open surgery. Note visualization of the L RV. (**f**) Exposure of the central vascular compartment after Cattel Braasch maneuver during laparoscopic surgery. Note visualization of the L RV. *AC* ascending colon, *IVC* inferior vena cava, *LoT* line of toldt, *SI* small Intestine, *RV* renal vein [5]

and vena cava, and the abdominal sympathetic chain (Fig. 1.2d).

The central vascular compartment is bounded posteriorly by the anterior spinous ligament (also referred to as the anterior longitudinal ligament), which overlies the vertebral spine, laterally by the perirenal space and its associated fascia, and anteriorly by both the midline connective tissue extension of Gerota's fascia and Toldt's fascia, which serves as the posterior connective tissue border of anterior pararenal compartment (Figs. 1.2 and 1.17). Of note, the crus of the diaphragm are also visualized posteriorly within the central vascular compartment as they insert onto the anterior-lateral aspects of the L1 and L2 vertebral body; the abdominal sympathetic chains can be seen emerging from underneath the crus bilaterally as they descend alongside the lateral aspect of the vertebral bodies (Fig. 1.17); thus, the crus serve as a valuable landmark when performing a nerve-sparing retroperitoneal lymph node dissection.

Aorta

The major branches encountered off the anterolateral aspect of the abdominal aorta when proceeding cephalad to caudad are the celiac trunk, the superior mesenteric artery, the left and right renal arteries, the left and right gonadal arteries, and the inferior mesenteric artery. The middle sacral artery is also encountered at the bifurcation of the aorta (Fig. 1.18).

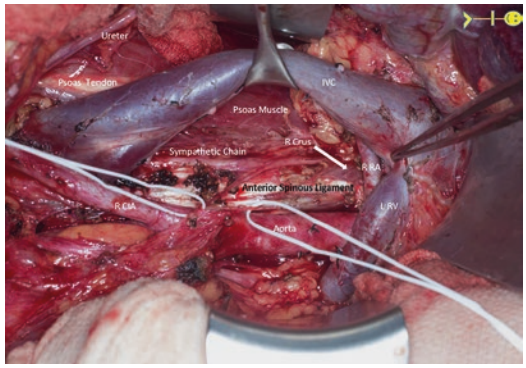

Fig. 1.17 Central vascular compartment. The anterior spinous ligament forms the posterior border of the central vascular compartment. The sympathetic chain can be seen emerging from underneath the cover the crus of the diaphragm and traveling caudally along the lateral edge of the anterior spinous ligament and medial border of the psoas muscle. Emanating from the sympathetic chain are the post-ganglionic splanchnic serves (encircled by white vessel loops), which on the right, travel beneath the IVC to arrive onto the anterior surface of the Aorta. *CIA* common iliac artery, *IVC* inferior vena cava, *RA* renal artery, *RV* renal vein

Superior Mesenteric Artery

The working space of urologic surgeons is most often limited superiorly by the renal hilar vessels; as such, the superior mesenteric artery (and the vessels above) is generally not exposed during open and laparoscopic urologic procedures. Nevertheless, the surgeon should be mindful of the superior mesenteric artery location given its close proximity to the renal hilar vessels. Indeed, the left renal vein crosses the midline anterior to the aorta, but posterior and inferior to the take-off of the superior mesenteric artery (Figs. 1.17 and 1.19). Similarly, the third and fourth portions of the duodenum, which reside within the anterior pararenal space, course posterior and inferior to the superior mesentery artery, and in doing so, lie directly anterior to both right and left renal veins (Fig. 1.19). In this regard, Kocherization [4] of the duodenum provides access to the right renal vein as well as the distal aspect of left renal vein as it enters the

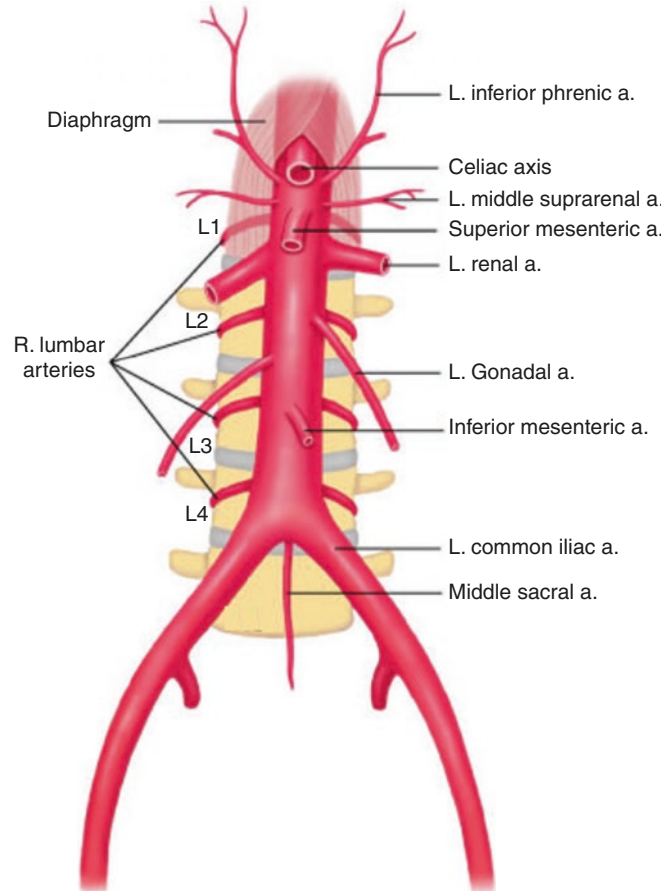

Fig. 1.18 Major vascular branches of the aorta

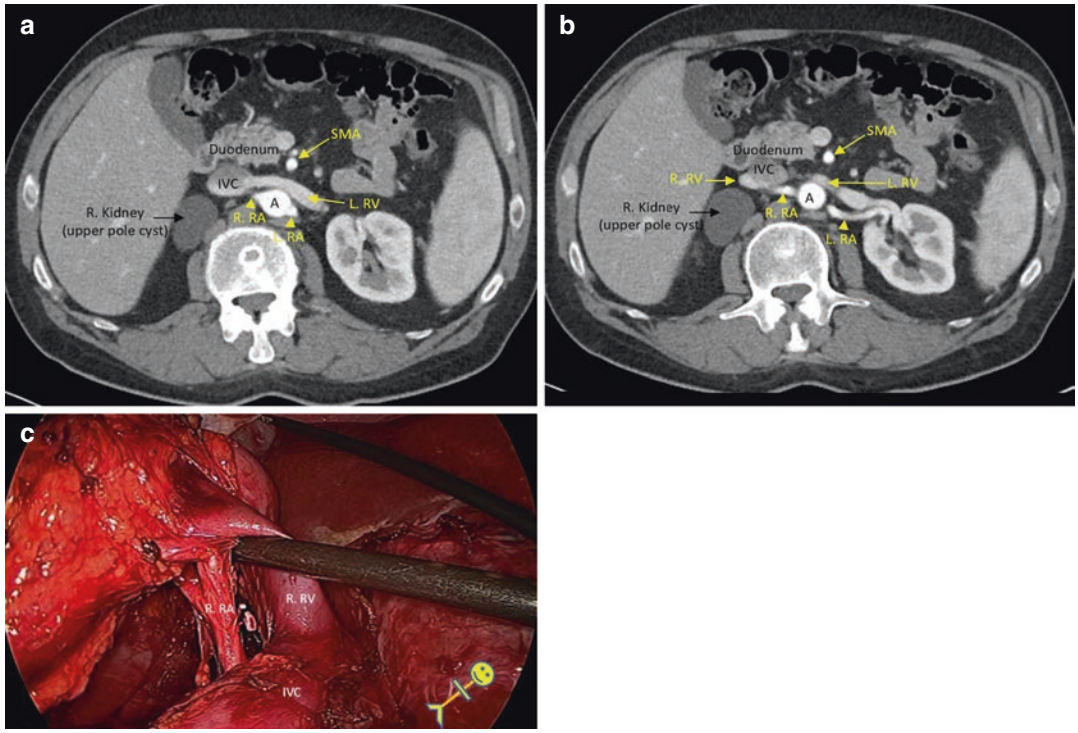

Fig. 1.19 Central vascular compartment. (**a**) The L RV courses anterior to the Aorta, and inferior and posterior to the SMA. The duodenum is immediately anterior to the IVC and L RV within the anterior pararenal space. (**b**) The R RA and L RA enter the hilum of the kidney posterior to the corresponding R LV and L RV. In doing so, the R RA travels posterior to the IVC. (**c**) Seen here within the right renal hilum is the R RV, which is the anterior most structure, and the R RA, emerging from behind the IVC. *A* aorta, *IVC* inferior vena cava, *RA* renal artery, *RV* renal vein, *SMA* superior mesenteric artery

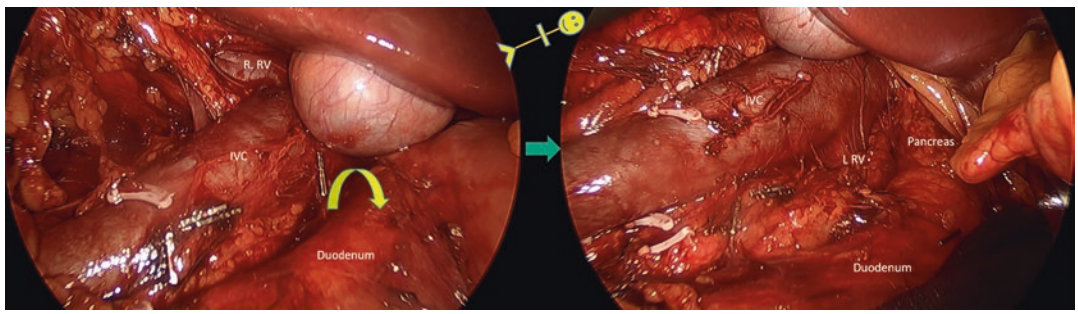

Fig. 1.20 More extensive medial reflection (e.g. Kocherization) of the duodenum off the medial edge of the IVC permits access to the interaortocaval space and the L RV. *IVC* inferior vena cava, *RV* renal vein

inferior vena cava (Fig. 1.20) while medial and cephalad displacement of the anterior pararenal compartment, specifically during the Cattel-Braasch maneuver, lifts the duodenum along with the SMA off the left renal vein, exposing its more proximal extent (Fig. 1.17) [5].

Intraoperative injury to the superior mesenteric artery can be especially catastrophic as such circumstances would render the entirety of the small bowel and proximal colon vulnerable to ischemia. One possible scenario arises during the Cattel-Braasch maneuver, whereby

incision of the parietal peritoneum lateral to the ascending colon, around the cecum, and diagonally along the posterior peritoneal peritoneum towards the ligament of Treitz (duodenojejunal flexure) detaches the ascending colon and its mesocolon from the underlying Gerota's fascia and the broad-based small bowel mesentery from the posterior abdominal wall [5]. As aforementioned, this enables medial visceral rotation and exposes both the right perirenal space and central vascular compartment up to the level of the left renal vein (Figs. 1.16 and 1.17). Given that the superior mesenteric artery is the primary blood supply to the small intestine and right colon, this maneuver leaves the mobilized intestinal segments on a stalk formed by the SMA, which is referred to here as the root of the mesentery. Accordingly, the pulse of the SMA should be periodically assessed to ensure the vessel is not twisted or subject to excessive traction caused by retraction instruments being used to maintain exposure of these retroperitoneal spaces. An alternative scenario arises when performing a left nephrectomy, as care should be taken not to confuse the superior mesenteric artery for the left renal artery when obtaining hilar control.

Renal Artery

Branching off the lateral aspect of the aorta below the superior mesenteric artery are the left and right renal arteries (Fig. 1.19). Given that the IVC is situated slightly anterior to the Aorta, the renal arteries course posterior to their corresponding renal veins as they enter the renal hilum (Figs. 1.7 and 1.19). Moreover, the right renal artery arrives at the renal hilum by crossing the interaortocaval space behind the IVC (Figs. 1.17, 1.19, and 1.21). When performing nephrectomy for large renal masses that may encroach medially and obscure access to the renal hilum, the renal artery can be controlled in the interaortocaval space as it branches off of the aorta; this approach also helps ensure that control of the main renal artery is obtained as opposed to arterial branches, which commonly form more distally within the renal hilar location.

The urologic surgeon should be aware of the possibility for both accessory and supernumerary renal arteries. Accessory renal arteries, often referred to as polar vessels, most often emerge off the left side of the aorta and direct supply a polar region of the kidney where supernumerary arteries emerge off the aorta and enter the hilum alongside the main renal artery (Fig. 1.21).

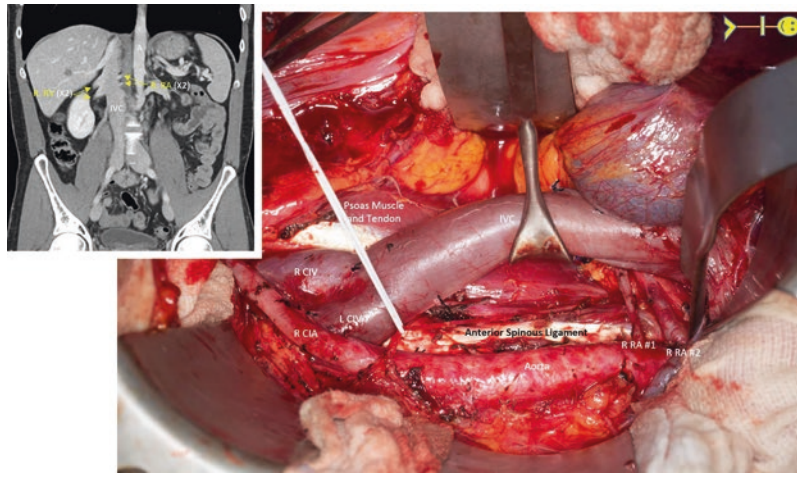

Fig. 1.21 Seen here within the interaortocaval space are two renal arteries (R RA #1 and RRA#2). R RA #1, given that it enters the renal hilum with the main R RA (RRA #2), is referred to as a supernumerary artery. Take note of the course of the R RA, traveling posterior to the IVC en route to the right renal hilum. *CIA* common iliac artery, *CIV* common iliac vein, *IVC* inferior vena cava, *RA* renal artery, *RV* renal vein

Accessory arteries most commonly supply the lower pole of the kidney whereas supernumerary vessels are usually found in a location superior to the renal vein. Radiographic assessment of the aorta and its branches in the preoperative setting is extremely valuable in this regard and aid in surgical planning (Fig. 1.21).

Gonadal Artery

The gonadal artery emerges off the anterolateral aspect of the aorta and joins its corresponding gonadal vein as they descend in the retroperitoneum within the perirenal space (Fig. 1.22a). It is important to be cognizant of the right gonadal artery as it crosses over the anterior surface of inferior vena cava, as inadvertent division during the "split-and-roll" maneuver during retroperitoneal lymph node dissections can result in bleeding. This is especially the case given that the gonadal artery is much narrower in caliber than its corresponding gonadal vein.

Inferior Mesenteric Artery

The final major branch of the abdominal aorta is the inferior mesenteric artery (IMA) (Fig. 1.23), which supplies the descending colon, sigmoid colon, and rectum. The IMA participates in two watershed regions of the large intestine, specifically at the level of the splenic flexure and the lower rectum. At the splenic flexure, the left colic artery of the IMA communicates with the middle colic artery of the SMA via two vascular arcades

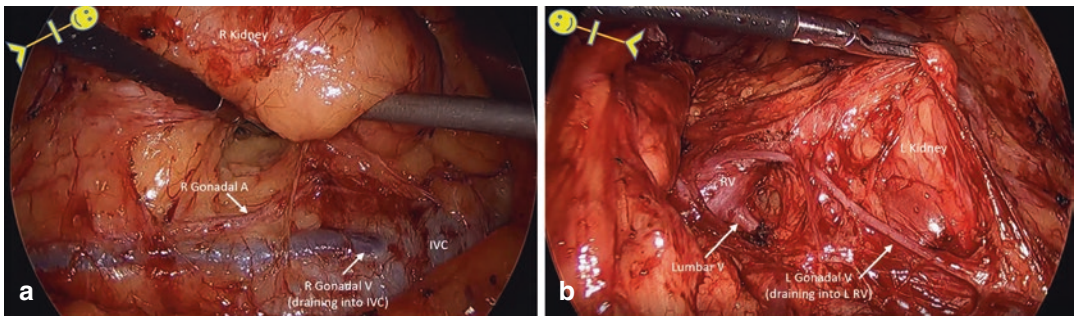

Fig. 1.22 Gonadal vessels. (**a**) The R Gonadal V drains directly into the IVC. Seen adjacent to it is the R Gonadal A, which is much narrower in caliber and courses over the IVC to the join the R Gonadal V. (**b**) The L Gonadal V drains directly into the L RV. *A* artery, *IVC* inferior vena cava, *RV* renal vein, *V* vein

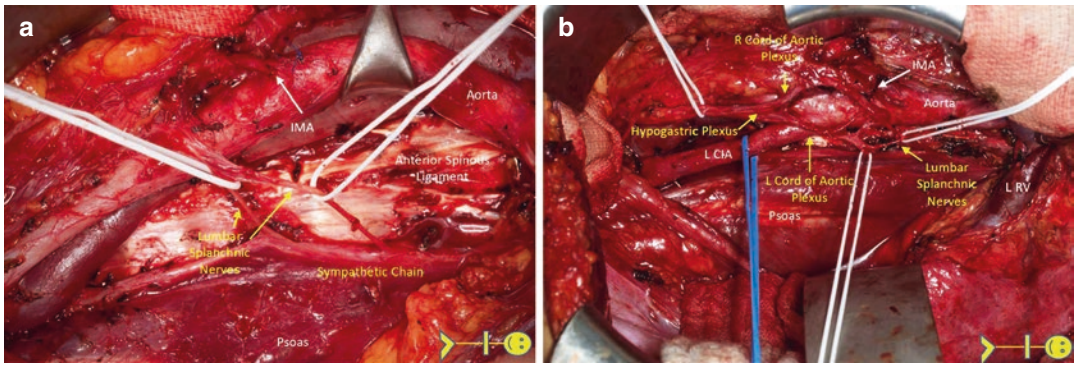

Fig. 1.23 Sympathetic nervous system structures within the central vascular compartment. (**a**) With the Aorta retracted medially, the left sympathetic trunk is seen traveling on the lateral edge of the anterior spinous ligament and medial border of the psoas muscle. Branching off the sympathetic trunk are the post-ganglionic lumbar splanchnic nerves (encircled by white vessel loops); they can be seen entering the cord of the aortic plexus below the level of the IMA. (**b**) The confluence of the L and R sympathetic cords of the Aortic plexus is seen below the level of the IMA, giving rise to the hypogastric plexus at the bifurcation of the Aorta. *CIA* common iliac artery, *IMA* inferior mesenteric artery, *RV* renal vein

within the colonic mesentery—the marginal artery of Drummond, which runs closest to the mesenteric border of the colon, and the meandering artery of the mesentery, which is closer to the root of the vessel (Fig. 1.11). Similarly, anastomoses between the superior rectal artery of the IMA with the middle and inferior rectal arteries coming off the internal iliac artery form the watershed region of the rectum.

The overlapping nature of the blood supply to the colon is an important anatomic consideration, particularly during a retroperitoneal lymph node dissection as ligation of the IMA may be necessary to ensure completeness of resection; although an effort should be made to preserve the IMA, ischemic damage to the colon is unlikely to occur in the event the IMA is compromised due to this robust vascular network that exists between its branches and those of the SMA and internal iliac artery.

Moreover, the IMA is a critical landmark during retroperitoneal lymph node dissection given that below the IMA, the right and left cords of the aortic plexus begin to convalesce so as to eventually give rise to the hypogastric plexus at the level of the aortic bifurcation (Fig. 1.23). Indeed, modified templates for retroperitoneal lymph node dissection for metastatic testicular cancer minimize dissection below the IMA to minimize disruption of the hypogastric plexus and aid in the preservation of antegrade ejaculation [6].

Lumbar Arteries

Situated posterolaterally along the abdominal aorta are the lumbar arteries. In general, there are four pairs of lumbar arteries in total, of which only three are encountered in the infrarenal location (Fig. 1.24). The lumbar arteries initially assume a lateral course upon branching off the aorta and then subsequently dive posteriorly to

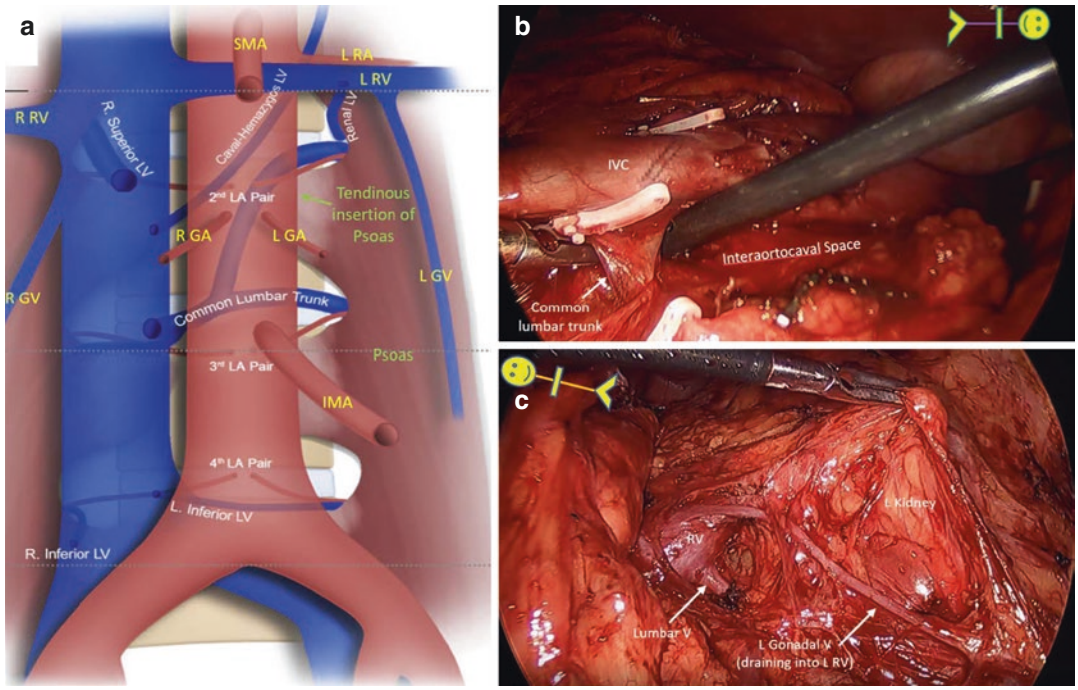

Fig. 1.24 Architecture of the lumbar vessels (arteries and veins). (**a**) Seen here is the relationship of the lumbar veins that drain into the IVC relative to the main venous branches of the IVC. Additionally, the anatomic distribution of the lumbar arteries is seen here relative to the major arterial branches of the Aorta. (**b**) Laparoscopic view of the common lumbar trunk within the interaortocaval space as it drains into the IVC. (**c**) Laparoscopic view of the renal lumbar vein draining into the posterior aspect of the L RV. *GA* gonadal artery, *GV* gonadal vein, *IMA* inferior mesenteric artery, *LA* lumbar artery, *LV* lumbar vein, *RA* renal artery, *RV* renal vein, *V* vein [6]

travel lateral to the anterior spinous ligament and alongside the lateral edges of the lumbar vertebral bodies. Given the aorta is lateralized slightly to the left of the vertebral spine, lumbar arteries emerging from the right edge of the aorta traverse the interaortocaval space underneath the inferior vena cava.

The two superior pairs of lumbar arteries dive behind the crus of the diaphragm as they course posteriorly whereas the two inferior pairs exit the central vascular compartment behind the sympathetic trunk and medial to the tendinous insertions of the psoas muscle along the lateral aspect of the L3-L5 vertebrae. Given that the infrarenal lumbar arteries (and corresponding veins) closely abut the medial edge of the psoas muscle belly upon exiting the retroperitoneum, medial traction placed directly onto the psoas muscle (i.e. with a sponge stick) can help tamponade bleeding that occurs during division of the lumbar vessels.

Inferior Vena Cava

Renal Vein and Gonadal Veins

The renal vein is the anterior most structure of the renal hilum, overlying the renal artery as it exits the perirenal space and enters the central vascular compartment (Fig. 1.7). The left renal vein, which is longer than the right, courses anterior to the aorta en route to the IVC and is situated below the takeoff of the SMA (Figs. 1.17 and 1.19). Anatomic variations of the left renal vein include a retroaortic left renal vein, which travels posterior to the aorta, and a circumaortic left renal vein, which is comprised of two veins traveling both anterior and posterior to the aorta.

Unique to the left renal vein is the drainage it receives from both the left gonadal vein and left adrenal vein, as well as in many cases the second right lumbar vein (Fig. 1.22b). This is unlike the case on the right, where the gonadal vein, renal vein, and adrenal vein independently drain into the inferior vena cava (Fig. 1.22a). The drainage pattern of the left renal vein is of clinical relevance when performing retroperitoneal surgery, especially left nephrectomy, as the left gonadal vein may be traced superiorly to aid in identification of the left renal vein. Another consideration related to the anatomy of the gonadal venous drainage involves the risk for avulsion of the right gonadal vein off the IVC when performing a right nephrectomy, particularly via a minimally-invasive approach. Given that the gonadal veins descend in the perirenal compartment parallel to the ureter, anterior traction placed on the ureter and surrounding perirenal fat to separate these structures from the lateral edge of the IVC and lift off the psoas fascia can cause traction on the right gonadal vein, resulting in avulsion; as such, this maneuver should be performed in a manner where the Gerota's fascia is entered lateral to the vein, leaving it in a medial position adjacent to the inferior vena cava.

Transperitoneal access to the right renal vein is gained primarily through medial mobilization and Kocherization [4] of the second portion of the duodenum (Fig. 1.14), whereas the left renal vein can be accessed a multitude of ways. The most conventional approach, employed when performing a left nephrectomy, involves medial reflection of the descending colon and its mesocolon along with the tail of the pancreas (Fig. 1.25). Alternatively, exposure can be obtained from the right through more extensive Kocherization [4], whereby the duodenum and pancreatic head are both medially and anteriorly reflected off the connective tissue overlying the central vascular compartment (Fig. 1.20), or the Cattel-Braasch maneuver (Fig. 1.16) [5]. In general, maneuvers to expose the renal veins offer good accessibility to the renal arteries; the exception is when performing nephrectomy for a large right renal mass,

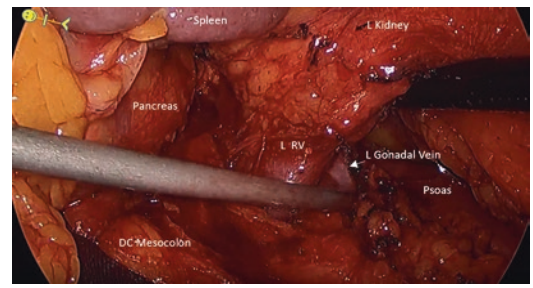

Fig. 1.25 Access to the left perirenal space and exposure of the left renal hilum involves medial reflection of the DC and its mesocolon as well as medial reflection of the pancreatic tail. *DC* descending colon

where medial encroachment by the tumor may necessitate control of the right renal artery in the interaortocaval space.

Lumbar Veins

The lumbar veins drain into the posterolateral inferior vena cava, but unlike the lumbar arteries, they do not necessarily occur in pairs and are variable in location and number. Along the infrarenal IVC, generally three lumbar veins are encountered on the right whereas two lumbar veins occur on the left (Fig. 1.24).

The right superior lumbar vein, which is large in caliber, is seen just below the confluence of the right renal vein and IVC and above the entry of the right gonadal vein. The right middle lumbar vein, which is variably present, is mid-way between the renal vein and IVC bifurcation, and may form a common trunk with the corresponding left lumbar vein. The right inferior lumbar vein is encountered just above the confluence of the right common iliac vein and IVC.

The primary lumbar vein on the left IVC occurs mid-way between the left renal vein and iliocaval junction, approximately at the level of the IMA, which can serve as a landmark. This vein, often referred to as the common lumbar trunk, forms from the convalescence of several tributaries (up to 3) that course behind the aorta and across the interaortocaval space; as such, proximal control of this vein may involve only a single suture tie while distal control may require multiple branches to be clipped in the interaortocaval location and then again the paraaortic location as they emerge lateral to the edge of the anterior spinous ligament from behind the left sympathetic trunk. The second left lumbar vein is situated more inferiorly at the iliocaval junction, just superior to where the right common iliac artery drapes over the left common iliac vein.

The lumbar veins emerge from behind the sympathetic trunk and tendinous insertions of the psoas muscle (or the right crus in the case of the right superior lumbar vein), lateral to the anterior spinous ligament. The left lumbar veins run posterior to the aorta as they cross the interaortocaval space to drain into the IVC.

Sympathetic Plexus

From a urologic perspective, the sympathetic nerve plexuses within the retroperitoneum are important for maintenance of antegrade ejaculation. Understanding the anatomy of this neural network is particularly relevant when performing nerve-sparing retroperitoneal lymph node dissection given the intimate association between these nerves and the major vessels within the central vascular compartment. The sympathetic system can be divided into four major structures for the ease of understanding what needs to be preserved when nerve-sparing is attempted: the abdominal sympathetic chain, the infrarenal lumbar splanchnic nerves, the right and left cords of the aortic plexus, and the hypogastric plexus (Fig. 1.23) [6].

The abdominal sympathetic chain emerges from under the crus of the diaphragm and descends the posterior central vascular space in the paravertebral location, along the lateral edge of the anterior spinous ligament and anteromedial to the tendinous insertions of the psoas muscles to the L3-L5 vertebrae. The IVC and Aorta overly the right and left sympathetic chains, respectively. Two main lumbar splanchnic nerves emerge from each sympathetic trunk from between the level of the L1-L4 vertebrae and join their respective cord of the aortic plexus, which run longitudinally along anterior surface of the aorta; in many cases, accessory splanchnic nerves can be seen branching off the sympathetic trunk and entering the aortic plexus below the IMA [6]. Both lumbar splanchnic nerves on the right course posterior to the IVC and travel across the interaortocaval space to join the right cord of the aortic plexus. Thus, a paracaval lymph node tissue can be dissected off the adventitia of the IVC with relative impunity given the nerves do not traverse this space.

The superior right lumbar splanchnic nerve comes off the sympathetic trunk at the level of the right renal vein above where the right superior lumbar vein drains and can be seen coursing obliquely across the interaortocaval space so as to enter the right cord of the aortic plexus below the right gonadal artery. The inferior right lumbar splanchnic nerve emerges from the sympathetic trunk just

below the level of the right gonadal vein and can also be seen in the interaortocaval space superior to the left common lumbar trunk [6]; it enters the right cord of the aortic plexus at or below the level of the IMA. As such, during the interaortocaval lymph node dissection, the nerves should be prospectively identified and isolated to avoid inadvertent injury as the lumbar vessels are ligated and/or fibroadipose tissue is dissected off the adventitia of the medial edges of the IVC and aorta.

On the left, the superior lumbar splanchnic nerve emerges from below the level of the left renal vein and courses anteriorly and inferiorly through the paraaortic fibroadipose tissue to join the left cord of the aortic plexus at the origin of the left gonadal artery. The inferior lumbar splanchnic nerve branches off the sympathetic trunk more caudally, and often just superior to where the third left lumbar artery dives posteriorly behind the sympathetic trunk into the psoas muscle; it intersects the left cord of the aortic plexus at or below the level of the IMA [6].

Neural crosstalk between the right and left cords of the aortic plexus increases below the level of the IMA, but their true convalescence is appreciated at the level of the aortic bifurcation, where the hypogastric plexus is formed.

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Gross and Laparoscopic Anatomy of the Lower Tract and Pelvis

2

Bastian Amend and Arnulf Stenzl

Introduction

An overview of the gross and laparoscopic anatomy of the lower urinary tract should summarize both long-standing anatomic knowledge and current scientific findings. In few fields has the anatomic understanding grown as much as urology, especially concerning anatomy of the lower urinary tract. Whereas the gross anatomy is already well known, now research is increasingly contributing to our understanding of the microscopic level. This concerns especially the detailed anatomy and topography of the sphincter mechanism of the urinary bladder, the routing and function of the neural structures in the pelvis and, for example, the anatomic structure of the pelvic floor. The transmission of these new findings in combination with traditional anatomic knowledge into urological practice, including the growing field of laparoscopic surgery, is essential to maintain and improve the success of treatments for our patients. The following chapter gives a clear, detailed and informative summary of the anatomy of the lower urinary tract, especially considering of laparoscopic and endoscopic surgery.

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The History of the Study of the Urological Anatomy

The historiography of urology goes back to 1000 BC in Egypt. The first description of a bladder catheter made of bronze dates to this time, and bladder stone surgery also seems to have been practiced. The prostate was first described by Herophilus of Chalcedon in 300 BC. Human cadaver sections enabled this first glimpse.

After the widespread rejection of anatomical studies up to the Middle Ages, detailed descriptions of human anatomy began to emerge again with the work of Leonardo da Vinci (1452–1519), Andreas Vesalius (1514–1564) from Brussels and their successor Eustachi (1500–1574). The anatomy of the urogenital tract was mainly revealed by Étienne de la Rivière of Paris with the description of the seminal vesicles, Marcellus Malpighi (1628–1694) with the exploration of renal functioning and Lorenzo Bellini (1643–1704) with the identification of the renal tubuli. The progress of microscopic examinations further advanced the basic anatomical knowledge. In 1684, Mery described the existence of the bulbourethral glands, which was later attributed to Cowper.

The founder of the study of the pathology of the urogenital tract was Giovanni Battista Morgagni (1682–1771) with his work "De sedibus et causis morborum." Giovanni Battista

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Morgagni is considered the first to describe prostatic hyperplasia.

One of the milestones in urology—urological endoscopy—goes back to Phillip Bozzini of Frankfurt who invented the first endoscope using candlelight in 1806. This made possible the exploration of the internal anatomical details of a living individual [1].

Topographic Anatomy of the Anterior Abdominal Wall

The increasing significance of laparoscopic procedures, especially for intrapelvic and prostatic surgery, necessitates a detailed understanding of the topographic anatomy of the anterior abdominal wall. Figure 2.2 illustrates the different structures in addition to a laparoscopic view of the male pelvis (Fig. 2.1) at the beginning of robotic-assisted radical prostatectomy. Beside topographic knowledge of specific anatomic landmark physiologic movement of intraabdominal structures, e.g. pulsation of arteries or undulated contraction of the ureters, and manipulation with introduced catheters (bladder neck visualisation during robot-assisted prostatectomy by catheter pull) help to identify relevant structures to proceed with surgery.

Five tissue folds subdivide the anterior abdominal wall. The former embryonic urachus forms the median umbilical ligament between the urinary bladder and the umbilicus. On both sides lateral to the median umbilical ligament, the remnants of the fetal umbilical arteries shape the medial umbilical ligaments/folds—the space in between is called the supravesical fossa. During cystectomy, the medial umbilical ligaments are the main structures to identify and control the superior vesical pedicle including the superior vesical artery. The inferior epigastric vessels underlie the lateral umbilical ligaments/folds. These structures have important significance regarding hernia classification. Medial to the lateral umbilical fold, the medial inguinal fossa represents the passage of direct inguinal hernias. The lateral inguinal fossa corresponds to the deep inguinal ring—the entry to the inguinal canal. An indirect inguinal hernia accompanies the components of the spermatic cord through the inguinal canal into the scrotum. In paediatric urology the Prentiss maneuver requires comprehensive knowledge of the inguinal canal and the course of inferior epigastric vessels to fascilitate adequate orchidopexy in boys with short spermatic cord.

The external iliac vessels and the iliopsoas muscle leave the pelvis below the inguinal ligament, which connects the anterior superior iliac spine to the pubic tubercle. The lacunar ligament is located directly medial to the external iliac vein connecting the inguinal ligament to the superior pubic ramus and represents the caudal

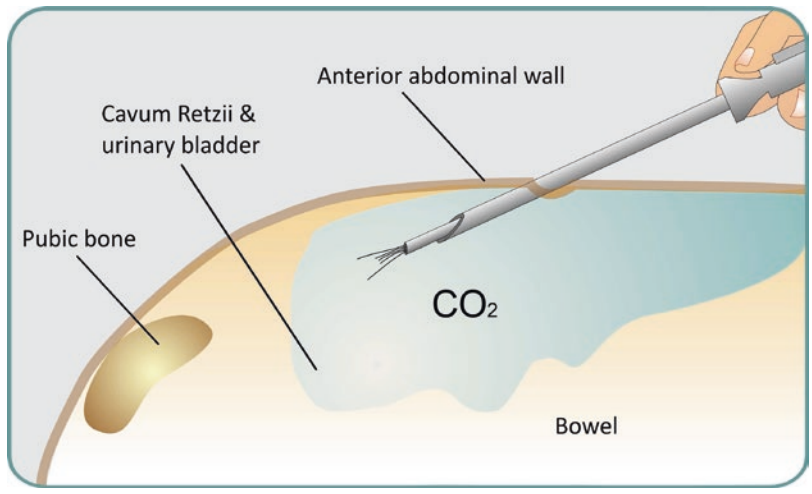

Fig. 2.1 The drawing illustrates the laparoscopic line of sight during pelvic or prostate surgery (illustrated by P.M. Weber, University Hospital of Tuebingen)

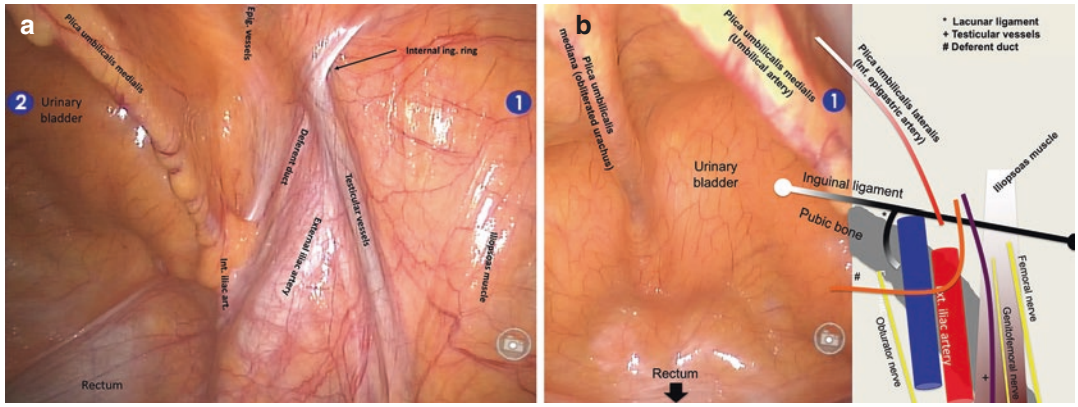

Fig. 2.2 (**a**) Laparoscopic view into the male pelvis with annotated anatomic landmarks. (**b**) Topographic anatomy of the male pelvis. Left: laparoscopic view at the beginning of robotic-assisted laparoscopic prostatectomy. Right: draft of the anatomical structures of the inguinal region in addition to the left intraoperative view (Reprinted from Amend et al. [55] with permission from Springer Nature)

extent during lymphadenectomy for prostate or bladder cancer. Lateral to the external iliac vessels the genitofemoral nerve dividing into two branches, the femoral nerve (laterally adjacent to the psoas major muscle) and the lateral femoral cutaneous nerve are at risk to be damaged during lymphadenectomy depanding on the extend of surgery (Fig. 2.2) [2, 3].

Female Pelvis

A plain promontorium and wide-open iliac wings characterize the female pelvic bone. The peritoneal pelvic cavity harbours the urinary bladder, the ureters, the uterus, the vagina, the ovaries, the Fallopian tubes and the rectum. The uterus, in between the urinary bladder and the rectum, leads to varying peritoneal conditions, starting from the anterior abdominal wall. The parietal peritoneum covers approximately the upper half of the urinary bladder, the uterus, the adnexa and the anterior wall of the rectum. Thereby the parietal peritoneum forms two parts of the abdominal cavity: the rectouterine excavation (Douglas' fold) and the vesicouterine excavation. A vaginal manipulator helps to expose these pelvic spaces during laparoscopic surgery. The peritoneal fold between the uterus/cervix and the pelvic wall is called the ligamentum latum or broad ligament, although these structures lack some of the typical features of a ligament in the anatomical sense. The uterine artery, the uterine venous plexus and parts of the distal third of the ureters are included in the broad ligament. Ovaries and the Fallopian tubes are also joined to the broad ligament by a peritoneal duplication. The ovaries receive their blood supply through the suspensory ligament (often also called infundibulopelvic ligament), and they are connected to the uterus by the (proper) ovarian ligament, which is part of the broad ligament and includes a secondary blood supply called ovarian branches of the uterine artery. At least, the round ligaments represent connections between the deep inguinal rings and the uterine horns. Embryogenetic, the round ligament corresponds to the gubernaculum testis in males.

The rectouterine folds mark the borders of the rectouterine pouch—they consist of fibrous tissue and smooth muscle fibers, and also include the inferior hypogastric plexus (Fig. 2.3).

The pelvic fascia with its parietal and visceral layer covers the borders of the subperitoneal space; the clinical synonym is "endopelvic fascia". The endopelvic fascia also forms the superior layer of the fascia of the pelvic and urogenital diaphragm. The urinary bladder is attached to the pubic bone/symphysis pubis via the pubovesical ligaments (analogous to the puboprostatic ligaments in male humans, see also below) with lateral connections to the superior layer of the fascia

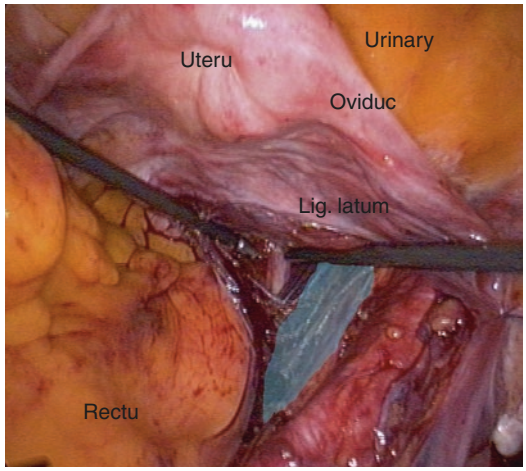

Fig. 2.3 Laparoscopic view into the female pelvis. The right rectovaginal fold is marked lucent blue

of the pelvic diaphragm. Between the different subperitoneal organs, connective and fatty tissue fills the resulting spaces (presacral, prevesical, paracervical, parametrial). The stability of the uterus and the cervix is guaranteed by the rectouterine (synonym, sacrouterine) ligament and the topography of the other pelvic organs. The cardinal ligaments (synonym, transverse cervical ligaments) on the base of the broad ligament, joining the cervix and the lateral pelvic wall, are not there at birth but are shaped throughout a lifetime by the increasingly compact and strong connective tissue. They increasingly support the topographical position of the cervix [2, 4–6].

Male Pelvis

In contrast to the female pelvis, in male humans the pelvic bone is narrower and marked by a more protruding promontorium, resulting in a heart-shaped pelvic entry. The pelvis accommodates the urinary bladder, the ureters, the prostate, the seminal vesicles, the deferent ducts and the rectum. The parietal peritoneum also covers the pelvic organs starting from the anterior abdominal wall to the anterior rectal wall. Between the urinary bladder and the rectum, the deepest point of the abdominal cavity forms the rectovesical excavation. On both sides the rectovesical fold confines the excavation and includes the inferior hypogastric plexus. The deferent ducts shape the paravesical fossa by raising a peritoneal fold.

The subperitoneal space in front of and lateral to the urinary bladder is clinically called the cavum retzii. A look at the existing literature concerning the anatomical conditions of the subperitoneal fascias, especially the prostate-surrounding tissue and the formation of the so-called Denonvilliers' fascia, demonstrates an inconsistent presentation and nomenclature. The following explanations will outline the most usually published anatomical findings and interpretations. The pelvic fascia in males also consists of two parts: a parietal layer, which covers the lateral wall of the pelvis, and a visceral layer covering the pelvic organs. The tendinous arch represents the transition between the parietal and visceral part. Often the visceral layer is clinically indicated as the endopelvic fascia, especially with regard to radical prostatectomy and nerve-sparing procedures. Whether the prostate is actually separated by its own prostatic fascia is under discussion. The absence of the fascia in the apical region of the prostate and the formation of the so-called puboprostatic ligaments by the endopelvic fascia suggest that the visceral layer of the pelvic fascia (=endopelvic fascia) and the fascia of the prostate (periprostatic fascia) correlate. Generally, the periprostatic fascia is described as a multilayered structure, which incorporates neurovascular structures, fatty and fibrous tissue. Interindividual and prostate aspect depended variations (fusion of fascias and prostate capsule) are common, especially with regard to the prostate gland size. The puboprostatic ligaments between the anterior aspect of the prostate and the pubic bone/symphysis pubis do not represent ligamentous structures in the proper sense. In fact, the puboprostatic ligaments are characterized by an aggregation of the pelvic fascia. Possibly muscle fibers (smooth or striated) also contribute to the configuration of the so-called puboprostatic ligaments. Especially in large prostates the correct identification of the dissection plane between the anterior prostate aspect and the puboprostatic ligaments may be difficult.

Similarly, there is a lack of clarity regarding Denonvilliers' fascia. The anatomical nomenclature

utilizes the description rectoprostatic fascia or septum. It represents a membranous separation between the rectum and the prostate/urinary bladder. The fascia emerges from two layers of a peritoneal cul-de-sac, ranging from the deepest point of the rectovesical excavation to the pelvic floor. Recent examinations report the termination of the Denonvilliers' fascia located at the junction of the prostate and the dorsal (fibrous) part of the rhabdosphincter. In addition, the presence of smooth muscle fibers inside the fascial layers has been reported. There has been extensive discussion about the possibility of surgical separation of both layers during radical prostatectomy. Currently it is evident that microscopically the rectoprostatic fascia consists of two formerly peritoneal layers, which often cannot be divided bluntly. It is assumed that authors illustrating techniques of fascia separation are referencing to the space between Denonvilliers' fascia and the rectal fascia propria (a part of the visceral layer of the pelvic fascia = endopelvic fascia). Furthermore, adhesions between Denonvilliers' fascia and the prostatic capsule, primarily at the base of the seminal vesicles, have been identified. These individual findings have to be taken into account for precise retro-prostatic preparation with regard to positive surgical margins during prostatectomy independent of the surgical approach. Periprostatic neural and vascular structures are focused on below [2, 4, 6–16].

Pelvic Floor

Two fibromuscular layers are responsible for the closure of the inferior pelvic aperture: the pelvic diaphragm and the urogenital diaphragm. It has to be emphasized at this point that the term urogenital diaphragm is not part of the anatomic nomenclature. Particularly the presence of a deep transverse perineal muscle was under extensive discussion, whereas recent studies confirm that a deep transverse perineal muscle is present.

The pelvic diaphragm consists of the levator ani muscle and the coccygeus muscle (M. ischiococcygeus). The levator ani muscle in turn consists of the following structures, which are named according to their origins and insertions: the pubococcygeus muscle, iliococcygeus muscle and puborectalis muscle. A superior and inferior fascia covers the levator ani muscle, the superior layer being part of the parietal layer of the pelvic fascia as described above. The levator ani muscle forms an archway-shaped opening for the anus and urethra in males, and the anus, vagina and urethra in females. Interestingly, the levator ani muscle thickness has been reported smaller and the steepness inside the pelvis greater comparing males to females. This might be dedicated to the general form of the bony pelvis and the physical necessities during pregnancy. The innervations for the striated muscles derive principally from the sacral plexus (S3 and S4); some nerve fibers reach the puborectal muscle via the pudendal nerve located in the pudendal canal. Even though the contributions of the shape topography and the contraction of the pelvic diaphragm to anal continence seem to be proven, it is still unclear to what extent these anatomical structures also affect urinary continence. Recent publications have reported the muscular independence between the pelvic diaphragm and the striated external urethral sphincter, whereas an association by connective tissue forming a tendinous connection starting from the inferior part of the external urethral sphincter in females could be demonstrated. Especially because of these interactions, authors suggest the necessity of an intact pelvic diaphragm for urinary continence.

The relevance of the rectourethralis muscle in males is regularly discussed with respect to post-prostatectomy urinary continence. Special incontinence tapes aim to repair the assumable posterior loss of the external urinary sphincter complex after prostatectomy, which is naturally guaranteed by muscular and fascial dorsal structures (Denonvilliers' fascia, rectourethralis muscle). Recent studies characterized the rectourethral muscle as the anterior branch of longitudinal fibers of the anterior smooth muscle component of the rectum, which directs through the deep transverse perineal muscle to the perineal body. The posterior branch of rectal longitudinal smooth muscles passes between the internal and external anal sphincter to the perineum (Fig. 2.4).

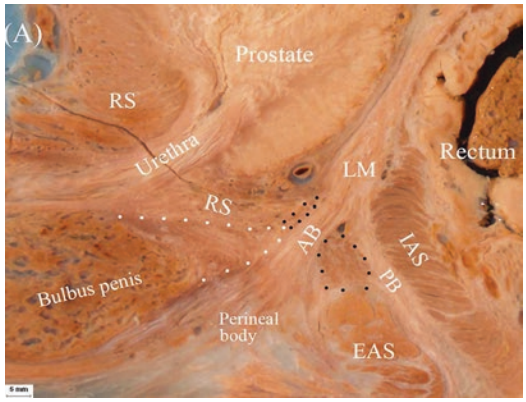

Fig. 2.4 Sagittal cross-section of celloidin fixed male human pelvic floor: deep transvers perineal muscle marked with black dots. Connective tissue of the penile bulb marked with white dots (*RS* rhabdosphincter, *LM* longitudinal muscle of the rectum, *AB* anterior bundle of LM, *PB* posterior bundle of LM, *EAU* external anal sphincter). (Reprinted from Zhai et al. [13] with permission from Elsevier)

Considering the urogenital diaphragm, the exact anatomical and histomorphological composition is still undefined. Almost all anatomical atlases report that the urogential diaphragm consists of the deep transverse perineal muscle (less developed in females) with a superior and inferior urogenital fascia. Additionally, the superficial transverse perineal muscle inserting at the perineal body (=central tendon of perineum), the striated external urethral sphincter and the surrounding connective tissue complete the traditional view of the urogenital diaphragm. In addition, as described above, smooth muscle fibers originating from the anterior rectal wall integrate into or perforate the urogenital diaphragm (rectourethralis muscle). With reference to the discussions of the existence of a deep transverse perineal muscle, prevailing descriptions in literature and also recent studies of human cadavers report the presence of the deep transvers perineal muscle (Fig. 2.4). The urogenital diaphragm is described as layers of connective tissue embedding the external urethral sphincter in conjunction with the perineal body, the deep transvers perineal muscle, the structures of the inferior pubic bone and the superficial transverse perineal muscle. Whether these findings about the muscular structures of the urogenital diaphragm are possibly due to age-related fatty degeneration of muscular tissue is under discussion and remains unexplained. The main vascular and neural structures—the internal pudendal artery and the pudendal nerve—are located directly below the urogenital diaphragm. The internal pudendal artery is a branch of the internal iliac artery and the pudendal nerve originates from the sacral plexus (S2-4). Both structures surround the sacrospinous ligament and follow the inferior pubic bone inside the pudendal canal as described below. The bulbourethral glands (Cowper's glands) are located laterally to the membranous urethra at the level of the urogenital diaphragm. They could be visible during deep urethral repair, perineal prostatectomy or gender reassignment surgery. The urethral sphincter mechanism is described out below [2, 6, 13, 17–26].

Urinary Bladder

The urinary bladder is a muscular, distensible organ for urine collection and controlled micturition. Macroscopically the urinary bladder is divided into the apex, corpus, fundus and collum. The average filling volume ranges between 300 and 500 cm^3. The mucosa is only loosely adherent to the subjacent muscular layers, except for the trigone where a direct adhesion to the submucosal layers can be found. A fold raised between the obliquely passing ureters on both sides forming the ureteral orifices characterizes the trigone.

The urinary bladder wall is structured as follows: mucosa (transitional cells), submucosa, detrusor muscle (three layers), and surrounding adipose and connective tissue. The detrusor muscle is subdivided into an external and internal longitudinal muscle layer, as well as an interjacent circular layer. The bladder neck, including the trigone, consists of two muscular layers. A specialized circular smooth muscle could not be found. The longitudinal muscle fibers in conjunction with the extending longitudinal fibers of both ureters extend below the bladder neck and reach the muscular layers of the urethra. In male humans these structures reach to the point of the seminal colliculus. Therefore, a closure of the

bladder neck to maintain continence, even in case of damage of the rhabdosphincter (e.g. traumatic urethral injury), or to ensure antegrade ejaculation is possible.

The blood supply of the urinary bladder generally derives from two main branches of each of the internal iliac arteries: the superior vesical artery and the inferior vesical artery—often named the superior and inferior vesical pedicle during surgery. The superior vesical artery descends from a common branch with the former umbilical artery, which is part of the medial umbilical ligament (landmark for the superior vesical pedicle during cystectomy). The inferior vesical artery arises from a common branch of the middle rectal artery. Prostatic branches generally derive from the inferior vesical artery. Varying distinct venous plexuses on both sides of the vesical base secure the blood drainage of the urinary bladder. These venous vessels communicate extensively with the prostatic venous plexus in male and the vaginal venous plexus in female humans. Both, the thin venous vessel wall (especially in case of neoplastic vascularization) and the numerous venous interconnections might result in demanding vascular control during radical surgery.

Organs of the pelvis, in contrast to other regions, present a widespread field of lymph node drainage. The urinary bladder drains its lymph fluid through external iliac lymph nodes, internal iliac lymph nodes, lymph nodes in the obturator fossa and common iliac lymph nodes (Fig. 2.5).

A complex neural system facilitates the correct functioning of the urinary bladder as a storage and drainage system. Interactions between independent reflex pathways and arbitrary actions are necessary for a precise process. Both the autonomous and the somatic nervous system contribute to carrying out the tasks of bladder filling and emptying.

Anatomic nerve fibers reach the urinary bladder (and adjacent organs) through the inferior hypogastric plexus (=pelvic plexus). The inferior hypogastric plexus thus comprises the parasympathetic and sympathetic nerve tracts. Anatomically the inferior hypogastric plexus

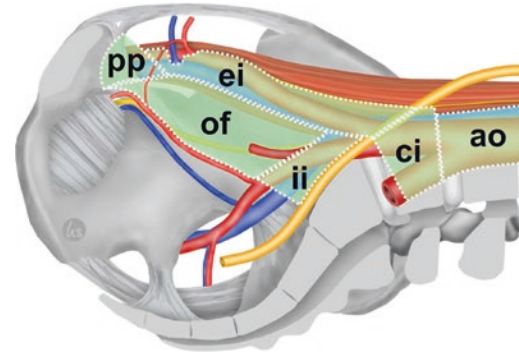

Fig. 2.5 Areas of lymphadenectomy for pelvic surgery: post pubic (pp), external iliac (ei), obtorator fossa (of), internal iliac (ii), common ilica (ci), aortal (ao). (Reprinted from Schilling et al. [28] with permission from Wiley-Blackwell)

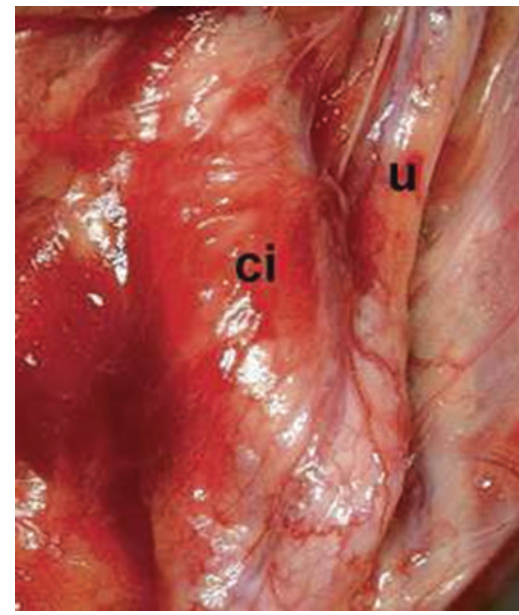

Fig. 2.6 Nerve course of the sympathetic fibers deriving from the superior hypogastric plexus (*ci* common ilica artery, *u* ureter). (Reprinted from Schilling et al. [28] with permission from Wiley-Blackwell)

derives from the singular superior hypogastric plexus, which reaches the pelvis proximally and medial to the crossing of the distal ureter and the common iliac artery on both sides (Fig. 2.6). The inferior hypogastric plexus is part of the bilateral rectouterine or rectovesical fold beside the pouch of Douglas (Fig. 2.3). The plexus extends laterally to the rectum, the vagina (in females), the

bladder neck and the seminal vesicles (in males) in a sagittal direction. The continuing course of nerve fibers along the prostate is described in the next chapter. An allocation of nerve fibers within the plexus to innervated targets seems to be possible. Roughly, the anterior part is responsible for urogenital innervations, and the posterior part serves the rectum.

The sympathetic fibers of the inferior hypograstric plexus originate from the superior hypogastric plexus, which is fed by nerve fibers from the lumbar sympathetic trunk condensed in 2–3 lumbar splanchnic nerves, as well as from sacral splanchnic nerves, which derive straight from the sacral part of the sympathetic trunk.

Sympathetic excitation generally results in inhibition of the detrusor muscle and stimulation of the smooth muscle sphincter cells, which leads to a filling of the urinary bladder. The parasympathetic fibers derive from the sacral spinal cord (S2-S5) and reach the inferior hypogastric plexus via pelvic splanchnic nerves exiting from the foramina of the sacral bone. Sensory afferent nerve fibers of the urinary bladder (and most probably of the proximal urethra as well) run along the parasympathetic nerves. Contraction of the detrusor muscle is mediated through the parasympathetic nervous system. The pudendal nerve is part of the somatic nervous system and innervates the striated parts of the external urethral sphincter. The pudendal nerve courses in the pudendal canal (Alcock's canal) at the bottom of the inferior pubic bone after the distribution of the lumbosacral plexus (S2–4). The variation of an intrapelvic nerve branching off the pudendal nerve prior to entering the pudendal canal and running on the inside of the levator muscle has been described. Stimulation results in increased contraction of the external urethral sphincter and adjacent segments of the levator ani muscle. Complex interconnections on different sections of the central nervous system, including Onuf's nucleus (located in the sacral part of the spinal cord), the periaqueductal grey, the pontine micturition center and the frontal lobe of the cerebrum, are involved in the process of filling and emptying. For example, it could be demonstrated that pelvic floor training for stress urinary incontinence not only influences the competence of the sphincteric mechanisms, but the training also results in restructuring of supraspinal central nervous system components [2, 4, 27–32].

Prostate, Seminal Vesicles and Deferent Ducts

The prostate is often compared to a chestnut of about 20 g. With the base aligned to the urinary bladder and the apex proximate to the external urinary sphincter, the prostate incorporates the prostatic urethra with a length of about 3 cm.

As a result of benign prostatic hyperplasia sizes up to 300 g are possible, which influences topography to the adjacent organs and structures (periprostatic nerves, striated and smooth muscle of the sphincter complex) as well as the distribution of the subsequently described prostatic zones.

McNeal defined the different zones of the prostate based on histopathological analysis: the peripheral zone, the central zone, the transitional zone and the anterior fibromuscular zone. This definition has to be separated from the macroscopic classification into lobes.

The ejaculatory ducts are paired tubes formed on each side by fusion of the deferent duct and the duct of the seminal vesicle. The orifices of the ejaculatory ducts are located on the seminal colliculus (also called the verumontanum). 15–30 orifices of ducts of the prostate glands are located beside the seminal colliculus.

The seminal vesicles are located lateral to the deferent ducts. Dorsally and laterally fibers from the inferior hypogastric plexus engulf the vesicles. The space between Denonvillier's fascia dorsally and the fascia covering the posterior wall of the bladder is called the spatium urovesicale (urovesical space). Recent studies describe smooth muscle fibers merged longitudinally into the Denonvillier's fascia, which connect the urinary bladder to the prostate at the entry of the ejaculatory ducts. This so-called vesicoprostatic muscle has to be identified and dissected during radical prostatectomybladder (neck preparation) (Fig. 2.7). Branches of the inferior vesical

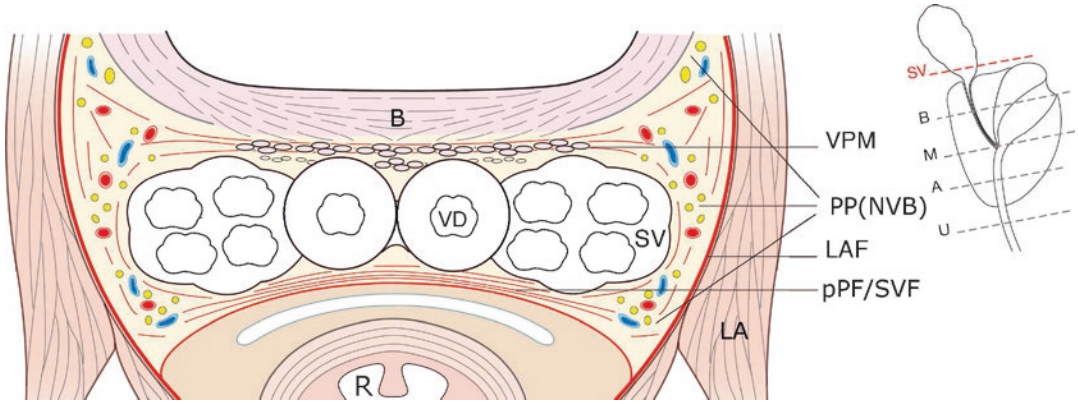

Fig. 2.7 Axial cross-section of the pelvis at the level of seminal vesicles (SV) illustrates the relation of deferent duct (VD), seminal vesicle, bladder (B), neurovascular bundle (NVB) and rectum (R) to the posterior pelvic fascia (synonymic seminal vesical fascia (SVF) or Denonvilliers' fascia), the vesicoprostatic muscle (VPM) and the levator ani fascia (LAF). (Reprint of Walz et al. [16] with permission of Elsevier)

artery, the middle rectal artery and the artery of the vas deferens usually reach the seminal vesicle at its tip.

The deferent duct is characterized by a dilatation prior to the confluence with the duct of the seminal vesicle called the ampulla. The deferent duct is accompanied by one or two separate arteries (arteries of the vas deferens), which derive from the inferior vesical artery. These arteries play an important role (beside additional cremasteric arteries) to ensure testicular blood supply during two-staged Fowler-Stephens procedure to treat cryptorchism with intraabdominal testis and the need to divide the main testicular vessels.

The inferior vesical and the middle rectal artery contribute to the blood supply of the prostate. The main vessels enter the prostate on both sides at the dorsolateral aspect close to the base of the prostate. Smaller vessels perforate the prostate capsule directly. Venous drainage moves from the surrounding prostatic venous plexus.

Accessory pudendal arteries can be found in about 25% of the patient population undergoing radical prostatectomy. An accessory pudendal artery is defined as a vessel starting above the level of the levator ani muscle, running down to the penile structures below the symphysis pubis and the pubic bone, respectively. Some authors subdivide the accessory arteries into lateral (alongside the anterolateral aspect of the prostate) and apical (inferior and lateral to the puboprostatic ligaments) accessory pudendal arteries. The extent of their contribution to the erectile function of the penis is still under investigation and discussion.

The puboprostatic complex includes the puboprostatic ligaments, the prostatic venous plexus and their correlation to the prostate and the external urethral sphincter. The puboprostatic ligaments formed by the endopelvic fascia, first described by Young, are described above. The prostatic venous plexus communicates extensively with the distinct venous plexus of the urinary bladder cranially and the superficial/deep dorsal veins of the penis. The proper name (Santorini's plexus) refers to their initial discovery by Giovanni Domenico Santorini in 1724. The venous plexus is imbedded in the fibrous structure of the so-called puboprostatic ligaments. The puboprostatic plexus directly covers the anterior elevated part of the external urethral sphincter (see also following chapter). The proximate neighborhood of sphincter structures, periprostatic nerves continuing beside the urethra and big venous vessels explains the risk of functional damage by an uncontrolled dissection of the Santorini's plexus.

The description of the anatomic affiliations of pelvic lymph nodes to the drainage field was originally based on lymphographic studies.

Recent findings are the results of sentinel lymph node studies. The injection of ^{99m}Tc-labeled nanocolloid into the prostate facilitates the identification of sentinel lymph nodes either by surgery or by radiological imaging (Fig. 2.8). The lymph nodes of the obturator fossa, the external iliac lymph nodes, the internal and finally the common iliac lymph nodes are responsible for the drainage of the prostate gland (Figs. 2.8 and 2.9).

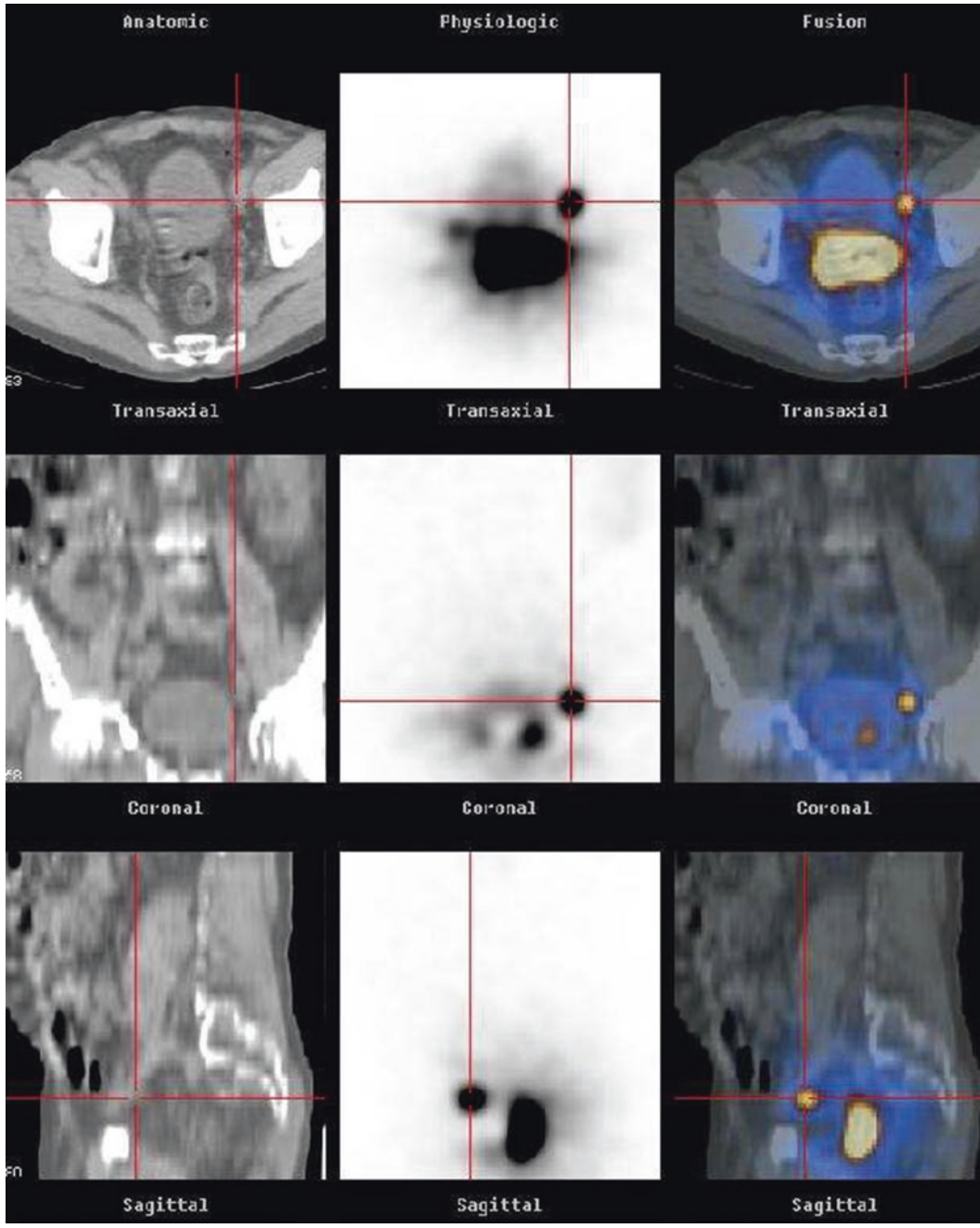

Fig. 2.8 Radiological image of sentinel lymph nodes after injection of ^{99m}Tc-labeled nanocolloid into the prostate. Left column: CT scan images, middle column: SPECT images, right column: CT/SPECT fused images. Sentinel lymph node located inside the red indicator

Although oncological aspects are still the main concern of every radical prostatectomy treating prostate cancer, quality of life aspects including erectile function as well as continence have become important. The existence of the endopelvic fascia equipollent to the visceral layer of the pelvic fascia has been outlined above. Most authors would agree that the neurovascular structures are located between the prostate surface with its fibromuscular capsule and the visceral layer of the pelvic fascia, which extends to Denonviellers' fascia at the dorsolateral aspect of the prostate (Fig. 2.10). Some studies describe a merger between the different parts of the multilayered fascia as described above. Whether nervous tissue can also be found in the fold between the visceral and the parietal layer of the pelvis remains unclear. In 1985, Donker, Walsh et al. were the first to extensively describe the neurovascular bundle. The technique of nerve-sparing radical prostatectomy and cystectomy was adapted regarding these anatomical findings. Especially the course of these periprostatic nerves has resurfaced as a focus of academic interest the last decade. The entry of the inferior hypogastric plexus into the pelvis and its location lateral to the seminal vesicles, including the convergent fibers of the sacral splanchnic nerves (sympathetic) and pelvic splanchnic nerves (parasympathetic), has been referred to above. Furthermore, the presence of somatic nerves with a percentage of about 5% has been detected. This might explain in conjunction with the confirmation of sensory fibers, responsible for innervation of the membranous/proximal penile urethra, that uni- or bilateral nerve-sparing also influences post-prostatectomy continence (Fig. 2.10).

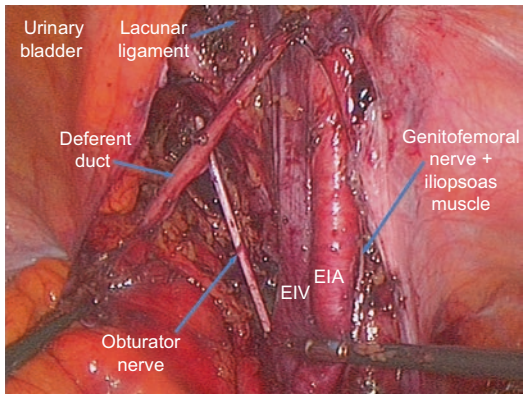

Fig. 2.9 Situs after laparoscopic lymphadenectomy for prostate cancer; EIV: external ilic vein, EIA: external iliac artery. The lacunar ligament as the distal extent of lymphadenectomy

In contrast to a separate dorsolateral nerve bundle, several authors reinvestigated the anatomy and described different nerve dispersions. The periprostatic nerves proceed divergently especially in the mid-part of the prostate; therefore, a varying amount of nerve tissue can be found also in the anterior and anterolateral aspect of the prostate in addition to the known accumulation in the dorsolateral course (Figs. 2.11 and 2.12). Characteristically the nerve fibers converge towards the apex located at the posterior

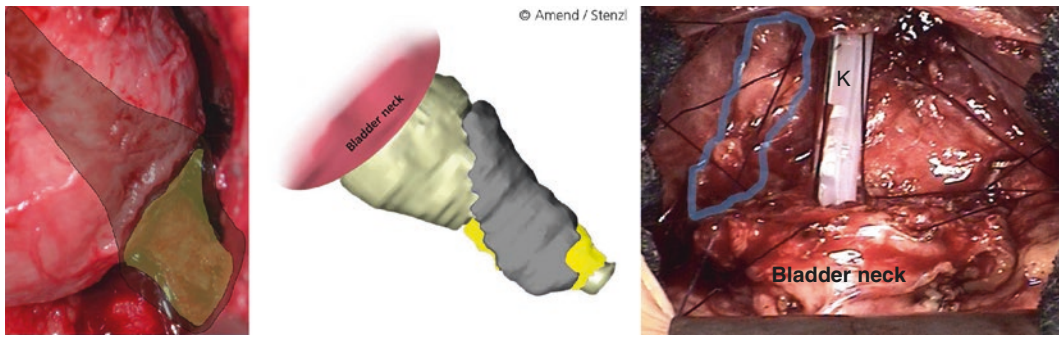

Fig. 2.10 Retropubic radical prostatectomy. Left: prostate after apical preparation with isolated membranous urethra (yellow shade). The grey shade outlines the area of the rhabdosphincter. Right: nerve-sparing procedure on left side (marked in blue) and partial nerve-sparing procedure on right side before anastomosis (K: transurethral catheter)

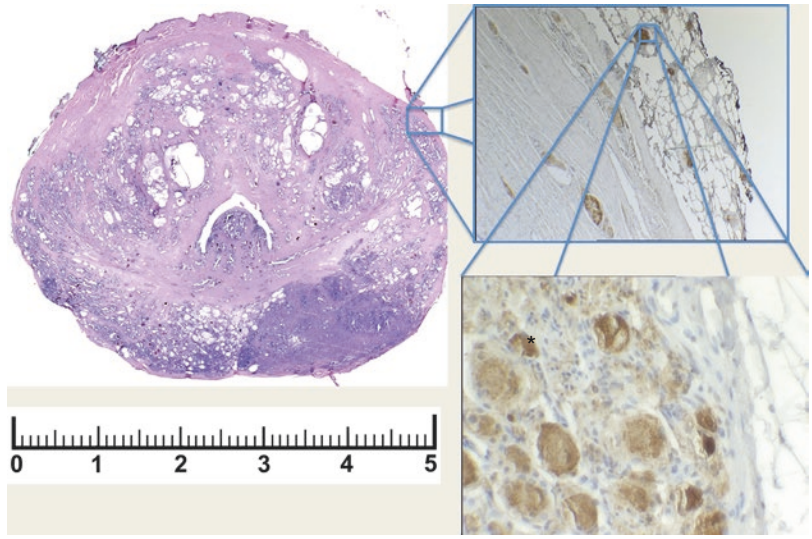

Fig. 2.11 Whole mounted horizontal section (left side, HE staining) of the prostate (∗prostate carcinoma). Staining with protein-gene-product (PGP) 9.5 antibodies illustrates the existence of nerve fibers anterior-lateral [42]

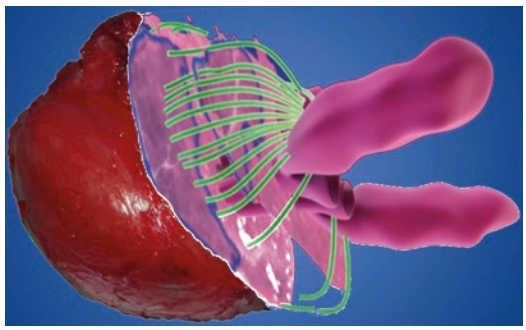

Fig. 2.12 3D reconstructions of nerve courses (right side: green lines) based on prostate specimens (left side) and whole mounted sections (middle part)

and posterolateral side of the apex and the urethra, respectively. In addition, parts of the periprostatic nerves leave the craniocaudal course and enter into the prostate for innervations. Initial investigations demonstrated the correlation of neural impulses routed through the nerve fibers on the anterior aspect of the prostate and erectile function. Beside the description of somatic periprostatic nerves additional emerging studies clarified the different nerve quantities surrounding the prostate gland. Relevant portions of parasympathetic and sympathetic fibers have been found anterolaterally at the level of the prostate base with subsequent condensation to a posterolateral course at the prostatic apex. The data supports a higher release of the periprostatic tissue for nerve-sparing with emphasis to the prostatic base-if the oncologic situation justifies this approach (Fig. 2.13) [2, 4, 7–12, 16, 19, 30, 33–50].

Urethra

Male Urethra

The urethra is subdivided into four different parts: the intramural part (=pre-prostatic urethra) at the bladder neck, the prostatic urethra, the membranous urethra and the spongy urethra surrounded by the corpus spongiosum. Transitional cells in large sections characterize the mucosa. The distal part near the navicular fossa is marked by a stepwise transition over stratified columnar cells to stratified squamous cells. The muscle layer is divided into an inner longitudinal, a middle circular and an inconsistently described outer longitudinal stratum. The bulbourethral artery, a branch of the internal pudendal artery entering at the level of the penile bulb, supplies the spongy urethra.

Female Urethra

The female urethra is about 3–5 cm long. The histology is equivalent to the male urethra.

Aspects of the urethral closure mechanisms are focused on in the following paragraph.

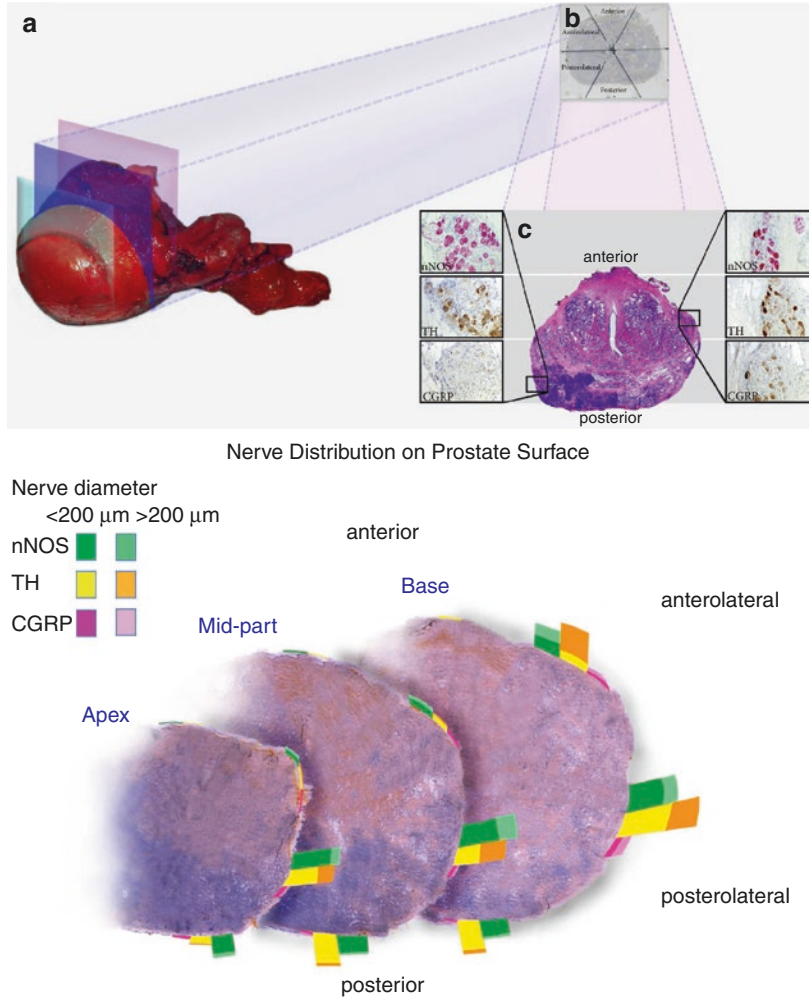

Fig. 2.13 Upper image illustrates prostate cross-sections with sectored quantification of nNOS+, TH+ and CGRP+ periprostatic nerves. Lower image illustrates the nerve distribution of the different qualities ranging from base to apex. (Reprint of Sievert et al. [49] with permission of John Wiley and Sons)

Sphincter Mechanisms

Traditional anatomy reports two muscular structures to achieve continence of the lower urinary tract: the voluntary, striated, external urethral sphincter (rhabdosphincter) located in the urogential diaphragm and the autonomous, smooth internal sphincter (lissosphincter) located in the bladder neck. However, the anatomical and functional understanding of the sphincter complex has changed over time (Fig. 2.14). In comparison to the periprostatic anatomy, various descriptions have been published. The contribution of three different components to the sphincter complex is commonly accepted: the detrusor muscle fibers of the bladder neck including the trigone, the

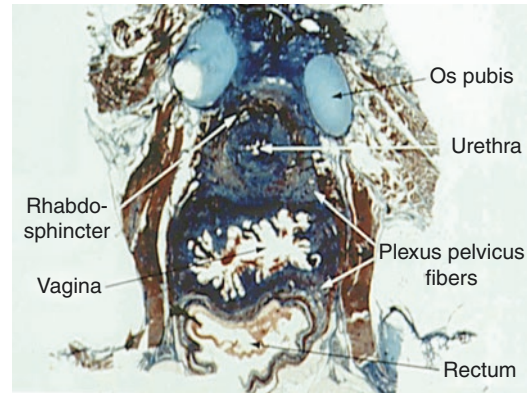

Fig. 2.14 Fetal female pelvis illustrating the omega-shaped rhabdosphincter surrounding the urethra and the topographical location of plexus pelvicus fibers. (Reprinted from Colleselli et al. [51] copyright 1998, with permission from Elsevier)

intrinsic smooth muscle fibers of the urethral wall and the external urethral sphincter. The description of the systematic anatomical circumstances and the interaction of the mentioned components vary with different authors.

The Bladder Neck Component

The presence of the circumscribable, circularly oriented smooth muscle sphincter at the outlet of the urinary bladder was denied by different authors 200 years ago. It has been demonstrated both that the detrusor muscle fibers condense especially in the direction of the trigone and that the smooth intrinsic fibers of the urethral wall arrange a complex interacting network of muscle strands at the bladder outlet. In male humans, as reported before, the detrusor fibers reach the point of the seminal colliculus. The bladder neck component is thought to be innervated by the autonomic nervous system.

The Urethral Wall Component

The smooth muscle fibers of the urethral wall do not act as a detached actor. In fact, they can be interpreted as a continuance of the muscular complex of the bladder neck. The urethral muscular layer consists of longitudinally (inner and (inconsistently described) outer layer) and circularly (middle layer) oriented muscle fibers. Reports of the exact anatomical condition vary. Also, these smooth muscle fibers receive autonomic innervations.

The External Urethral Sphincter

Many authors have shaped the anatomical understanding of the external urethral sphincter, but an overall accepted anatomical and functional definition is still lacking. Consensus of opinion exists regarding the three-dimensional profile of the external sphincter. The terms omega-shaped and horseshoe-shaped are most often used to illustrate the external sphincter in male as well as female humans (Figs. 2.15 and 2.16). Muscle fibers are located in the anterior and lateral part of the urethra—only fibrous tissue forms the dorsal interconnection between the dorsolateral "ends" of the external sphincter. In the same way, authors concur that the external sphincter is not part of an urogential diaphragm (deep transverse perineal muscle) and that the external sphincter only has a fibrous connection to the surrounding tissue (including the pelvic diaphragm).

There is extensive discussion about the vertical extend and the histological constitution of the external urethral sphincter.

The participation of striated muscle fibers in the configuration of the external sphincter has

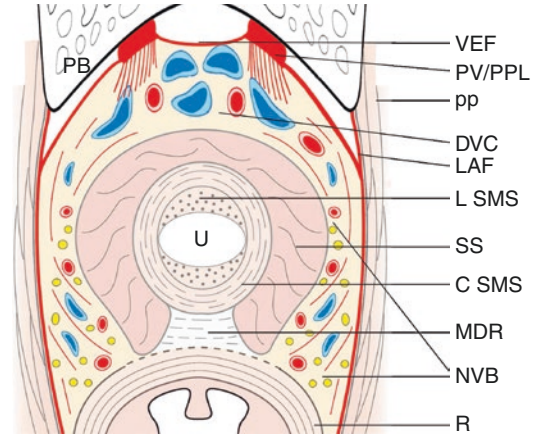

Fig. 2.15 Schematic illustration of the u-shaped rhabdosphinter (SS) (pubic bone (PB), visceral endopelvic fascia (VEF), puboprostatic ligament (PPL), puboperinealis muscle (PP), dorsal vein complex (DVC), levator ani fascia (LAF), longitudinal lissosphincter (L SMS), circular lissosphincter (C SMS), median dorsal raphe (MDR), neurovascular bundle (NVB) and rectum (R)). (Reprint of of Walz et al. [16] with permission of Elsevier)

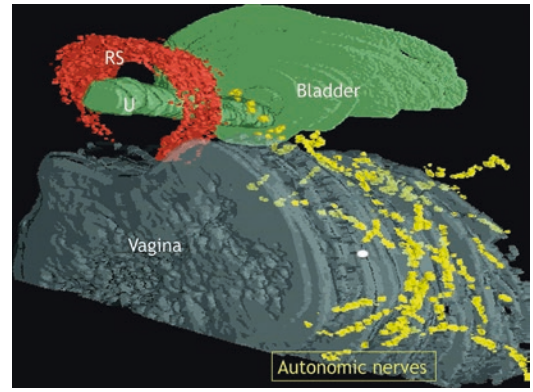

Fig. 2.16 3D reconstruction of the rhabdosphincter (RS) and the autonomic nerve supply based on female fetal pelvic studies. *U* urethra. (Reprinted from Colleselli et al. [51] copyright 1998, with permission from Elsevier)

long been well known. Essentially the external sphincter has to secure continence continuously as well as during rapid abdominal pressure. Whereas some authors favor the existence of two different striated muscle fibers ("slow twitch fibers" for basic pressure of the external sphincter and "fast twitch fibers" for rapid pressure increases), others report the existence of a smooth muscle component located inside the coat of the striated external sphincter. Therefore, the description internal urethral sphincter (in contrast to the internal vesical sphincter) is used. It is accepted that the pudendal nerve (somatic nervous system) is responsible for the innervations of the voluntary striated external sphincter. Whether autonomous fibers resulting from the inferior hypogastric plexus or lately described somatic fibers (routed through the periprostatic plexus) with potential impact after nerve sparing radical prostatectomy are involved in the sphincter innervations is still under investigation.

In male humans it is assumed that the striated muscle fibers of the pronounced anterior part of the sphincter disperse below the puboprostatic ligaments (Fig. 2.15). It is still unclear if striated muscle fibers communicate with the structures of the bladder neck. In females it could be demonstrated that parts of the striated external sphincter could only be found in the two distal thirds of the urethra. In addition, striated muscle fibers also surrounding the lateral aspect of the vagina have been recently reported [2, 4, 10, 17, 19, 20, 22, 23, 25, 51–54].

Summary

Knowledge of the anatomy of the lower urinary tract was substantiated by comprehensive investigations long ago. Over time, many consolidated findings have been refuted and then recognized again. Current urological treatments are based on these anatomical conclusions. It has been shown that while some irrevocable facts have been substantiated in several fields of urological anatomy, extensive exploration is still taking place. Especially the complex sphincter mechanism in both females and males as well as the pelvic neuroanatomy are examples of these interesting research subjects. Only functional studies will validate whether these upcoming new aspects of anatomy will also lead to better treatment outcomes for our patients.

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Male Reproductive Physiology

3

Peter N. Schlegel and Michael A. Katzovitz

The Male Reproductive Axis

This chapter will present a broad overview of the main features of male reproductive axis physiology, which axis controls male reproductive function. The male reproductive hormonal axis is organized into three tiers: the hypothalamus of the brain, the pituitary gland, and the testis. Both the hypothalamus and the pituitary gland produce endocrine signaling act eventually at the level of the testis. In the preoptic area of the hypothalamus are neurons with axons that project to the median eminence. These neurons secrete gonadotrophin-releasing hormone (GnRH) into the hypothalamo-hypophysial shunt, a portal system of blood vessels leading to the pituitary. Within the anterior pituitary gland (or adenohypophysis) are specialized cells known as pituitary gonadotropes that, upon stimulation, secrete gonadotrophins. When stimulated by GnRH, the pituitary gonadotropes secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). FSH secretion is also stimulated by activating, a dimeric peptide locally produced within the pituitary [1]. **FSH and LH travel via the blood stream to the testis where LH stimulates Leydig cells in the interstitium to produce testosterone, and FSH stimulates Sertoli cells in the seminiferous epithelium to support spermatogenesis.**

The rates of testosterone and sperm production are regulated by a network of negative feedback relationships between the testis and upper levels of the reproductive axis. For example, testosterone and its metabolite, estradiol, suppress the secretory activity of hypothalamic neurons and gonadotropes. Feedback from the testis is delivered in part by, inhibin β, a 32-kilodalton glycoprotein hormone secreted by human Sertoli cells, that suppresses FSH release. Inhibin B suppresses FSH secretion in gonadotropes by preventing the transcription of the gene encoding the β subunit of FSH [2]. There is controversy surrounding the clinical use of inhibin B as a marker of impaired testicular function [3]. Whereas some studies have proposed that inhibin B can be used as a predictor of the presence of spermatozoa within the testis, other studies have suggested inhibin B levels are more sensitive than those of FSH. This relationship is clinically of interest in detection of sperm production from men with severely impaired sperm production, where no sperm are present in the ejaculate (non-obstructive azoospermia.) For these men, Inhibin B and FSH are poor predictors of the presence of sperm for NOA patients. However, both FSH and inhibin B, in inverse relationship, appear to grossly reflect both Sertoli cell and germ cell number. Men with high FSH rarely have substantial numbers of germ cells within the testes.

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has been suggested that inhibin B and FSH levels may predict the presence of spermatozoa in the testes of infertile men [4]. Activins, 30-kilodalton proteins closely related to inhibin, also suppress FSH secretion in gonadotropes. Futhermore, activin activity is negatively regulated by a binding protein called follistatin [1]. There is no clinical role for activins or follistatin measurement in the management of clinical male infertility.

Hypothalamus

Hypothalamic neurons receive input to secrete GnRH from neurons in other parts of the brain such as the amygdala and both the visual and olfactory cortex. GnRH output is affected by three forms of rhythmicity: seasonal, circadian, and pulsatile. The seasonal rhythmicity is measured on a timescale of months and peaks in the spring. The circadian rhythmicity results in testosterone levels peaking in the early morning hours. The pulsatile rhythmicity peaks on average every 90–120 min. **The seasonal and circadian rhythms are controlled by melatonin signaling. This signaling comes from, respectively, the pineal gland and neural connections arising from the suprachiasmatic nucleus. The suprachiasmatic nucleus functions in mammalian species as an internal 24-h clock. The neurons that compromise the GnRH pulse generator have not yet been identified. During embryonic development, the precursors of GnRH neurons migrate from the olfactory placode to their positions in the hypothalamus.** In cases of congenital hypogonadotropic hypogonadism, the GnRH precursor neurons migrate abnormally to the hypothalamus, which results in the diminished ability of hypothalamic GnRH secretion. This condition is known as Kallman's syndrome, when hypogonadotropic function exists together with midline defects such as olfactory deficiency (anosmia) cleft palate or other midline defects.

Pituitary

The pituitary is composed of the posterior and anterior lobes. The posterior lobe, or the neurohypophysis, arises during development as a ventral outpocket of the hypothalamus. Neural stimuli promote the secretion of oxytocin and vasopressin, two neurohypophysial hormones. The anterior pituitary, or adenohypophysis, is a glandular structure regulated instead by blood-borne factors. **Gonadotropes within the anterior pituitary secrete LH and FSH.** The anterior pituitary also contains specialized cells for the secretion of other glycoprotein hormones, four of which have detectable effects on some components of male reproductive function. These specialized cells and their respective secreted glycoprotein hormone are: corticotropes which secrete adrenocorticotrophic hormone (ACTH), lactotropes which secrete prolactin (PRL), somatotropes which secrete growth hormone (GH), and thyrotropes which secrete thyroid stimulating hormone (TSH). A murine investigation of the effect of ACTH on fetal Leydig cell steroidogenesis indicated a common embryonic origin of adrenocortical and Leydig cells from mesenchymal stem cells in the mesonephros [5]. However, the natural function of ACTH in the adult human male reproductive system remains unclear. LH, FSH, PRL, and GH, are four glycoproteins with known significant effects on male reproductive function. For instance, in cases of chronic over secretion of prolactin due to pituitary adenomas, the suppression of spermatogenesis has been observed [6].

The normal secretion of LH occurs on average once every ninety minutes to two hours, and the amplitude of each pulse is six International Units per liter [7]. The tonic level of LH in the blood stream is 10 International Units per liter. Normal testosterone levels are thus maintained at approximately 5 ng/mL [7].

Steroid Feedback on the Hypothalamus Pituitary

GnRH levels are regulated by a negative feedback mechanism predominantly involving testosterone. Testosterone suppresses the release of GnRH through androgen receptors present in both hypothalamic neurons and the pituitary. Aromatase and 5α-reductase metabolize testosterone into estradiol and dihydrotestosterone, respectively.

Steroid negative feedback likely results from testosterone and DHT binding to androgen receptors and estradiol binding to estrogen receptors. *Testosterone provides feedback primarily at the hypothalamic level, whereas estrogen provides feedback predominantly at the pituitary to regulate gonadotropic secretion in response to GnRH surges* [8]. These findings reflect the profound influence of selective estrogen receptor modulators (e.g., clomiphene or tamoxifen) as well as aromatase inhibitors on the pituitary. These medications decrease estrogen-associated feedback to the pituitary, resulting in increased LH and FSH secretion. In the male, effects of gonadotropin secretion varies depending on the steroid. For example, testosterone exerts negative feedback on LH secretion primarily in its androgenic form, whereas testosterone exerts negative feedback on FSH secretion primarily by its aromatized form, estradiol. In other words, FSH secretion is predominantly regulated in the male by estradiol. Steroid hormone receptors also exist in various isoforms. An investigation of the effects of the estrogen receptor ERβ on the negative feedback of estradiol found no correlation [9]. Moreover, the A and B forms of AR vary in their ligand binding and transcriptional activation properties, but it remains unknown whether these two forms are differentially expressed in the hypothalamus [10].

Development of the Male Reproductive Axis

The development of the male body plan is determined at fertilization when a Y chromosome from the father's sperm combines with an X chromosome from the mother's oocyte. At the start of embryogenesis, male and female embryos are morphologically indistinguishable. Gonadal differentiation will occur during embryogenesis in discrete steps and begins with the thickening (or placode) of the coelomic epithelium on the primitive kidney (mesonephros). The placode develops into a gonadal ridge, followed by the migration of primordial germ cells from the yolk sac (allantois) into the epithelium.

Primordial germ cells use pseudopodial motion to migrate to the genital ridge and locate their correct positions using chemotactic signals and tracks of extracellular matrix proteins. During the indifferent gonad stage, the gonadal ridge then develops medullary cords composed of epithelial tissue. **Differentiation of the ovarian and testicular pathways begins with the movement of the primordial germ cells into the medullary cords, which occurs at about seven weeks post-conception.** Sertoli cell precursors surround the primordial germ cells, which are henceforth referred to as seminiferous cords. This transition of seminiferous cords and intracord spaces establishes the two compartments within the testis: seminiferous and interstitial.

The *SRY* (Sex-determining Region on the *Y* chromosome) gene controls the morphogenetic events of early testis differentiation. The *SRY* gene encodes for a nuclear transcription factor that acts in unison with other transcription factors, including WT-1, SOX-9, and DAX-1 to promote male sexual differentiation [11, 12]. The discovery of the *SRY* gene product as the testis-determining factor resulted from studies of Y chromosome deletions involving the *SRY* gene. Males with such Y chromosome deletions were phenotypically female. Likewise, the translocation of the *SRY* gene into an X chromosome conferred a male phenotype in a genetic XX female. Additional studies of the involvement of the *SRY* gen in testicular development have found that approximately 10% of 46 XX males have no detectable *SRY* gene (*SRY*-). Evidence suggests that some men who are 4It 6,XX (SRY-) have endogenous activation of downstream targets of male gonadal development such as SOX9 that allow this developmental pathway to "bypass" SRY activation [13].

Cells from the mesonephros migrate into the testis and provide the source of mesenchymal stem cells that will eventually become Leydig cells. **The regression of the anlagen of the female reproductive tract structures is mediated by hormone signaling [14]. The hormone, Mullerian inhibiting substance, or anti-Mullerian hormone, is secreted by Sertoli cell precursors. Fetal Leydig cells, meanwhile,**

secrete testosterone, which stimulates the differentiation of the Woflian duct system. Later on in embryological development, this system will develop into the epididymis, vas deferens, and sex accessory glands. *SRY* also mediates steroidogenic factor-1 (SF-1) production, a transcription factor that induces the expression of cytochrome P450 steroidogenic enzymes in Leydig cells, and is also involved in differentiation of Sertoli cells and pituitary gonadotropes [15].

Endocrinology of the Testis

The hormonal control of testis function was thought to be a simple, two-compartment model: **FSH stimulates Sertoli cells to nurture germ cells as they undergo spermatogenesis, while LH stimulates Leydig cells to release testosterone.** Though this understanding holds true with respect to Leydig cells, mutational studies of males with decreased FSH action suggest that FSH may not be essential for spermatogenesis. One study found that male mice remained fertile despite knockout mutations in the FSH and FSH receptor genes [16]. These findings are corroborated by the fact that some men with defective FSH receptors remain fertile, though it should be noted that their sperm output is quantitatively reduced [17]. Recent studies suggest a negative correlation between testes function and increased conversion of testosterone to estradiol (reflected as the T/E-2 ratio). Although some of this excess conversion may occur because of relative clumping of Leydig cells within dysfunctional testes with limited seminiferous tubular tissue. In addition, this condition can be treated by using an aromatase inhibitor to reduce the conversion of testosterone to estradiol [18]. Transgenic studies in the rodent model have also suggested the importance of stem cell factor in spermatogenesis [19]. Stem cell factor is a local, or paracrine, signaling molecule in the testis that is secreted by Sertoli cells. The factor binds to the cell surface receptors of spermatogonia, spermatocytes, and round spermatids. The cell-cell interactions that promote germ cell differentiation within the seminiferous tubules suggest the complexity of the endocrine control of spermatogenesis. In order to provide a framework for understanding endocrine and paracrine controls, the cellular organization of the testis will be reviewed.

The highly specialized spermatozoa are produced and transported by the testis, epididymis, and ductus deferens to the ejaculatory duct. A spermatozoa is ready for ejaculation and fertilization only after undergoing weeks of changes post the initial mitotic division. During this incredible transformation, certain highlights include (1) initial mitotic divisions that maintain a set of stem cells relatively resistant to external injury as well as a population of rapidly proliferating germ cells destined to become spermatozoa; (2) meiosis, that occurs inside tight junctions between Sertoli cells that produce a unique intratesticular environment shielding the forming haploid gamete from systemic influences; and (3) the dramatic differentiation of the prospective gamete into a specialized cell ideally suited for transit through the female reproductive tract and ultimately, fertilization.

The spermatozoon will obtain its overall shape and size in the testis, but it is further modified both structurally and functionally as it passes through the epididymis before acquiring the ability to naturally fertilize an oocyte and the capacity for substantial intrinsic motility. Of note, sperm retrieved directly from the testis may have twitching motility and capacity to fertilize an oocyte if injected intracytoplasmically into an oocyte.

By the seventh week of gestation, Leydig cells differentiate from mesenchymal precursor cells in the connective tissue stroma of the testis between the seminiferous tubules. This event is detected by the presence of androgens in circulation. Leydig cell steroidogenesis occurs in conjunction with androgen-dependent differentiation of the male reproductive system. A gonadotropin similar to LH, human chorionic gonadotropin (hCG) is secreted by the placenta and thought to stimulate the development of fetal Leydig cells based on observations that Leydig cells differentiate in abnormal, amencephalic fetuses in which there is no internal LH secretion.

Fetal Leydig cell differentiation regresses after birth due to a lack of continuous hCG stimulation. However, two to three months post-birth, a second wave of Leydig cell differentiation occurs, driven by gonadotropin production from the neonatal pituitary that briefly elevates male infant testosterone levels. This neonatal surge of LH and subsequent testosterone has been suggested from anecdotal observations to hormonally imprint the hypothalamus, liver, and prostate such that they respond appropriately to androgen stimulation later in life. It is also thought that androgen production during this time period in neonate development also hormonally imprints the phallus and scrotum. Therefore, the absence of an androgen surge in a male neonate may impair normal development [20]. After this second wave of Leydig cell differentiation in neonate development, the Leydig cells regress and the testis will remain dormant during childhood.

The hypothalamus develops the ability to emit pulses of GnRH at puberty, which is around twelve years of age. At this time, the pineal gland decreases its nocturnal melatonin production, providing partial explanation for why pubertal onset of GnRH pulses tends to initially occur at night. The pattern of GnRH pulses matures so that pulses remain more frequent at night than during the day. The "gonadostat" hypothesis for puberty proposes in addition to the suppression of melatonin inhibition, androgen negative feedback is also delayed by converting testosterone to androgens such as androstanediol, which have a weak affinity for ARs, via enzymes such as 5α-reductase and 3α-hydroxysteroid dehydrogenase. These reactions delay androgen negative feedback until sufficient development of steroidogenic capacity of the testes.

Other factors that influence puberty are the growth rate and nutritional status of the body. For instance, there are clear stimulatory effects of growth hormone and its paracrine mediator, insulin-like growth factor-I (IGF-1), on reproductive function [21]. It is now theorized that leptin, an adipocyte hormone, affects the timing of puberty [22]. This hormone regulates the size of fat stores in the boy.. Once the body has acquired sufficient nutritional resources, reproductive development may occur. Though it remains unclear the exact mechanism by which leptin exerts control over reproduction, leptin has been shown to exhibit stimulatory effects on gonadotropin secretion [23]. In addition, leptin receptors present in the testis appear to exert inhibitory effects [24].

Aging of the Hypothalamic and Pituitary Axis

Serum testosterone levels begin to decline in men beyond 50 years in age. This declined output may result from the declining health status in older men, but aging also exerts a specific effect on hormone levels. Though basal levels of LH in the blood increase as men age, LH pulsatility is dampened, indicating that aging has an effect on the GnRH pulse generator. Moreover, the steroidogenic capacity of Leydig cells also decreases with age. Men older than 40 years of age have a lower fecundity, measured as a 50% lower probability of achieving a pregnancy with their partners within one year, compared to men younger than 25, possibly related to the fact that high testicular concentrations of testosterone are essential for maintaining spermatogenesis [25]. Therefore, male fertility may be impacted by the age-related decline in Leydig cell steroidogenesis. Accumulated oxidative stress in aging men may affect both sperm production and sperm quality as well [26].

Testis

Gross Structures and Vascularization

The average ovoid testis in healthy, young men measures at 15–22 cm^3 in volume and 4.5–5.1 cm in longitudinal length [27, 28]. Testicular parenchyma is enveloped in a capsule composed of three layers that encompass the tunica albuginea with vascular, and contractile capacity as well as notable sensory capacity for pressure. Due to the fact that the testicular artery traverses the capsule at an oblique angle, smooth muscle

control of the capsule may impact blood flow into the testis in not only man but also several other species [29]. The removal of the testicular capsule in the rate rete testis did not inhibit seminiferous fluid flow; therefore, it is unclear the extent to which capsular smooth muscle contractions influences the flow of seminiferous tubule fluid out of the testis [30, 31]. **The testicular arties penetrate the tunica albuginea just medial to the caput epididymis (allowing cooling of the epididymis in its lateral position) and the vessels then travel inferiorly along the posterior surface of the testicular parenchyma, which then branches passing anteriorly in a variable transverse fashion over the testicular parenchyma. The inferior pole of the testis therefore has** major testicular artery branches that makes the lower pole a poor site to place orchiopexy sutures. The vessels then, passing anteriorly and branching out over the surface of the testis. There is clinical significance to knowing the location of these vessels, as they may be injured during orchiopexy or testis biopsy procedures [32, 33]. In comparison with the anterior and inferior sections of the testis, the medial and lateral midsection contain few vessels. Individual artieres to tubules travel parallel to and within the septae that contain each seminiferous tubule, making dissection between seminiferous tubules feasible with preservation of blood flow to the seminiferous tubules—a factor utilized during the sperm retrieval procedure of microdissection TESE (testicular sperm extraction).

The testis is organized into compartments within the capsule that are separated by the septae. Each septum separates seminiferous tubules. Within the septum, there is at least one centrifugal artery. This organization is clinically important, as it allows microdissection to occur of testicular tissue, preserving the integrity and blood supply of seminiferous tubules within these septa. This is the principal for microTESE, where nearly all testicular tissue can be examined under an operating microscope. The individual seminiferous tubules that contain the developing germ cells and interstitial tissue. Interstitial tissue contains Leydig cells, mast cells, and macrophages as well as nerves, blood and lymph vessels. **In humans, 20–30% of the total testicular volume is comprised of interstitial tissue in normal men** [34] whereas men with severely defective spermatogenesis have up to 60–70% of the testis composed of interstitial tissue [35].

The seminiferous tubules are extremely coiled and looped, and their ends typically meet at the rete testis. **It has been estimated that the 600–1200 tubules in the human testis that, when combined, would reach a total length of about 250 m** [36]. **The 6–12 ductuli efferentes are tubules formed from the rete testis through which testicular fluid and spermatozoa travel to the caput epididymis** [37]. The identification of the efferent ducts allows an ideal site for microsurgical epididymal aspiration for azoospermic obstructed patients, including those with congenital absence of the vas. In men with the disease of cystic fibrosis, often the only component of epididymis that is present for these men.

There is no somatic innervation in the testis, but the testis does receive autonomic innervation primarily from the intermesenteric nerves and renal plexus, that are associated with the testicular artery to the testis, providing abdominal sensation of testicular pressure or inflammation [38]. As androgens suppress immune system function, interleukins acting in the brain during an infection could stimulate an appropriate immune response through the inhibition of Leydig cells. Other investigations suggest the nervous system exerts control over the vascular tone in the testis [39]. In man, the functional significance of testicular innervation remains unclear.

Approximately 9 mL of blood per 100 g of tissue circulate per minute in the human testicular parenchyma [40]. An investigation of blood flow to the testes in man found that blood flow to the left testis varies from 1.6 to 12.4 mL/per 100 mg per minute. Interestingly, blood flow to the right testis varies from 3.2 to 38.5 mL/per 100 g per minute [41]. However, it remains unknown the clinical significance of variation if blood flow to the testes.

Three reviews are recommended as excellent, in-depth discussions of the vasculature of the mammalian testis [34, 42, 43]. The human testis

and epididymis receives blood from three arterial sources: the internal spermatic testicular artery, the deferential vasal artery, and potentially from the external spermatic or cremasteric artery [44]. The spermatic artery enters the spermatic cord above the inguinal ring. The artery develops from the abdominal aorta just below the renal artery. It is closely associated with a network of veins that come together to form the pampiniform plexus. Within the pampiniform plexus, the artery and veins counterflow and are at time separated only by their vascular walls. This vascular arrangement permits the exchange of heat and small molecules, such as testosterone that diffuses passively from the vein (low concentration) to the artery (high concentration) [45, 46]. The vascular arrangement in the spermatic cord enables the counter-current exchange of heat, which lowers the temperature of blood circulating to the testis 2–4 °C in comparison to the rectal temperature of a normal individual [47]. As a result, the intratesticular temperatures are measured to be 3–4 °C lower than rectal temperatures in health individuals [48]. The loss of this temperature gap has been linked to testicular dysfunctions in humans such as idiopathic infertility as well as varicocele and cryptorchidism [49–51].

Though the internal spermatic artery branches in some males before entering the testis, the interconnections between the internal spermatic and deferential arteries facilitate the maintenance of testicular viability. **In 56% of the cases, a single artery entered the testis; in 31% of cases, two branches entered the testis; and in 13% of cases, three or more branches entered the testis** [52]. These findings offer practical insight into the number of testicular arteries present in the spermatic cord at the inguinal level. Jarow et al. compared the number of arteries found in intraoperative dissections versus cadaveric dissections and reported an average of 2 arteries and 2.4 arteries, respectively [53]. Another study investigating the number of internal spermatic arteries in intraoperative dissections found using ×10–15 magnification that in over 100 spermatic cords, a single internal spermatic artery was present in 50% of cases, two arteries were found in 30% of cases, and three arteries were found in 20% of cases [54]. The branching of the testicular artery typically occurs as it passes through the inguinal canal [55, 56]. The larger testicular artery broanches into a series of centrifugal arteries that run along the septa, penetrating the testicular parenchyma. The testicular artery derives its blood supply predominantly from internal spermatic artery with some support from the deferential arteries. There is limited evidence of any direct support of the external spermatic vessels to testicular blood supply. In certain cases, up to 90% of the testicular blood supply has been found to derive from the testicular artery. In such cases, a hindrance in testicular blood supply may result in testicular atrophy [57]. The intertubular capillaries are within the columns of interstitial tissue, whereas the rope ladder-like peritubular capillaries run near the seminiferous tubules.

Several mechanisms regulate testicular blood flow. Myogenic activity of the testicular capsular may play a role in autoregulation of arterial blood flow [58]. **While the total testicular blood flow is thought to remain fairly constant, flow at the regional level of the testis varies substantially to fit varying local metabolic needs**. At least in rodents, LH may affect testicular as well as cytokine release [59, 60]. In addition, the microvasculature of the testis appears to be capable of highly specialized functions [61].

Intratesticular veins are unusual in that they do not run alongside their corresponding arteries. The small veins within the parenchyma empty either to the veins under the capsule of the testis or to a group of veins near the mediastinum that run toward the region of the rete [34]. These veins together with the deferential veins form the pampiniform plexus. The testicular venous system was described by Ishigami et al. as stagnate due to the spermatic veins being thin-walled and poorly muscularized. Excluding the inflow points into the inferior vena cava or the renal vein, the venous system was also described as lacking effective valves [62], an observation that leads to clinical varicoceles due to reflux of blood within a substantial proportion of men, especially infertile men.

The human testis contains prominent lymphatic ducts [63, 64]. These ducts originate from lymph capillaries, which are within the intertubular space and do not penetrate the seminiferous tubules. The fact that the obstruction of the lymphatic ducts in the spermatic cord causes dilation of the interstitium but not the seminiferous tubules suggests the extracellular space of the interstitium, but not the seminiferous tubules, is drained via the lymphatics. The hindrance of lymphatic flow can also result in hydrocele formation, which is a recognized complication of inguinal or spermatic cord surgery, including non-microscopic varicocelectomy [65].

Extracellular fluid flows from the seminiferous tubules through the rete to form the rete testis fluid. This fluid is transported into the caput epididymis. Rete fluid was thought to have originated from both primary secretions with the seminiferous tubules and epithelial secretions [66–68]. However, Setchell proposed "the majority of the fluid leaving the rete, originates in the tubules" [34]. Though the origins of the rete testis fluid remain debated, the fluid is a dilute suspension that is isosmotic with plasma and contains spermatozoa. Estrogen seems to have a regulatory effect on the reabsorption in the rete testis and efferent ducts. A study of rodents found that the knocking out of estrogen receptors (ERKO) impaired intratubular fluid reabsorption [69]. In addition, the resulting build-up of fluid within the seminiferous tubules was observed to result in seminiferous tubular dysfunction.

Rete testis fluid contains a unique composition of ions, carbohydrates, amino acids, and proteins in comparison to those in blood plasma or lymphatics. Setchell and Waites remarked "**differences in composition between the fluid inside the seminiferous tubules and excurrent ducts of the testis and blood plasma or testicular lymph make it clear that substances do not diffuse freely into and out of tubules**." These findings contributed to the conception of the blood-testis barrier, which has been observed not only in man [70] but also in numerous species. The blood-testis barrier will be reviewed in further detail later in this chapter.

Cytoarchitecture and Function of the Testis

Interstitium

The interstitium contains blood vessels, lymph vessels, fibroblastic supporting cells, macrophages, and mast cells. Cytologically, Leydig cells are predominant. Macrophages have been observed to assist in the regulation of parenchymal cells, such as Leydig cells, within the testis [71]. Resting macrophages promote testosterone biosynthesis by secreting the steroid precursor, 25-hydroxycholsterol [72]. Testicular macrophages that have been activated due to disease, though, have been observed to suppress Leydig cell function through the release proinflammatory cytokines, such as interleukin-1 [73]. The role of macrophages in human testicular dysfunction has not been elucidated.

A stereologic analysis of the testis of a 20-year-old man was found to contain approximately 700 million Leydig cells [74]; whereas a broader evaluation of males suggested 4000–6000 million Leydig cells per testis [35]. These cells singlehandedly account for 5–12% of the total testicular volume in humans [74, 75]. Huhtaniemi conducted a review of the mechanisms by which Leydig cells mature and develop [76]. Leydig cells obtained from rat testes were ablated with ethane dimethyl sulfonate (EDS), and evidence from the ablation suggest that paracrine factors within the testis and pituitary LH affect the differentiation of Leydig cells from their precursor cells [77, 78]. Precursors of rat and mouse Leydig cells were observed to express steroidogenic enzyme before becoming sensitive to LH [79, 80]. Therefore, insulin-like growth factor-1 and other paracrine factors may play an important role in the induction of LH sensitivity [81].

The Leydig cell produces the majority of testicular steroid production. The principle steroid produced by the testis is testosterone, which is synthesized from the steroid precursor cholesterol [82]. In addition to testosterone, other C_{18}, C_{19}, and C_{21} steroids are reduced in the testis [82, 83]. It has not yet been discerned which source of cholesterol, blood plasma or de novo biosynthe-

sis, supplies the majority of the cholesterol used in testosterone biosynthesis [84, 85]. Cholesterol is transported from the metabolically active pool to the mitochondria, where an enzymatic reaction takes place that cleaves cholesterol into pregnenolone and the C6 fragment isocaproaldehyde.

The binding of LH to Leydig cells promote protein synthesis, and the newly synthesized steroidogenic acute regulatory protein (StAR) encodes a signal sequence that allows it to be weaved through the outer mitochondrial membrane [86]. It has not yet been determined the significance of this signal sequence in the cholesterol transport function of StAR. In addition, peripheral-type benzodiazepine receptor (PBR) creates a channel for cholesterol in the mitochondrial membrane [87]. It has not yet been determined whether StAR and PBR function independently, though a recent analysis of cells with both of these proteins fluorescently labeled did reveal a close association between them [88]. After exiting the mitochondrial membrane, pregenolone is transported to the smooth endoplasmic reticulum and is converted into testosterone. The four major enzymes involved in testosterone biosynthesis are cholesterol side-chain cleavage enzyme, 3β-hydroxysteroid dehydrogenase, cytochrome P450 17α-hydroxylase/C_{17-20}-lyase, and 17β-hydroxysteroid dehydrogenase. For more details on the enzymology, human chromosomal locations, and molecular genetics of StAR and PBR, see Payne and Hales [89]. Mutations in the genes encoding StAR and PBR have been investigated; though, sexual ambiguity in normal XY is very rarely attributed to disorders of androgen biosynthesis [90]. Post-synthesis, testosterone likely diffuses across the cell membrane where it is secured in the extracellular fluid and blood plasma by steroid-binding macromolecules.

There have been extensive reviews of Leydig cell steroidogensis [75, 91–98]. It is clear, though, that LH plays a key rule in the regulation of testosterone production. LH binding promotes the transport of cholesterol into the mitochondria, through intracellular events such as the generation of cyclic adenosine monophosphate. In addition, the efflux of chloride ions [99], the influx of calcium [99], and the release of arachidonic acid from phospholipids [100] influence the acute stimulation of steroidogenesis. Other peptides secreted by the pituitary that exert modifying effects on the LH-stimulated testosterone increase are follicle-stimulating hormone and prolactin [95]. Other nonpituitary factors that influence the Leydig cell production of steroids include LHRH [101], inhibin and activin [102], the growth factors EGF, IGF-I, and TGF-beta [103, 104] prostaglandins [93], and adrenergic stimulation [93, 94]. It should be noted, though, that such information has been obtained from in vitro experiments using laboratory animals, and that the role of these factors on normal testicular function in humans remains unclear. Autocrine and paracrine effectors of Leydig cells have been investigated (see [105–107]). Lastly, it has been proposed that Leydig cell steroidogensis may be inhibited directly by estrogens and androgens [95, 108].

Testosterone concentrations in peripheral blood fluctuates significantly during the life cycle of man. During 12–18 weeks of gestation, the first testosterone peak will occur in the blood of the human fetus. At approximately two months of age, another testosterone peak occurs. Sometime during the second or third decade of life, testosterone levels will peak. Thereafter, levels will plateau, and decline with age. Testosterone levels also change rhythmically on an annual and daily scale. There are also irregular changes to testosterone levels in peripheral blood that occur. For a more in depth discussion of testosterone concentrations in peripheral blood, see the review by Ewing et al. [109].

With regards to the species whose testosterone levels have been thoroughly investigated, the key stages of testosterone production correlate to an orderly sequence of temporal signals. **The first major stage of testosterone production is the differentiation and development of the fetal reproductive tract. The second stage correlates with neonatal organization, or "imprinting" of androgen-dependent target tissues, which assures their appropriate response later in puberty and adulthood. The third stage is marked by the masculinization of the male at puberty, and the fourth stage entails the maintenance of growth and function of**

androgen-dependent organs in the adult. One can attribute these major epochs in testosterone production to the intricate interaction between the pituitary gland and the testis. For a more in-depth review of this topic, see [110–113].

Seminiferous Tubules

The seminiferous tubule is a unique environment for germ cell production due to the fact that it contains both germinal elements and supporting cells. The supporting cells are the sustentacular cells of the basement membrane and the Sertoli cells. The germinal elements are the population of epithelial cells, which include the slowly dividing primitive stem cell populations, the rapidly proliferating spermatogonia, spermatocytes undergoing meiosis, and the metamorphosing spermatids. The components of the seminiferous tubule as well as the environment formed by the "blood-testis barrier" in the seminiferous tubule will be discussed in further detail below.

Peritubular Structures

Several layers of peritubular tissue surround the human seminiferous tubule [114]. An outer adventitial layer of fibrocytes separates the interstitial tissue from the tubule. The following layer is composed of myoid cells scattered among connective tissue lamellae. The third peritubular layer is a thick, inner lamella that is rich in collage and lies directly adjacent to the basement membrane underlying the seminiferous epithelium.

Human myoid cells are thought primarily to be contractile cells [115]. An investigation of rat myoid cells found their contractile functions responsive to both their thermal and endocrine environments. Within five days of establishing the experimental cryptorchidism, the contractions not only ceased but also the peritubular structures thickened [116].

Myoid cells secrete a multitude of substances, including fibronectin and collagen type 1, which are both components of the extracellular matrix [117]. It is likely that the myoid cells synthesize a considerable amount of the third, collagenous peritubular layer that separates the myoid cells from the basement membrane. Peritubular myoid cells release a paracrine factor called P-Mod-S (pertibular modifies Sertoli) that has been isolated in vitro [118]. The effects of P-Mod-S on Sertoli cell differentiation and synthesis have even been deemed more influential than those of FSH in culture. In vitro analysis of human peritubular cells have reported them to have steroidogenic functions. These functions include the ability to secrete testosterone, associate with Sertoli cells in a specific mesenchymal-epithelial interaction, and play a role in the regulation of the secretory activity of Sertoli cells [119]. Sertoli cells have been observed in culture to create cords similar to seminiferous tubules upon the addition of certain extracellular matrix components, which further stresses the important role that peritubular cells play in spermatogenesis [120, 121].

The Sertoli Cell

Both the nanostructure and morphological features of the human Sertoli cell have been thoroughly reviewed [122–124]. The defining features of the Sertoli cell are the uniquely shaped nucleus, prominent nucleolus, low mitotic index, Sertoli-germ cell connections, and the tight junctional complexes between adjacent Sertoli cell membranes that define the predominant component of the blood-testis barrier. **The Sertoli cell is located on the basement membrane of the seminiferous tubule and projects filamentous cytoplasmic ramifications toward the lumen.** Germinal cells exist between these cytoplasmic extensions. The undifferentiated spermatogonia can be found near the basement membrane of the seminiferous tubule, while the more differentiated spermatocytes and spermatids are located towards the higher levels of the epithelium. **The Sertoli cell therefore acts as a polarized epithelium with its base located in a plasma environment and its apex in an environment unique to the seminiferous tubule** [109].

It is proposed that Sertoli cells assist germ cell development with the following features: (1) the creation and maintenance of the adluminal compartment of the seminiferous epithelium, which functions as a unique

microenvironment (2) the existence of gap junctions between Sertoli and germ cells (3) the facilitation of germ cell migration in the seminiferous tubule. The microenvironment is actually a component of the previously mentioned "blood-testis barrier." This barrier is in fact found at various levels within the testis. Gap junctions entail the cytoplasmic connection of Sertoli and germ cells, and the specific junctions between Sertoli and germ cells include an "opening" and "closing" mechanism that promotes communication amongst cells and migration of germ cells to the adluminal surface [125].

One of the molecules Sertoli cells secrete is androgen-binding protein (ABP) [126, 127]. This protein transports androgens intracellularly within the Sertoli cell. The protein may also store androgenic hormones for the seminiferous tubule and potentially the epididymis. ABP also serves as a useful marker for in vitro analysis of the hormonal regulation of Sertoli cell function. There has not yet been a correlation found between the production of ABP or other known Sertoli cell products that mark Sertoli cell function, and male infertility [128].

In addition to ABP, the Sertoli cell also secretes components of the extracellular matrix, including lamin, collagen type IV, and collagen type I. Other secretory products include proteins such as cerulopasmin, transferrin, glycoprotein 2, plasminogen activator, somatomedin-like substabces, T proteins, inhibin, H-Y antigen, clusterin , cyclic proteins, growth factors, and somatomedin (see [125] for an additional review of Sertoli cell function). Sertoli cells also produce steroids such as dihydrotestosterone, testosterone, androstenediols, 17β-estradiol, and other C-21 steroids [109, 129]. While the functions of each Sertoli cell secretory product have yet to be fully revealed, such information may clarify how Sertoli cells generate the microenvironment in which spermatogenesis occurs.

Both FSH and testosterone have been observed to contribute to Sertoli cell function regulation, including the production of ABP [109, 130–133]. Inhibin B, a secretory product of Sertoli cells, is responsible for the feedback inhibition of FSH secretion in the human male. Both the molecular forms and the clinical values of inhibin B have been reviewed in the beginning of this chapter. Other regulatory molecules that enable maximal ABP secretion in vitro include progesterone, hydrocortisone, insulin, EGF, transferrin, and vitamins A and E [129]. Lastly, as previously mentioned, Sertoli cell function has been shown in vitro to be stimulated by testicular peritubular cell products [134, 135]. However, the exact mechanisms by which these effector molecules regulate Sertoli cell function as well as their physiological roles remains unclear. The production of feedback molecules including Inhibin B, and subsequent FSH suppression, from Sertoli cells appear to reflect both the number of Sertoli cells and germ cell/Sertoli cell complexes. So, men with normal volume testes and maturation arrest or Sertoli cell-only may still have normal inhibin B and low FSH levels.

The Blood-Testis Barrier

The notion of a "blood-testis barrier" resulted from the observations that many substances when injected into the blood stream would be rapidly detected in testicular lymph but not in rete testis fluid [136]. Ultrastructural investigations not only man but also other species have revealed specialized junctional complexes between Sertoli cells that subdivide the seminiferous epithelium into: the basal and adluminal compartments [137]. There seems to be three levels of the blood-testis barrier within the testis. The primary level is formed from the tight junctions between Sertoli cells and functions to organize the premeiotic germ cells (spermatogonia) from other germ cells. The two additional layers of the barrier are defined by endothelial cells in capillaries and peritubular myoid cells.

The basal compartment of the seminiferous epithelium contains the spermatogonia and young spermatocytes and separates them from the blood-testis barrier. The adluminal compartment contains the mature spermatocytes and spermatids above the barrier. During the first three substages of meiotic prophase (leptotene, zygotene, pachytene), the spermatocyte will travel from the basal compartment into the adluminal compartment of the seminiferous tubule. The migration

of the spermatocyte in the rat testis was detailed by Russel [138]. Russel observed this adluminal-to-luminal migration to occur when "Sertoli cell processes undermine the young spermatocytes to separate them from the basal lamina, and as the processes meet they form junctions impermeable to substances from the blood." In addition, "in those stages where young spermatocytes (leptotene, zygotene) move toward the lumen, these germ cell types are noted in regions where occluding junctions exist both above and below the germ cell." This described region of tight junctions that is above and below the germ cell was described by Russell as the "intermediate compartment" and was thought to be "a transit chamber in which cells may move from one compartment to another without disrupting the integrity of the blood-testis barrier."

The blood-testis barrier starts developing at the initiation of spermatogenesis; though, germ cells need not be present for the barrier to begin development [139, 140]. It was observed that in cases of males with hypogonadotropic hypogonadism, the administration of gonadotropins correlated with the formation of inter-Sertoli cell junctions [141]. However, the underlying factors regulating the development of the blood-testis barrier remain unclear.

The functional importance of the blood-testis barrier is currently primarily speculative. It may be functionally significant for meiosis due to the fact that the fluid bathing the germinal cells has a different composition to that of the compartments outside the barrier. Moreover, the barrier may separate the haploid male gamete, which the male immune system does not recognize as "self." Only after puberty can the clinical value of the blood-testis barrier be discerned. "Antigens" on germ cells undergoing meiosis only appear once puberty begins. As a result, if testicular damage due to events such as by biopsy, torsion, or trauma occurs pre-pubertaly, antisperm antibodies may not be induced. An injury resulting in the physical disruption of the blood-testis barrier and consequently the immune system coming into contact with advancing germ cells could theoretically cause an immune system reaction to germ cell-associated (including sperm) antigens. An important consideration is the potential for different drugs to access cells behind the barrier, which includes the use of chemotherapeutic agents to target neoplastic cells within the seminiferous tubule. It is not clear if the risk of developing antisperm antibodies can be prevented, for example, post-torsion. Further, it appears that antibodies may resolve with avoidance of sperm exposure to the circulation, for example, after successful vasectomy reversal.

Sertoli Cell–Germ Associations

Investigations on laboratory animals have revealed cell communication within the testis to be a complex network. Interactions between Leydig cells and Sertoli cells, between Leydig cells and peritubular cells, between Sertoli cells and peritubular cells (see previous discussion on peritubular structures), and between Sertoli cells and germinal cells have all been identified in investigative studies. For a more in-depth review of these complex interactions and the paracrine factors that regulate them, see [142]. This discussion will focus exclusively on Sertoli cell-germ cell interactions.

Sertoli cell-germ cell specialized junctions were once believed not to exist; however, it is currently accepted that are multiple types of Sertoli cell-germ cell associations within the mammalian testes [143–148]. For a more extensive review of this topic, see [142, 149, 150].

Russell [150] noted "desmosome-like contacts function as attachment devices that maintain the integrity of the seminiferous epithelium and at the same time assure that germ cells are transported in an orderly fashion, toward the tubular lumen by virtue of configurational changes of the Sertoli cell." He also added, "ectoplasmic specializations are complex surface specializations that appear to hold elongated spermatids within deep recesses of the Sertoli cell." Moreover, he remarked that that "both the Sertoli cell and spermatid participate in the formation of tubulobulbar complexes that appear in the few days preceding sperm release." Russell interpreted such observa-

tions to indicate that spermatids lose the majority of their cytoplasm by Sertoli cell phagocytosis of tubulobulbar complexes.

The associations between Sertoli cells and germ cells may aid in the migration of germ cells upward towards the lumen of the seminiferous tubule. In addition, the associations between the condensing spermatid and the apex of the Sertoli cell during spermiogenesis is associated with the loss of residual cytoplasm from developing spermatid. Overall, it is clear that the junctions between Sertoli-cells plays an important role in forming the blood-testis barrier.

The Germinal Epithelium

About 123×10^6 spermatozoa are produced in the human male on a daily basis [151]. **Sperm production, or spermatogenesis, entails the division of spermatogonia either to both maintain their number (stem cell renewal) as well as to make cells that will develop meiotically. Daughter cells will become spermatocytes and undergo reduction division, which results in the production of haploid spermatids. The spermiogenic phase includes the morphological changes associated with the size and shape of the spermatid as it develops into a mature spermatozoa**. The following discussion of spermatogenesis will a general one and references will not necessary be made to original research due to space limitations, lack of information pertaining to human research, and the overall complexity of the topic. The discussion will rely on outstanding reviews [109, 110, 152, 153].

Histological evaluation of the human testis demonstrate substantive numbers of germ cells organized among Sertoli cells and developing as they migrate from the basement membrane to the lumen of the seminiferous tubule. Morphologic analysis indicated at least 13 types of identifiable germ cells present in the testis. These different types of germ cells were thought to depict the different stages of the developmental process. The germ cells were named in the order of least to the most differentiated. The order is dark Type A spermatogonia (Ad), pale Type A spermatogonia (Ap), Type B spermatogonia (B), preleptotene primary spermatocyte (R), leptotene primary spermatocytes (L), zygotene primary spermatocytes (z), pachytene primary spermatocytes (p), secondary spermatocytes (II), and Sa, Sb1, Sb2, Sc, Sd1, and Sd2 spermatids.

Spermatogonial Development

Primitive testicular chords form during the prenatal development of the testis. Primordial germ cells migrate to the gonadal ridge where they associate with Sertoli cells to the cords. For many species, after this event a period of high mitotic activity follows in the fetal testis. This period of rapid cell division will lead to an increase in germ cell numbers, though they remain the minority cell population within the testis. **Primordial germ cells of the undifferentiated gonad are known as gonocytes once seminiferous cords form and the gonad differentiates into a testis. Once gonocytes have migrated to the periphery of the seminiferous tubule, they are classified as spermatogonia** [154].

Between the 8th and the 22nd week of pregnancy, a sharp increase in the number of germ cells per tubule (from 1.1 to 3.5) occurs. After this period of development until about 4 months after birth, the ratio of germ cell to Sertoli cell production will decrease. The lower level of germ cell production is associated with limitations in the proliferative activity of immature Sertoli cells [155]. There are negligible morphological changes to the human testis until about 7 years of age. **Between the ages of 7–9, gonocyte mitotic activity occurs and spermatogonia begin to populate the base of the seminiferous tubule and increase in numbers equal to that of Sertoli cells** [156]. Morphological changes in spermatogonia will again remain minimal until the onset of puberty and the initiation of spermatogenesis. Additional investigations of gonocyte maturation, their migration to the base of the seminiferous tubule, and the factors that impact these changes, may provide insight into clinical problems affecting the testis, such as cryptorchidism.

Spermatogonial Proliferation and Stem Cell Renewal

The basal compartment of the seminiferous tubule forms from overextended Sertoli-Sertoli tight junctions and is also where Pale Type A spermatogonia are found. Ap spermatogonia undergo division in 16-day intervals in humans and produce B spermatogonia, which are developmentally committed to becoming spermatocytes [152]. During this mitotic event, cytoplasm will usually not separate completely after nuclei have divided, which results in the formation of cytoplasmic bridges between adjacent spermatogonia. Cytoplasmic bridges continue into meiotic stages and have been observed during all stages of germ cells [109]. While their functional significance has yet to be determined, cytoplasmic bridges may play an important role in the synchronization of cellular division, differentiation, gene expression in haploid cells.

The population of undifferentiated spermatogonia must be replenished (stem cell renewal), though the mechanism by which spermatogonia both replenish their population while also producing precursors for spermatogenesis is not well understood. A research study found evidence of a growth factor/receptor called kit ligand/c-kit receptor system that plays a role in spermatogonial stem cell renewal. The c-kit receptor has even been used as a marker for type A spermatogonia in rats (Reviewed by Dym [157]. During this process, some type A_4 spermatogonia differentiates, eventually becomes a type B spermatogonia, and continues undergoing spermatogenesis. Other A_4 cells, though, will instead replenish the stem cell population of type A_1 spermatogonia [158]. The mechanisms by which approximately 2/3 of all spermatogonia undergo programmed cell death is yet to be elucidated; this could either be an opportunity for enhanced sperm production or, alternatively, a critical quality control step in human spermatogenesis [159, 160].

Meiosis

Type B spermatogonia, with their intact cytoplasmic bridges, undergo mitosis and form primary spermatocytes that will undergo meiosis. This process has been reviewed in general by Ewing et al. [109] and specifically in humans by Kerr and deKretser [123]. **As a result of these cytoplasmic bridges, mature spermatocytes will be interconnected in chains behind the blood-testis barrier formed from Sertoli-Sertoli cell tight junctions within the adluminal compartment of the seminiferous tubule.** In many species, meiotic divisions are proceeded by an equatorial division that results in a pair of daughter cells with haploid chromosomes. These daughter cells will contain unique genetic information, though, due to recombination. In humans, these events result in the production of the round, Sa spermatid.

Spermiogenesis

The last stage of spermatogenesis is spermiogenesis. The meiotic products of this stage are round Sa spermatids, which undergo metamorphosis and mature into spermatids. *Though this metamorphic process entails significant changes to the spermatid cytoplasm and nucleus, the spermatid will not undergo cell division*. For a detailed review of this metamorphosis and the changes that occur, including the loss of cytoplasm, the formation of the acrosome and flagellum, and the movement of cytoplasmic organelles to locations characteristic of mature spermatozoa, see [123]. In the rat, the daughter spermatids remain connected via cytoplasmic bridges and to Sertoli cells via ectoplasmic specializations.

It takes roughly 64 days for human spermatogenesis to occur from start to finish [152]. **During this 64 day time period, there are six identifiable cellular associations (stages of the cycle of the seminiferous epithelium) that take place if spermatogenesis is observed from a fixed point within the seminiferous tubule** [161]. The stage of spermatogenesis that entails the differentiation of Ap to B spermatogonia, also known as the proliferative phase, occurs every 16 days in this 64-day time frame. Consequently, the human testis will potentially contain two cohorts of spermatogonia, spermatocytes, and spermatids. Millions of spermatozoa are able to be produced daily as a result of the efficiency of stage-specific spermatogonia production.

The stages of spermatogenesis have been observed in rats to repeatedly occur from start to finish along a given portion of the tubule. The wave of seminiferous epithelium refers to a complete series of these tubule segments that represent all cellular associations (stages) of spermatogenesis. The wave of seminiferous epithelium was not thought to occur in man [161–163]. Instead, cellular associations took up only a portion of the circumference of the tubule and formed a mosaic, rather than a clear, linear progression of the stages of spermatogenesis. However, this understanding has been challenged by Schulze who used computer-generated 3D imagine to view the arrangement of the stages of spermatogenesis in humans. The reports described the stages to be oriented obliquely and in a helical arrangement. Thus, the precise arrangement of cellular associations in humans remains unclear.

Hormonal Regulation of Spermatogenesis

Testosterone levels in man and other mammals increase around 100-fold in the testis in comparison to that measured in the peripheral circulation [164, 165]. Clinical and genetic data indicate that some 46,XX (SRY-) men have activation of downstream targets of STY including SOX9 that allow the normal gonadal developmental pathway to "bypass" SRY activation [13]. Though testosterone and other GnRH agonists have been explored as potential male contraceptives, limitations to these treatments include their failure to completely inhibit FSH secretion by the pituitary.

Hypophysectomy, or the surgical removal of the pituitary, in many species [166] including man [167–169] results in testicular atrophy. The fact that intratesticular injections of testosterone microsphere almost fully recovered spermatogenesis rates in rats previously treated with GnRH agonists further stresses the significant role that testosterone plays in supporting spermatogenesis. Testosterone regulates sperm production through its effects on the Sertoli cell [170]. **Androgens not only initiate but also maintain human spermatogenesis.** A case study of a 6-year-old boy with an androgen-secreting Leydig cell tumor affirmed testosterone's impact on spermatogenesis [171]. Despite the lack of gonadotropin production, spermatogenesis was occurring in the testicular tissue exposed to the tumor. The contralateral testis was not exposed to the tumor, and no sperm production was observed in this area. Such findings suggest sperm production was initiated and maintained by the androgenic steroids secreted by the tumor.

For young men with congenital hypogonadotropic hypogonadism, early treatment with hCG may optimize testicular growth and subsequent spermatogenic potential, whereas treatment with exogenous testosterone and subsequent adult administration of hCG does not result in the same quantitative sperm.

For more in-depth reviews of pituitary gonadotropins and their effects on sperm production, see [109, 110, 166, 172]. The only known effect that luteinizing hormone has been observed to have on spermatogenesis is the stimulation of endogenous testosterone production.

In contrast, the effects of FSH on spermatogenesis have been more highly contested over the years. Cases of human males with severely defective FSH receptors have been reported to be fertile, though testicular volume, sperm concentration, and morphology were all significantly reduced [17]. In addition, cases of men with hypogonadism that do not produce FSH were also recorded to be fertile. Though the mechanism by which FSH exerts these effects remains unclear, it has been proposed that it aids in the initiation of spermatogenesis in pubertal males and also in the reinitation of spermatogenesis post germinal epithelium regression in animals who have undergone hypophysetomy [109, 110, 166]. Though spermatogenesis can begin without the presence of FSH in cases of human males with hypogonadotropic hypogonadism, FSH enhances quantitative and qualitative sperm production treatment. Spermatogenesis can occur without FSH, but it is the combination of FSH and testosterone that enables quantitatively normal sperm production.

Genetic Bases of Spermatogenesis

There are many ongoing investigations seeking to identify genes critical for spermatogenesis. The fact that about 5–10% of azospermic men have been found to also contain microdeletions on interval 6 of the Y chromosome led scientists to focus their attention on this area as the location of a critical factor (**Az**oospermic **F**actor) for spermatogenesis [173, 174]. **A specific gene referred to as DAZ (deleted in azoospermia) was located in the AZFc region of the long arm of the Y chromosome** [175]. Other regions of the Y chromosome where deletions are strongly associated with azospermia are AZFa and AZFb region deletions. Complete deletion of the entire AZFa region has been linked uniformly to Sertoli cell-only and azoospermia. *DBY*, a DEAD-box protein that functions as a regulator in transcription, is a gene in the AZFa region of the Y chromosome that is deleted in all cases of severe impairments of sperm production, suggesting its critical role in maintenance of spermatogenic cells [176]. Moreover, the AZFb region of the Y chromosome has been identified as crucial to the completion of spermatogenesis. No men with complete AZFb deletions have had full spermatozoal development usable for assisted reproduction [55, 56]. It is likely that other genetic defects will cause defects in sperm production, and studies, at least in limited populations, have demonstrated common defects [177].

Recent investigations have found compelling evidence to suggest that certain male gamete characteristics may have a significant effect on embryonic development. In addition, studies have identified important inter-species variation of embryonic growth**. In the case of human embryonic development, mitotic activity of the embryo seems to organized normally by the paternally-inherited centrosome** [178, 179]. Observations of human embryonic development support the notion that sperm not only provide genetic material but also assist in regulating mitotic activity via the male gamete centrosome. Cases in which embryos have not inherited the male gamete centrosomes have entailed chaotic mitotic activity and the lack of viable embryos [180]. As a result, further investigations are needed in order to identify the exact components of the male gamete that are vital for normal embryo development.

Summary

Under adequate hormonal conditions, spermatogenesis will lead to the production of a new cohort of spermatogonia (Type Ab-B) every 16 days at any one location of the seminiferous epithelium. Following this event, certain spermatogonia (Ap-Ap) will undergo mitosis and provide stem cells for a future cohort of differentiating spermatogonia. As it takes 64 days for any one cohort to mature into Sd2 spermatids, four cohorts of maturing sperm cells are observed in the seminiferous epithelium. The various stages of differentiation amongst these cohorts of cells in a 64 day time internal reveals six unique stages of spermatogenesis. These stages can be observed with histologic examination of the human testis.

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4 Clinical Evaluation of the Lower Urinary Tract

Christopher R. Chapple

Introduction

The urinary tract consists of two distinct and mutually dependent components:

Upper Tract: Comprising The Kidneys and Ureters

Both kidneys continuously produce greater than 0.5 mL of urine per kg of body weight per hour (i.e. >35 mL per hour in a 70 kg man) when functioning properly and adequately hydrated. This urine empties into the kidney's collecting systems which drain via the ureters.

The ureters function as low-pressure distensible conduits with intrinsic peristalsis, which transport urine from the kidneys to the bladder. The urine drains into the bladder at the vesicoureteric junction (VUJ) at the termination of each ureter. Each junction, if correctly functioning, only allows the one-way flow of urine and contains a mechanism to prevent retrograde transmission of urine back into the ureters from the bladder. This serves to protect the upper tract from the high pressures encountered within the bladder during voiding and to prevent infection entering the upper tracts.

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Lower Tract: Comprising the Urinary Bladder and Urethra

These provide a highly sophisticated system of conduits and a reservoir that converts the continuous involuntary production of urine by the kidneys into the intermittent, consciously controlled voiding of urine (micturition at a convenient time and place). A thorough evaluation and detailed understanding of the structure, function and control of the lower urinary tract is vital for the accurate interpretation of urodynamic investigations.

Clearly the bladder is a hollow, muscular organ. It has two main functions:

- Low pressure storage of urine
- Expulsion of urine at an appropriate time and place.

Histologically the bladder is composed of four distinct layers:

1. **Serosa**—an outer adventitial connective tissue layer.
2. **Detrusor muscle**—a middle smooth muscle layer, comprising a functional syncytium of interlacing muscle bundles with fibres running in all directions. Adequate functional contraction of the bladder is essential for effective bladder emptying. Despite the commonly held view it seems unlikely that the detrusor muscle is the primary target of

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therapy designed to treat the overactive bladder symptom complex but the effects of antimuscarinics and botulinum toxin A on the detrusor muscle are likely to represent an unwanted 'bystander' effect.

3. **Urothelium**—an innermost lining composed of transitional cell epithelium providing an elastic barrier that is impervious to urine and which has a high metabolic rate and an important role in the control of bladder function. In particular there is non neuronal release of a number of putative neurotransmitters from this layer triggered by distension of the bladder and consequent stretching of the urothelium.
4. **Suburothelial layer**—this lies immediately beneath the urothelium, is also highly active metabolically and acts in concert with the urothelium to subserve a key afferent role. It is this afferent function which is the target for all therapies directed at overactive bladder syndrome and detrusor overactivity.

The base of the bladder extends circumferentially from the ureteric orifices. This region contains the trigone which is a small triangular muscular area between the two ureteric orifices and the bladder neck. The trigone contains a complex plexus of nerves. Above the ureteric orifices is the main body of the bladder.

The bladder neck is an important functional and genital sphincter in the male, it is less well developed in women.

The urethra has two main functions:

1. To provide an effective continence mechanism, for the majority of the time (storage phase).
2. To allow adequate emptying from the bladder with the minimum of resistance during micturition (voiding phase).

A further role for the urethra which seems likely but remains hypothetical is to provide afferent feedback which may have important implications in influencing bladder function. The innermost mucosal layer in both sexes is organized in longitudinal folds and during the storage phase when the urethra is 'closed' this appears in a stellate configuration on cross section. Such a configuration allows significant distensibility, which is necessary during urethral 'opening'.

The submucosal layer contains a vascular plexus which may be involved in improving the seal of a 'closed urethra' by transmitting the tension of the urethral muscle to the mucosal folds.

Apart from the obvious anatomical differences there are important differences in the configuration of the sphincter mechanisms between males and females (Fig. 4.1 and Table 4.1).

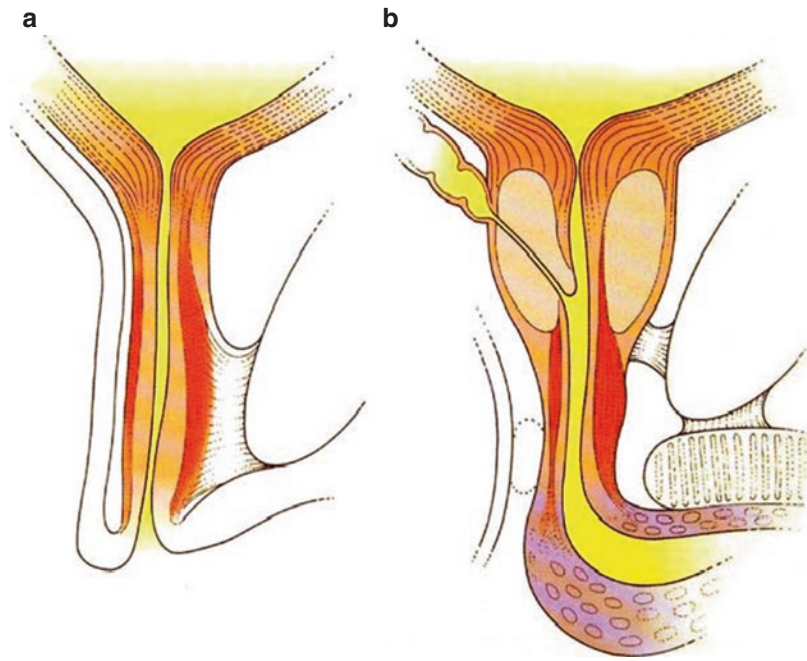

Fig. 4.1 (**a**) Anatomy of the female urethra. The bladder neck is both anatomically and functionally poorly developed. (**b**) Anatomy of the male urethra. There is a powerful bladder neck, distal to which is the prostatic urethra and just below that the distal sphincter mechanism with both internal and external components

Table 4.1 The principal innervation of the lower urinary tract

The principal innervations of the lower urinary tract					
	Type	Origin	Detrusor muscle	Sphincteric muscle	Principal neurotransmitter
Hypogastric	Sympathetic	T10-L2	Relaxes	Contracts sphincteric smooth muscle	Noradrenaline
Pelvic	Parasympathetic	S2-S4 (spinal micturition Centre)	Contracts	Relaxes	Acetylcholine
Pudendal	Somatic	S2-S4 (Onuf's nucleus)	N/A	Contracts sphincteric striated muscle and pelvic floor	Acetylcholine

Note the longer urethra, a prostate and two powerful sphincter mechanisms in the male compared to the single weaker intrinsic sphincter mechanism with a weaker bladder neck and also a shorter urethra in the female.

Male Sphincteric Mechanisms

In the male there are two important sphincteric mechanisms:

1. A proximal 'bladder neck mechanism'.
2. A distal urethral mechanism at the apex of the prostate.

The proximal sphincter in the male bladder neck provides a powerful mechanism in both maintaining urinary continence and also preventing retrograde ejaculation of semen during sexual activity. In patients with a damaged distal urethral sphincter (e.g. a pelvic fracture-associated urethral disruption) continence can be maintained solely by the proximal bladder neck mechanism. Ultrastructurally it consists of a powerful inner layer of muscle bundles arranged in a circular orientation.

The distal sphincteric mechanism is also extremely important, as evidenced by its ability to maintain continence even when the proximal bladder neck mechanism has been rendered totally incompetent by surgical bladder neck incision or a prostatectomy. It is confined to the 3–5 mm thickness of the wall of the membranous urethra from the level of the verumontanum down to the distal aspect of the membranous urethra. It is composed mainly of extrinsic striated muscle which is capable of the sustained contraction necessary for continence and to a lesser degree by intrinsic smooth muscle.

Prostate Gland

The prostate is made up of smooth muscle and glandular tissue, with the proportion of smooth muscle being increased in benign prostatic hyperplasia (BPH). The prostatic smooth muscle is controlled by the sympathetic nervous system, which acts by releasing noradrenaline onto α_{1a}-adrenoceptors located on the smooth muscle cells; the resulting contraction increases the bladder outlet resistance and further aids continence in the male.

Female Sphincteric Mechanisms

Females are much more likely to suffer from urinary incontinence due to sphincteric deficiency than males, due to the much less powerful sphincteric mechanisms. The bladder neck is a far weaker structure than the male bladder neck and is often incompetent, even in nulliparous young women. The bladder neck is poorly defined with the muscle fibres having a mainly longitudinal orientation.

Urinary continence is usually reliant upon the integrity of the urethral sphincteric mechanism, which like the male distal mechanism is composed of a longitudinal intrinsic urethral smooth muscle and a larger extrinsic striated muscle component. This sphincter extends throughout the proximal two-thirds of the urethra, being

most developed in the middle one-third of the urethra. Damage to the sphincter or its innervation (in particular the pudendal nerve) by obstetric trauma reduces the effectiveness of this mechanism and predisposes to stress urinary incontinence.

Pelvic Floor Muscles

In females the pelvic floor muscles also have an important role in maintaining continence. The pelvic floor is composed primarily of the levator ani muscle group, the endo-pelvic fascia and the supporting ligaments. The pelvic organs are maintained in the correct position by this pelvic floor. These tissues form a supporting 'hammock' beneath the urethra and during increases in intra-abdominal pressure (such as coughing, sneezing) the urethra is compressed against this hammock, thereby keeping the urethra closed and the patient continent.

Failure of this mechanism causes descent (prolapse) and also hyper-mobility of the bladder neck and is an important cause of stress urinary incontinence as is denervation of the urethral sphincter mechanism.

Function of the Lower Urinary Tract

The function of the lower urinary tract can be split into two distinct phases(Table 4.2).

1. The storage (filling) phase.
2. The voiding phase.

Table 4.2 The phases of bladder function

Urodynamics in practice
Storage phase
• Bladder fills passively—Detrusor muscle is relaxed
• Urethral sphincter mechanisms are 'closed'—Urethral and pelvic floor muscles are contracted
Voiding phase
• Bladder actively expels urine under conscious voluntary control—Detrusor muscle is contracting
• Urethral sphincter mechanisms are 'open'—Urethral and pelvic floor muscles are relaxed

For the majority of the time (greater than 99%) the lower urinary tract will be in the storage phase, whilst less than 1% of time is spent voiding.

Storage Phase

During the storage phase the bladder is filled with urine from the ureters. The bladder needs to accommodate the increase in volume without an appreciable rise in bladder (intra-vesical) pressure. This receptive relaxation property is called the 'compliance' of the bladder. Factors that contribute to compliance are:

- The passive elastic properties of the tissues of the bladder wall.
- The intrinsic ability of smooth muscle to maintain a constant tension over a wide range of stretch.
- The neural reflexes which control detrusor tension during bladder filling.

During the storage phase the urethra and sphincteric mechanisms should be closed, thereby maintaining a high outlet resistance and continence.

Voiding Phase

During the voiding phase the reverse activity to that seen during the storage phase must occur. The bladder must cease relaxing and instead contract to expel the urine and the urethra and sphincteric mechanisms must 'open' to decrease the outlet resistance and allow passage of urine. Voiding should be efficient and there should be minimal or no urine remaining in the bladder at the end of the voiding phase.

During voiding:

1. Urethral relaxation preceeds detrusor contraction.
2. Simultaneous relaxation of the pelvic floor muscles occurs.

3. 'Funnelling' of the bladder neck occurs to facilitate flow of urine into the proximal urethra.
4. Detrusor contraction occurs to forcefully expel urine.

Return to Storage Phase

At the end of voiding the proximal urethra is closed in a retrograde fashion, thus milking back the urine into the bladder. This 'milkback' is seen during contrast studies of the lower urinary tract when the patient is asked to stop voiding. Following this the bladder returns to a state of relaxation.

Neuronal Control of the Lower Urinary Tract

Control of the lower urinary tract is executed via a complex series of peripheral and central neuronal pathways. These pathways:

- Co-ordinate the activities of the bladder and the urethral/sphincter mechanisms
- Control receptive relaxation of the bladder (compliance)
- Sense bladder fullness
- Maintain continence with increasing fullness of the bladder
- Initiate voluntary voiding.

Motor (Efferent) Control

- The storage phase is under predominant sympathetic control.
- The voiding phase is under predominant parasympathetic control.

The peripheral innervation of the lower urinary tract is principally from three groups of nerves.

1. Hypogastric
2. Pelvic
3. Pudendal.

Sensory (Afferent) Control

Afferent signalling from the lower urinary tract also occurs along the hypogastric, pelvic and pudendal nerves. These nerves transmit information regarding the fullness of the bladder as well as the presence of any noxious (chemical or cold) stimuli.

Afferent signalling is involved in:

- Involuntary reflexes
- Conscious sensation of bladder fullness.

In certain neurogenic or inflammatory conditions there is up-regulation of some of these afferent nerves, causing bladder pain and it is thought that type C and Ad afferent nerve fibres are implicated in the involuntary stimulation of detrusor contractions (detrusor overactivity). In fact it is likely that it is the sensory nerves which are the main target of all contemporary therapy for overactive bladder symptom complex.

Involuntary Storage Reflexes

A number of involuntary reflexes exist, which are mainly located in the lumbo-sacral spinal cord. With increasing bladder fullness these reflexes will increase sympathetic activity and inhibit parasympathetic activity and also activate the pudendal (somatic) neurons. These reflexes therefore enhance storage by relaxing the bladder and maintain continence by increasing both intrinsic and extrinsic sphincter tone (guarding reflex).

Voiding reflexes are not confined to the spinal cord and there are a number of supra-spinal reflexes involved in co-ordinating lower urinary tract activity that have been discovered in experimentally produced high spinal cord transections.

Desire to Void

After infancy, voluntary control of voiding is achieved, thus allowing voiding to be initiated only in appropriate circumstances. To achieve

this, information regarding bladder fullness must be sent to the brain, and when appropriate to void the brain must override the peripheral storage reflexes and 'switch' the lower urinary tract into the voiding phase.

Once a threshold level of fullness has been achieved (which will depend upon circumstances and vary between individuals) there will be increasing afferent activity emanating from sensory neurons in the suburothelial plexus associated with the bladder wall. Parasympathetic afferents in the pelvic nerve will communicate this activity via the spinal cord to the periaqueductal gray (PAG) area in the midbrain. At the PAG the bladder filling information is processed and from here the signals are sent to the pontine micturition centre (PMC) in the brainstem and the suprapontine areas of the brain.

The suprapontine areas of the brain comprise the frontal cortex, the hypothalamus, the paracentral lobule, the limbic system and the cingulate gyrus. These are important in the conscious and unconscious control of the PMC. They have a role in delaying micturition, inhibiting premature detrusor contractions and in initiating voiding at an appropriate time.

Voluntary Control of Voiding

The PMC is an essential control centre in coordinating the micturition process and is itself under the control of the suprapontine area.

If the bladder is sensed to be full but it is inappropriate to void then the PMC will send descending signals to inhibit parasympathetic activity, increase sympathetic activity and increase the pudendal somatic activity to contract the urethral sphincter mechanism and pelvic floor muscles. These mechanisms voluntarily 'tighten up' the bladder outlet and so maintain continence until an appropriate time and place is found to void.

If the bladder is sensed to be full and it is appropriate to void then the PMC will 'switch' the lower urinary tract into the voiding phase by sending descending signals to increase parasympathetic activity and inhibit sympathetic and somatic activity.

Once voiding is initiated, secondary reflexes in the urethra, activated by urine flow also further facilitate bladder emptying.

Neuronal Interactions

The account of the neuronal control of the lower urinary tract given above is a simplification; there are extensive interactions between the neuronal populations at all levels in both the peripheral, spinal and higher central areas. These complex neuronal interactions have led to much controversy regarding the motor control of the lower urinary tract and also more recently regarding the sensory feedback. In particular the role of the sub-urothelial layer in afferent feedback involving a variety of neurotransmitters is currently the focus of much research. In recent years it has been recognised that stretch of the urothelial mucosa can lead to the nonneuronal release of a number of neurotransmitters such as acetylcholine, nitric oxide and ATP. In addition, an important group of cells, so called 'interstitial cells', have also been identified and these undoubtedly have an important role in the coordination of lower urinary tract function. This remains an evolving area with continuing research into the mechanisms underpinning lower urinary tract function.

Clearly a broad understanding of lower urinary tract function and its control is vital to accurately interpret urodynamic investigations and in understanding the pathophysiology and treatment of urinary tract disorders such as incontinence, bladder outlet obstruction and neurogenic dysfunction (Table 4.3).

Principles of Evaluation

The bladder and the urethra comprise the lower urinary tract and act as a single (vesico-urethral) unit during normal lower urinary tract function. The role of this unit is to:

- Adequately store urine (storage)
- Efficiently empty urine (voiding).

Table 4.3 Comparison of male and female sphincteric mechanisms—showing why females are much more likely to develop an incompetent urethral mechanism and be prone to urinary incontinence from intrinsic sphincter deficiency (ISD)

Comparison of male and female sphincteric mechanisms		
	Male	Female
Proximal bladder neck mechanism	Powerful	Weak
Distal urethral mechanism/ urethal sphincter mechanism (in the female)	Powerful	Prone to the effect of exogenous influences such as pelvic floor weakness and damage or denervation consequent upon childbirth
Prostate	Further increases bladder outlet resistance	Not present
Urethra	Long	Short (~3.5 cm)

If the function of this vesico-urethral unit is disturbed then urinary dysfunction along with associated lower urinary tract symptoms (LUTS) may occur. Management of lower urinary tract dysfunction is based on the findings of:

- A focused history and physical examination
- Appropriate laboratory studies
- Endoscopy and radiography—to provide structural information when clinically indicated
- Urodynamic studies—to provide functional information when clinically indicated.

Focused History and Physical Examination

First and foremost, a focused history establishes a working diagnosis, helps formulate clinical questions and directs subsequent investigations and management. Previously a plethora of overlapping and confusing terms relating to lower urinary tract dysfunction were in usage; however the International Continence Society (ICS) have published terminology reports to standardize the terms used when describing LUTS, thus enabling consistent and accurate reporting of symptoms as well as enabling further investigations and management to be appropriately directed. It is recommended that only standardized terminology is used when describing LUTS.

Table 4.4 Lower urinary tract symptoms

Lower urinary tract symptoms		
Storage	Voiding	Post-micturition
Urgency Increased daytime frequency Nocturia Urinary incontinence Altered bladder sensation	Hesitancy Intermittency Slow stream Splitting or spraying Straining Terminal dribble	Feeling of incomplete emptying Post-micturition dribble

The ICS have broadly categorized LUTS into three groups (Table 4.4) related to their timing within the bladder (voiding) cycle. The three stages of the bladder cycle are:

1. Storage—during which passive filling of the bladder occurs, either naturally from urine produced by the kidneys or artificially during a urodynamic study.
2. Voiding—during which the vesico-urethral unit actively expels the bladder contents.
3. Post-micturition—immediately after voiding when the bladder returns to storage function.

Specific definitions for lower urinary tract symptoms are listed at the end of this chapter.

The bladder is frequently said to be an 'unreliable witness'. There are a number of reasons why this statement accurately reflects the situation. First, lower urinary tract symptoms are not disease specific and diverse patho-physiologies can produce similar lower urinary tract symptoms. Second, patients express symptoms in different ways and this is influenced both by what they are experiencing and how they interpret the symptoms they are experiencing. Lastly, as clinicians we all take histories differently and interpret the clinical picture based on our own experience and prejudices.

Clearly however, a careful history with emphasis on allocating symptoms to the appropriate stage of the bladder cycle is an important starting point. Failure to store can be due to overactivity of the bladder, underactivity of the bladder with overflow, or weakness of the bladder outlet. Likewise, while voiding symptoms tend to be associated in many people's minds with bladder outlet obstruction, they can of course also occur in the context of poor bladder function.

Without a bladder diary it is not possible to assess nocturia and determine whether there is excessive production of urine at night time—so called nocturnal polyuria—where more than 33% of 24 h urine production is produced at night (in a younger age group it may be less than this—e.g. <20% below the age of 20).

In addition, in assessing a post voiding urinary residual it is essential to have information from a frequency volume chart to assess the voiding efficiency. Interpretation of the significance of a post voiding residual needs to take account of, and hence be related to, the functional bladder capacity. (Voiding Efficiency = Residual/ Voided Volume + Residual Volume. Normally <40% is accepted).

In some circumstances it is necessary to assess the anatomical bladder capacity by assessing capacity under a general anaesthetic—e.g. severe frequency in cases where shrunken bladder needs to be excluded such as post TB, ketamine abuse, or sensory bladder disorders.

Having taken a careful history and carried out an appropriate clinical examination; laboratory, endoscopic or radiographic tests should be performed prior to urodynamic assessment as clinically indicated. Clearly evaluation of a mid stream urine examination and appropriate investigation of haematuria is essential.

Urodynamic Evaluation

Appropriate urodynamic tests can only be interpreted after taking an adequate history, with the formulation of specific clinical questions; since the principal aims of the urodynamic assessment are to answer the clinical questions by evaluating the function of the vesico-urethral unit. Urodynamics is particularly of benefit in objectively identifying functional abnormalities of the lower urinary tract such as urinary incontinence and bladder outflow obstruction (BOO). However (particularly with video cystometry) it may also assist in identifying structural abnormalities such as a prolapse associated with stress urinary incontinence (SUI), vesico-vaginal fistulae, urethral diverticula, upper tract vesico-ureteric reflux; or in the context of the male patient, it can be useful in demonstrating attenuation of the prostatic urethra in association with prostatic outlet obstruction or confirming the diagnosis of bladder neck obstruction.

The term 'urodynamics' encompasses any investigation of lower urinary tract dysfunction from the simple to the sophisticated, these include:

- Frequency/volume chart (FVC).
- Pad testing.
- Uroflowmetry ± ultrasound residual estimation.
- Pressure/flow studies:
- Urethral pressure studies.

The most frequently performed tests are frequency volume charts (FVC)/bladder diaries, uroflowmetry and pressure/flow studies.

Generally the term 'urodynamics' has become synonymous with pressure/flow studies, with most clinicians referring to either cystometry or video cystometry when they use the term "urodynamics".

Urodynamics in Practice

Urodynamics:

- Can only be interpreted in association with a comprehensive history and examination of the patient, where they are valuable adjuncts in the investigation of patients who have LUTS/ lower urinary tract dysfunction
- Have become synonymous with pressure/flow studies, with most clinicians referring to either cystometry or video cystometry

- Are objective functional tests of bladder and urethral function (and may provide some associated structural information)
- May help indicate the most appropriate therapy.

Indication and Interpretation of Urodynamics

The information acquired from accurately interpreted and well performed urodynamic studies can be used to:

- Diagnose the underlying cause of the lower urinary tract dysfunction
- Characterize the lower urinary tract dysfunction
- Formulate treatment strategies
- Improve therapeutic outcomes
- Educate patients regarding their condition.

An experienced clinician with an understanding of urodynamic techniques should carry out the urodynamic study and should interpret the study in the context of the patient's symptoms. As with all practical skills there is a learning curve, with the interpretation becoming easier with increasing experience. The true clinical value or 'art' of urodynamics is in applying the objective findings of a well executed study to the individual patient, taking into consideration subtleties in the history and physical examination that may be clinically important.

Lower Urinary Tract Symptom Terminology

It is essential to use standardized terminology when discussing lower urinary tract symptoms (LUTS) (Table 4.4) and the results of urodynamic investigations, to allow accurate exchange and comparison of information for clinical and research purposes. The official terminology suggested by the International Continence Society (ICS) in 2002 is used in this chapter [1]. The ICS terminology for LUTS is summarized below and the terminology for urodynamic parameters are defined in later chapters. Further information regarding terminology can be found on the ICS website (www.icsoffice.org). Reference to urodynamics parameters in the ICS standardisation report is recommended [2].

Storage Symptoms

- Increased daytime frequency: the complaint by the patient who considers that he/she voids too often by day (term is equivalent to pollakisuria used in many countries).
- Nocturia: the complaint that the patient has to wake at night one or more times to void.
- Urgency: a sudden compelling desire to pass urine which is difficult to defer.
- Urinary incontinence (UI): any involuntary leakage of urine.
- Stress urinary incontinence (SUI): involuntary leakage on effort or exertion, or on sneezing or coughing.
- Urge(ncy) urinary incontinence (UUI): involuntary leakage accompanied by or immediately preceded by urgency (urge urinary incontinence is a misnomer since it is urgency that is associated with this incontinence and we therefore believe it should be called 'urgency incontinence', not urge incontinence).
- Mixed urinary incontinence (MUI): involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing (a mixture of urgency urinary incontinence and stress urinary incontinence symptoms).
- Mixed urinary symptoms: involuntary leakage associated with exertion, effort, sneezing or coughing; combined with urgency but not urge(ncy) incontinence
- Enuresis: any involuntary loss of urine (similar to definition of urinary incontinence).
- Nocturnal enuresis: loss of urine occurring during sleep (involuntary symptom, as opposed to 'nocturia' which is a voluntary and 'conscious' symptom).
- Continuous urinary incontinence: the complaint of continuous leakage.
- Other types of urinary incontinence: may be situational, for example incontinence during sexual intercourse, or giggle incontinence.

Bladder Sensations During Storage Phase

- Normal bladder sensation: aware of bladder filling and increasing sensation up to a strong desire to void.
- Increased bladder sensation: aware of an early and persistent desire to void.
- Reduced bladder sensation: aware of bladder filling but does not feel a definite desire to void.
- Absent bladder sensation: no awareness of bladder filling or desire to void.
- Non-specific bladder sensation: no specific bladder sensation but may perceive bladder filling as abdominal fullness, or spasticity (these are most frequently seen in neurological patients, particularly those with spinal cord trauma or malformations of the spinal cord).

Voiding Symptoms

- Slow stream: the perception of reduced urine flow, usually compared to previous performance or in comparison to others.
- Splitting or spraying: description of the urine stream.
- Hesitancy: difficulty in initiating micturition, resulting in a delay in the onset of voiding after the individual is ready to pass urine.
- Intermittent stream (intermittency): urine flow which stops and starts, on one or more occasions, during micturition.
- Straining: the muscular effort used to either initiate, maintain or improve the urinary stream.
- Terminal dribble: a prolonged final part of micturition, when the flow has slowed to a trickle/dribble (compare to post-micturition dribble).

Post-micturition Symptoms

- Feeling of incomplete emptying: a feeling experienced by the individual after passing urine.
- Post-micturition dribble: the involuntary loss of urine immediately after an individual has finished passing urine, usually after leaving the toilet in men, or after rising from the toilet in women (compare to terminal dribble).

Other Symptoms

- Symptoms associated with sexual intercourse: e.g. dyspareunia, vaginal dryness and incontinence (should be described as fully as possible—it is helpful to define urine leakage as: during penetration, during intercourse, or at orgasm).
- Symptoms associated with pelvic organ prolapse: e.g. ‘something coming down’, low backache, vaginal bulging sensation and dragging sensation (may need to digitally replace the prolapse in order to defaecate or micturate).
- Genital and lower urinary tract pain: pain, discomfort and pressure may be related to bladder filling or voiding or may be felt after micturition, or even be continuous. The terms ‘strangury’, ‘bladder spasm’, and ‘dysuria’ are difficult to define and of uncertain meaning and should not be used, unless a precise meaning is stated. Dysuria literally means ‘abnormal urination’. However, it is often incorrectly used to describe the stinging/burning sensation characteristic of an urinary infection (UTI).

Painful Bladder Syndrome Symptoms

- Bladder pain syndrome/Painful bladder syndrome/interstitial cystitis (BPS/PBS/IC): subrapubic pain related to bladder filling and associated with other lower urinary tract symptoms, usually increased frequency ((but not urgency) (diagnosed only in the absence of UTI or other obvious pathology)). This is a specific diagnosis usually confirmed by typical cystoscopic and histological feature.

Overactive Bladder (OAB)

This is a non specific symptom complex where only a proportion of patients have detrusor overactivity. It is characterised by the symptom of urgency, which in a third of women leads to urgency incontinence (Fig. 4.2). Indeed detrusor overactivity is only present in 40 and 60% of women and is present in 60 and 90% of men who are dry and have incontinence respectively.

Benign Prostatic Hyperplasia (BPH)

BPH is a histological condition, it is a term mistakenly applied to men who are thought to have symptoms resulting from benign enlargement of the prostate. In fact the majority of these men present with symptoms of OAB. The complexity of this condition is demonstrated in (Figs. 4.3a and 4.3b).

Female Incontinence

A similar picture is evident when considering women with incontinence. Consideration has to be given to the presence or absence of genito-urinary prolapse, but in addition to the medical factors noted above, one needs to determine the presence or absence of sphincteric weakness, sensory bladder disturbance and overactive bladder symptoms. (Fig. 4.4).

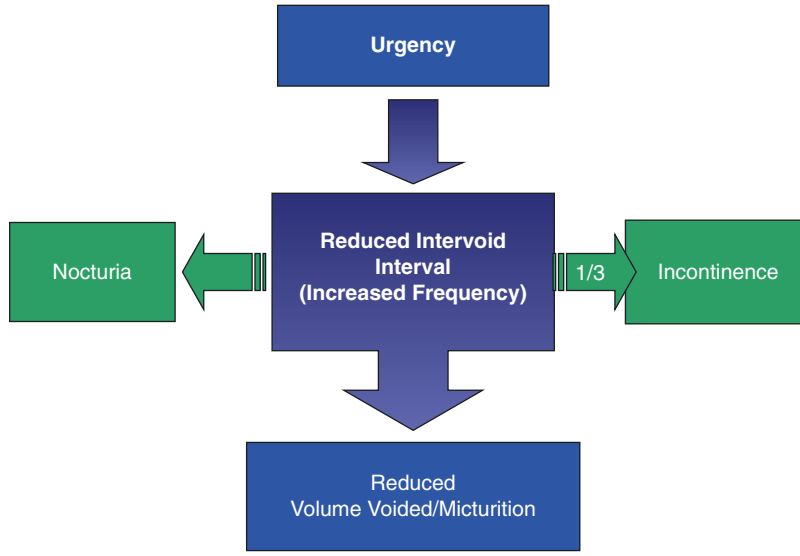

Fig. 4.2 Diagrammatical representation of the symptoms in the overactive bladder symptom complex

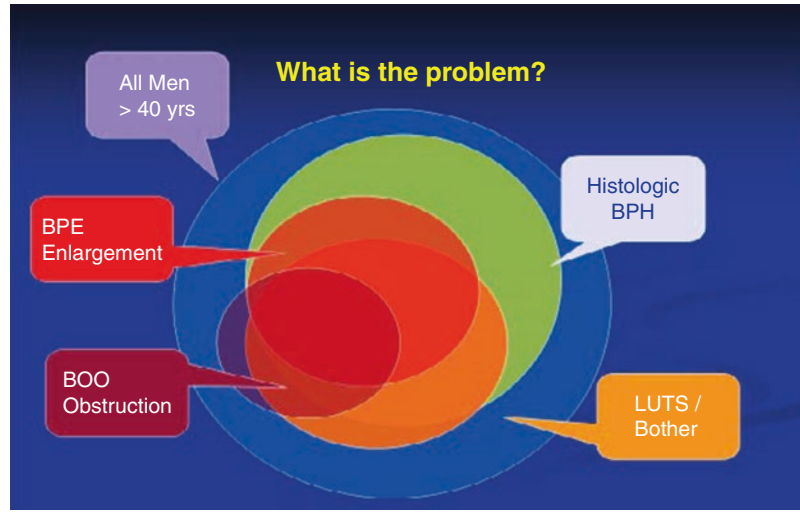

Fig. 4.3a The clinical problem

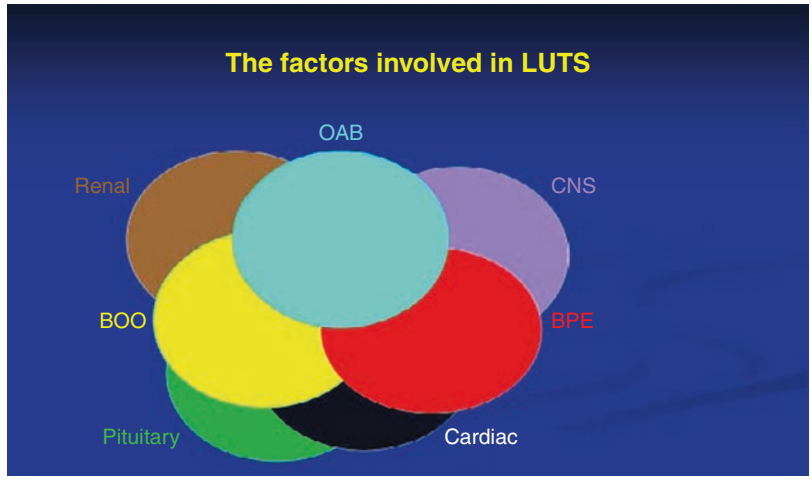

Fig. 4.3b The associated medical factors

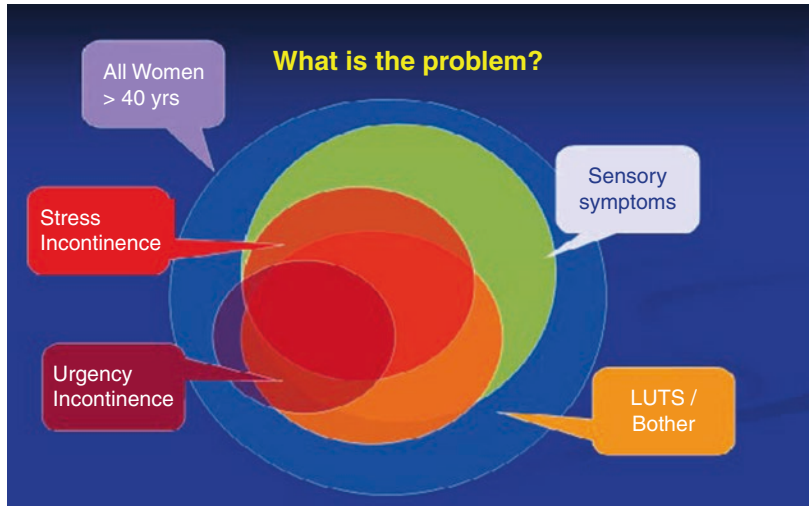

Fig. 4.4 The clinical problem in women

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5 Ureteral Physiology and Pharmacology

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Ureteral Anatomy

The ureters are retroperitoneal structures that carry urine from the kidney to the bladder. They travel inferiorly from the renal pelvis at the ureteropelvic junction (UPJ), course anteriorly along psoas major, pass over the pelvic brim at the level of the common iliac artery bifurcation, and then run along the lateral pelvic sidewall to enter the urinary bladder. In adults they are typically 22–30 cm in length and 1.5–6 mm in diameter. Radiologically, the ureter is divided into three segments: proximal (UPJ to sacroiliac joint), middle (overlying sacrum), and distal (lower border of sacroiliac joint to bladder) [1].

The terminal ureter near the bladder is enveloped by a muscular layer called the Waldeyer sheath and then pierces the bladder. It travels 1.2–2.5 cm intramurally in adults before opened up into the bladder inferiorly and medially along the trigone as the ureteral orifice. Detrusor fibers coalesce with the Waldeyer sheath such that increased intravesical pressure prevents reflux of urine from the bladder to the ureter [1].

Blood supply to the ureter above the pelvic brim (proximally) arises medially from the renal artery, abdominal artery, gonadal artery, and common iliac artery. Below the pelvic brim (distally), the blood supply to arises laterally from the branches off the internal iliac artery [1].

Microscopically, the ureter is composed of three distinct layers: the mucosa (innermost layer), muscularis (middle layer), and adventitia (outermost layer). The mucosa is made up of transitional epithelium (urothelium) atop the lamina propria, and is usually 4–6 cell layers thick when the ureter is contracted [1]. The urothelium acts both as a protective barrier and a sensor of mechanical and chemical changes, which then signal the muscular layers [2]. The muscularis is made up of two layers of smooth muscle: an inner helical layer and an outer mesh-like layer. The inner layer is responsible for peristalsis while the outer layer is thought to offer structural support [3]. Finally, the adventitial layer contains a dense network of collagen and elastic fibers, including blood vessels and unmyelinated nerve fibers [1] (Fig. 5.1).

Initiation of Peristalsis

Precise coordination of ureteral smooth muscle is required for downstream propagation of urine between the kidneys and the bladder. As with all smooth muscle, the contraction of the ureter is the result of depolarization of the cell membrane. In the ureteral smooth muscle cell, the resting membrane potential is −33 to −70 mV as a result of the distribution of potassium (K^+) ions across

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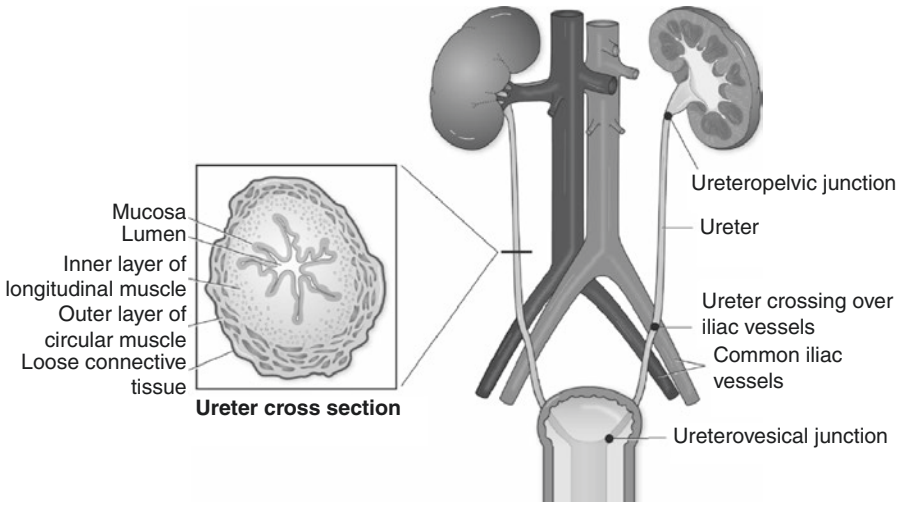

Fig. 5.1 Basic retroperitoneal anatomy with cross section of the ureter

the cell membrane. When stimulated, the membrane becomes less permeable to K^+ and more permeable to calcium (Ca^{2+}). The Ca^{2+} influx into the cell then activates calmodulin, which binds to myosin light chain kinase and leads to myosin phosphorylation. Phosphorylated myosin then migrates up actin filaments, resulting in smooth muscle contraction [4].

Ureteral peristalsis originates in the renal pelvis, specifically at the pelvicalyceal junctions [5]. The initiation of peristalsis involves three types of cells: atypical, typical, and interstitial cells of Cajal-like cells (ICC-like cells). Atypical smooth muscle cells are considered to be pacemaker cells and are clustered at the pelvicalyceal junctions [6]. Compared to non-pacemaker cells, these cells have a lower resting membrane and undergo slow spontaneous depolarization caused by opening and slow closure of voltage gated L-type Ca^{2+} channels [7]. The autorhythmicity generated by these atypical cells are then modulated by surrounding ICC-like cells. ICC-like cells express both c-kit receptor positivity as well as hyperpolarization-activated cation-3 (HCN3) channels, both of which work to modify contractility based on the influence of the nervous system, prostaglandins, and other hormones [8, 9]. These modulated signals finally pass onto typical smooth muscle cells, which fire at a rate of 3–5/minute in a coordinated fashion. Typical smooth muscle cells make up the vast majority of urinary smooth muscle. Nearly all ureteral smooth muscle have typical cells, whereas 97.5% and 83% of the smooth muscle cells in the distal renal pelvis and proximal renal pelvis are made up of typical cells, respectively [10] (Fig. 5.2).

Mediators that increase intracellular calcium cause ureteral smooth muscle contraction. Interactions with 1,4,5-triphosphate and diacylglycerol cause increased contraction, whereas mediation of G-protein coupled receptor complexes via cAMP and cGMP reduce contraction by lowering calcium levels [11].

Additional work demonstrates that peristalsis is initiated not by neurons but by smooth muscle itself, as experiments using tetrodoxin or autonomic nerve blockers fail to block ureteral contractions [12]. In addition, denervated transplant ureters have been shown to maintain contractility [13] and normal antegrade peristalsis has been shown to continue after reversal of the ureter in situ [14].

Modulation of Peristalsis

While initiation of ureteral contraction is to some degree independent from the nervous system, modulation of peristalsis relies heavily on the autonomic and sensory nervous system, as well

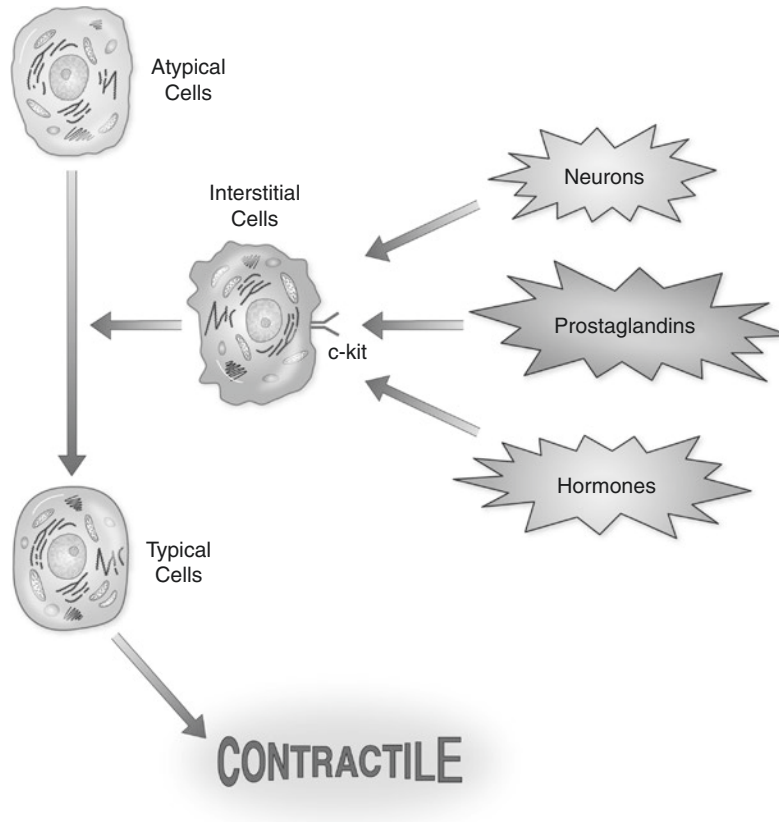

Fig. 5.2 Autorhythmicity is first generated by atypical smooth muscle cells. These pacemaker signals are then modulated by surrounding interstitial cells of Cajal-like cells (ICC-like cells). Modulation occurs under the influence of multiple factors, including neuronal, prostaglandin, and hormonal stimulation. These modulated signals finally pass onto typical smooth muscle cells that result in a coordinated firing action, initiating ureteral peristalsis

as prostaglandins. Ureteral contraction can vary with regard to rate and contractility.

The autonomic nervous system influences ureteral contraction through both parasympathetic and sympathetic fibers. The parasympathetic nervous system acts on muscarinic receptors, with acetylcholine as its major neurotransmitter via postganglionic cholinergic fibers. The cholinergic innervation is especially rich in the distal and intravesical ureter [15]. Significant evidence indicates that the effect of such cholinergic stimulation varies by species, with decreased ureteral activity noted in dogs and increased activity noted in a pig model [16, 17]. However in humans, cholinergic agonists have demonstrated an excitatory effect on the ureter and renal pelvis, increasing both the frequency and force of contractions [18–20]. This is supported by excitatory effects on the ureter found with the use of anticholinesterases such as physostigmine and neostigmine [18, 21], along with some inhibitory effects of ureteral contraction noted with atropine, a competitive muscarinic antagonist [22].

The sympathetic nervous system affects ureteral function by modulating and mediating ureteral contraction. The ureter contains both excitatory alpha-adrenergic along with inhibitory beta-adrenergic receptors [19, 23]. There are four α_1-adrenergic receptor subtypes (α_{1A} to α_{1D}), with the α_{1A} subtype being the primary receptor subtype that participates in contraction of the human ureter [24–26]. It is understood that agents that activate these α_1-adrenergic receptors, such as norepinephrine and phenylephrine, increase ureteral and renal pelvic contractile activity [18, 19, 23]. Furthermore, the highest density of α_1-adrenergic receptors are found in the distal ureter, as evidenced by the greater contractile force seen in the distal versus proximal human ureter with the administration of phenylephrine, an alpha-adrenergic agonist [26]. Conversely, stimulation of the beta-adrenergic receptors causes ureteral and renal pelvic relaxation, as seen with the use

of beta-adrenergic agonists such as isoproterenol and orciprenaline [27–29]. Further support of these findings was seen when norephinephrine, a primary alpha-adrenergic agonist with some beta-adrenergic agonistic activity, was found to increase the force of ureteral contraction. However, when administered with phentolamine, a potent alpha-adrenergic antagonist, norepinephrine was found to decrease the force of ureteral contractions. This reversal of action is likely due to the unopposed beta-agonistic effect of norepinephrine on the ureter given the alpha-blockade provided by phentolamine [23, 27].

Sensory nerves are able to modulate peristalsis via capsaicin-sensitive fibers. The sensory nerves found in the ureter are unmyelinated C fibers and poorly myelinated A-delta fibers [9]. Sensory afferent nerve fibers release several molecules that influence peristalsis. Among these are tachykinins and calcitonin gene-related-peptides (CGRP). Tachykinins are released in response to painful stimuli and cause smooth muscle contraction via G-protein coupled receptors, specifically the NK receptors in the ureter [30, 31]. Examples of tachykinins are neurokinins A, neurokinin K, and substance P [32]. Therefore, the presence of neurokinins and substance P are associated with increased contraction in the proximal and distal ureter [32, 33, 34]. Neurokinin A has been shown to be the most potent of the tachykinins, and treatment of ureters in vitro with a neurokinin antagonist decreased ureteral contraction by 80% [34]. Capsaicin-sensitive sensory nerves also contain and release CGRP in response to low levels of capsaicin, which inhibit electrical and contractile activity in the ureter [31]. CGRP cause ureteral relaxation by opening ATP-sensitive K+ channels, which cause membrane hyperpolarization and resultant blocking of the Ca2+ channels needed for generating a contraction [35, 36].

In addition to the nervous system, prostaglandins (PG) have been shown to play a role in ureteral contractility. PGs originate from arachadonic acid as a result of cyclooxygenase (COX) activity. COX exists in two isoforms: COX-1 and COX-2. The expression of COX-1 is relatively consistent, whereas COX-2 expression is heavily influenced by outside stimuli such as inflammation and obstruction. The effect of PG release varies between obstructed and unobstructed ureters. COX-2 expression is upregulated in obstructed ureters as compared to unobstructed ureters [37]. There are several subtypes of PG, and each has been studied independently regarding their effect on ureteral contraction. It has been shown in vitro that $PGF_2\alpha$, PGD_2, and TXA_2 increase ureteral contraction. PGE_2 is unique in that it has been shown in pig and human models to have a condition-dependent effect on ureteral contractility, namely, inducing contractility in the obstructed ureter while promoting relaxation in the unobstructed ureter [38].

Physiologic Implications of Obstruction

Obstruction, whether from an intrinsic or extrinsic source, results in an increase in ureteral stretch due to the increase both in the volume of retained urine and intraluminal pressure. Afferent sensory neurons react to this stretch and contractility, eliciting a significant pain response [39]. The effect of obstruction on ureteral physiology is largely dependent on the duration of obstruction. Initially in obstruction, there is a transient increase in the amplitude and frequency of peristaltic contractions. Within a few hours after obstruction, intraluminal pressure reaches a peak and then declines to a level slightly higher than baseline [40]. This is largely attributable to changes in renal hemodynamics causing reduced renal blood flow, reduced glomerular filtration rate, and accordingly reduced intraluminal pressure [41].

Over time however, with persistent obstruction, ureteral diameter and length increases due to continued buildup of retained urine. The ureteral smooth muscle itself undergoes hypertrophy and increased contractile force, however due to the large increases in diameter, the ureter is unable to coapt its lumen to propel the urinary bolus forward [40]. Chronically obstructed ureters furthermore start to exhibit a reduction in the number of interstitial smooth muscle cells, resulting in a lack of peristaltic integration [42].

Abnormalities of innervation and an increase in collagen expression have also been identified in obstructed ureteral segments [43]. Furthermore, as illustrated in animal models, prolonged obstruction in excess of 6 weeks results in complete and irreversible loss of function in the obstructed renal unit [44].

The Effects of Ureteral Stenting

Ureteral stents provide drainage of the upper tracts in cases of obstruction. There have been multiple studies investigating flow patterns in the stented ureter. There had been conflicting prior reports of stents achieving drainage via larger luminal size with more fenestrations [45], while other in vitro studies showed drainage occurring around the stent versus through it [46]. Subsequent studies later demonstrated that fluid actually drains both through and around the stent, with similar flow patterns amongst all double pigtail stents regardless of specialty stent design or luminal size [47].

Ureteral stenting has been shown to impair short-term ureteral peristalsis in several animal models. In a porcine model of the stented ureter, normal peristalsis disappeared for days 1 and 2, and then became irregular after day 5 [48]. Evidence of ureteral dilation and ineffective peristalsis was seen to persist 3 weeks after stenting in pigs [49] and up to 16 weeks in dogs [50]. Drainage certainly is improved in obstructed ureters post stenting, however this is likely due to passive drainage secondary to hydrostatic pressure in the collecting system [51].

The histopathological changes to the ureter with stenting are significant. Stenting of normal rabbit ureters revealed mild hydroureteronephrosis with short-term stenting, progressing to moderate to severe hydroureteronephrosis with prolonged stenting over 3 weeks. Short-term stenting for less than 1 week did not show any harm, however prolonged stenting resulted in renal function deterioration in 2 of 18 renal units due to severe hydroureteronephrosis or infection. Histological examination revealed dilation of the entire collecting system and renal tubules, infiltration of the kidney and ureter with inflammatory cells, mucosal ulceration, and ureteral muscular hypertrophy [52]. To date there have been no physiologic studies to show the effects of stented ureter over the long term, therefore the timeline for reversal of these changes has not been elucidated.

Ureteral Pharmacology

The significant visceral pain brought about by ureteral obstruction has been largely attributed to the increase in associated ureteral contractility, spasm, and pressure. It has been shown that partial ureteral obstruction causes a 478% increase in the amplitude of ureteral contractions in a rat model, eliciting the severe associated colicky pain [39]. Several pharmacologic therapies therefore have been studied in an attempt to reduce the severity of these symptoms.

Opioids are commonly used to control the symptoms associated with ureteral obstruction. They work by activating *mu*-receptors and thus block the afferent pain pathways caused by ureteral obstruction. Interestingly, some studies have shown that narcotic analgesics increase both the tone and amplitude of ureteral contractions [18, 53]. Other studies however have failed to observe any type of effect on ureteral function [22, 54]. Overall, it appears that the role of opioids in the treatment of colic is largely dependent on their central nervous system actions and is not related to ureteral relaxation.

The main PGs (PGE_1, PGE_2, and $PGF_2\alpha$) are derived from arachidonic acid via COX-1 and COX-2. As mentioned previously, they have a variety of different biologic functions however for the most part promote ureteral contractility. Furthermore, COX-2 activity in particular has been shown to be upregulated in obstructed and inflamed ureters [55]. Agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) have been successful in inhibiting ureteral contractility in multiple studies [56]. Both nonselective COX inhibitors (such as diclofenac and indomethacin) along with selective COX-2 inhibitors (such as celecoxib) have been shown to be equally

efficacious in inhibiting contractions in both the pig and human ureter [57, 58]. Two randomized controlled trials assessed stone passage rates with diclofenac and indomethacin. Both trials demonstrated that patients did not experience improved stone passage rates or decreased time to passage. They did however require significantly less amount of narcotic analgesic requirement [59, 60]. Despite the clear effect on ureteral contractility, the clinical use of NSAIDs should be considered cautiously due to their effect on renal function. PGs promote renal vasodilation, therefore use of these COX inhibitors has the potential to cause renal insufficiency [17].

Phosphodiesterase (PDE) inhibitors block the degradation of cAMP and cGMP in smooth muscle, leading to smooth muscle relaxation by activation of protein kinase A and phosphorylation of myosin light chain kinase. The action of PDE inhibitors on the ureter causes a reduction in the frequency of peristaltic waves [61], and in vitro experiments have shown a reversal of tension along human ureteral smooth muscle, with vardenafil having the highest efficacy [62]. Furthermore, the presence of isoforms PDE-1, 4, and 5 were isolated in cytosolic solutions of human ureteral tissue [63], with PDE-4 being identified as having the greatest effect on ureteral relaxation [64]. Rolipram, a PDE-4 inhibitor, caused marked ureteral relaxation in a rabbit in vivo model without any of the deleterious hemodynamic effects seen with non-specific PDE-inhibitors, making this a promising target for further investigation [64]. In a recent meta-analysis, PDE-5 inhibitors were found to be superior to placebo in the rates of successful medical expulsive therapy for distal ureteral stones. There is also some evidence to suggest a reduction in the episodes of colic along with the need for analgesia, however further study is required to solidify this conclusion [61].

Calcium channel blockers inhibit the influx of extracellular calcium needed to generate an action potential and thereby limit the degree of smooth muscle contraction. They have therefore been studied extensively in the setting of obstructing ureteral calculi to minimize ureteral spasm and pain while encouraging spontaneous passage [65]. Calcium channel blockers, such as nifedipine, verapamil, and diltiazem, have been shown to inhibit ureteral contraction in guinea pigs and humans [66, 67]. Nifedipine and verapamil in particular were found to inhibit fast phasic contractions while preserving slow phasic contractions, thus preventing painful ureteral spasm while maintaining normal peristalsis [68]. With respect to stone passage, randomized controlled trials have shown efficacy when nifedipine is combined with corticosteroid therapy. One randomized double-blind trial of 86 patients comparing nifedipine and versus placebo (with methylprednisolone given to both) demonstrated an increased stone expulsion rate (86% vs. 65%) and less mean time to passage (11.2 days vs. 16.5 days) in the nifedipine group versus placebo group, respectively [69]. Another randomized trial compared a control group treated with analgesia alone versus a nifedipine and prednisone treatment arm. The treatment arm similarly was found to have a higher passage rate than the control arm (86% vs. 54%) after 7 days of treatment [70]. In a more recent series, 96 patients with distal ureteral stones received either deflazacort and nifedipine or conservative management. Stone expulsion rate in the nifedipine group was 79% compared to 35% in the conservatively managed group. Mean time to stone passage was 7 days in the nifedipine group versus 20 days in the conservative group [71]. Despite this evidence of increased stone passage rate, there is no evidence that calcium channel blockers contribute to pain control from obstruction. One study evaluated nifedipine versus placebo in 30 patients with renal colic and found no significant difference in pain control [72]. With respect to steroid therapy, they were found to provide some benefit as expulsive therapy when combined with other agents but not alone [73].

Alpha adrenergic antagonists, or alpha blockers, work by blocking adrenergic activation of smooth muscle cells, resulting in a reduction in both the frequency and amplitude of contractions. As described earlier, α_1-adrenergic receptors are found throughout the ureter with the highest concentration being in the distal ureter. Therefore, in the setting of ureteral calculi, alpha

blockers can aid in facilitating spontaneous passage. Alpha blockers can be broadly grouped as either selective or nonselective, depending on their affinity especially for α_{1A} and α_{1D} receptors, which are abundant in the ureter [74]. Both selective (tamsulosin) and nonselective (terazosin, doxazosin) alpha blockers have been shown to be equally efficacious in reducing ureteral spasm and improving stone passage rates [75]. There is evidence to suggest analgesic benefit of alpha blockers, as seen with the use of tamsulosin in patients post shockwave lithotripsy and particularly with the development of steinstrasse [76, 77].

Numerous randomized studies have examined tamsulosin compared to either nifedipine or placebo for expulsive therapy. In these studies, the stone passage rate was 97–100% compared to 64–70% in the placebo groups [78, 79]. Tamsulosin offered a 20% increase in passage rate when compared to nifedipine [80]. In 2006, Hollingsworth and colleagues published a meta-analysis of nine randomized controlled trials investigating the use of nifedipine and alpha blockers. Compared with the control groups, patients treated with nifedipine or alpha blockers had an overall 65% greater likelihood of stone passage with an absolute risk reduction of 31% [73]. A subsequent meta-analysis from the combined AUA/EUA ureteral stone guidelines demonstrated a statistically significant absolute increase of 29% in stone passage rate of tamsulosin when compared to controls. Nifedipine had an absolute increase of 9% when compared to controls, which was deemed to not be statistically significant [81]. A more recent meta-analysis of 47 randomized controlled trials demonstrated higher and faster expulsion rates when the alpha blocker and nifedpine groups were pooled and compared to controls. Lower analgesic requirements, fewer colic episodes, and fewer hospitalizations were also observed with the treatment groups [82]. A Cochrane review was also conducted recently of 67 studies with over 10,000 participants comparing alpha blockers to placebo. Stone clearance in the alpha blocker group was significantly higher (RR 1.45, 95% CI 1.36–1.55), and remained high still (RR 1.16, 95% CI 1.07–1.25) after a subset of better quality subset of placebo controlled trials was extracted from the main body. Similar to previous analyses, the alpha blocker groups experienced shorter expulsive times by 2–4 days, used less analgesia, and required fewer hospitalizations. The need for surgery was found to be similar between the two groups. Subgroup analyses further suggested that alpha blockers could be less effective for stones <5 mm than for larger stones >5 mm [83].

A multicenter, randomized, placebo-controlled trial (referred to as the SUSPEND trial) recently published some contradictory findings. 1167 patients at over 24 centers in the UK with a single ureteral stone ≤10 mm in size were randomly assigned to placebo, nifedipine, or tamsulosin groups. Spontaneous stone passage within 4 weeks, without the need for additional interventions, was defined as the primary outcome. The percent of patients who did not require further intervention by 4 weeks was 80% in the placebo group, 81% in the tamsulosin group, and 80% in the nifedipine group. No difference was noted between the active treatment and placebo groups, or between the tamsulosin and nifedipine groups. No differences were noted in secondary outcomes of pain score or time to stone passage. The authors concluded that tamsulosin and nifedipine were not effective at decreasing the need for further treatment to achieve stone clearance in 4 weeks [84]. The quality of the trial was considered to be very good as it was well-powered, had centralized randomization, and was multicenter. A notable criticism of the trial was that the rates of stone clearance for stones >5 mm was slightly more pronounced for tamsulosin, however because the majority of the patients assessed (24.8%) had stones >5 mm. The trial may have therefore been underpowered to detect the utility of medical expulsive therapy for stones >5 mm, and that the potential benefits of medical therapy may have been diluted by inclusion of smaller stones [85]. Other criticisms included lower response rates for questionnaires to evaluate the secondary outcomes and well has lack of monitoring for medication adherence [86]. Overall however, this trial does challenge the current dogma of medical

Table 5.1 The effect of various substances on the ureter

	Ureteral contraction	Ureteral relaxation
Endogenous substance	Acetylcholine Tachykinins Prostaglandins ($PGF_2\alpha$, PGD_2, TXA_2, [a]PGE_2) Alpha agonists	Prostaglandins (PGE_1) Beta agonists
Drugs	Alpha agonists	Non-steroidal anti-inflammatory drugs (NSAIDs) Phosphodiesterase (PDE) inhibitors Calcium channel blockers Alpha blockers

[a]PGE_2 causes contraction in the obstructed ureter, relaxation in the normal ureter

expulsive therapy. Whether future trials yield similar findings will remain to be seen.

Other pharmacologic agents have been contenders for further study. Neurokinin receptor antagonists have been studied in vitro as alternative agents to modulate ureteral contractility. The three neurokinin receptors, NK-1, NK-2, and NK-3 have affinity for substance P, neurokinin A, and neurokinin B, respectively [87]. Blockage of these receptors prevents phospholipase C synthesis and ultimately calcium influx into the smooth muscle cell. The result is ureteral relaxation. NK-2 is the predominant receptor in the human ureter, and its inhibition in vitro prevents ureteral contractility [87]. NK-2 blockade has yet to be studied clinically, but if safe may decrease obstruction-related pain and increase stone passage rates.

Nitric oxide (NO) is a major inhibitory neurotransmitter in the ureter. Based on axons that stain positive for nitric oxide synthase in the human ureter, it has been suggested that nitric oxide may play a role in ureteral relaxation [88]. In vitro, it has been shown that NO inhibits ureteral contractility in rats [89]. Interestingly, NO seems to play a specific role at the ureterovesical junction, where it has been postulated to regulate the valve-like effect in this area [90].

Histamine can cause the release of catecholamines from sympathetic nerves and act directly on smooth muscle receptors. Although it likely has a species specific effect on the ureter [91] the majority of studies have shown an excitatory effect of histamine on ureteral function [18]. The excitatory effect is mediated by H1 receptors, as evidenced by inhibition of ureteral activity with H1-receptor antagonists [92]. H2 receptors mediate inhibitory effects of histamine, as evidenced by the H2-receptor agonists relaxing a pre-contracted ureteral segment. These effects are reversed by cimetidine, an H2-reeptor antagonist. Further study is needed for clinical utilization of these agents in ureteral obstruction (Table 5.1).

The Effect of Special Conditions on Ureteral Physiology

Infection of the upper tract has been shown in vitro and in vivo to impair ureteral contraction. As early as 1913, Primbs demonstrated that toxins released by *Escherichia coli* and staphylococcal species inhibited contractions of in vitro guinea pig ureteral segments [93]; these findings have been reproduced in subsequent studies. In humans, decreased peristalsis and even absent peristalsis has been documented in the ureter in cases of infection, and can be a radiographic disease hallmark [94]. Furthermore, ureteral dilation has been reported to result from infectious processes in adjacent organs, such as in appendicitis or regional enteritis [95].

Age is an important factor in the response of the ureter to different physiologic stressors. More marked degrees of ureteral dilation are observed at a younger age as opposed to in adulthood. In vitro studies have observed that an intraluminal pressure load will cause more deformation and compliance in a neonatal rabbit ureter than in an adult rabbit ureter [96]. In addition, there seems to be a decrease in the response of the ureter to beta-adrenergic agents with age, an event likely mediated by decreased cAMP levels [97].

Pregnancy has been known to cause hydroureteronephrosis in the mother that begins in the second trimester and resolves by the first month after delivery. It is usually more prominent and severe on the right. Mass effect of the gravid uterus causing obstruction is thought to be the reason for this hydroureteronephrosis. Evidence in favor of this includes the fact that pregnant women demonstrate elevated resting pressures in the ureter above the pelvic brim, which can be reversed with positional changes. Additionally, normal ureteral contractile pressures recorded during pregnancy suggest hormonally induced ureteral atony is not the main factor in ureteral dilation with pregnancy. Lastly, hydronephrosis of pregnancy does not occur in quadriplegic women, whose uterus hangs away from the ureters [98]. Hormonal affects are also thought to play a role in hydroureteronephrosis of pregnancy, particularly of progesterone. There have been conflicting data in the past, however for the most part progesterone has been shown to produce mostly smooth muscle relaxation in the urinary system [99]. In general, obstruction appears to be the primary factor in hydroureteronephrosis of pregnancy, with hormones playing a potential secondary role.

Conclusion

Ureteral physiology involves a complex interplay between various stimuli, cells, receptors, and proteins. The ability to modulate ureteral physiology continues to be a major area of study especially in the clinical management of ureteral colic and calculi. Going forward, more work on the subject will be necessary to determine the optimal treatment strategy for diseases affecting the human ureter.

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Symptoms Complexes in Urology

6

Kyle J. Wilson and Nadir I. Osman

Introduction

Traditionally, the terminology that was used in functional urology was based on the likely underlying pathophysiological cause. Terms like 'prostatism' and 'detrusor instability' were used to describe the group of symptoms associated with what we now recognize as benign prostatic obstruction and detrusor overactivity (DO) respectively. The development and widespread acceptance of urodynamic studies as a clinical diagnostic tool led to the recognition that symptoms do not reliably predict the underlying pathophysiological problem. This was neatly summarized by Patrick Bates who, whilst working with Richard Turner-Warwick at the Middlesex Hospital, coined the term "the bladder is an unreliable witness" [1]. The term lower urinary tract symptom (LUTS) was introduced by Paul Abrams in 1994, which largely replaced the terms in usage at the time such as prostatism and BPH when describing urinary symptoms [2].

Consequently contemporary urological practice has moved away from using definitions tied to pathophysiology, favoring a symptoms-based approach instead [3, 4]. In addition to not presuming cause, this approach provides a clear set of symptoms on which to base a clinical diagnosis and initiate basic treatment without the need for expensive and invasive tests. This approach has not been without its critics who have suggested this approach has led to the medicalisation of normal voiding patterns and may favour commercial interests.

It is helpful to frame any discussion on symptom complexes in the context of how lower urinary tract symptoms (LUTS) are classified in contemporary practice. Wein was the first to classify lower urinary tract dysfunction on the basis of the phases of the micturition cycle: storage and voiding [5]. This approach has been adopted by the International Continence Society which now classifies LUTS into three groups: storage, voiding and, in addition, post-micturition. Typical storage symptoms include frequency, urgency, nocturia and incontinence. Hesitancy, intermittency, slow stream and straining are representative of typical voiding symptoms. Post-micturition symptoms include a 'feeling of incomplete emptying' and 'post-micturition dribble' [6]. In this chapter we discuss and critique the principal symptom-complexes encountered in modern urological practice: the overactive bladder, the underactive bladder and bladder pain syndrome.

From a semantic point of view, it is important to distinguish the term syndrome from symptom complex. A syndrome refers to a grouping of symptoms and clinical signs which relate to the deviation of the function of an organ or a lesion

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in the organ. A symptom complex is a grouping of symptoms or clinical signs without any consideration for a lesion or functional disturbance of particular organ. As OAB and, in theory, UAB describe a grouping of symptoms which may or may not occur in association without a demonstrable urodynamic abnormality they are considered to be symptom complexes.

The Overactive Bladder

Definitions and Terminology

The overactive bladder (OAB) is the oldest recognized symptom complex in functional urology. It is defined by the ICS as "urgency, with or without urge incontinence, usually with frequency and nocturia" [6]. The *sine qua non* of OAB is urinary urgency, "a sudden and compelling desire to void that is difficult to defer". The term OAB-wet is used when patients are incontinent whereas OAB-dry is used when patients remain continent. The term OAB was introduced by Paul Abrams and Alan Wein in 1996 who proposed that a symptom-based definition should be used, based upon the fact that many patients who were bothered by symptoms did not exhibit DO on filling cystometry [3]. In addition, it did not seem necessary that all patients with symptoms should have to undergo invasive testing before commencing readily available and relatively safe drug treatment [2, 3]. The simplicity of the term OAB compared to the previous urodynamic terms renders it easier for patients to understand, which has contributed to the growing profile of OAB and arguably led to increased research in the field and a subsequent rise in the number of agents available to manage the condition. The term "detrusor overactivity" (DO) continues to be used as a descriptor in urodynamic studies [7].

The ICS definition has received some criticisms. It does not differentiate different causes of the symptom complex, which some have argued is necessary in order to provide the most appropriate management. Similarly, it does not quantify how many voids per day or night constitute frequency or nocturia, respectively, which could result in over-medicalisation of the extremes of normal [7]. Similarly, the inclusion of terms such as "usually" and "with or without" makes aspects of the definition vague. A further criticism was highlighted by Wein, who notes that the inclusion of the word urgency, fails to include those with unaware urinary incontinence and demonstrable DO [4]. Urgency, which is a sensory symptom, is also often difficult to interpret and differentiate from the normal urge to pass urine when the bladder is full. Some have suggested a "fear of leakage" is necessary to separate pathological urgency from a normal urge to pass urine [8], though this is not part of the current definition. Another important issue is that that urgency and urge cannot be differentiated in many languages which limits the application of the definition in some countries.

Epidemiology

The specificity of the OAB symptom complex for underlying DO is an important question which several investigators have tried to address. These studies comprise of mainly of small observational studies of patients undergoing urodynamic studies (see Table 6.1). Together these studies show that the OAB symptom complex is more strongly associated with DO in men as compared to women. In both sexes, OAB-wet is more strongly associated with DO than OAB-dry. The weaker correlation with OAB-wet with underlying DO in women as compared to men is likely related to the relatively weaker bladder outlet in the former [7].

Several major epidemiological studies have been undertaken to attempt to quantify the prevalence of OAB and the incidence of the specific symptoms, as well as their effect on quality of life [17–21]. Together these studies have shown that OAB is common in both women and men, with a prevalence as high as 24.7% in the EpiLUTS survey of 20,000 adults aged >40 years [20]. OAB has also been shown to increase in prevalence with increasing age in both sexes, with the EPIC study (>19,000 respondents) showing a rise from 10.8% of men and 12.2% of women in the general population, to 13.1% and 14.8% in

Table 6.1 Studies assessing the relationship between OAB and DO

Study	OAB definition	No. of subjects	OAB-dry patients with DO (%)	OAB-wet patients with DO (%)	Overall OAB patients with DO (%)
Al Ghazo et al. [9]	ICS 2002 [5]	Male: 92	63	93	76
		Female: 117	61	70	59
Digesu et al. [10]	ICS 1988 [16]	Female: 843	–	–	54.2
Giarenis et al. [11]	ICS 2002	Female: 556	–	–	43
Hashim and Abrams [12]	ICS 2002	Male:[a]	69	90	–
		Female:[a]	44	58	–
Hyman et al. [13]	Urge incontinence	Male: 28	–	–	75
Jeong et al. [14]	ICS 2002	Female: 513	–	–	32.6
Sekido et al. [15]	ICS 2002	Male: 12	–	–	75
		Female: 38	–	–	37

[a]Not specified

respectively in those >40 years [17, 18]. These studies have been criticized as overestimating the scale of the problem, in view of the rather subjective methods, such as telephonic interviews and online questionnaires, that were used to assess symptoms. In addition to its significant prevalence in the population, several studies have demonstrated that OAB may have detrimental impact on mental health and sexual function, as well as on employment and productivity [21]. The economic impact of OAB is perhaps best demonstrated in the EPIC study's cost analysis of OAB which estimated the cost-per-country at USD 13 billion per year, comprising investigation and treatment, treatment of depression secondary to OAB, nursing costs and lost productivity [17].

Pathophysiology

No single aetiology has been identified as causative of OAB. The mechanisms can be broadly categorised into two main groups: increased afferent activity and dysregulated afferent signal management. The first involves abnormal afferent signalling and may be related to either urothelial receptor dysfunction and neurotransmitter release or to detrusor myocyte hyperexcitability. In the latter there may be increased activation of voiding pathways or a defect in normal centrally-mediated inhibition. In reality the cause in any given individual is likely to be complex and multifactorial, encompassing components from each of the hypotheses.

The Myogenic Hypothesis

An early myogenic theory of bladder overactivity suggested a 'denervation hypersensitivity' whereby bladder outlet obstruction (BOO) caused denervation of the detrusor with subsequent increased myocyte electronic coupling and widespread excitation throughout the detrusor [22]. Later work suggests that this electronic coupling occurs through gap junction channels, composed primarily of connexin proteins. Increased Cx43 expression has been demonstrated in patients with urgency symptoms [23]. The role of connexin proteins remains a subject for further study. Furthermore, it has been suggested that the arrangement of the detrusor muscle into modules allows for a coordinated response to detrusor excitability mediated by a peripheral myovesical plexus [24].

The Urothelial Hypothesis

The urothelium and associated suburothelium, comprising nerves, vessels and connective tissue contributes to bladder modulation [25]. Responses to mechanical and chemical stimuli are mediated through an array of receptors which have been identified in urothelial cells, triggering neurohormonal stimulation of closely-related afferent nerve fibres. It is proposed that abnormalities in urothelial cell signalling could cause increased afferent signalling, with resultant increases in efferent signalling and detrusor activity [26]. As urgency itself is a sensory symptom it is possible that the afferent signalling alone is sufficient to cause symptoms.

The Neurogenic Hypothesis

During the storage phase of the voiding cycle, aberrant central signalling may result in inappropriate detrusor contractions. Central nervous system (CNS) damage may result in reduced inhibitory signalling and inappropriate activation of primitive voiding reflexes [27]. The former have been linked to suprapontine cortical lesions affecting the central inhibitory centres. Observations of patients with Parkinson's and multiple sclerosis have led to the suggestion that disruption of the basal ganglia and lesions of the cervical spinal cord, especially the posterior and lateral columns, may lead to the development of neurogenic detrusor overactivity (NDO). Similarly, it has been observed that inappropriate activation of unmyelinated C fibres involved in the mediation of the sacral spinal reflex may result in NDO [28].

Conclusions

OAB is perhaps the best understood of the symptom complexes in urology. Despite this it continues to provide significant challenges to the research community. Further research is required to tie together the current hypotheses on the pathophysiological basis of the condition,. Epidemiological analysis reveals just how significant a problem OAB continues to be, with the least conservative estimates suggesting almost one quarter of the population > 40 years are affected. The high economic cost of the problem, emphasises the importance public and academic attention to the symptom complex.

The Underactive Bladder

Definitions and Terminology

Recently there has been growing interest in the problem of impaired bladder emptying not related to bladder obstruction. As with OAB, a urodynamic concept and terms became established before the development of symptom complex. The term Detrusor underactivity (DUA) was adopted by the ICS in the 2002 standardization of terminology document, where DUA is defined as 'a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time frame' [4]. This definition, while succeeding in its provision of a clear conceptual outline, fails to provide defined parameters for what constitutes 'prolonged bladder emptying' or 'a normal timeframe', neither does it detail how these parameters might change according to patient demographics. Nevertheless, this definition is the one most commonly cited in the literature and in practice [29]. It must also be noted that, despite attempts at standardisation, a plethora of terms are still used in the literature to refer to DUA, including detrusor failure, atonic bladder and chronic retention.

Recently a symptom-based counterpart of DUA has been proposed. An ICS working group have proposed that UAB is a 'symptom complex suggestive of detrusor underactivity and is usually characterised by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and a slow stream' [30]. Whether this definition is sufficiently specific to exclude those with similar symptoms arising as a result of other pathologies, such as BOO or OAB remains to be established. The apparent absence of a pathognomic symptom (c.f. urgency in OAB) is a key issue which may hamper practical application [29]. While it is unlikely that this definition of UAB is sufficiently robust for diagnostic purposes in current clinical practice, it may be helpful for promoting further clinical research [31]. Further studies are needed to validate this definition and establish its specificity, before further refinement, if possible, can be made.

Epidemiology

Understanding the epidemiology of UAB has been limited by the lack of a concrete definition, or a simple and accurate proxy measure such as urinary retention or post void residual. Thus, researchers have initially had to look at the group of patients with LUTS who have undergone urodynamic studies to first understand the preva-

lence of DUA, albeit this is a highly selected population. A review of the literature found that DUA was common in this group, being present in 9–45% of men and 12–45% of older women (>55 years) being investigated for non-neurogenic LUTS [32].

Recently some questionnaire-based populations studies have attempted to clarify the prevalence of voiding LUTS, with 'difficulty in bladder emptying' reported by 23% of individuals from the general population (age range 33–92 years, mean 74.3 years) [33]. In addition, investigators have attempted to identify the prevalence of individual symptoms associated with DUA in order to differentiate UAB from the normally functioning bladder and the symptoms associated with BOO. A group from Bristol (UK) found that men with DUA are more likely to have decreased and/or interrupted urinary stream, hesitancy, feeling of incomplete bladder emptying, palpable bladder, feeling of incomplete bowel emptying, absent and/or decreased sensation, and always straining to void compared with controls with urodynamics studies. The symptoms of decreased stream, hesitancy and urgency were more common in BOO than DUA, with DUA being further distinguished by the increased prevalence of abnormal sexual function, stress incontinence, enuresis, palpable bladder, absent and/or decreased sensation, always straining to void, bowel straining, feeling of incomplete bowel emptying, and poor bowel control. Women with DUA were distinguished from controls with normal urodynamics by decreased and/or interrupted urinary stream, hesitancy, feeling of incomplete bladder emptying, palpable bladder, absent and/or decreased sensation, enuresis, and impaired mobility in the same study [34]**.** This work informed the initial attempts at refining the definition of UAB.

Pathophysiology

DUA is traditionally considered to be the result of impaired detrusor activity through impaired parasympathetic efferent signalling or through structural changes in the muscle itself, neurogenic and myogenic hypotheses, respectively [29]. Recent work has suggested that other aetiological factors are also at play the pathogenesis of DUA, and indeed its symptom-based counterpart [31]. It is important to recognise that UAB, as a symptom complex, does not necessarily correlate with DUA and that afferent signalling may a play a more significant role in the pathophysiology of UAB.

Urothelial Dysfunction

Recent work to establish the role of the urothelium in normal and abnormal bladder functioning has provided some interesting insights into the potential aetiology of UAB/DUA. Bladder biopsies taken from men with DUA (defined as bladder contractility index (BCI) <100) compared to those of controls (BCI >100) showed that those with DUA have significantly lower levels of adenosine triphosphate (ATP), with a significant correlation between ATP level and detrusor pressure at maximum flow [35]. Jiang and Kuo established deficiencies in E-cadherin expression, muscarinic receptors (M2 and M3), P2X3 receptors and endothelial nitric oxide synthase when comparing urodynamically-confirmed DUA to urodynamically-confirmed stress urinary incontinence. Conversely, DUA patients had elevated levels of mast cells, apoptotic cells and increased expression of the β3-adrenoreceptor [36]. While it remains to be seen if these changes are causative or representative of DUA, these studies do succeed in demonstrating a link between DUA and urothelial dysfunction, suburothelial inflammation and altered sensory transduction.

Neurogenic Dysfunction

The role of afferent signals from the bladder and urethra in monitoring bladder filling during storage and voiding is recognised and it has been suggested that failure of this signalling could result in premature termination of the micturition reflex in DUA [37]. Similarly, afferent signals from the urethra have been shown to play a significant role in bladder functioning, with urethral anaesthesia having been shown to impair bladder emptying and urethral electrical stimulation succeeding in stimulating bladder contraction [38, 39]. The identification of serotonin receptors on urethral sensory fibres led Coelho et al. to infuse serotonin into the urethras and bladders of

anaesthetised rats. Urethral infusion caused bladder contraction, whereas bladder infusion did not. The effect of urethral infusion was mitigated by urethral anaesthesia and serotonin-receptor blockade [40]. This work may prove particularly important as it represents a potential pharmacological target.

Pelvic Ischaemia

Work on rabbits suggests that bladder ischaemia secondary to pelvic arterial insufficiency can lead to ultrastructural damage and denervation, secondary to oxidative stress [41]. More recent work looking at the syndromes induced by this ischaemia found that rats with pelvic arterial insufficiency developed DO at 8 weeks and DUA at 16 weeks, with associated changes in muscarinic receptor expression and neural damage. This could support the hypothesis that ischaemia underpins both pathologies and that DUA is positioned as the end-stage of a spectrum of ischaemia [42].

Conclusions

UAB remains poorly understood. The difficulty of defining a symptom complex without a pathognomic symptom has led to epidemiological estimates that may not accurately reflect the scale of the problem. The utility of UAB as a symptom complex separate to its urodynamic counterpart, DUA, is that it facilitates discussions at an academic level until such a time as a definition sufficiently specific to differentiate UAB from alternative diagnoses is reached and, more importantly, it facilitates discussions with patients, for whom the term is much easier to understand.

Bladder Pain Syndrome

Definitions and Terminology

It could be said that Interstitial cystitis (IC) is to the bladder pain syndrome (BPS) as DO is to OAB or DUA is to UAB. While the defining characteristics of IC are not observed during urodynamics, it has previously been defined by the National Institute of Diabetes and Digestive and Kidney Diseases (USA) using strict and directly observable features such as glomerulations and Hunner ulcers observed during cystoscopy [43]. Later work suggested the requirement for a move towards a symptom-based definition, with the strict criteria failing to diagnose over 60% of patients in whom experienced clinicians felt that a diagnosis of IC was at least likely [44].

BPS is the most poorly understood and difficult to manage of all the symptom complexes in urology, it is defined as "suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or any other obvious pathology" [6]. The American Urological Association includes in its similar definition a required time-frame of at least 6 weeks [45, 46]. It should be noted that while this text summarises the current knowledge relating to BPS, several urological pain syndromes have been defined by the ICS, including pain syndromes of the urethra, vulva, vagina, scrotum, perineum and pelvis [6]. They are connected insomuch as they are all chronic pain syndromes with poorly understood aetiology associated with symptoms of a urogynaecological nature and/or sexual dysfunction.

Epidemiology

The prevalence of IC/BPS appears to be rising, though whether this is a genuine phenomenon or related to the varying definitions of IC/BPS over time is difficult to distinguish [47]. It is likely that the combination of a symptom-based definition and greater public and clinician awareness is responsible. This increased awareness was demonstrated by Davis et al. who used Google Trends data to show that the number of searches for IC/BPS has increased annually since 2005 [48].

A large study of census data from the United States evaluated the prevalence of symptoms that could result in a diagnosis of BPS using two definitions, one with high sensitivity and one with high specificity. This work estimated the prevalence

as somewhere between 2.7% and 6.5% among adult females. Interestingly, of these patients less than 10% had a formal diagnosis of IC/BPS, suggesting that under diagnosis is a major problem [49]. A separate study evaluated a managed-care population in the Pacific Northwest of the United States and showed the prevalence of physician-made diagnoses to be 197 and 41 per 100,000 in women and men, respectively, with a female:male ratio of 5:1, much lower than previously thought [50]. Nevertheless, female sex remains the only clear risk factor for developing IC/BPS [48].

Pathophysiology

Several theories on the aetiopathogenesis of BPS have been offered, though to date no definitive process by which the pathology develops has been agreed upon. Some of the major recent theories are outlined below.

The Glycosaminoglycan Layer Hypothesis

The glycosaminoglycan (GAG) layer is formed from an extracellular matrix of polysaccharide molecules, collagen, elastin, fibronectin and laminin and covers the bladder urothelium [51]. It has been proposed that its role is to protect the urothelium from the effects of electrolytes, microorganisms and other solutes [52]. Infectious and inflammatory processes may damage the GAG layer, allowing passage of harmful substances into the bladder wall, with resultant pain, frequency and urgency [53].

The Epithelial Permeability Hypothesis

The role of urothelium is bladder modulation is just beginning to be fully appreciated [25]. Neuromodulation following signals from ATP and acetylcholine (ACh) receptors are thought to provide information to the central nervous system on bladder filling, in addition to a role in the regulation of blood flow and detrusor contractions [53]. It has been suggested that a loss in urothelial permeability can result in BPS, as well as OAB [54]. The effect of nitric oxide (NO) on the urothelium has also been implicated in the bladder functioning [55]. Differences in levels of ATP and NO in the bladder mucosa of rat models was positively and negatively correlated with bladder activity, respectively [56]. This demonstrated the importance of a normally functioning urothelium. Importantly, permeability changes may result in increased antiproliferative factor (APF) activity, associated with increased apoptosis and decreased cellular proliferation [57].

The Inflammation Hypothesis

It has been postulated that dysfunctional urothelium is a major activator of mast cells, which release several active molecules including histamine and serotonin, as well as inflammatory cytokines, potentially resulting in inflammation, pain, fibrosis and detrusor contraction in IC/BPS [53]. Histamine and its metabolites have been detected in greater quantities in patients with IC/BPS than healthy controls [53]. The urine of patients with IC/BPS has also been shown to contain neutrophils and eosinophils [48]. Though these findings suggest an inflammatory component, understanding the processes by which mast cells are activated and which underpin the inflammatory response in IC/BPS remains a topic for future research.

The Neural Up-Regulation Hypothesis

The inflammatory response is regulated by neuroendocrine pathways, including the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis [53].

Neuroendocrine changes have been reported in the SNS of cats with Feline Idiopathic Cystitis (FIC), widely regarded as a cat model for IC/BPS [58, 59]. FIC cats have been shown to have elevated levels of thyroxin hydroxylase in the nucleus coreolus, an enzyme responsible for increased catecholamine production [60]. Similarly, elevated levels of noradrenaline (NE) have been demonstrated in the urine of FIC cats and in humans [58, 59].

An altered stress function in IC patients was demonstrated by Dimitrakov et al. who used interleukin-6 (IL-6) to stimulate corticotropin-releasing hormone (CRH) from the hypothalami of

IC patients and age-matched controls. Following administration of IL-6, IC patients had a delayed adrenocorticotrophic hormone (ACTH) release. They were also noted to have higher baseline levels of NE and an exaggerated NE response. Decrease in NE levels was greater in IC patients following the administration of amitriptyline, known to inhibit SNS activity [61]. Taken together these results may represent a defect in hypothalamic CRH neuronal function and support a theory of altered stress response in IC/BPS. HPA-axis abnormalities were further suggested by a study of FIC cats that demonstrated significantly smaller adrenal glands and suggested a mild primary adrenal insufficiency [62]. Further research is required to confirm this in humans.

Further to the above, Liu et al. demonstrated increased expression of transient receptor potential vallinoid receptor subtype 1 (TRPV1) nerve fibres in the suburothelium of IC patients. TRPV1 nerve fibre density correlated well with the severity of symptoms such as pain, urgency and frequency [63].

Presently it is not clear whether these neuroendocrine alterations occur as a result of previously described pathological processes, or whether they directly contribute to the pathogenesis of IC/BPS.

Conclusions

With some estimating as many as 60% of patients with likely IC/BPS being missed following the strict criteria of the 1990s the need for a symptom complex became clear. However, despite increasing prevalence and increasing public awareness (as demonstrated by the Google Trends data for Internet searches of IC/BPS) relatively little is known about the condition. Current prevalence estimates vary wildly, and while there are several accepted hypotheses regarding the pathogenesis, clear relationships of cause and effect remain to be elucidated. That being said, recent work has uncovered some exciting new avenues for future research, offering hope in the future to those presently suffering with this often debilitating and troublesome condition.

Summary

The genesis of the OAB symptom complex has arguably raised the profile of the most bothersome LUTS, namely the storage symptoms. This has facilitated the conduct of epidemiological research which has highlighted the scale of the problem and the impact upon quality of life of patients. Along with this there has been a rise in investment in basic and clinical research and the development of several new pharmacological agents. The symptom complex approach has been criticised in that it may medicalise individuals who may be normal and consequently may serve commercial rather than patient interests. The counter point to this argument is that the symptom complex has allowed patients to be treated initially by the non-specialist practitioner without the need for invasive testing. The UAB and BPS symptom complexes are at much earlier stage in their development, and it remains to be seen whether a definition with sufficient specificity is possible so as to exclude patients with BOO in the case of UAB, and whether new simple effective treatments can be developed for both.

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7 Anatomy, Physiology and Pharmacology of the Lower Urinary Tract

Karl-Erik Andersson and Alan J. Wein

Introduction

Storage and elimination of urine requires a regulated interplay of reciprocal contraction and relaxation of bladder and outflow region and these structures are working as a functional unit [1, 2]. The interaction is controlled by neural circuits in the brain and spinal cord, which coordinate the activity of the detrusor smooth muscle as well as of the smooth and striated muscles of the outflow region [2, 3]. The peripheral nervous mechanisms for this control involve a complex pattern of efferent and afferent signaling in parasympathetic, sympathetic, and somatic nerves. Even if vesical and urethral functions are dependent on autonomic reflexes, the voluntary control of micturition, regulated by higher cortical centers, differentiates these organs from other viscera innervated by the autonomic nervous system. This review will briefly discuss the anatomy of the lower urinary tract and the principles of nervous control of micturition, and then focus on the peripheral, physiological and pharmacological mechanisms involved in the contraction and relaxation of bladder and urethra.

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Anatomy

The gross anatomy of the bladder and urethra is shown in Fig. 7.1. Main bladder components are the base (fundus), body and the trigone. The smooth muscle of the bladder (detrusor) remains continuous and inseparable from the urethra at the urethra-vesical junction. Details on the morphology of these structures can be found in many reviews and textbooks [1, 4–7].

Bladder

Bladder wall. The bladder wall has three well-defined layers: the mucosa (innermost portion), the muscularis propria, and the adventitia/serosa [8]. The mucosa defined as urothelium, basement membrane and lamina propria, also contains within the lamina propria some smooth muscle cells, muscularis mucosae. These cells are sometimes used to separate the mucosa from the "submucosa". Since the muscularis mucosa cells often do not form a distinct layer and is not very well defined in the human bladder (and sometimes seems to be absent), it may be questioned whether the human bladder, unlike the gut, has

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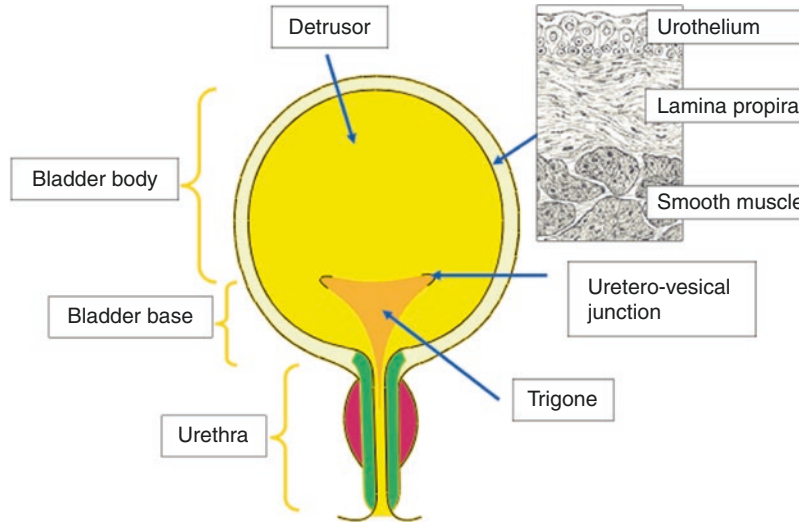

Fig. 7.1 The gross anatomy of the bladder and urethra (from Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. Physiol Rev. 2004;84(3):935–86)

a true "submucosal" layer. However, the term is sometimes used to denote the part of the lamina propria closest to the muscularis propria.

Urothelium. The uroepithelium, or urothelium, lines the renal pelvis, ureters, bladder, upper urethra, and glandular ducts of the prostate, and forms the interface between the urinary space and the underlying vasculature, connective, nervous, and muscular tissues [8]. There are at least three urothelial lineages consisting of the ureter/renal pelvis, detrusor/trigone, and bladder neck/proximal urethra. The functional significance of these findings has yet to be determined. The urothelium of the detrusor/trigone is a transitional epithelial tissue, composed of at least three layers: a basal cell layer attached to a basement membrane, an intermediate layer, and a superficial or apical layer composed of large hexagonal cells (diameters of 25–250 μm) known as "umbrella cells" [9, 10]. The apical surface of umbrella cells possesses a unique asymmetric unit membrane (AUM), whose protein components (uroplakins) have been well studied. Tight junctions, localized between the superficial umbrella cells, are composed of multiple proteins such as the occludins and claudins. These proteins, along with uroplakins, which are crystalline proteins that assemble into hexagonal plaques, contribute to the urothelial barrier function. There appears to be little difference between the urothelium of the trigone and the detrusor.

In the proximal urethra, the urothelium transitions to a stratified or columnar epithelium accompanied by a lack of urothelial-specific differentiation markers. Urethral epithelial cells express microvilli on the apical surface. The presence of cilia or microvilli may have a number of functions including ability to increase the cell surface area, as well as affect bacterial adherence and fluid transport.

A urothelial glycosaminoglycan (GAG) layer covers the umbrella cells and has been suggested to contribute to urothelial barrier function [11].

Lamina propria. The lamina propria (LP) lies between the basement membrane of the mucosa and the muscularis propria (detrusor muscle) and is composed of an extracellular matrix containing several types of cells, including fibroblasts, adipocytes, interstitial cells, and sensory nerve endings [12]. In addition, LP contains a rich vascular network, lymphatic channels, elastic fibers, and smooth muscle fascicles (muscularis mucosae). Notably, the thickness of the LP varies within the bladder. The morphological characteristics of the LP, muscularis mucosae, and the detrusor muscle are important for pathological tumor staging of bladder cancer. However, LP is not only a landmark, but also a functionally active structure.

The roles of the LP and its components in bladder function have not been definitively established [13], although it has been suggested to be the capacitance layer of the bladder, determin-

ing bladder compliance and enabling adaptive changes to increasing volumes. However, the bladder LP may also serve as a communication center, with an important integrative role in signal transduction to the central nervous system (nociception, mechano-sensation). The LP may also, by means of its different components, make it possible for the urothelium to transmit information to other components of the bladder wall, contributing to activation of the detrusor muscle. In addition, the LP may serve as a source for production of factors influencing the growth of both the overlying urothelium and the underlying detrusor muscle.

A dense layer of spindle-shaped cells has been described in bladder upper lamina propria in both humans and animals [14]. These cells have been categorized heterogeneously as interstitial cells (ICs), interstitial cells of Cajal (ICC), interstitial Cajal-like cells (ICLC) cells, myofibroblasts, or telocytes. Even if significant progress has been made in the study of bladder ICs' cellular markers, ion channels and receptor expression, electrical and calcium signaling, their specific functions in normal bladder filling and emptying remain elusive.

Different types of nerves have been described in the LP. The highest density of mucosal innervation was found in the neck and the initial part of the urethra. In human bladder, intramural ganglion cells were demonstrated both in the LP or embedded among the detrusor muscle bundles. The majority of the ganglia were small in size and contained from one to six neurons. These ganglion cells possessed fine structural characteristics of parasympathetic nerve cells. Smet et al. [15] showed that in the human bladder, peptidergic (CGRP; tachykinin) nerves are localized mainly within the sub-epithelium, surrounding the vasculature as well as intramural ganglia. While these nerves have not been detected within the detrusor smooth muscle, vasoactive intestinal polypeptide (VIP)-containing nerves have been localized within both the sub-urothelial plexus as well as the detrusor muscle bundles.

Detrusor muscle. The detrusor is a smooth muscle layer, comprising interlacing muscle fibres running randomly in all directions [4, 5]. Only close to the internal urethral meatus do the fibres orientate themselves into three specific layers (inner longitudinal, middle circumferential, outer longitudinal), thus forming the proximal bladder neck sphincter. The detrusor muscle in the male is better developed than in the female as greater pressure needs to be generated to overcome the resistance posed by the longer male urethra. Detrusor muscle remains continuous and inseparable from the urethra at the urethra vesical junction. Its smooth fibers form the bladder neck and the internal urethral sphincter (IUS).

Trigone. The trigone consists of the triangular region between the ureteral orifices and the bladder outlet [4, 16]. Muscular extensions of the two distal ureters blend to form a thin triangular muscular sheet, designated as the trigonal muscle (so-called *superficial trigone*). This muscle is spread over the base detrusor and tapers off at the vesicourethral junction. The trigonal muscle and the similarly innervated, predominantly longitudinally helical muscularis of the distal ureters have been designated as the uretero-trigonal muscle. It contracts during bladder filling to keep the ureteral orifices opened and the bladder neck closed and relaxes during micturition to help funnel urine into the outlet and prevent ureteric reflux.

Vasculature. The arterial supply to the bladder is primarily from the superior, middle and inferior vesical arteries which arise from the hypogastric (anterior) trunk of the internal iliac artery [13]. Small branches also arise from the obturator and inferior gluteal arteries and in females also from the uterine and vaginal arteries, to provide a contribution to the lower bladder. A plexus of veins surrounds the bladder and in the male form a vesico-prostatic (Santorini's) plexus between the bladder and the prostate, which empties into the hypogastric (internal iliac) veins.

Lymphatics. Lymphatics that drain the bladder begin in mucosal, intermuscular and serosal plexuses. There are three sets of collecting vessels (the trigone, superior and inferolateral surface of the bladder) draining lymph into the para/vesical, hypogastric (internal iliac), external iliac and common iliac lymph nodes. Minute nodules of lymphoid tissue may occur along the vesical lymph vessels. Using antibodies against

the lymphatic vessel endothelial hyaluronan receptor (LYVE-1), Matsumoto et al. [17] demonstrated the distribution of lymphatic vessels in the human bladder. Small lymphatics expressing LYVE-1 were distributed in all layers of the normal bladder except for the urothelium. The border areas—the LP and detrusor or the detrusor and adventitia—showed the greatest distribution of these vessels. The small vessels were irregular in shape and without thick walls. The density of the lymphatics in the detrusor was significantly greater than in other parts of the bladder wall.

Urethra

Internal urethral smooth muscle sphincter (IUS). At the level of the bladder neck, the IUS surrounds the proximal urethra and is seen as a continuation of the detrusor smooth muscle, therefore favoring proximal urethral closure by constricting its lumen [18]. Smooth muscle fibers within the IUS are arranged in a horse-shoe shaped arrangement, but Wallner et al. [19] describe the superior part of the urethra to have a completely circular arrangement of smooth muscle. Layers of striated muscle, arranged in a circular configuration and thought to be derived from levator ani, surround the smooth muscle layer of the IUS in the midportion of the urethra [18, 20].

External urethral striated muscle sphincter (EUS.) Skeletal muscle, derived from the inner fibers of the levator ani muscle, surrounds the urethra as it traverses the deep perineal pouch therefore forming the EUS. In males, the EUS covers the inferior side of the prost ate and is located at the level of the membranous urethra [20] where fibers are oriented in a horse-shoe shape and without anatomical fixation to the levator ani muscle. This implies that voluntary closure of the urethra in males is executed by the EUS alone, without any involvement of the levator ani muscle [21]. The EUS is under voluntary control via the pudendal nerve. In females, the EUS begins at the inferior end of bladder and includes (1) sphincter urethrae muscle, (2) the compressor urethrae muscle, and (3) the urethrovaginal sphincter [20, 22]. Dorsolateral extensions of the inferior portion of the sphincter urethrae muscle are continuous with compressor urethrae muscle, whose contraction causes compression of the ventral part of urethra. The urethrovaginal sphincter is a thin, broad and flat muscle. As the inferior portion of EUS, the urethrovaginal sphincter encircles both the anterolateral parts of urethra and lateral aspect of vagina [20]. Based on their findings from fetal pelves, Wallner et al. [19] observed the following urethral closure mechanism in females: (1) the con- traction of levator ani muscle compresses the vagina against the posterior urethra above the level of EUS, (2) the simultaneous contraction of EUS and levator ani muscle induces an anteriorly convex bend in the midurethra, (3) the contraction of the inferior part of the EUS induces a posteroinferior force on the urethra as a result of the tendinous connection between the inferior part of the EUS and the puborectalis portion of levator ani [19]. Histological [23] and magnetic resonance imaging [22] studies have demonstrated the smooth muscle component of the IUS and the striated muscle component of the EUS to be maximally thick in the middle third of the urethra, therefore forming the true annular sphincter surrounding the urethra.

Basic Bladder Physiology/ Pharmacology

Details of the autonomous nervous control of the bladder storage and emptying functions have been discussed in several reviews [1, 2, 24, 25]. The bladder and the outflow region work as a functional unit and micturition requires the integration of autonomic and somatic efferent mechanisms to coordinate the activity of the bladder and urethral smooth muscle with that of urethral striated muscles. Micturition is under voluntary control and depends on learned behavior whereas many other visceral functions are regulated involuntarily. Despite extensive research, a number of both central and peripheral nervous control mechanisms are yet incompletely understood.

Nervous Control Mechanisms

Central control. The central nervous mechanisms for regulation of micturition are still not completely known. The normal micturition reflex is mediated by a spinobulbospinal pathway, passing through relay centers in the brain. In principle, the central pathways are organized as on-off switching circuits [3, 26, 27]. The reflex circuits involved consist of five basic components. Studies in humans and animals have identified three areas in the brainstem and diencephalon that are specifically implicated in micturition control: (1) The Barrington's nucleus or the pontine micturition center (PMC) in the dorsomedial pontine tegmentum directly excites bladder motoneurons and indirectly inhibits urethral sphincter motoneurons via inhibitory interneurons in the medial sacral cord. (2) The periaqueductal grey (PAG) receives bladder-filling information, and (3) the pre-optic area of the hypothalamus is assumed to be involved in determining the beginning of micturition. According to PET-scan studies in humans, these supraspinal regions are active during micturition [3, 26, 27].

Peripheral control (Fig. 7.2). The peripheral nervous mechanisms for bladder emptying

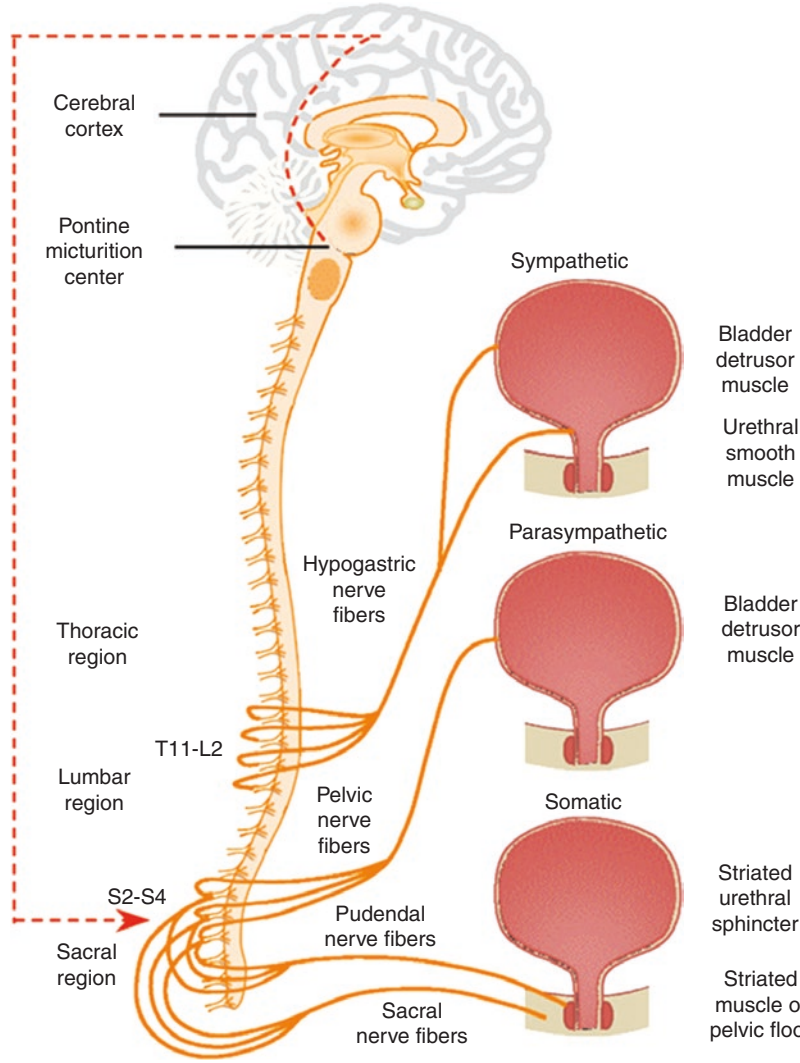

Fig. 7.2 Peripheral nervous control (from Penn Clinical Manual of Urology, Hanno P et al. 2014, Elsevier (Saunders), Philadelphia, p. 341)

and urine storage involve a complex pattern of efferent and afferent signaling in three sets of peripheral nerves: the p*arasympathetic*, *sympathetic* and *somatic* nerves. These nerves activate or deactivate bladder and outflow region in a reciprocal order, coordinated by reflex pathways. They either maintain the bladder in a relaxed state, while the outflow region is activated and enable urine storage at low intravesical pressure, or they initiate micturition by relaxing the outflow region and contracting the bladder smooth muscle. Parasympathetic action excites the bladder and relaxes the outflow region, sympathetic activation inhibits the bladder body and excites bladder outlet and urethra. Somatic nerves activate the external sphincter. The *sensory* innervation transmits information about bladder filling and contractions to the spinal cord.

Parasympathetic nerves. Parasympathetic neurons, mediating contraction of the detrusor smooth muscle and relaxation of the outflow region, are located in the sacral parasympathetic nucleus in the spinal cord at the level of S2-S4 [28]. The axons pass through the pelvic nerve and synapse with the postganglionic nerves in either the pelvic plexus, in ganglia on the surface of the bladder (vesical ganglia), or within the walls of the bladder and urethra (intramural ganglia) [29]. The preganglionic neurotransmission is predominantly mediated by acetylcholine (ACh) acting on nicotinic receptors. The transmission can be modulated by adrenergic, muscarinic, purinergic, and peptidergic presynaptic receptors [28]. The postganglionic neurons in the *pelvic nerve* mediate the excitatory input to the human detrusor smooth muscle by releasing ACh acting on muscarinic receptors. However, an atropine-resistant component, which is not mediated by cholinergic receptors has been demonstrated, particularly in functionally and morphologically altered human bladder tissue (see below). The pelvic nerve also conveys parasympathetic fibres to the outflow region and the urethra. These fibres exert an inhibitory effect and thereby relax the outflow region. This is mediated partly by nitric oxide [30], although other transmitters might be involved [31–33].

Sympathetic nerves. Most of the sympathetic innervation of the bladder and urethra originates from the intermediolateral nuclei in the thoracolumbar region (T10-L2) of the spinal cord. The axons travel either through the inferior mesenteric ganglia and the *hypogastric nerve* or pass through the paravertebral chain and enter the pelvic nerve. Thus, sympathetic signals are conveyed in both the hypogastric and pelvic nerves.

There are well-known anatomical differences between the male and female urethra, and this is also reflected in the innervation. In the human male, the smooth muscle surrounding the pre/prostatic part of the urethra is richly innervated by both cholinergic and adrenergic nerves [34]. This part is believed to serve as a sexual sphincter, contracting during ejaculation and thus preventing retrograde transport of sperm. The role of this structure in maintaining continence is unclear, but probably not essential. In the human female, there is no anatomical urethral smooth muscle sphincter, and the muscle bundles run obliquely or longitudinally along the length of the urethra. In the whole human female urethra, and in the human male urethra below the preprostatic part, there is a scarce supply of adrenergic nerves [34, 35]. Fine varicose terminals can be seen along the bundles of smooth muscle cells, running both longitudinally and transversely. Adrenergic terminals can also be found around blood vessels. Colocalization studies in animals have revealed that adrenergic nerves, identified by immunohistochemistry (tyrosine hydroxylase) also contain NPY [36]. Chemical sympathectomy (6-OH-dopamine) in rats resulted in a complete disappearance of tyrosine hydroxylase-immunoreactive (IR) nerves, whereas NOS-containing nerve fibers did not appear to be affected by the treatment [37]. This suggests that NOS is not contained within adrenergic nerves.

The predominant effects of the sympathetic innervation of the lower urinary tract in man are inhibition of the parasympathetic pathways at spinal and ganglion levels, and mediation of contraction of the bladder base and the urethra. However, in several animals, the adrenergic innervation of the detrusor is believed to inactivate the contractile mechanisms in the detrusor directly (see [24]).

Noradrenaline is released in response to electrical stimulation of detrusor tissues *in vitro*, and the normal response of detrusor tissues to released noradrenaline is relaxation (see [24]).

Somatic motoneurons. The innervation of the striated muscle of the external urethral sphincter (EUS), commonly referred to as Onuf's nucleus, originates in a specific region of the lateral ventral horn of the sacral spinal cord, generally centered in the human at the S2 segment, but also in the caudal end of the S1 segment and the middle of S3 [38]. Motoneurons in Onuf's nucleus send axons through the pudendal nerve to the pelvic floor muscles, including the external anal and external urethral sphincter [3]. These neurons are cholinergic, releasing acetylcholine to activate postjunctional nicotinic receptors on the sphincter striated muscle fibers. EUS also receives adrenergic innervation and is the only one to receive both autonomic and somatic stimuli [34, 39, 40]. Like all autonomic, but not somatic, EUS motoneurons also receive afferents from the paraventricular nucleus of the hypothalamus [41].

Afferent pathways. The *sensory* nerves monitor the urine volume and amplitude of bladder contractions during urine storage by afferent axons, which transmit the information to the lumbosacral cord [2, 40, 42]. Most of the sensory innervation of the bladder and urethra reaches the spinal cord via the pelvic nerve and dorsal root ganglia. In addition, some afferents travel in the hypogastric nerve. The sensory nerves of the striated muscle in the rhabdosphincter travel in the pudendal nerve to the sacral region of the spinal cord [2, 29]. Bladder afferent nerves are comprised of two types, myelinated Aδ fibers and unmyelinated C-fibers. Aδ fibers, located primarily in the detrusor smooth muscle layer, respond to detrusor stretching during bladder filling and convey fullness sensations. Thus, Aδ fibers respond to stretch of the bladder wall as the bladder fills with urine and to bladder contraction when voiding occurs [43]. They have a relatively low threshold pressure, approximately 5–15 mmHg [44], which corresponds to the pressure in the bladder when most humans first report sensations of bladder filling. Unmyelinated sensory C fibers are more widespread than Aδ fibers and reside in the detrusor muscle, close to the urothelium in the lamina propria and directly adjacent to urothelial cells. They have very high thresholds for firing and are not activated by physiologically relevant bladder pressures and are generally labeled as silent. C-fibers respond to nociceptive stimulation by chemicals, such as capsaicin or menthol, cold [45] or in response to inflammation [46].

Local Bladder Control

Cholinergic Mechanisms

The parasympathetic part of the autonomic nervous system is composed of neurons arising from the brainstem and sacral spinal cord. The main transmitter is acetylcholine (ACh), which is released at both ganglionic synapses and at postganglionic neuroeffector junctions. Nerves containing ACh are called cholinergic, a term introduced by Dale to describe neurons that liberate ACh. It should be remembered, however, that such nerves may contain other transmitters and that they can also be found postjunctionally in the sympathetic part of the autonomic nervous system (sweat glands and prostate). In all ganglia, released ACh stimulates nicotinic receptors. However, the postjunctional effects of ACh released from cholinergic nerves, mediating important functional actions in smooth muscle and other structures of the urogenital region, are mediated via muscarinic receptors [24, 25]. ACh may be released not only from cholinergic nerves; in isolated human bladder tissue, a basal ACh release of nonneuronal origin has also been demonstrated [47]. The released ACh was at least partly generated by the urothelium.

Cholinergic nerves. Although histochemical methods that stain for ACh-esterase (AChE) are not specific for ACh-containing nerves [29], they have been used as an indirect indicator of cholinergic nerves. The vesicular ACh transporter (VAChT) is a marker specific for cholinergic nerve terminals [48]. In e.g., rats, bladder smooth muscle bundles were supplied with a very rich number of VAChT- positive terminals also containing NPY, NOS and VIP [49]. Similar findings have been made in human bladders of

neonates and children [50]. The muscle coat of the bladder showed a rich cholinergic innervation and small VAChT-immunoreactive neurons were found scattered throughout the detrusor muscle. VAChT-immunoreactive nerves were also observed in a suburothelial location in the bladder. The function of these nerves is unclear, but a sensory function or a neurotrophic role with respect to the urothelium cannot be excluded [50].

Muscarinic receptors. Muscarinic receptors comprise five subtypes, encoded by five distinct genes [51, 52]. The five gene products correspond to pharmacologically defined receptors, and M1 through M5 are used to describe both the molecular and pharmacological subtypes. Muscarinic receptors are coupled to G-proteins, but the signal transduction systems vary. M1, M3, and M5 receptors couple preferentially to Gq/11, activating phosphoinositide hydrolysis, in turn leading to mobilization of intracellular calcium. M2 and M4 receptors couple to pertussis toxin-sensitive Gi/o, resulting in inhibition of adenylyl cyclase activity. In the human bladder, the mRNAs for all muscarinic receptor subtypes have been demonstrated [52, 53], with a predominance of mRNAs encoding M2 and M3 receptors [53, 54]. In most animal species, detrusor smooth muscle contains muscarinic receptors of the M2 and M3 subtypes [55–57].

The M3 receptors in the human bladder are believed to be the most important for detrusor contraction and to cause contraction through phosphoinositide hydrolysis [58, 59]. The main pathway for muscarinic receptor activation of the detrusor via M3 receptors may be calcium influx via L-type calcium channels, and increased sensitivity to calcium of the contractile machinery produced via inhibition of myosin light-chain phosphatase through activation of Rho-kinase. The functional role for the M2 receptors has not been clarified, but it has been suggested that M2 receptors may oppose sympathetically mediated smooth muscle relaxation, mediated by β-ARs [60]. M2 receptor stimulation may also activate nonspecific cation channels [61] and inhibit KATP channels through activation of protein kinase C [62, 63].

Muscarinic receptors may also be located on the presynaptic nerve terminals and participate in the regulation of transmitter release. The inhibitory prejunctional muscarinic receptors have been classified as M2 in the rabbit [64, 65] and rat [66], and M4 in the guinea pig [67], rat [68], and human [69] bladder. Prejunctional muscarinic facilitation has also been detected in human bladders [70].

The muscarinic receptor functions may be changed in different urological disorders, such as outflow obstruction, neurogenic bladders, bladder overactivity without overt neurogenic cause, and diabetes [52]. However, it is not always clear what the changes mean in terms of changes in detrusor function.

Urothelial cells and cells in the lamina propria express several types of muscarinic receptors, and stimulation of these receptors may affect detrusor function [8]. The porcine urothelium was found to express a high density of muscarinic receptors, even higher than the bladder smooth muscle [71], and, in the rat and human urothelium, the receptor proteins and mRNAs, respectively, for all muscarinic receptor subtypes (M1–M5) were demonstrated [72]. In these studies, not only the urothelium but also part of the lamina propria was included in the tissues investigated. However, the expression pattern of the different subtypes in the human urothelium was reported to differ: the M1 receptors on basal cells, M2 receptors on umbrella cells, M3 and M4 receptors homogenously, and M5 receptors with a decreasing gradient from luminal to basal cells [73]. Mansfield et al. [74] found, using Real Time-Polymerase Chain Reaction (RT-PCR) analysis, an abundant expression of muscarinic M2 receptors in the human bladder mucosa (urothelium/lamina propria). Some of these receptors may occur at other locations than the urothelium, e.g., on suburothelial interstitial cells of Cajal (ICC; [75–77]). The physiological significance of what appears to be a cholinergic signaling system in the mucosa is unclear. Ikeda and Kanai [78] suggested that muscarinic receptors within the mucosa were involved in urotheliogenic signaling, enhancing intrinsic detrusor contractions. Isolated strips of porcine urothelium with lamina

propria were shown to exhibit spontaneous contractile activity that was increased by stretch. The mechanism appeared to involve endogenous ACh release acting on M3 receptors [79]. It has also been suggested that cholinergic mechanisms may be involved in the urothelial release of an unknown inhibitory factor [71, 80].

Adrenergic Mechanisms

Fluorescence histochemical studies have shown that the body of the detrusor receives a relatively sparse innervation by noradrenergic nerves. The density of noradrenergic nerves increases markedly towards the bladder neck, where the smooth muscle receives a dense noradrenergic nerve supply, particularly in the male [34, 35]. The importance of the noradrenergic innervation of the bladder body has been questioned since patients with a deficiency in dopamine β-hydroxylase, the enzyme that converts dopamine to noradrenaline (NA), void normally [81]. Noradrenergic nerves also occur in the lamina propria of the bladder, only some of which are related to the vascular supply. Their functional significance remains to be shown.

α-Adrenoceptors. The human detrusor contains both α1-ARs and α2-ARs [82]. β-ARs dominate over α-ARs and the normal detrusor response to NA is relaxation [24]. α2-ARs, mainly their α2A-subtype, are expressed in bladder, urethra and prostate. They mediate prejunctional inhibition of neurotransmitter release and also a weak contractile effect in the urethra of some species, but not humans. Their overall post-junctional function in the lower urinary tract remains largely unclear.

α1-ARs are activated by adrenaline and NA. They mediate smooth muscle contraction and other functions through members of the Gq/11 family of G proteins that stimulate the hydrolysis of inositol phosphate, liberation of calcium from the endoplasmic reticulum, and activation of genes [83].

α1-ARs have been identified and characterized extensively by functional, radioligand-binding, and molecular biological techniques. Molecular clones have been isolated and characterized for three α1-subtypes (α1a, α1b, and α1d) [84]. The subtypes can be distinguished pharmacologically on the basis of their affinity for a1-adrenoceptor antagonists [83]. The α1A-subtype generally regulates smooth muscle tone in the prostate and bladder neck, whereas the α1B-subtype contributes to regulate blood pressure via contraction of the small resistance vessels. The α1D-subtype may be involved in the bladder function and spinal cord innervations [83].

In the human detrusor α1-ARs are only poorly expressed and play a limited functional role [83, 85]. Levin et al. [86] found that in the human bladder neck region, the predominating postjunctional α-AR subtype seemed to be α1. Walden et al. [87] reported a predominance of α1A-AR mRNA in the human bladder dome, trigone, and bladder base. This contrasts with the findings of Malloy et al. [88], who found that among the high affinity receptors for prazosin, only α1A and α1D-mRNAs were expressed in the human bladder. The total α1-AR expression was low, 6.3 ± 1.0 fentomol/mg, but very reproducible. The relation between the different subtypes was α_{1D}: 66 % and α1A: 34 % with no expression of α1B.

Even if α1-ARs probably play a limited functional role in the normal detrusor they seem to be involved in the peripheral control of sympathetic supply to the bladder [82]. Thus, stimulation of the hypogastric nerve has been shown to facilitate cholinergic transmission at the level of the pelvic ganglia by the actions of α1-adrenoceptors [89] and thus also bladder contractions. Intravenous injection of α1-AR antagonists inhibited the sympathetic control of the bladder by reducing hypogastric nerve activity [90, 91] and somatic activity to the urethra [92].

Okutsu et al. [93] evaluating the effects of tamsulosin on bladder blood flow (BBF) in the normal and outflow-obstructed rats found that α1-ARs expressed in the vesical artery were α1A- > α1D with almost no expression of the α1B-subtype. Experimental findings in humans have indicated involvement of the a1D-adrenoceptor subtype in storage symptoms [83]. Thus, the α1-AR is considered responsible for the dynamic component of voiding and storage symptoms.

Expression of α-ARs in the urothelium has been well documented. Ishihama et al. [94] found

the presence of α1D-adrenoceptors in the rat urothelium and suggested that activation of these adrenoceptors facilitates the micturition reflex. They suggested that endogenous catecholamines act on α1D-receptors in the urothelium to facilitate mechanosensitive bladder afferent nerve activity and reflex voiding.

Even if the α-ARs have no significant role in normal bladder contraction, there is evidence that this may change after, e.g., bladder outlet obstruction, parasympathetic decentralization, and in hyperactive bladders [1].

β-Adrenoceptors. The β-ARs of the human bladder were shown to have functional characteristics typical of neither β_1-, nor β_2- ARs [95, 96]. Normal (as well as neurogenic) human detrusors are able to express β_1-, β_2-, and β_3-AR mRNAs and selective β_3-AR agonists effectively relaxed both types of detrusor muscle [97, 98]. An investigation comparing the subpopulation of β-AR in research animals revealed significant differences amongst species [99]. Based upon quantitative PCR experiments, it appears that the β3-AR accounts for more than 95% of all β-AR mRNA in the human bladder [100]. If the amount of mRNA reflects the population of receptor protein, β_3 ARs should mediate bladder relaxation). This is in accordance with several in vitro studies [97, 98] and it seems that atypical β-AR-mediated responses reported in early studies of β-AR antagonists are mediated by β_3-ARs. It may be speculated that in bladder overactivity, there is a lack of an inhibitory β-AR-mediated noradrenaline response.

The physiological role of the sympathetic system for bladder relaxation remains unclear, however, β-AR stimulation is an effective mechanism to increase bladder capacity, as illustrated by the clinical use of the β3-AR agonist mirabegron for treatment of the overactive bladder [101]. At the mRNA level, all three subtypes are detectable in the bladder. Whereas in the rat bladder, the abundance of the three subtypes appears similar [102], in the human bladder, >95% of all β-AR mRNA belongs to the β3 subtype [100]. At the protein level, β1- and β2-ARs have been identified by radioligand binding in the bladder of humans [85] and several animals species [83], whereas a lack of β3-ARs detection is primarily attributable to a lack of suitable tools rather than a lack of presence of this subtype. Bladder smooth muscle relaxation upon β-AR stimulation has been demonstrated in many species including rats, rabbits, guinea pigs, ferrets, cats, dogs, pigs, monkeys, and humans; the maximum relaxation appears similar across species, but agonist potency may differ between them [83]. Moreover, efficacy and potency of β-AR agonists depends markedly on the stimulus used to induce bladder contraction [83, 103]. Of note, bladder relaxation occurs mainly in the detrusor and not necessarily in the bladder neck.

Non-adrenergic, Non-cholinergic Mechanisms (NANC)

In most mammalian species, part of the neuronally-induced bladder contraction is *resistant to atropine*, which blocks cholinergic muscarinic receptors [24, 52]. The proportion of NANC-mediated response to the total contraction seemed to vary with species and the frequency of stimulation. Thus, in rats and guinea-pigs, atropine has little effect on the response to single nerve stimuli, but at 20 Hz, it inhibits about 25% of the response. Corresponding figures for rabbit and pig were 40% and 75%, respectively. In strips of normal human bladders, the reported degrees of atropine resistance have varied from a few % to up to 50 % ([104]; see [25]). Luheshi and Zar [105] investigated whether the full atropine-sensitivity of the human detrusor, reported by some investigators, was due to a genuine absence of a non-cholinergic element in its motor transmission, or if it was dependent on the experimental protocols. Using a specially designed stimulation protocol, they found that part of the electrically induced response (about 30%) was resistant to atropine. Most probably, normal human detrusor muscle exhibits little atropine resistance. This does not exclude that atropine resistance can increase in morphologically and/or functionally changed bladders, and that it plays a role in the activation of the bladder.

Adenosine 5′-triphosphate. Evidence has been presented [24] that the atropine-resistant contractile component evoked in human detrusor

by electrical stimulation can be abolished by α,β-methylene ATP, suggesting that the NANC mediator is ATP. Husted et al. [106] showed that ATP produced a concentration-dependent contraction in isolated human detrusor muscle, but also that ATP influenced the responses to transmural nerve stimulation, probably by both prejunctional and postjunctional effects. The contractile effects of ATP are mediated through stimulation of P_{2X} receptors.

Two P_{2X} receptor subtypes are suggested to play a role in the bladder, P_{2X1} and P_{2X3}. Using RT-PCR, Hardy et al. [107] demonstrated the presence of the P_{2X1} receptor subtype in the human bladder, and confirmed that activation of purinergic P_{2X} receptors, putatively P_{2X1}, may be important in the initiation of contraction in human detrusor. Purinergic transmission seemed to be more important in muscle taken from patients with bladder instability. Their results also indicated the possibility that human bladder expresses multiple isoforms of the P_{2X1} receptor which may be potential sites for modifying or regulating putative purinergic activation of the human bladder. Supporting such a concept, mice deficient in P_{2X3} receptors exhibited a marked urinary bladder hyporeflexia, characterized by decreased voiding frequency and increased bladder capacity, but normal bladder pressures [108–110]. This could be caused by decreased afferent and/or efferent signaling. Immunohistochemical studies localized P_{2X3} receptors to nerve fibres innervating the urinary bladder of wild-type mice and showed that loss of this receptor subtype did not alter sensory neuron innervation density. P_{2X3} receptors thus seemed to be critical for peripheral afferent pathways (urothelial signaling) controlling urinary bladder volume reflexes. Available results suggest that ATP may contribute to excitatory neurotransmission in the bladder, both by stimulation of the detrusor and afferent nerves. The importance of this for the emptying contraction of the human bladder under normal and pathophysiological conditions remains to be established.

However, ATP is released not only from parasympathetic nerves, but also from the urothelium [109, 111]. During bladder filling, the urothelium is stretched and ATP is released from the umbrella cells thereby activating mechanotransduction pathways. ATP release can also be induced by various mediators present in the urine and and/or released from nerves or other components of the lamina propria. Urothelial release of ATP is mainly attributable to vesicular transport or exocytosis and, to a smaller extent, to pannexin hemichannel conductive efflux. After release, ATP acts on P2X3 and P2X2/3 receptors on suburothelial sensory nerves to initiate the voiding reflex and to mediate the sensation of bladder filling and urgency. ATP also acts on suburothelial interstitial cells/myofibroblasts generating an inward Ca2+ transient that via gap junctions could provide a mechanism for long-distance spread of signals from the urothelium to the detrusor muscle.

Neuropeptides. The functional roles of the many neuropeptides that have been demonstrated to be synthetized, stored, and released in the human lower urinary tract [112–115] have not been established. Neuropeptide-containing, capsaicin-sensitive primary afferents in the bladder and urethra may not only have a sensory function ("sensory neuropeptides"), but also a local effector or efferent function. In addition, they may play a role as neurotransmitters and/or neuromodulators in the bladder ganglia and at the neuromuscular junctions. As a result, the peptides may be involved in the mediation of various effects, including micturition reflex activation, smooth muscle contraction, potentiation of efferent neurotransmission, and changes in vascular tone and permeability. Evidence for this is based mainly on experiments in animals. Studies on isolated human bladder muscle strips have failed to reveal any specific local motor response attributable to a capsaicin-sensitive innervation [114]. However, cystometric evidence that capsaicin-sensitive nerves may modulate the afferent branch of the micturition reflex in humans has been presented [116]. In a small number of patients suffering from bladder hypersensitivity disorders, intravesical capsaicin produced a long-lasting, symptomatic improvement [117].

Tachykinins are fast-acting peptides. Three endogenous tachykinins, Substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) are widely distributed in the central and peripheral nervous system and bind to the three tachykinin-receptors (NK_1, NK_2 and NK_3). Nociceptive transmission is mainly mediated through NK_1-receptors. In the urinary tract they are suggested to act in afferent as well as efferent pathways [112].

Tachykinins have contractile effects in the human bladder [112, 118]. The potency of neurokinins was shown to be NKA > NKB » SP. This, and results with subtype selective agonists [118], suggested that the tachykinin receptor mediating contraction in the human bladder is of the NK_2 type.

Substance P (SP) and various related peptides were shown to have contractile effects in isolated bladder smooth muscle from various species. The potential role of SP in the atropine resistant component of the contractile response induced by electrical stimulation has been studied by several investigators (see [24]). With few exceptions, these studies did not favor the view that SP, released from postganglionic nerve-terminals, has an excitatory transmitter role. Evidence has been presented, on the other hand, that SP may play a role in the afferent, sensory branch of the micturition reflex [24, 115].

*Vasoactive intestinal polypeptide (VIP)*was shown to inhibit spontaneous contractile activity in isolated detrusor muscle from several animal species and from humans, but to have little effect on contractions induced by muscarinic receptor stimulation or by electrical stimulation of nerves (see [24, 115]). In isolated rat bladder, VIP had no effect, and in isolated guinea-pig bladder, VIP produced contraction. Stimulation of the pelvic nerves in cats increased the VIP output from the bladder, and increased bladder blood flow, although moderately [119]. VIP injected i.v. induced bladder relaxation in dogs [120]. On the other hand, VIP given i.v. to patients in a dose causing increases in heart rate, had no effect on cystometric parameters [121]. Plasma concentrations of VIP were obtained which, in other clinical investigations, had been sufficient to cause relaxation of smooth muscle [121].

Calcitonin gene-related peptide (CGRP) is a widely distributed in nerve endings in the bladder and considered a sensory neuromodulator [114, 115]. However, the role of CGRP in control of bladder motility is controversial. In pig detrusor CGRP did not alter the response to potassium, carbachol, substance P, or EFS [122]. In hamsters, CGRP caused dose-dependent inhibition of the response to EFS, but about 20% of the preparations were non-responders [123]. In human detrusor strips the relaxing effect of CGRP on carbachol-induced contraction was negligible, despite a slight increase in cGMP levels [124].

Neuropeptide Y (NPY). The human bladder is richly endowed with NPY containing nerves [125, 126]. NPY and noradrenaline are stored in separate vesicles at sympathetic nerve terminals, NPY is preferentially released at high frequency stimulation. It seems as if NPY can be found in adrenergic as well as cholinergic nerves.

The presence of functional NPY receptors in human bladder was investigated by [127]) using peptide YY (PYY) as the agonist and [^{125}I] PYY as the radioligand, and they found that human bladder expresses only very few if any functional NPY receptors. In neonates and children, Dixon et al. [50] found small ganglia scattered throughout the detrusor muscle of urinary bladder. Approximately 75% of the intramural neurons were VAChT immunoreactive, whereas approximately 95% contained NPY and approximately 40% contained NOS. VAChT-immunoreactive nerves were also observed in a sub-epithelial location in all the organs examined, the majority containing NPY, whereas a small proportion contained NOS. In animal bladders, NPY-containing nerves were shown to be present in abundance in the rat detrusor (see [24]). Available in formation on the effects of NPY on detrusors from different species is conflicting [128–130]. Even if it has been suggested that NPY may have an important role in the neural control of the lower urinary tract in the rat [131], there is no convincing information that this is the case in humans.

Prostanoids. Prostaglandin synthesis in detrusor and mucosa is initiated by several stimuli, as stretch, injury, nerve stimulation, and mediators of inflammation. PGE_2 has been shown

to mediate bladder contraction and increase bladder pressure after intra-arterial as well as intravesical application in rats and humans [24, 132, 133]. The mechanism of action is still not fully established, but most likely the effects are caused via influences on neurotransmission. It appears that prostanoids cause the release of tachykinins from nerves, which stimulate NK-1 and NK-2 receptors, as the above effects were blocked by selective NK-1 and NK-2 receptor antagonists [132].

Nitric oxide. Evidence has accumulated that L-arginine-derived nitric oxide (NO) is responsible for the main part of the inhibitory NANC responses in the lower urinary tract [24, 30]. In biopsies taken from the lateral wall and trigone regions of the human bladder, a plexus of NADPH-diaphorase containing nerve fibers was found [134]. Samples from the lateral bladder wall contained many NADPH-reactive nerve terminals, particularly in the subepithelial region immediately beneath the urothelium; occasionally they penetrated into the epithelial layer. Immunohistochemical investigations of pig bladder revealed that the density of NO synthase (NOS)-immunoreactivity was higher in trigonal and urethral tissue than in the detrusor [30].

In small biopsy preparations of the human detrusor James et al. [135] found that electrical stimulation evoked relaxations sensitive to N^G-nitro-L-arginine, but insensitive to tetrodotoxin. They suggested that NO might be generated from the detrusor and an important factor for bladder relaxation during the filling phase. However, others have been unable to obtain relaxation in rat isolated detrusor muscle precontracted by carbachol or potassium in response to electrical field stimulation [136, 137].

In the pig detrusor, the NO-donor, SIN-1, and NO relaxed carbachol and endothelin-1 contracted preparations by approximately 60%, but isoprenaline was about 1000 times more potent than SIN-1 and NO and caused complete relaxation. Nitroprusside, SIN-1, and NO were only moderately effective in relaxing isolated rat, pig, and rabbit detrusor muscle, compared to their effects on the urethral muscle [138]. These results agree well with those of [139], who found that in rabbits, cyclic GMP is mainly related to urethral relaxation and cyclic AMP to urinary bladder relaxation. Thus, it is unlikely that NO has a role as a neurotransmitter causing direct relaxation of the detrusor smooth muscle, since the detrusor sensitivity to NO and agents acting via the cyclic GMP system is low. This does not exclude that NO may modulate the effects of other transmitters, or that it has a role in afferent neurotransmission.

TRP Channels. Detailed information on TRP channels and LUT function can be found in several recent reviews [140–144]. These studies have indicated that several transient receptor potential (TRP) channels, including TRPV1, TRPV2, TRPV4, TRPM8 and TRPA1, are expressed in the bladder and may act as sensors of stretch and/or chemical irritation. They are highly expressed in, but not restricted to, primary afferent neurons. Thus, the urothelium [145], some interstitial cells and detrusor muscle also express several TRP channels [143, 146, 147]. There seem to be several links between activation of these channels and bladder dysfunction, and the therapeutic potential for TRPV1 channel agonists (capsaicin, resiniferatoxin) has been convincingly demonstrated. Animal studies have shown that inhibition of these pathways can be effective for the reduction in bladder activity. However, the roles of these channels for normal function and in pathological states have not been established. Nevertheless, TRP channels still may be most exciting targets for future LUT drugs. LUT dysfunction may not have been given the highest priority in TRP drug development, but research carried out for nonbladder diseases may be possible to apply also to LUT disorders.

TRPV1. TRPV1 is the best-characterized member of the TRPV subfamily TRPV1-6) in terms of expression pattern, properties, and clinical translation of its manipulation [148]. It is a non-selective cationic channel with high Ca^{2+} permeability allowing the passage of cations, mainly calcium, upon activation by vanilloids, noxious heat and low pH [149, 150]. TRPV1 expression has been observed in neuronal and non-neuronal human and rat LUT tissues including the urothelium, suburothelial nerve plexus, detrusor smooth

muscle, ICC, and sensory afferent neurons. There is evidence for TRPV1 expression in small diameter bladder afferent fibres in close proximity to the urothelium and in bladder sensory neurons in the dorsal root ganglia (DRG). However, the expression in the bladder particularly in the urothelium, has been controversial [143].

Despite extensive information on morphology and function in animal models, the role of TRPV1 in normal human bladder function is still controversial. However, its role in the pathophysiology and treatment of particularly neurogenic DO (NDO) is well established [140–142, 144].

TRPV2. TRPV2 is a nonselective cation channel with high Ca2+ permeability; it acts as a heat sensor with a temperature threshold of 50–52 8C and is activated by agonists such as 2-aminoethoxydiphenyl borate and D9-tetrahydrocannabinol (THC) [151]. In vascular smooth muscle cells TRPV2 is stretch-activated channel and can increase stretch-induced [Ca2+] i [152]. In rat urinary bladder TRPV2 mRNA is expressed in urothelial and smooth muscle cells and the channel is also functionally expressed in mouse urothelial cells [153, 154]. In the human bladder, Caprodossi et al. [155] found TRPV2 expression in normal human urothelial cells and bladder tissue specimens. The TRPV2 channel is also highly expressed in sensory DRG neurons. Even if TRPV2 channels are expressed in different parts of the bladder, its functional significance is still unclear. It has been suggested that TRPV2 has a role as a sensor of urothelium stretch and a pivotal role in bladder cancer development [146].

TRPV4. TRPV4 is a Ca^{2+}-permeable stretch-activated cation channel, which is expressed in rat and mouse urothelial and detrusor muscle cells. The activation of TRPV4 induces significant increases in $[Ca2+]_i$ in rat urothelial cells, leading to ATP release and modulation of afferent nerve activity in response increases in intravesical pressure. Ca2+ influx through TRPV4 appears to activate BK channels to suppress spontaneous contractions and thus a functional coupling of TRPV4 with BK channels may act as a self-limiting mechanism for bladder contractility during its storage phase [156]. Supporting this, Lee et al. [157] demonstrated that Ca^{2+} influx throughTRPV4 channels can activate SK channels in PDGFRα+ cells and prevent bladder overactivity during filling.

TRPV4 has been suggested to be an important urothelial mechanosensor for bladder distension [146, 153, 154]. Gevaert et al. [158] raised the possibility that TRPV4 plays a critical role in urothelium-mediated transduction of intravesical mechanical pressure. Mochizuki et al. [159] suggested that the TRPV4 channel participates in the mechanosensory pathway in urinary bladder and that mechanical stimulus-dependent activation of TRPV4 in urothelial cell layers is a key event for ATP signaling in the micturition reflex pathway.

Takaoka et al. [160] using rats with bilateral pelvic nerve crush and showing characteristics of detrusor underactivity (DU), and this model intravesical application of the TRPV4 agonist GSK1016790A significantly decreased ICI, bladder capacity, voided volume, and PVR without increasing non-voiding contractions (NVCs), and these effects were blocked by the TRPV4 antagonist RN1734. In contrast, GSK1016790A had no significant effects on CMG parameters in normal rats. Deruyver et al. [161], using female wild-type and Trpv4 knockout rats that underwent sham surgery or bilateral pelvic nerve injury. Rats with nerve injury showed DU with low-amplitude voiding contractions, decreased voiding frequency, and increased postvoid residual. Intravesical application of GSK1016790A increased voiding frequency and reduced postvoid residual in wild-type, but not Trpv4−/−, rats. In isolated bladder strips, GSK1016790A did not induce relevant contractions. These studies suggested a potential for TRPV4 for treatment of DU.

TRPA1. TRPA1 is the only mammalian member of the Ankyrin TRP subfamily. TRPA1-channels are predominantly expressed in sensory afferent nerve endings [162], but their expression and sensory function in the epithelial cells is species-specific, with a virtual absence of TRPA1 expression in the detrusor smooth muscle (DSM) cells [163]. In addition to being present in nerve endings, TRPA1-channels can be found in the mucosa of the human bladder. Agonists of TRPA1-channels are known to induce

concentration-dependent contraction of isolated muscle strips of the rat bladder via stimulation of TRPA1-expressing sensory fibers [164]. The contractile effect of TRPA1 on detrusor smooth muscle (DSM) may to be due to release from sensory afferents of inflammatory factors—tachykinins and prostaglandins. Streng et al. [165] investigated the effects of H_2S and known TRPA1 activators on micturition in conscious rats. The found that intravesical TRPA1 activators initiate detrusor overactivity indicating that TRPA1 may have a role in sensory transduction in this organ.

TRPM8. TRPM8 channels are known to be activated by low temperatures (<18–28 °C) and chemical agents such as menthol [166]. It has been reported that TRPM8 channels are expressed in urothelial cells and in sensory nerve fibres located in the urothelium and suburothelial space of the bladder and L6 dorsal root ganglia (DRG) of the rat and guinea-pig. TRPM8 may have a role in activation of bladder afferent pathways during filling of the bladder in the normal rat [167], an effect that at least partlyseems to be mediated via mechanosensitive C-fibres. TRPM8 channels may be involved in the bladder cooling reflex I humans [146, 168], and TRPM8 channels may have a role in activation of bladder afferent pathways during filling of the bladder in the normal rat. The positive correlation between the density of TRPM8 in the bladder mucosa and voiding frequency in detrusor overactivity, and also increased TRPM8 expression in bladder pain patients, led to the suggestion that this channel was involved in the symptomatology and pathophysiology of these disorders [75, 77].

Basic Urethral Physiology/ Pharmacology

Under normal conditions, there is a reciprocal relationship between the activity in the detrusor and the activity in the outlet region. Sufficient contraction of the urethral smooth muscle is an important key function in order to provide continence during the storage phase of the micturition cycle. Equally important is a coordinated and complete relaxation during the voiding phase. During voiding, contraction of the detrusor muscle is preceded by a relaxation of the outlet region, thereby facilitating bladder contraction. In humans, the normal pattern of voiding is characterized by an initial drop in urethral pressure followed by an increase in intravesical pressure [24].

Many factors have been suggested to contribute to urethral relaxation and to urethral closure, including urethral smooth muscle tone, and the properties of the urethral lamina propria [169, 170]. The role of NA as a main contractant factor is well established. In contrast, the mechanisms involved in urethral relaxation seem to be more complicated and several factors may contribute. One possibility is that the fall in intraurethral pressure is caused by stimulation of muscarinic receptors on noradrenergic nerves diminishing NA release and thereby tone in the proximal urethra. Another is that contraction of longitudinal urethral smooth muscle in the proximal urethral, produced by released ACh, causes shortening and widening of the urethra, with a concomitant decrease in intraurethral pressure. A third possibility is that a NANC mechanism, including NO, mediates this response [24, 169, 170].

Adrenergic Mechanisms

Adrenergic nerves. The well-known anatomical differences between the male and female urethra are also reflected in the innervation. In the human male, the smooth muscle surrounding the preprostatic part of the urethra is richly innervated by both cholinergic and adrenergic nerves [34], and considered the "sexual sphincter", contracting during ejaculation and thus preventing retrograde transport of sperm. The role of this structure in maintaining continence is unclear, but probably not essential.

In the human female, the muscle bundles run obliquely or longitudinally along the length of the urethra, and in the whole human female urethra, as well as in the human male urethra below the pre-prostatic part, there is only a scarce supply of adrenergic nerves [35, 171]. Fine varicose terminals can be seen along the bundles of smooth muscle cells, running both longitudinally

and transversely. Adrenergic terminals can also be found around blood vessels. Colocalization studies in animals have revealed that adrenergic nerves, identified by immunohistochemistry (tyrosine hydroxylase; TH) also contain neuropeptide Y (NPY) [36]. Chemical sympathectomy (6-OH-dopamine) in rats resulted in a complete disappearance of TH-immunoreactive (IR) nerves, while NO synthase (NOS)-containing nerve fibres were not affected by the treatment [37]. This suggests that NOS is not contained within adrenergic nerves.

α_1-Adrenoceptors. In humans, up to about 50% of the intraurethral pressure is maintained by stimulation of α-ARs, as judged from results obtained with α-AR antagonists and epidural anesthesia in urodynamic studies [172, 173]. In human urethral smooth muscle, both functional and receptor binding studies have suggested that the α_1-AR subtype is the predominating postjunctional α-AR (see [24, 174]). Most in vitro investigations of human urethral α-ARs have been carried out in the male, and the results support the existence of a sphincter structure in the male proximal urethra, which cannot be found in the female. Other marked differences between sexes in the distribution of α_1-and α_2-ARs (as can be found in e.g., rabbits), or in the distribution of α_1-AR subtypes, do not seem to occur [175]. Separating the entire length of the isolated female human urethra into seven parts, from the external meatus to the bladder neck, it was found that NA (α_1-and α_2), but not clonidine (α_2), produced concentration-dependent contractions in all parts, with a peak in middle to proximal urethra [176].

Among the three high-affinity α_1-AR subtypes (α_{1A}, α_{1B}, $\alpha_{1\Delta}$) identified in molecular cloning and functional studies, α_{1A} seems to predominate in the human lower urinary tract [175, 177, 178].

Urethral α_2-ARs are able to control the release of NA from adrenergic nerves as shown in in-vitro studies. In the rabbit urethra, incubated with [^{3}H]NA, electrical stimulation of nerves caused a release of [^{3}H] which was decreased by NA and clonidine, and increased by the α_2-AR antagonist rauwolscine [179]. Clonidine was shown to reduce intraurethral pressure in humans [180], an effect that may be attributed partly to a peripheral effect on adrenergic nerve terminals. More probable, however, this effect is exerted on the central nervous system with a resulting decrease in peripheral sympathetic nervous activity. The subtype of prejunctional α_2-AR involved in [^{3}H] NA secretion in the isolated guinea-pig urethra was suggested to be of the α_{2A}-subtype [181].

Prejunctional α_2-AR regulation of transmitter release is not confined to adrenergic nerves (see [24]). It was found that electrical field stimulation (EFS; frequencies above 12 Hz) of spontaneously contracted smooth muscle strips from the female pig urethra, evoked long-lasting, frequency-dependent relaxations in the presence of prazosin, scopolamine, and the NOS inhibitor, N^G-nitro-L-arginine (L-NOARG), suggesting the release of an unknown relaxation-producing mediator [182]. Treatment with the selective α_2-AR agonist UK-14 304 markedly reduced the relaxations evoked by EFS at all frequencies tested (16–30 Hz). The inhibitory effect of UK-14 304 was completely antagonized by rauwolscine, and the results suggested that the release of the unknown mediator in the female pig urethra can be modulated via α_2-ARs.

β-Adrenoceptors. The presence of β-AR protein in the urethra of rabbits and humans has been reported by radioligand binding studies [83]. In pigs, urethral relaxation by isoprenaline is mediated by both β2- and β3-ARs but the predominant β-AR subtype present in both the bladder and urethra was the β3-AR [183]. β-AR agonists can reduce urethral pressure in vivo in rats [184], cats [185], and humans [186]. While such urethral relaxation and hence reduction of bladder outlet resistance may be undesirable in the treatment of overactive bladder and urgency incontinence, the smaller magnitude of effects in the urethra as compared to those in the bladder make it unlikely that direct effects on the urethra limit the usefulness of β-AR agonists, specifically β3-selective drugs, in the treatment of bladder dysfunction. Alexandre et al. [187] investigated the effects of β3-AR agonist mirabegron in mouse urethra and found that effects were the result of β3-ARagonism together with α1A and α1D-AR antagonism. Although this effect might be an interesting pharmacological in vitro observation,

it seems to have no relevance for the clinical use of mirabegron in the treatment of the overactive bladder [142, 144].

Although the functional importance of urethral β-ARs has not been established, they have been targets for therapeutic interventions. Selective β_2-AR agonists have been shown to reduce intraurethral pressure [188–190], but β-AR antagonists have not been shown to influence intraurethral pressure acutely [186]. The theoretical basis for the use of β-AR antagonists in the treatment of stress incontinence is that blockade of urethral β-ARs may enhance the effects of NA on urethral α-ARs. Even if propranolol has been reported to have beneficial effects in the treatment of stress incontinence, this does not seem to be an effective treatment. Selective β_2-AR antagonists have been used as a treatment of stress incontinence, it seems paradoxical that the selective β_2-AR agonist, clenbuterol, was found to cause significant clinical improvement and increase in maximal urethral pressure in women with stress incontinence. The positive effects were suggested to be a result of an action on urethral striated muscle and/or the pelvic floor muscles [191].

Cholinergic Mechanisms

Cholinergic nerves. The urethral smooth muscle receives a rich cholinergic innervation of which the functional role is largely unknown. Most probably, the cholinergic nerves cause relaxation of the outflow region at the start of micturition by releasing NO and other relaxant transmitters. Co-localization studies in the pig urethra revealed that ACh esterase (AChE) positive and some NOS-IR nerves had profiles that were similar. These nerves also contained NPY and VIP immunoreactivity. NOS-containing nerves were present in a density lower than that of the AChE positive nerves, but higher than the density of any peptidergic nerves [192]. Coexistence of ACh and NOS in the rat major pelvic ganglion was demonstrated by double immunohistochemistry using antisera raised against NOS and choline acetyltransferase [49]. In the rat urethra, co-localization studies using VAChT antibodies confirmed that NOS and VIP are contained within a population of cholinergic nerves. Investigating the distribution of immunoreactivities to neuronal NOS (nNOS), heme oxygenases (HO), and VIP, HO-2 immunoreactivity was found in all nerve cell bodies of intramural ganglia, localized between smooth muscle bundles in the detrusor, bladder base and proximal urethra [193]. About 70% of the ganglionic cell bodies were also NOS-immunoreactive, whereas a minor part was VIP-immunoreactive.

Muscarinic receptors. The distribution and number of muscarinic receptors in different parts of the urethra seems to vary. Compared to the bladder, the number of muscarinic receptor binding sites in the rabbit urethra was lower [194], and by autoradiography, it was demonstrated that muscarinic receptors were abundant in the outer parts of the urethral wall and decreased in density in luminal direction [195]. Muscarinic receptor agonists contract isolated urethral smooth muscle from several species, including humans, but these responses seem to be mediated mainly by the longitudinal muscle layer [24, 35]. Taki et al. [176], investigating the whole length of the female human urethra, found that ACh contracted only the proximal part and the bladder neck. If this contractile activation is exerted in the longitudinal direction, it should be expected that the urethra is shortened and that the urethral pressure decreases. Experimentally, in vitro resistance to flow in the urethra was increased only by high concentrations of ACh [196, 197]. Prejunctional muscarinic receptors may influence the release of both noradrenaline and ACh in the bladder neck/urethra. In urethral tissue from both rabbit and humans, carbachol decreased and scopolamine increased concentration dependently the release of [^{3}H] noradrenaline from adrenergic and of [^{3}H] choline from cholinergic nerve terminals [179]. At least theoretically, this would mean that released ACh could inhibit noradrenaline release, thereby decreasing urethral tone and intraurethra l pressure. However, in humans, tolerable doses of the muscarinic receptor agonist, bethanechol [198], and the antagonist, emeprone [199], had little effect on intraurethral pressure. The muscarinic receptor subtypes involved in contractile effects

on smooth muscle, or controlling transmitter release in the urethra, have not been established. It has been reported that M1, M2, and M3 receptors all mediate contraction of the circular muscle of the rabbit urethra after stimulation with carbachol [200, 201].

Non-adrenergic, Non-cholinergic Mechanisms (NANC)

The mechanical responses of the cat urethra to autonomic nerve stimulation and to intraarterial ACh injection were analysed by Slack and Downie [202]. Sacral ventral root stimulation produced an atropine-sensitive constriction when basal urethral resistance was low, but dilatation when resistance was high. The latter response was reduced, but not abolished, by atropine. When urethral constriction had been produced by phenylephrine, injection of ACh produced a consistent decrease in urethral resistance, which was not reduced by atropine. It was suggested that parasympathetic dilatation of the urethra may be mediated by an unknown NANC transmitter released from postganglionic neurons. There are reasons to believe that this transmitter is NO.

Nitric oxide. NO appears to be an important inhibitory neurotransmitter in the lower urinary tract [24, 203]. NO-mediated responses in smooth muscle preparations are found to be linked to an increase in guanosine 3′,5′-cyclic monophosphate (cyclic GMP) formation, which has been demonstrated in the rabbit and pig urethra [139, 204–206]. Subsequent activation of a cyclic GMP-dependent protein kinase (cGK) has been suggested to hyperpolarize the cell membrane, probably by causing a leftward shift of the activation curve for the K^+-channels, thus increasing their open probability [207, 208]. There have also been reports suggesting that NO in some smooth muscles, might act directly on the K^+-channels [209, 210]. Other mechanisms for NO-induced relaxations, mediated by cyclic GMP, might involve reduced intracellular Ca^{2+} levels by intracellular sequestration, or reduced sensitivity of the contractile machinery to Ca^{2+} [211], both mechanisms acting without changing the membrane potential.

Electrophysiological registrations from urethral smooth muscle are scarce, probably due to the technical difficulties caused by the large amounts of connective tissue. However, Ito & Kimoto reported a hyperpolarization following NANC-stimulation in some preparations of urethral smooth muscle from male rabbits [212]. Furthermore, KRN 2391, a combined NO-donor and K^+-channel opener, had a pronounced relaxant effect accompanied by a hyperpolarization in the female rabbit urethra [213]. These effects were suggested being mediated predominantly through NO-dependent mechanisms, since the relaxant effect was less sensitive to K^+-channel blockade. However, it cannot be excluded that the hyperpolarization was a pure K^+-channel opening effect, and not mediated by NO.

It appears reasonable to believe that the relaxant effect of NO in rabbit and pig urethra is mediated by increased levels of cyclic GMP. Evidence for this has been demonstrated by several investigators [139, 204–206]. Accordingly, the cyclic GMP-analog, 8-Br-cyclic GMP, was able to induce relaxation of rabbit urethra, further supporting the view of cyclic GMP as a mediator of relaxation also in this tissue. The mechanisms by which cyclic GMP induces relaxation probably involves stimulation of a cGK, which phosphorylates K_{Ca} channels and thus increases their open probability, leading to an hyperpolarization [208]. Furthermore, cyclic GMP might affect the sequestering of intracellular Ca^{2+}, affect Ca^{2+} extrusion pumps and/or decrease the sensitivity for Ca^{2+} [211]. The latter may occur without changing the membrane potential. Thus, cyclic GMP may be able to induce relaxation in different ways in different tissues.

The role of NO for urethral relaxation was further investigated in mice lacking cGK type I (cGKI) [214]. In urethral preparations of cGKI+/+ mice, EFS elicited frequency-dependent relaxations. The relaxations were abolished by L-NOARG, and instead a contractile response to stimulation was generally found. In cGKI−/− urethral strips, the response to EFS was practically abolished, but a small relaxation generally appeared at high stimulation frequencies (16–32 Hz). This relaxant response was not

inhibited by L-NOARG, suggesting the occurrence of additional relaxant transmitter(s).

The rich occurrence of NOS-IR nerve fibres also supports the present view of NO as the main inhibitory NANC-mediator in rabbit urethra [205]. To localize target cells for NO, cyclic GMP antibodies have been used and Waldeck et al demonstrated spindle-shaped cyclic GMP-IR cells, distinct from the smooth muscle cells, forming a network around and between the urethral smooth muscle bundles [215]. These results confirmed the findings of Smet et al. [216] who found similar cyclic GMP-IR interstitial cells in the guinea-pig and human bladder/urethra. In contrast to the results of Waldeck et al. [215], Smet et al. [216] also found smooth muscle cells with cyclic GMP-immunoreactivity in the urethra. The occurrence of cyclic GMP-immunoreactivity in smooth muscle cells seems logical, since NO is believed to stimulate guanylyl cyclase with subsequent cyclic GMP-formation in the cells. The function of the interstitial cells has not been established, but since they have morphological similarities to the interstitial cells of Cajal in the gut, it has been speculated that they also may have a similar function. There seems to be no experimental basis for this speculation.

Carbon monoxide. The role of CO in urethral function is still controversial. It has been assumed, but not proven, that CO causes relaxation through the cGMP pathway [217]. Waldeck et al. [215] found only weak relaxant effects of exogenous CO in the rabbit urethra, compared to NO, concluding that CO is not an important mediator of relaxation in this tissue [215]. Nonetheless there are known interspecies differences of urethral relaxant responses to CO. In guinea pigs the maximal relaxant response to CO did not exceed 15 ± 3%, compared to 40 ± 7% in pigs [193, 206]. The distribution of the CO producing enzymes haem oxygenases, HO-1 and –2, was studied by immunohistochemistry in the pig lower urinary tract [182]. HO-2 immunoreactivity was observed in coarse nerve trunks in the urethra, and HO-1 immunoreactivity was seen in nerve cells, coarse nerve trunks and varicose nerve fibres within urethral smooth muscle. In urethral smooth muscle preparations, exogenously applied CO evoked a small relaxation associated with a small increase in cyclic GMP, but not cyclic AMP, content. CO-evoked relaxations were not significantly reduced by treatment with methylene blue, or by inhibitors of voltage-dependent (4-aminopyridine), high (iberiotoxin, charybdotoxin) and low (apamin) conductance Ca(2+)-activated, and ATP-sensitive (glibenclamide) K+ channels.

The inhibitory innervation of guinea-pig urethral smooth muscle was investigated histochemically and functionally [193]. HO-2 immunoreactivity was found in all nerve cell bodies of intramural ganglia, localized between smooth muscle bundles in the detrusor, bladder base and proximal urethra. In rabbit urethral smooth muscle, CO produced a small relaxant effect without change in membrane potential, and it was concluded that CO is less likely to be involved in the inhibitory neurotransmission in this tissue [215].

Taken together, available results do not support a transmitter role of CO in urethral smooth muscle. However, a messenger function CO cannot be excluded. Naseem et al. [217] found a weak relaxation by CO (compared to NO) in the rabbit urethra. In the presence of hydrogen peroxide, the urethral relaxation responses to both CO and NO were significantly increased, and it was suggested that hydrogen peroxide may amplify NO and CO-mediated responses. In the female pig urethra an even more pronounced increase in relaxant response to CO was found, using YC-1, a stimulator of sGC, suggesting a possible role for CO as possible messenger function for urethral relaxation [206].

Adenosine 5′-triphosphate. ATP is widely considered is an inhibitory neurotransmitter in the urethra since EFS of intramural nerves in strips of urethra or bladder neck smooth muscle produced relaxation that was mimicked by ATP and inhibited by purinergic receptor antagonists. ATP was suggested to cause smooth muscle relaxation via G-protein coupled P2Y receptors [177] and in hamster urethra, Western blotting analysis showed expression of both P2Y1and P2Y2. The relaxant response to ATP in this preparation could be mediated via these receptors [218] but

ATP may also induce relaxation via breakdown to adenosine [218–222].

Spontaneous myogenic tone in the urethra were shown to be associated with spontaneous transient depolarizations and large, regularly occurring slow waves [223, 224]. Sergeant et al. [225] suggested that this activity originated in specialized pacemaker cells (interstitial cells of Cajal: ICC). The frequency of pacemaker activity in ICC was increased by noradrenaline [226] and decreased by NO leading to the suggestion that ICC may also act as targets for neurotransmitters in the urethra [227].

Contractile responses to ATP or related compounds have also been described [228, 229]. Bradley et al. [229], found that exogenous application of ATP evoked robust contractions of strips of rabbit proximal urethral smooth muscle. These contractions were inhibited by the P2 blocker suramin and the selective P Y1 receptor antagonist MRS2500 and the authors suggested that they were mediated by the activation of P2Y receptors on interstitial cells of Cajal. Further study showed that stimulating purinergic nerves in rabbit urethral smooth muscle induced contractions via the activation of P2X receptors on smooth muscle cells [230].

Neuropeptides. *[*231*]* found abundant VIP-, CGRP-, SP-, and NPY-immunoreactive nerve fibers in the adventitia, muscularis, and lamina propria of proximal and distal segments of the mouse urethra. A proportion of fibers were closely associated with blood vessels, glands, and cells immunoreactive for PGP9.5. The epithelium contained abundant nerve fibers immunoreactive for CGRP and/or SP. Abundant fibers were traced from L5-S2 DRG to all urethral regions and the authors concluded that spinal afferent endings in the urethra would impact urethral function. However, the functional importance of most of the peptides described has not been established.

Vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are expressed in the neural pathways regulating the lower urinary tract [115, 232]. VIP-immunoreactivity (IR) is present in afferent and autonomic efferent neurons innervating the bladder and urethra, whereas PACAP-IR is present primarily in afferent neurons.

In various species, VIP-containing urethral ganglion cells have been demonstrated, and numerous VIP-IR nerve fibres have been observed around ganglion cells, in the bladder neck, in the urethral smooth muscle layers, in lamina propria, and in association with blood vessels [29]. Several investigators have shown that VIP is able to relax urethral smooth muscle from various species, including man, and the peptide was suggested to be responsibe for NANC-mediated urethral relaxation (see [24]). Sjögren et al. [233] showed that VIP had a marked inhibitory effect on the isolated female rabbit urethra contracted by NA or EFS. No effect was found on NA release. In the pig urethra, VIP and NOS seem to be partly co-localized within nerve fibres (Persson et al., 1995). Waldeck et al. [215] showed that VIP-IR nerve fibres occurred throughout the smooth muscle layer of the rabbit urethra, although the number of nerves was not as high as that of NOS-IR structures. Marked relaxation of the isolated rabbit urethral muscle was reported [215], and the relaxant mechanism for VIP seemed to be independent of changes of the membrane potential. The ability of VIP to relax K^+-contracted preparations strengthens the hypothesis that the relaxant mechanism is independent of hyperpolarization [215].

Both pelvic and hypogastric nerve stimulation in dogs increased the bladder venous effluent VIP concentration [120], which supports the view that VIP can be released also from urethral nerves. In human urethral smooth muscle, relaxant responses were less consistent, but a modulatory role in neurotransmission could not be excluded [233]. Infusion of VIP in humans in amounts that caused circulatory side effects, had no effects on urethral resistance [121]. Plasma concentrations of VIP were obtained which, in other clinical investigations, had been sufficient to cause relaxation of the lower esophageal sphincter and to depress uterine contractions [121]. Therefore, the physiological importance of VIP for the lower urinary tract function in humans was questioned [121], and it is still unclear whether or not VIP contributes to NANC-mediated relaxation of the urethra.

Overview of the Micturition Cycle: Simplified Summary [234]

Bladder accommodation during normal filling is a primarily passive phenomenon, dependent on the elastic and viscoelastic properties of the bladder wall and the lack of parasympathetic excitatory input. An increase in outlet resistance occurs via the striated sphincter somatic "guarding reflex". In some species a sympathetic reflex contributes to storage by (1) increasing outlet resistance by increasing tension on the smooth sphincter, (2) inhibiting bladder contractility through an inhibitory effect on parasympathetic ganglia, and (3) causing a decrease in tension of bladder body smooth muscle. Continence is maintained during increases in intraabdominal pressure (IAP) by intrinsic competence of the bladder outlet and urethral compression against a suburethral supporting layer. A further increase in striated sphincter activity, on a reflex basis, is also contributory during increases in IAP (e.g. by coughing or straining). Emptying (voiding) can be voluntary or involuntary and normally involves an inhibition of the spinal somatic and sympathetic reflexes and activation of the vesical parasympathetic pathways, the organizational center for which is in the brainstem. Initially, there is a relaxation of the outlet musculature, mediated not only by the cessation of the somatic and sympathetic spinal reflexes but probably also by a relaxing factor, very possibly NO, released by parasympathetic stimulation or by some effect of bladder smooth muscle contraction itself.

A highly coordinated parasympathetically induced contraction of the bulk of the bladder smooth musculature occurs, with shaping or funneling of the relaxed outlet, due at least in part to a smooth muscle continuity between the bladder base and proximal urethra. With amplification and facilitation of the bladder contraction from other peripheral reflexes and from spinal cord supraspinal sources, and the absence of anatomic obstruction between the bladder and the urethral meatus, complete emptying will occur. Whatever disagreements exist regarding the anatomic, morphologic, physiologic, pharmacologic, and mechanical details involved in both the storage and expulsion of urine by the LUT, agreement is found regarding certain principles. First, the micturition cycle involves two relatively discrete processes: bladder filling/urine storage and bladder emptying/voiding. Second, whatever the details involved, these processes can be summarized succinctly from a conceptual point of view.

Bladder filling/urine storage require the following:

1. Accommodation of increasing volumes of urine at a low intravesical pressure (normal compliance) and with appropriate sensation
2. A closed bladder outlet at rest which remains so during increases of IAP.
3. Absence of involuntary bladder contractions (DO)

Bladder emptying/voiding requires the following:

1. Sustained coordinated contraction of the bladder smooth musculature of adequate magnitude and duration
2. Concomitant lowering of resistance at the level of the smooth and striated sphincter (absence of functional obstruction)
3. Absence of anatomic obstruction

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Physiology and Pharmacology of the Prostate

8

Matthias Oelke

Introduction

The prostate is located in the lower pelvis and positioned between the bladder neck and pelvic floor. The prostate is a tubulo-alveolar gland, part of both the reproductive and urinary system, and universally present in mammals. The urethra of humans runs in cranio-caudal direction through the prostate (i.e. prostatic urethra) and the ejaculatory ducts run on both sides from dorso-cranial to ventro-caudal direction towards the prostatic urethra. The prostate grows and matures during puberty under the influence of testosterone from a small gland of 2–5 cm^3 in childhood to a gland volume of approximately 20–25 cm^3 in early adolescence [1]. Approximately 15–30 ejaculatory ducts disembogue at the verumontanum which is located on the dorsal side halfway through the prostatic urethra. Based on the position of the verumontanum, the prostatic urethra can be divided into a proximal and distal part which has in the young healthy adult a length of approx. 1 cm each. Starting at the verumontanum and ventrally directed, the proximal prostatic urethra has an angle of approximately 35° [2, 3].

A total of 30–50 glands are embedded in the prostate. The glandular tubes contain epithelial cells which coat the lumen and are responsible for the secretion during ejaculation. Prostatic glands are surrounded by interstitial tissue which accommodates smooth muscle cells, fibrocytes, elastic and collagen fibers, blood and lymph vessels, as well as nerves (Fig. 8.1). According to the structure and alignment of the glands as well as the microscopic shape of epithelial cells, the prostate can be divided into four distinct zones (Fig. 8.2) [4, 5] which can be visualized by ultrasound [7] or MRI [8, 9]:

1. Anterior zone: this area does not have glands and only contains muscular and fibrotic cells. The aglandular prostate forms the ventral surface of the prostate and is inseparable fused with the glandular prostate. The function of this area remains unknown but strong muscular components suggest contracting abilities.
2. Central zone: constitutes approximately 25% of the glandular prostate in young, healthy adults, has a conical shape with the tip of the cone directed towards the verumontanum and the base towards the seminal vesicles. Glandular tubes run parallel to the intra-prostatic ejaculatory duct and disembogue in the center of the verumontanum. The glands are oriented in a coronal plane and contain wide chambers. The epithelium of the glands has multiple rows.
3. Peripheral zone: constitutes approximately 70% of the glandular prostate in young,

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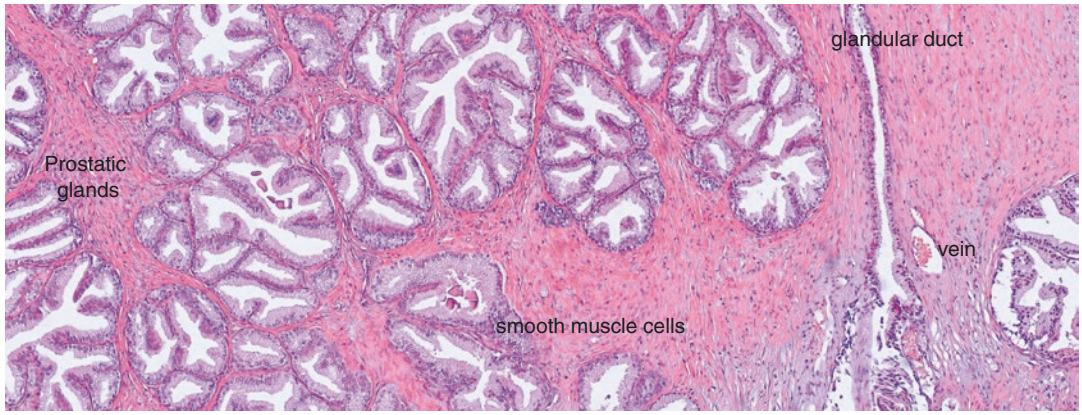

Fig. 8.1 TUR specimen of a patient with benign prostatic hyperplasia demonstrating the different tissue components of the transition zone (hematoxylin eosin staining, enlargement 150-fold). Prostatic glands with single layer epithelial cells appear blue and the lumen white (without secretion, washed out during fixation). The glands are separated by interstitial tissue with a large amount of smooth muscle cells (red). A glandular duct with single layer epithelial cells runs in vertical direction through the tissue. Elastic and collagen fibers as well as lymphatic vessels and nerves are not stained and remain invisible on this image (courtesy of Dr. S. Afram, Pathological Institute Gronau, Germany)

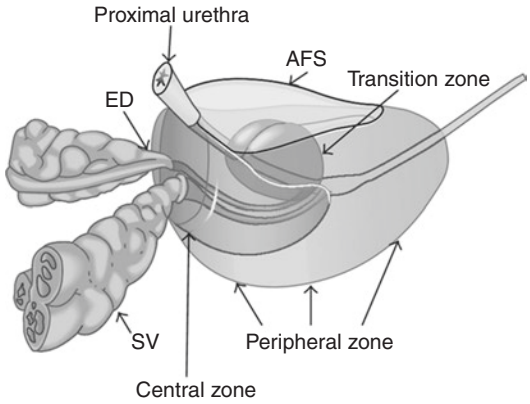

Fig. 8.2 Schematic illustration of the gross anatomy of the prostate, imaged 45 degrees from the left (zonal anatomy according to McNeal [4, 5]). The anterior fibromuscular stroma (AFS) is positioned ventrally. The central zone is located dorsally of the urethra and is surrounded by the peripheral zone. The transition zone is positioned at the proximal urethra (proximal of the verumontanum, i.e. the location where the ejaculatory ducts (ED) disembogue into the urethra). The seminal vesicles (SV) are located dorso-laterally of the prostate on both sides (modified according to Roehrborn et al. [6])

healthy adults and surrounds the central zone from the base to the apex. The ducts radiate laterally from the urethra and disembogue lateral and distal of the verumontanum. The glands have a uniform configuration, only a few branches and a round lumen. The epithelial cells are long and positioned in a single row and have a uniform shape as well as a light cytoplasm.

4. Transition zone: constitutes approximately 5% of the glandular prostate in young, healthy adults and is positioned on the dorsal side of the proximal prostatic urethra. The transition zone only has a few ducts which run parallel to the urethral axis. The glands are straight and the epithelial cells have a similar shape compared to those of the peripheral zone; however, the interstitial tissue is irregular.

The different morphology of the prostatic glands and different appearances of epithelial cells in different zones indicate different functions within the glandular prostate [10, 11]; however, it remains largely unknown which zones are responsible for particular functions or secretions in the context of ejaculation and reproduction.

Different diseases develop in different zones. Prostate cancer and prostatitis begin in the peripheral zone [12], whereas benign prostatic hyperplasia (BPH) originates in the transition zone [13]. However, the cause of BPH remains largely unknown. The prevalence of BPH increases with aging [1] and may result in enlargement of the transition zone and secondarily in enlargement of the entire prostate (i.e. benign prostatic enlargement, BPE), elongation of the proximal prostatic urethra (>1 cm), increase of the ventrally directed

angle of the proximal prostatic urethra (>35°), increased urethral resistance of urine flow (i.e. benign prostatic obstruction, BPO) and lower urinary tract symptoms (LUTS) [2, 3, 14, 15].

Physiology of the Prostate

The prostate is—next to the seminal vesicales and the bulbourethral glands (Cowper)—part of the male accessory sex glands and produces seminal fluids. Smooth muscle cells of the prostate contract during orgasm in order to expel ejaculate through the urethra [16]. Epithelial cells of the prostatic glands produce a secretion that empties during ejaculation through the glandular ducts into the prostatic urethra where they mix with semen from the testes and epididymes as well as with secretions from the seminal vesicales [16].

Prostatic secretion is an important component of the ejaculate and constitutes approximately 25–30% of the ejaculate volume (~0.5 mL). The prostatic secretions are a milky white mixture of simple sugars (e.g. fructose and glucose), proteins, minerals and alkaline chemicals which protect and nourish sperm. The sugars secreted by the prostate function as nutrition for the spermatozoa while they pass into the female body to fertilize eggs [16]. Protein content is less than 1% of the total prostatic secretion and includes proteolytic enzymes, prostate-specific antigen (PSA), prostatic acid phosphatase and β-microseminoprotein [17]. PSA, a glycoprotein and member of the kallikrein-related peptidase family produced and secreted in prostatic epithelial cells, and other enzymes break down seminal proteins to free spermatozoa from the viscous semen, thereby making semen thinner and allowing sperm cells to swim freely. Additionally, PSA can also dissolve cervical mucus in order to give sperm cells free passage to the uterus to fertilize eggs. The secretions also contain zinc with a concentration 500–1000 times the concentration in blood [16]. The alkaline chemicals in prostatic secretions (~pH 7.8) neutralize acidic vaginal secretions to promote the survival and prolong the lifespan of spermatozoa in the female body, thereby increasing their chance of successfully fertilizing an egg [16].

The prostate needs hormones (androgens) to function properly. The predominant male sex hormone is testosterone which is mainly produced by the Leydig cells of the testes, to a lesser amount also in the adrenal glands. Testosterone is metabolized into the active hormone dihydrotestosterone (DHT) inside prostatic epithelial cells by the enzyme 5α-reductase (see Section "Androgens").

Pharmacology of the Prostate

The prostate contains several tissue types (especially smooth muscle cells and epithelium) which are rich of receptors and enzymes. Targeting these receptors/enzymes helps treating LUTS/BPH or PCa. LUTS/BPH is the fourth most common disease in men aged ≥50 years and prostate cancer is the most common malignancy in males [18]. Therefore, the following targets and the selective manipulation of these became most important for all urologists and also general practitioners.

Adrenergic Receptors (Adrenoceptors)

The Sympathetic Nerve System

The general principal in the human body is that the tone of the smooth musculature is under control of the autonomic (vegetative) nervous system [19, 20]. Depolarization of sympathetic nerves leads to noradrenaline release at the terminal postganglionic neuron into the synaptic gap where adrenoceptors are located at the pre- and postsynaptic membrane (Fig. 8.3). Two main types of adrenoceptors exist, the α- and β-adrenoceptors, which can further be divided into α_1- and α_2- as well as β_1-, β_2- and β_3-adrenoceptors [22]. Stimulation of the adrenoceptors at the postsynaptic membrane results in g-protein induced activation of phospholipase C and production of inositol-triphosphate and diacetylglycerol (second messengers) which release Ca^{2+} from the sarcoplasmatic reticulum, thereby initiating smooth muscle cell contraction [23]. Because different organs in the human body typically express different subtypes and concentrations of adrenoceptors, stimulation of

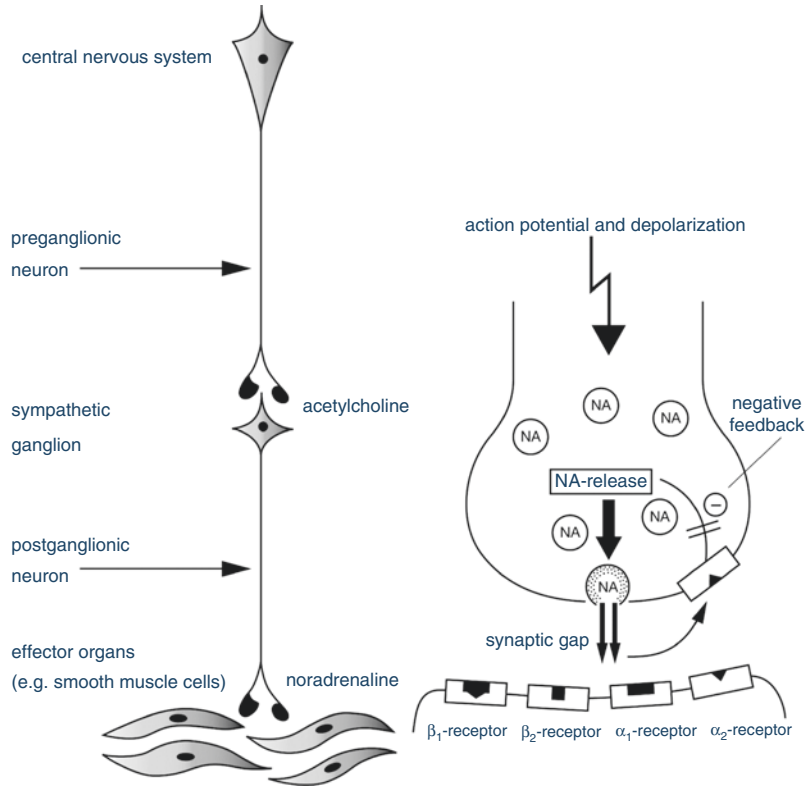

Fig. 8.3 Schematic illustration of the sympathetic nervous system (left) and enlargement of the neuromuscular connection (right). After depolarization of the postganglionic neuron, noradrenaline (NA) is released into the synaptic gap. NA molecules bind to α- and β-adrenoceptors on the postsynaptic membrane where they initiate effects (e.g. smooth muscle cell contraction). NA release is terminated via a negative feedback mechanism mediated by α_2-andrenoceptors on the presynaptic membrane (modified according to Oelke et al. [21])

these postsynaptic adrenoceptors results in various responses in different organs (e.g. prostate, internal urethral sphincter, blood vessels, heart, gastro-intestinal tract). Noradrenaline in the synaptic gap inhibits further noradrenaline release at the presynaptic membrane via α_2-adrenoceptors (negative feedback), thereby terminating the sympathetic response at the effector organ. Learmonth could already show in the year 1931 that stimulation of the pre-sacral (hypogastricus) nerve leads to a contraction of the prostatic musculature [24], and organ bath studies demonstrated a contraction of prostate strips after addition of noradrenaline [25].

α_1-Adrenergic Receptors

The human prostate predominantly contains α_1-adrenoceptors, to a lesser amount also α_2-adrenoceptors [26–29]. α_1-Adrenoceptors are located on smooth muscle cells (proportion of α_1:α_2 = 4:1), whereas α_2-adrenoceptors are mainly located in the epithelium and blood vessels [26, 28, 30]. Functional studies clarified that smooth muscle cell contraction in the prostate is mediated by α_1-adrenoceptors [31–35]. Hyperplastic prostatic tissue (BPH) has more smooth muscle cells (absolute and in percentage) and carries more α-adrenoceptors than normal prostate tissue [34, 36, 37]. However, the content of α_1-adrenoceptors in the prostate of BPH-patients with LUTS is identical to BPH-patients without LUTS; therefore α_1-adrenoceptors do not seem to be the origin of LUTS [32].

Pharmacologically interesting for the treatment of LUTS/BPH are especially the α_1-adrenoceptors of which three subtypes have been

identified, the α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors [38–40]. Historically, the α_{1C}-adrenoceptor was also described but turned out to be identical with the α_{1A}-subtype; therefore, the exact specification of this α_1-adrenoceptor subtype was abandoned [41, 42]. Approximately 70% of α_1-adrenoceptors in the prostate are α_{1A}-subtypes [43] which are predominantly located on smooth muscle cells [41]. The α_{1A}-adrenoceptors increase numerically and the proportion of α_{1A}:α_{1B}:α_{1D} adrenoceptor subtypes changes from 63:6:31 in normal prostatic tissue to 85:1:14 in BPH tissue [44]. Inhibition of the α_{1A}-adrenoceptor subtype results in smooth muscle cell relaxation. The α_{1B}-adrenoceptor is mainly located in blood vessels and inhibition of this adrenoceptor subtype is associated with vasodilation [45, 46]. The α_{1D}-adrenoceptor is predominantly expressed in the bladder, peripheral ganglia and spinal cord; inhibition of this adrenoceptor subtype results in direct or indirect (peripheral ganglia, spinal cord) relaxation of the detrusor [47–49].

α_1-Adrenergic Receptor Antagonists (α_1-Blockers)

It was shown in patients with BPH that smooth muscle cells account for ~39% of the cellular volume of the prostate and ~51% of the stroma volume [50]. The aim of the treatment of LUTS/BPH is to relax smooth muscle cells of the prostate and bladder neck by inhibition of α_{1A}-adrenoceptors which eventually decrease urethral resistance. Inhibition of the adrenergic innervation of the prostate can reduce the intra-prostatic urethral pressure by approx. 47% [51–53] and can improve the detrusor pressure at maximum urine flow ($P_{det.Qmax}$) by approximately 11.4 cm H_2O, maximum urine flow (Q_{max}) by 2.3 mL/s as well as bladder outlet obstruction index (BOOI = $P_{det.Qmax} - 2Q_{max}$) by 14.2 cm H_2O [54].

Initially, the unselective α_1-/α_2-adrenoceptor antagonists phenoxybenzamine and phentolamine were used to treat LUTS/BPH (Fig. 8.4); although significant and relevant LUTS reduction was achieved with both α-blockers in clinical trials, adverse events and especially blood pressure decrease were too pronounced for routine clinical use [55, 56]. Prazosin was the first selective α_1-adrenoceptor antagonist used and licensed for the treatment of LUTS/BPH [57]. Later, the more α_{1A}-adrenoceptor subtype specific α_1-blockers doxazosin and terazosin were introduced to treat LUTS/BPH but these drugs still showed relevant

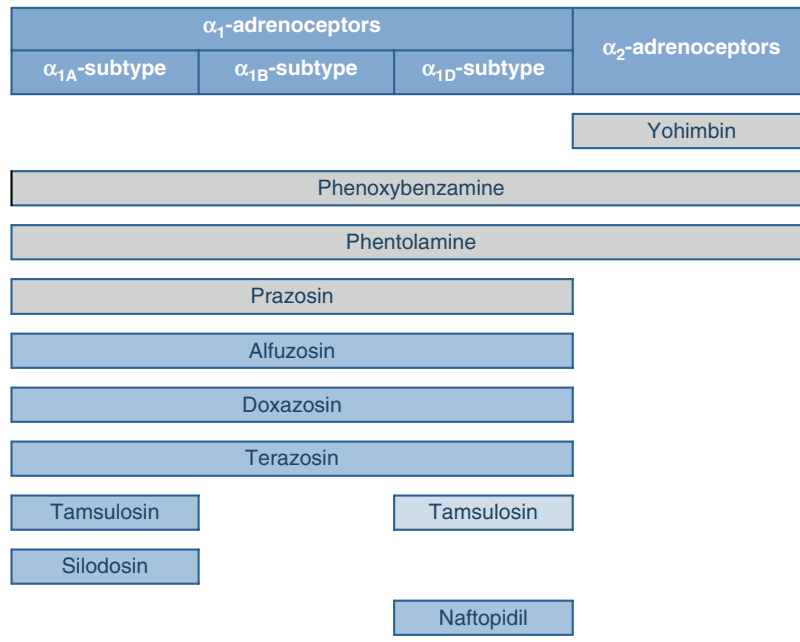

Fig. 8.4 Commercially available α-adrenoceptors antagonists and their subtype selectivity. Only the α_1-adrenoceptor antagonists in blue color are currently licensed for the treatment of "symptoms or signs of BPH" (modified according to Oelke et al. [21])

blood pressure decrease, the reason why these two α_1-blockers were also used to treat arterial hypertension alone or in combination with LUTS/BPH. The strategy to treat both diseases with one α_1-blocker was abandoned in the year 2000 because the *ALHAT* (Antihypertensive and Lipid-Lowering treatment to prevent Heart ATack) trial demonstrated that doxazosin cannot prevent cardio-vascular events (angina pectoris, myocardial infarction or heart insufficiency); therefore, α_1-blockers were considered inappropriate to treat arterial hypertension alone [58–61]. Later, the "uroselective" α_1-blockers alfuzosin and tamsulosin were developed which showed more pronounced α_{1A}-adrenoceptor inhibition and especially a lower incidence of arterial hypotension. The development of α_1-blockers has currently ended with the development of specific antagonists of the α_{1A}-adrenoceptor subtype (silodosin) and the α_{1D}-adrenoceptor subtype (naftopidil; only licensed in Asia).

The pharmacokinetic profiles of currently available α_1-blockers to treat LUTS/BPH are listed in Table 8.1. Once-daily formulations (extended release, modified release, gastrointestinal therapeutic system [GITS] or oral controlled absorption system [OCAS]) aim to slowly release the α_1-blocker into the intestinal tract which results in a more stable and consistent serum concentration, avoiding serum peaks and unwarranted side effects such as arterial hypotension [63–65]. Additionally, once-daily formulations are likely to increase the intake compliance and adherence to the drug [66].

Clinical Efficacy of α_1-Blockers

Although LUTS and urine flow improvements take a few weeks to fully develop, statistically significant and clinically relevant differences compared to placebo were already documented within a few hours or days after first drug intake [67]. α_1-Blockers show a similar efficacy, expressed as percent improvement in the International Prostate Symptom Score (IPPS) questionnaire, in patients with mild, moderate or severe LUTS [68]. RCTs demonstrated that α_1-blockers reduce LUTS (both storage and voiding symptoms) by ~30–40% and increase Q_{max} by ~20–25% after the placebo run-in period [62]. In observational studies (without a placebo run-in period), IPSS improved by ~50% and Q_{max} by ~40%. Indirect comparisons and limited head-to-head comparisons between α_1-blockers indicate that all α_1-blockers have a similar efficacy when used in appropriate doses [69, 70]. However, a recent network meta-analysis suggested that some α_1-blockers reduce LUTS to a greater extent than others [71]; mean IPSS reduction was −7.1 points for doxazosin and −6.8 points for terazosin, whereas mean IPSS reduction for silodosin, alfuzosin, tamsulosin and naftopidil was −5.8, −5.5, −5.5 and − 5.4 points, respectively. This preliminary data needs confirmation by independent analyses, especially considering the different doses and formulations of the individual α_1-blockers.

α_1-Blockers do not reduce prostate size and, additionally, prostate size does not affect α_1-blocker efficacy in studies with follow-up period

Table 8.1 Key pharmacokinetic properties and standard doses of α_1-blockers licensed in Europe for the treatment of "signs or symptoms of BPH" [62]

Drug	t_{max} (h)	$t½$ (h)	Recommended daily dose (mg)
Alfuzosin IR	1.5	4–6	3 × 2.5
Alfuzosin SR	3	8	2 × 5
Alfuzosin ER	9	11	1 × 10
Doxazosin IR	2–3	20	1 × 2–8
Doxazosin GITS	8–12	20	1 × 4–8
Silodosin	2.5	11–18	1 × 4–8
Tamsulosin MR	6	10–13	1 × 0.4
Tamsulosin OCAS	4–6	14–15	1 × 0.4
Terazosin	1–2	8–14	1 × 5–10

t_{max} time to maximum plasma concentration, $t½$ elimination half-life, *IR* immediate-release, *SR* sustained release, *GITS* gastrointestinal therapeutic system, *MR* modified release, *OCAS* oral controlled absorption system

of ≤1 year [62, 72]. Q_{max} at baseline does not have relevant influence on LUTS reduction [73]. Long-term efficacy of α_1-blockers was documented for a period of longer than 4 years [74]. Nevertheless, α_1-blockers are not able to prevent acute urinary retention (AUR) in the long run, especially in patients with a prostate volume >40 cm^3 (see Section "Androgens") [74, 75].

Men with BPH can develop AUR due to increased bladder outlet resistance (BPO) and/or insufficient detrusor function (detrusor underactivity). The incidence rate is approximately 2.2 cases/1000 patient-years in asymptomatic and 18.3–35.9 cases/1000 patient-years in symptomatic men [76]. The use of α_1-blockers in these patients allows approx. 60% of men to void spontaneously again compared to approx. 38% using placebo (successful trial without catheter, TWOC), which measures up to a 55% increase in the success rate [77].

For further reduction of LUTS, α_1-blockers can be combined with drugs of other drugs classes, e.g. with phosphodiesterase type 5 inhibitors (PDE5i; see Section "Phosphodiesterases") [78–80], 5α-reductase inhibitors (5ARIs; see Section "Androgens") [75, 81], muscarinic receptor antagonists (antimuscarinics) [82, 83] or β_3-receptor agonists [84].

Adverse Event Profile of α_1-Blockers

Although alfuzosin, doxazosin and terazosin have a similar molecular structure (quinazoline-based derivatives) and do not selectively inhibit specific α_1-adrenoceptor subtypes, the adverse event profile of alfuzosin is more similar to tamsulosin (non-arylamine sulfonamide derivative) than to doxazosin or terazosin. The mechanisms underlying such differential tolerability are not fully understood but may involve better penetration and/or tissue distribution by alfuzosin and tamsulosin [62]. Other factors, such as subtype selectivity and the pharmacokinetic profiles of certain formulations, may also contribute to the adverse event profile of individual drugs.

The most frequently reported adverse events of α_1-blockers are asthenia, dizziness and (orthostatic) hypotension which can be explained by the inhibition of α_{1B}-adrenoceptor subtypes in vessels, leading to vasodilation and blood pressure decrease [85]. At least some of the observed asthenia and dizziness can be attributed to blood pressure decrease. In particular, patients with cardiovascular co-morbidity and/or vasoactive co-medication appear to be prone to vasodilatation during α_1-blocker treatment [86]. This includes anti-hypertensive drugs, such as diuretics, Ca^{2+}-channel blockers, β-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists but also phosphodiesterase type 5 inhibitors (PDE5i) prescribed for erectile dysfunction or male LUTS. Vasodilatation is more pronounced with immediate-release doxazosin and terazosin but less common for alfuzosin or tamsulosin (odds ratio for vascular-related adverse events 3.3, 3.7, 1.7 and 1.4, respectively; the latter two not reaching statistical significance [87]). In contrast, blood pressure decrease or prevalence of orthostatic hypotension with the α_{1A}-selective blocker silodosin is comparable with placebo [85, 88] and, therefore, this drug can safely be used with anti-hypertensive co-medication [89].

The intraoperative floppy iris syndrome (IFIS) was only discovered in 2005 in the context of cataract surgery [90]. IFIS consists of a typical triad of the following intraoperative characteristics: (1) a flaccid iris stroma leading to fluttering and billowing of the iris, (2) a tendency for the floppy iris stroma to prolapse through the surgical incision and (3) a progressive pupil constriction despite standard perioperative pharmacologic measures for prevention. Most patients, however, manifest an incomplete form of this triad displaying only one or two signs [85]. The basis of IFIS is thought to be antagonism of the α_1-adrenoceptor subtype located in the iris dilator muscle. The incidence varies between 30 and 88% for tamsulosin, 15 and 70% for alfuzosin, and 2 and 45% for doxazosin users. In a meta-analysis, alfuzosin, doxazosin, tamsulosin and terazosin had an increased risk for IFIS [91]. The odds-ratio for IFIS was 393 for tamsulosin, 9.7 for alfuzosin, 6.4 for doxazosin and 5.5 for terazosin. Silodosin has yet not been associated with IFIS [85]. α_1-Blocker treatment should not be initiated prior to scheduled cataract surgery, and the ophthalmologist should

be informed about previous or current α_1-blocker use [85]. Important to mention is that the occurrence of IFIS may complicate cataract surgery and make it technically more challenging but no reports about increased health risks of these patients have been published.

A systematic review concluded that α_1-blockers do not adversely affect libido, sometimes have a small beneficial effect on erectile function (e.g. doxazosin) but can cause abnormal ejaculation [92]. Originally, abnormal ejaculation was thought to be retrograde but more recent data demonstrate that it is due to (relative) anejaculation (i.e. reduction or absence of seminal fluids during ejaculation). Abnormal ejaculation seems to be caused by α_{1A}-adrenoceptor subtype selective inhibition of smooth muscle cells in the prostate, seminal vesicles, ejaculatory ducts and spermatic cords and is more frequently observed with silodosin and tamsulosin than with other α_1-blockers. LUTS reduction was shown to be higher in men with abnormal ejaculation compared to men without [93]. The apparently greater risk for abnormal ejaculation with tamsulosin is intriguing as even the more α_{1A}-selective drug silodosin carries an even greater risk [94, 95]. However, all α_1-blockers are dosed to block α_{1A}-adrenoceptors effectively; therefore, the mechanism underlying abnormal ejaculation still remains to be elucidated.

A dose-dependent increased risk of dementia for tamsulosin was only recently described (2018) in a cohort analysis of more than 250,000 US-American patients after a follow-up of 20 months (hazard ratio 1.11–1.20; 38.8 cases/1000 patient years) [96]. In contrast, an increased risk for dementia was not seen for other α_1-blockers (alfuzosin, doxazosin or terazosin) or 5ARIs (finasteride or dutasteride). Another recently published cohort study (2019) with approx. 60,000 Korean patients with a follow-up of 52 months could not confirm the results seen in the North American study [97]. However, the daily standard dose for tamsulosin in Asian patients is only 0.2 mg, and differences in pharmacokinetics, metabolism and genetic/ethnicity may have contributed to these controversial results. Therefore, the association between α_1-blocker use and dementia still needs to be clarified in future studies.

Phosphodiesterases

The NO/NOS: Phosphodiesterase System

Nitric oxide (NO) is a universal and important non-adrenergic, non-cholinergic neurotransmitter which is involved in signal transmission in the human lower urinary tract [98]. NO is synthesized from the amino acid L-arginine by NO synthases (NOS) [99]. NO diffuses into cells and stimulates the synthesis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which are synthesized from the corresponding nucleoside triphosphates by adenylyl- or guanylyl-cyclases (Fig. 8.5). The intracellular increase of cAMP or cGMP triggers a signal transduction cascade involving activation of cyclic nucleotide-dependent protein kinases (PKA or PKG), subsequent phosphorylation of the actin-myosin system, as well as Ca^{2+} channels and ATP-driven Ca^{2+} pumps located in the outer cell membrane or the membrane of the sarcoplasmatic reticulum [98]. This cascade leads to a reduction in cytosolic Ca^{2+} and, finally, to smooth muscle relaxation [102]. NO may also be involved in the micturition cycle by inhibiting reflex pathways in the spinal cord and neurotransmission in the urethra, prostate and urinary bladder [103]. The effects of cAMP and cGMP are terminated by PDE isoenzymes, a heterogeneous group of enzymes which catalyze the hydrolysis of cAMP or cGMP into their inactive forms.

PDEs are classified according to their preferences for cAMP or/and cGMP, kinetic parameters of cyclic nucleotide hydrolysis, sensitivity to the inhibition by various compounds, allosteric regulation by other molecules, and chromatographic behavior on anion exchange columns [99]. In total, 11 families of PDE isoenzymes have been identified in humans (PDEs 1–11). Some of these isoenzyme families have more than one gene and some genes are alternatively spliced so that

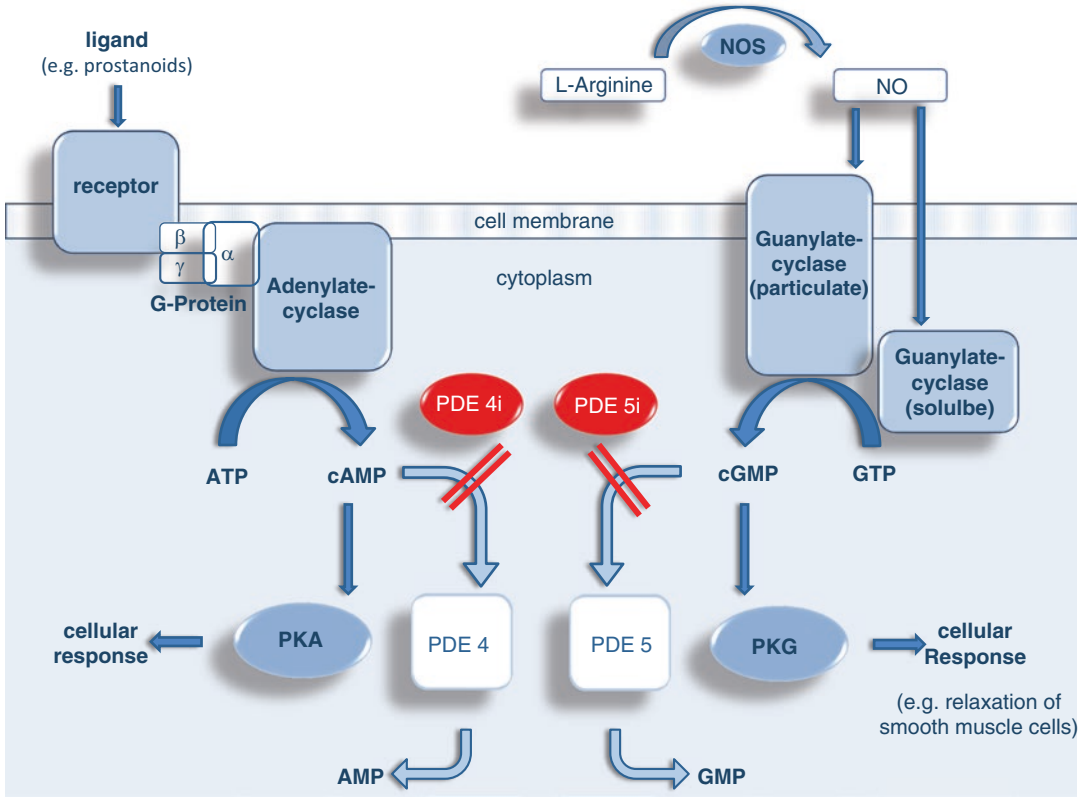

Fig. 8.5 Cellular responses (e.g. smooth muscle cell relaxation) after activation of protein kinase A (PKA) by cyclic adenosine monophosphate (cAMP-pathway, left) or protein kinase G (PKG) by cyclic guanosine monophosphate G (cGMP-pathway, right). The effect of cAMP is terminated by phosphodiesterase type 4 (PDE 4) and the effect of cGMP is terminated by phosphodiesterase type 5 (PDE 5). PDE 4 inhibitors (PDE 4i; e.g. rolipram, Ro 20-1724 or RP 73401) block the degradation and thus inactivation of cAMP. PDE 5 inhibitors (PDE 5i; e.g. avanafil, sildenafil, tadalafil, udenafil or vardenafil) block the degradation and thus inactivation of cGMP, which results in accumulation of cyclic monophosphates and prolonged cellular responses (modified according to Ghofrani et al. [100] and Lincoln et al. [101]). *AMP* adenosine monophosphate, *cAMP* cyclic adenosine monophosphate, *ATP* adenosine triphosphate, *GMP* guanosine monophosphate, *cGMP* cyclic guanosine monophosphate, *GTP* guanosine triphosphate, *NO* nitric oxide, *NOS* nitrite oxide synthases, *PDE* phosphodiesterase, *PDEi* phosphodiesterase inhibitor, *PKA* protein kinase A, *PKG* protein kinase G

more than 50 isoenzymes or variants have been identified. Some PDE genes are also variably expressed in different tissues [104]; therefore, the distribution and functional significance of PDE isoenzymes vary in different organs and, consequently, isoenzyme-selective inhibitors have the potential to exert specific effects on target tissues. In the lower urinary tract, the cAMP- and/or cGMP-specific PDE isoenzymes PDE 1, PDE 2, PDE 4, PDE 5 and PDEs 7–10 have been identified of which PDE4 (cAMP-specific PDE) and PDE5 (cGMP-specific PDE) are the predominant ones in the prostate, bladder and urethra [105]. Immunohistochemistry showed that PDEs 4 and 5 are mainly located in stromal and glandular tissues of the transition zone. A clinical study with 30 men with moderate to severe LUTS awaiting transurethral resection of the prostate (TURP) were randomly divided to receive 20 mg tadalafil or 200 mg udenafil 1 h prior to TURP or TURP without the preceding administration of a PDE5i. The concentrations of the PDE5i and cGMP were measured in the plasma and resected prostate specimen and, afterwards, the prostate tissue/plasma ratio was calculated. The authors showed that (1) the PDE5i was predominantly distributed

in the prostate (transition zone) and (2) tadalafil and udenafil significantly increased cGMP levels in both the plasma and prostate tissue.

Organ bath studies demonstrated that, after α_1-adrenergic stimulation of smooth muscle cells with noradrenaline, the tension of prostate tissue strips was dose-dependently reversed by PDE4 inhibitors (e.g. rolipram, Ro 20-1724 and RP 73401) and PDE5 inhibitors (e.g. sildenafil, tadalafil and vardenafil) and accompanied by an increase of cAMP or cGMP levels in the tissue [105–107]. These results indicate that cAMP and cGMP as well as PDEs 4 and 5 are involved in relaxation of prostatic smooth muscle cells.

The NO/NOS- and cAMP/cGMP-systems can also relax smooth muscle cells outside the lower urinary tract, for example in arteries, leading to vasodilatation and increased blood circulation. This is an important hint because it has been postulated that hyperplasia of myocytes, fibrocytes and epithelial cells—as seen in BPH tissue—may be induced by hypoxia resulting from an age-related impairment of blood flow in the small pelvis. Consequently, a key role of urogenital ageing and subsequent alterations in the blood supply of the prostate has been suggested for the development of BPH [108]. Transrectal contrast-enhanced color Doppler ultrasound studies demonstrated that perfusion of the transition zone of the prostate was significantly lower and mean flow resistance index significantly higher in men with BPH than in healthy controls [109]. Thus, it seems likely that regular administration of PDE5i may, to a certain degree, overcomes ischemia due to vascular damage and increase local blood flow by relaxation of smooth muscle cells in pelvic arteries [110].

Phosphodiesterase Type 5 Inhibitors (PDE5i)

PDE5i have a similar structure to cGMP and inhibit the breakdown of NO-derived cGMP molecules by competitively binding the catalytic site of PDE5, thereby causing accumulation of cGMP in the cell (cytoplasm) for continuous activation of the NO/cGMP system and, hence, prolonged (prostatic) muscle cell relaxation (Fig. 8.5).

Four selective oral PDE5i (avanafil, sildenafil, tadalafil and vardenafil) have been licensed in Europe for the treatment of erectile dysfunction (udenafil has only been licensed in Asia) and two PDE5i for the treatment of pulmonary arterial hypertension (sildenafil and tadalafil) [62, 111]. However, only tadalafil has yet been licensed for the treatment of LUTS/BPH, although clinical trials with sildenafil, udenafil and vardenafil in men with LUTS were also conducted and showed similar favorable effects (Table 8.2). The available PDE5i differ primarily in their pharmacokinetic profiles; therefore, clinical differences between these PDE5Is are mainly related to the time to onset and duration of action [62]. All PDE5i are rapidly resorbed from the gastrointestinal tract, have a high protein binding in plasma, are metabolized primarily in the liver and eliminated predominantly into the feces. However, the half-lives of PDE5i differ substantially, reaching from approx. 4 h with sildenafil to more than 17 h with tadalafil. Therefore, tadalafil is suitable for once-

Table 8.2 Phosphodiesterase type 5 inhibitors (PDE5i) licensed in Europe for the treatment of "erectile dysfunction" and/or "signs or symptoms of BPH"; key pharmacokinetic properties and doses used in clinical trials [62, 112]

Drug	t_{max} (h)	$t½$ (h)	Recommended daily dose (mg)
Avanafil	0.4[a] (0.3–0.5)	5–11	1 × 50–200
Sildenafil[b]	1[a] (0.5–2)	3–5	1 × 25–100
Tadalafil[b]	2 (0.5–12)	17.5	1 × 5 (2.5–20)
Udenafil[b]	1.0[a] (0.8–1.3)	9–12	1 × 100–200
Vardenafil[b]	1[a] (0.5–2)	4–5	2 × 10

t_{max} time to maximum plasma concentration, $t½$ elimination half-life

[a]Pharmacokinetics dependent on food intake (i.e. slower resorption of the drug and increase of t_{max} by approximately 1 h after a fatty meal)

[b]Tested in clinical trials for the treatment of LUTS/BPH

Please note that only tadalafil (5 mg once daily) has been licensed for the treatment for LUTS/BPH

daily use (5 mg), whereas other PDE5i must be taken two or three times daily to result in similar intracellular cGMP and PKG concentrations.

Clinical Efficacy of PDE5i

PDE5i were developed to treat pulmonary arterial hypertension and erectile dysfunction [113]. However, a *post hoc* analysis of patients with erectile dysfunction treated with sildenafil demonstrated that PDE5i was also able to significantly improve concomitant LUTS/BPH and LUTS-related QoL [114, 115]. The improvement of LUTS was independent on the improvement of erectile function. Consequently, RCTs on the efficacy of sildenafil, tadalafil, udenafil and vardenafil were conducted and investigated the key parameters LUTS (IPSS), uroflowmetry (Q_{max}), and post-void residual urine [79, 116, 117]. Significant LUTS reduction was documented for all PDE5i, and both storage and voiding LUTS decreased during treatment [62, 79, 118]. Symptom bother directly impacts QoL and improvement of storage LUTS is mainly responsible for improved bother and QoL during tadalafil treatment [119]. A Cochrane meta-analysis showed that monotherapy with PDE5i in patients with LUTS/BPH was associated with a significant improvement of IPSS (mean difference compared with placebo −1.9 points) and BPH-Impact Index (mean difference compared with placebo −0.52 points) [120]. Tadalafil was equally effective in reducing LUTS compared to the α_1-blocker tamsulosin [121] but treatment satisfaction with tadalafil was significantly greater, most probably due to improved erectile function [122].

Significant effects on LUTS were detected for tadalafil as early as 1 week of treatment [121, 123]. In total, 70% of tadalafil-treated patients had a clinically relevant LUTS reduction of ≥3 IPSS points; 60% of responders passed this threshold already after 1 week and 80% after 4 weeks of treatment [123]. Significant and continuous LUTS reduction was documented for 52 weeks in an open 12-month trial [124]. On the standardized and validated 15-item International Index of Erectile Function (IIEF) questionnaire, tadalafil treatment resulted in improvements of erectile function of 6.0 points (IIEF-questions 1–5 + 15; range 0–30), ejaculation of 0.8 points (IIEF-9; range 0–5), orgasmic function of 1.5 points (IIEF-questions 9 + 10; range 0–10), satisfaction with sexual intercourse of 2.3 points (IIEF 6 + 7 + 8; range 0–15) and overall sexual satisfaction of 2.0 points (IIEF-questions 13 + 14; range 0–10), whereas the IIEF domains remained stable or even deteriorated with tamsulosin [125]. Q_{max} was not consistently improved in the individual studies but a *post hoc* analysis of all tadalafil trials demonstrated a significant mean increase of 1.1 mL/s with tadalafil 5 mg once daily compared to 0.4 mL/s with placebo [126].

PDE5i have no effects on prostate volume and prostate volume does not affect treatment response or efficacy of PDE5i. Post-void residual urine remains unchanged during PDE5i treatment. Efficacy with tadalafil differed between patients aged <75 vs. ≥75 years, with significant efficacy only in the <75-year age group. The older age group suffered of more concomitant diseases and used more drugs which seem to reduce tadalafil efficacy [127]. Patients with a history of more than one drug for arterial hypertension have a significantly lower LUTS response compared to men without; otherwise, cardio-vascular risk factors/comorbidities do not affect the magnitude of LUTS/BPH improvement during tadalafil treatment [128]. Placebo-adjusted least squares (LS) mean improvements in total IPSS were −1.2 in men using >1 antihypertensive drugs vs. −3.3 in men using only ≤1 antihypertensive drug.

Only a few trials with durations of 6–12 weeks compared the efficacy of PDE5i or α_1-blocker monotherapies against PDE5i + α_1-blocker combination therapy. The drug combination frequently improved IPSS, Q_{max}, and post-void residual urine to a greater extent than the single drug class alone. A meta-analysis on PDE5i trials demonstrated significantly improved LUTS/BPH (IPSS) when using α_1-blocker + PDE5i combination vs. α_1-blocker or PDE5i alone but the differences between mono- and combination therapies were small [118]. Therefore, it is still debatable whether combination therapy is justified in routine patients with LUTS/BPH, especially when considering the price for both drugs.

The drug combination of tadalafil (PDE5i) + finasteride (5ARI) was significantly more efficacious in reducing LUTS/BPH (IPSS) than finasteride alone after 6 months; IIEF-EF improved only in the tadalafil arm by 4.7 points, whereas IIEF-EF remained unchanged with finasteride monotherapy [129]. Treatment satisfaction at week 26 was significantly greater with tadalafil/finasteride combination therapy compared to finasteride monotherapy for the total treatment satisfaction scale score and satisfaction with efficacy subscore [130].

Adverse Event Profile of PDE5i

All PDE5i may cause headache, flushing, dizziness, dyspepsia, nasal congestion, myalgia, hypotension, syncope, tinnitus or conjunctivitis [62]. PDE3 hydrolyzes cAMP and is mainly found in cardiomyocytes but also in the corpora cavernosa. PDE5i can cross-react with PDE3 and increase the level of cAMP in the heart, thereby increasing the heart rate with a positive inotropic effect. In this respect, PDE5i can cause myocardial infarction in patients with coronary heart disease, especially in those using nitrates or potassium channel openers. The probability of developing priapism or AUR during PDE5i therapy is very low [62]. PDE5i can also cross-react with PDE6 in the cones and rods of retina. Inhibition of PDE6 may cause visual adverse effects, such as chromatopsia or blurred vision, as reported by patients using sildenafil or udenafil [131]. A systematic review and meta-analysis demonstrated that adverse events during PDE5i treatment are generally mild [132]. However, the frequencies of these adverse events vary between different PDE5i. Tadalafil typically causes headache, back pain, dizziness and dyspepsia in 2–3% of patients [121].

PDE5i are contraindicated in patients using nitrates or the potassium channel opener nicorandil due to additional vasodilatation, which might cause arterial hypotension, myocardial ischemia in patients with coronary artery disease, or cerebrovascular strokes [62, 133]. Additionally, all PDE5i should not be used in patients who use immediate-release doxazosin or terazosin, have unstable angina pectoris, recently had a myocardial infarction (previous 3 months) or stroke (previous 6 months), have myocardial insufficiency NYHA >2, arterial hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if non-arteritic anterior ischemic optic neuropathy (NAION) with sudden loss of vision is known or has appeared during previous use of PDE5i. Sildenafil and vardenafil are also contraindicated in patients with retinitis pigmentosa. Caution is advised when PDE5i are used together with other drugs which are metabolized by the same hepatic elimination pathway (CYP3A4), because these drugs can cause an increased serum concentration of PDE5i.

Androgens

The development of the prostate in the embryogenic period, prostate growth during puberty and prostate enlargement in elderly men with BPH are only possible with testicular androgens. The prostate is only rudimentary developed and remains free of BPH tissue in men with congenital hypopituitarism, congenital androgen-receptor defect, autosomal-recessive 5α-reductase deficiency (male pseudo-hermaphroditism) or castration before puberty. The prostate and seminal vesicales in these men are small or even missing, and prostate biopsies only show fibromuscular stroma without epithelial cells or glands. PSA is usually not detectable in the prostate, ejaculate or serum in the genetic diseases or are low in patients with early castration.

Testosterone is the predominant androgen in men. The active metabolite of testosterone is dihydrotestosterone (DHT) which results from 5α-reduction in the cytoplasm of the prostatic epithelial cells (Fig. 8.6). DHT has a stronger affinity to the nuclear bound androgen receptor and a 4- to 5-times higher androgenic potency than testosterone [135]. DHT accounts for approximately 90% of prostatic androgens. 5α-reductase, a NADPH-dependent enzyme, converts testosterone to DHT and exists in two isoforms [134, 136]:

- 5α-Reductase type 1 is encoded on chromosome 5 and has only minor expression and activity in the prostate but predominant

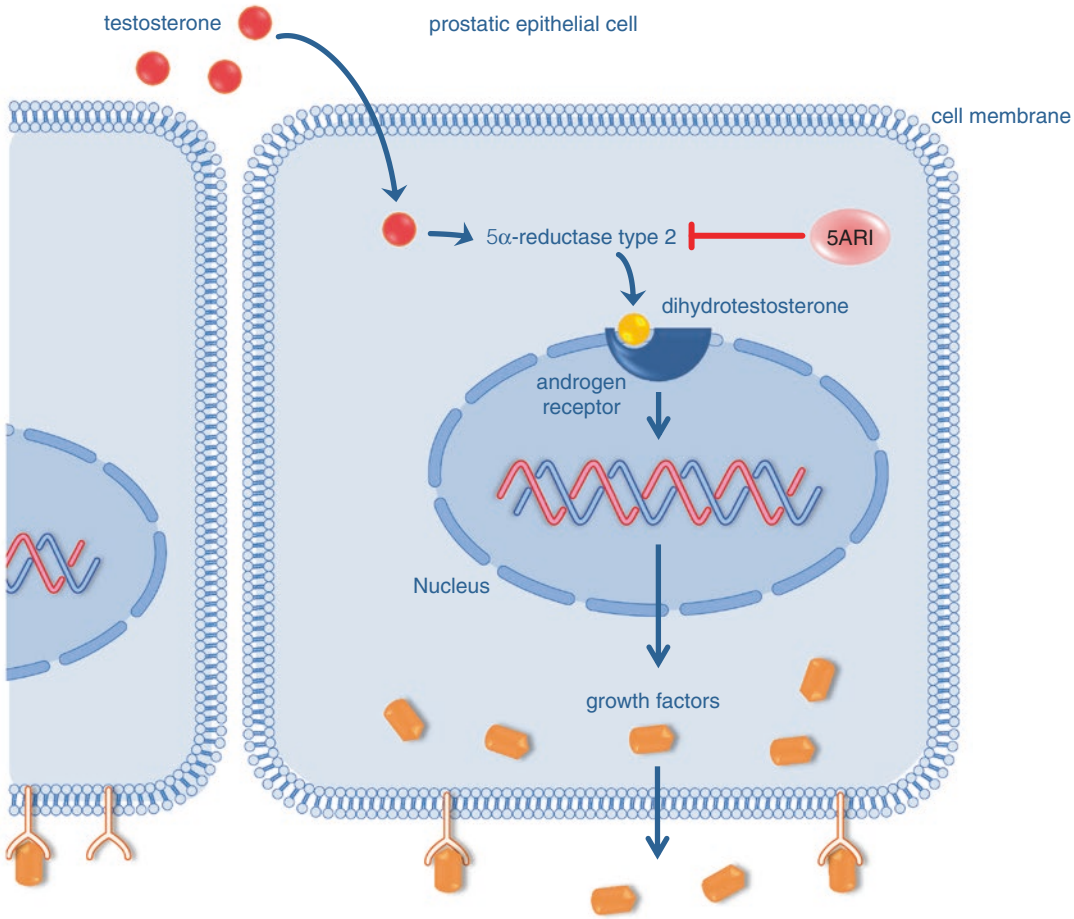

Fig. 8.6 The active metabolite of testosterone is dihydrotestosterone which results from 5α-reduction inside the prostatic epithelial cell. The dihydrotestosterone-androgen receptor complex initiates gene transcription resulting in protein and growth hormone synthesis as well as cell proliferation. 5α-Reductase type 2 inhibitors (5ARIs; dutasteride or finasteride) inhibit the conversion from testosterone to dihydrotestosterone and initiate apoptosis [134]

activity in extra-prostatic tissues, such as skin and liver.

- 5α-Reductase type 2 is encoded on chromosome 2, is predominantly expressed and active in the stromal and basal cells of the prostate, and also exists in hair follicles as well as in cells of the seminal vesicles. The conversion of testosterone to DHT by 5α-reductase type 2 is 25-times faster than by 5α-reductase type 1.

After synthesis of DHT, the active androgen binds to the androgen receptor on the nuclear membrane and migrates into the cell nucleus (together with a transportation complex), where the DHT-androgen receptor complex stimulates gene transcription which results in protein and growth hormone synthesis (e.g. PSA, epidermal growth factor [EGF] and vascular endothelial growth factor [VEGF]) as well as cell proliferation. Testosterone and DHT are important in the physiology of the muscle, fatty tissue, liver, bone, central nervous system as well as reproductive and sexual functions.

Hormonal and especially anti-androgenic therapies have a long tradition in the treatment

of prostatic diseases. It is known since the end of the nineteenth century that androgen withdrawal by castration leads to shrinkage of the prostate [137, 138]. Molecular studies in men with androgen deprivation therapy (ADT) demonstrated that epithelial cells of the prostate induce a genetic mechanism which is characterized by enzymatic splitting of the DNA and irreversible cell death (apoptosis), depletion of epithelial cells and decrease in prostate volume. ADT is possible with bilateral surgical orchiectomy, synthetic anti-androgens, LHRH-agonists or -antagonists, estrogens or anti-estrogens. ADT is used for the treatment of advanced prostate cancer. Different drugs interfere in the gonadotropin-testosterone axis and initiate apoptosis of hormone-sensitive prostate cancer cells (Fig. 8.7). ADT results in shrinkage of the prostate but, however, also decrease of the serum testosterone concentration. Therefore, severe and bothersome adverse events resulting from androgen deficiency appear frequently and are only acceptable during the treatment of advanced prostate cancer. Libido loss typically emerges during treatment with LHRH-agonists or -antagonists, steroidal anti-androgens and estrogens; hot flushes and painful nipples typically appear during treatment with anti-androgens and estrogens; cardiovascular events (e.g. myocardial infarction) are frequently seen during treatment with estrogens

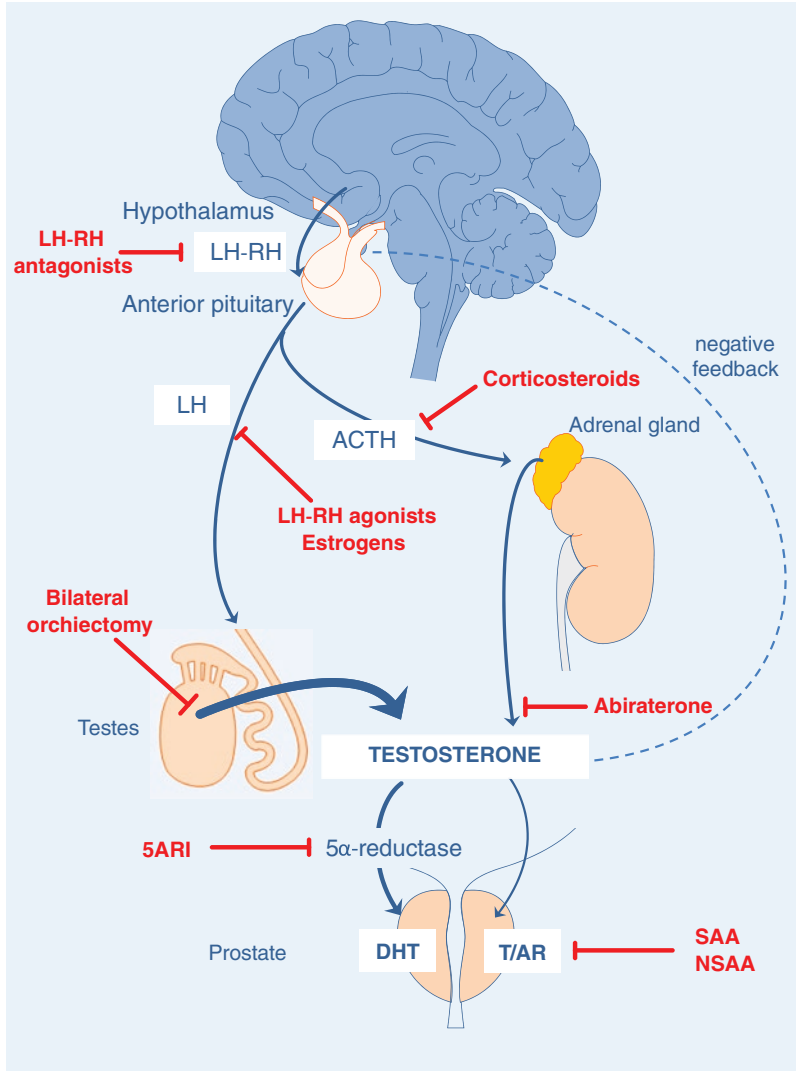

Fig. 8.7 Androgen deprivation therapy for the treatment of advanced prostate cancer. Different drugs or drug classes interfere with the gonadotropin-androgen axis to inhibit growth of androgen-sensitive prostate cancer cells (modified according to Raja et al. [139]). *5ARI* 5α-reductase inhibitor, *ACTH* adrenocorticotropic hormone, *DHT* dihydrotestosterone, *T/AR* testosterone/androgen receptor, *LH* luteinizing hormone, *LH-RH* luteinizing hormone-releasing hormone, *NSAA* non-steroidal antiandrogen (e.g. flutamide, nilutamide, bicalutamide, apalutamide, enzalutamide), *SAA* steroidal antiandrogen (e.g. cyproterone acetate)

or LHRH-agonists, and gastro-intestinal complaints or liver toxicity are observed during treatment with non-steroidal anti-androgens.

Only local blockade of the DHT synthesis inside prostatic cells by selective 5α-reductase inhibitors (5ARIs) is a viable treatment option of LUTS/BPH. Thus, selective inhibition of intracellular 5α-reductase can prevent systemic (anti-) hormonal adverse events. Although testosterone concentrations in the serum and prostate even increase up to 10% during 5ARI therapy [140], the elevated concentrations are functionally irrelevant because testosterone is 5-times less potent in the prostate than DHT. Serum gonadotropin concentrations during 5ARI treatment remain unchanged which validates the hypothesis that the negative feedback on the secretion of LHRH in the hypothalamus and LH in the hypophysis is regulated by testosterone and not DHT [141]. Normal serum testosterone concentration is responsible for the preservation of libido and sexual function of patients treated with 5ARIs [142].

5α-Reductase Inhibitors (5ARIs)

Two 5ARIs are commercially available for the treatment of LUTS/BPH: dutasteride and finasteride. The pharmacokinetic profiles of the 5ARIs are listed in Table 8.3. Additionally, finasteride in a lower dose (1 mg once daily) has been licensed for the treatment of hair loss (androgenetic alopecia); dutasteride has only been licensed for this indication in Japan and South Korea but not in North America or Europe, as of 2018. Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits 5α-reductase types 1 and 2 with similar potency (dual 5α-reductase inhibitor). Continuous long-term treatment with 5ARIs reduces serum DHT concentration by approximately 70% with finasteride and 95% with dutasteride [143]. However, intra-prostatic DHT concentrations are reduced to a similar level (85–90%) by both 5ARIs. Therefore, the clinical role of dual 5α-reductase inhibition remains unclear. Both 5α-reductase inhibitors are metabolized in the liver and excreted into the feces. The elimination half-time is longer for dutasteride (3–5 weeks) than finasteride (6–8 h); consequently, serum DHT concentration is still reduced after >16 weeks after cessation of dutasteride treatment, whereas serum DHT concentration returned to normal within 4 weeks after finasteride use [144].

Clinical Efficacy of 5ARIs

5ARIs primarily reduce prostate volume by apoptosis of prostatic epithelial cells. Significant differences of prostate volumes in patients treated with 5ARIs compared to placebo were already seen as early as 1 month of treatment with dutasteride or finasteride. The transition, central and peripheral zones shrink equally [145]. Prostate volume reduction (cm^3) is more pronounced in patients with greater volumes at baseline but volume reduction as percentage seems to be identical in patients with small, medium and large prostates [62]. Prostate volume continuously decreases within the first year of treatment with 5ARIs but, thereafter, remains more or less stable. After continuous 5ARI treatment >1 year, the prostate has lost ~18–28% of its original volume. Prostate volume reduction with 5ARIs is similar to the reduction seen with ADT (castration level) [146].

Clinically relevant effects secondary to prostate volume reduction and relative to placebo are only seen after minimum treatment duration of at least 6–12 months. After treatment for 2–4 years, 5ARIs reduce LUTS (IPSS) by approximately 15–30% and increase Q_{max} of free uroflowmetry by approximately 1.5–2.0 mL/s in patients with LUTS/BPE [62]. LUTS reduction by finasteride depends on initial prostate volume and may not be more efficacious than placebo in patients with

Table 8.3 5α-Reductase inhibitors licensed in Europe for treating 'benign prostatic enlargement (BPE) due to benign prostatic hyperplasia (BPH)'; key pharmacokinetic properties and standard doses [62]

Drug	t_{max} (h)	$t½$ (h)	Recommended daily dose (mg)
Dutasteride	1–3	3–5 weeks	1 × 0.5
Finasteride	2	6–8 h	1 × 5

t_{max} time to maximum plasma concentration, $t½$ elimination half-life

prostates <40 cm^3 [147]. Placebo effects appeared more frequently and were more pronounced in patients with prostate volumes <40 cm^3 [148]. Similar meta-analyses have not been conducted with dutasteride but a significant IPSS reduction and Q_{max} increase were also documented with prostate volumes between 30 and 40 cm^3 [149, 150]. Indirect comparison between individual studies and one direct comparative trial indicate that dutasteride and finasteride are equally effective in the treatment of LUTS/BPH [150–153].

Comparative studies with α_1-blockers demonstrated that 5ARIs reduce symptoms more slowly and, for finasteride, less effectively [81, 154–156]. A long-term trial with dutasteride in symptomatic men with prostate volumes >30 cm^3 (*CombAT trial*, mean prostate volume 55 cm^3) showed that 5ARIs reduced LUTS at least as much or even more effectively than the α_1-blocker tamsulosin [75, 157]. The greater the prostate volume (or the proxy parameter serum PSA-concentration) at baseline, the faster and more pronounced the symptomatic benefit of 5ARIs. IPSS reduction was significantly greater in men with a baseline prostate volume of ≥58 cm^3 (PSA ≥4.4 ng/mL) at treatment month 15 or later compared to lower prostate volumes or PSA concentrations. Patient age (<65 years vs. ≥65 years) had no influence on the efficacy or tolerability of 5ARIs [158], but a prostate median lobe protruding into the bladder had a significant impact on efficacy [159]. In the latter study, patients with a comfortably full bladder were investigated by transabdominal ultrasound and the distance between bladder base and tip of the prostate median lobe (i.e. intravesical prostatic protrusion, IPP) was measured. 82 men had IPP <10 mm (IPP grades 1 and 2) and 29 men IPP ≥10 mm (IPP grade 3) [160]. After treatment for 26 months with dutasteride, significant improvements concerning LUTS (IPSS), Q_{max}, post-void residual and serum PSA concentration were only seen in the group with IPP grades 1–2. Patients with IPP grade 3 even significantly deteriorated (IPSS and Q_{max}). It was concluded that patients with a prominent prostate median lobe are poor candidates for 5ARI therapy.

AUR occurs in 18.3–35.9 symptomatic men/1000 patient-years [76]. Risk factors for AUR (*MTOPS study* data) are age (>62 years), PSA (>1.6 ng/mL), prostate volume (>31 cm^3), Q_{max} (<10.6 mL/s), IPSS (>17 points) and post-void residual urine (>39 mL) [81]. Identical risk factors but slightly different threshold values for AUR were determined in the US-American *Olmsted County Study* and the German *Herne-LUTS Study* [161, 162]. Lately, the protrusion of the prostate median lobe into the bladder has been identified as another risk factor for AUR; patients with IPP ≥10 mm had a cumulative incidence rate for AUR or need for surgery during 3-year follow-up of 71.5% compared to 9.9% in patients with IPP <10 mm [159]. 5ARIs but not α_1-blockers are able to reduce the long-term (>1 year) risk of AUR or need for surgery [74, 81, 163, 164]. Prevention of disease progression by 5ARIs is already detectable after 4 months and also in men with prostate volumes considerably smaller than 40 cm^3 [75, 157]. The precise mechanism of action of 5ARIs in reducing disease progression is still unknown but it is most likely attributable to reduction of bladder outlet resistance due to shrinkage of the prostate and widening the prostatic urethra [62]. Accordingly, open-label computer-urodynamic trials demonstrated relevant reductions of voiding parameters in patients with long-term finasteride treatment (≥3 years) [165, 166]. The relative risk reduction with 5ARIs compared to placebo is approximately 50–67% for AUR and 30–64% for prostate surgery [74, 167, 168]. Therefore, 5ARIs should be used if prevention of disease progression is intended.

Combination therapy of α_1-blockers together with 5ARI aims to couple the beneficial effects of both drug classes, i.e. fast symptom reduction within days or weeks with the α_1-blocker and prevention of disease progression with the 5ARI. Initial studies with follow-up periods between 6 and 12 months consistently demonstrated that the α_1-blocker was superior to finasteride in symptom reduction, whereas the combination treatment was not superior to the α_1-blocker alone. In studies with a placebo arm, the α_1-blocker was consistently more effective than placebo, whereas finasteride was not [154–156]. However, long-term combination

therapy, as shown for finasteride + doxazosin in the 4-year *MTOPS trial* and dutasteride + tamsulosin in the 4 year *CombAT trial*, is superior to either monotherapy with regards to reduction of LUTS/BPH (IPSS), increase of Q_{max} and reduction of the risk of disease progression [75, 81, 157]. *CombAT* showed that combination treatment was superior to either monotherapy with regards to improvement of LUTS/BPH and Q_{max} starting from month 9 and superior to the α_1-blocker with regards to the reduction of the risk of AUR as well as need for surgery after month 8 [75]. 5ARIs alone reduced prostate volume as effectively as combination treatment (−20 to −27%). Combination therapy was superior to monotherapy in both the *MTOPS* and *CombAT trials* in preventing overall clinical progression, as defined by IPSS increase ≥4 points, AUR, urinary tract infection, incontinence, or an increase in serum creatinine >50% compared to baseline values. For combination therapy in the *MTOPS* vs. *CombAT trials*, the following relative risk reductions were observed [62]:

- Overall risk of disease progression: −66% vs. −44%
- Symptomatic progression: −64% vs. −41%
- AUR: −81% vs. −68%
- urinary incontinence: −65% vs. −26%
- BPH-related surgery: −67% vs. −71%

Nevertheless, monotherapy with 5ARIs reduced the risk of AUR and prostate-related surgery as effectively as combination therapy (differences not significant), although the prevention was more pronounced with combination therapy. These two long-term trials indicated that α_1-blocker +5ARI combination treatment should be initiated in patients with moderate-to-severe LUTS, baseline characteristics of disease progression and when long-term treatment (>12 months) is intended [62].

Short-term use of 5ARIs (4 weeks) before scheduled prostate operations (e.g. TURP) can reduce microvessel density of prostatic tissue and, therefore, can decrease total blood loss, blood loss per gram resected prostate tissue, blood transfusions and concentration of vascular endothelial growth factor (VEGF, see above). A meta-analysis of 17 RCTs with a total of 1489 patients confirmed these beneficial effects for finasteride [169]. However, short-term use of finasteride was not able to not reduce the operation time, prostate volume or resected gland weight. A single center study recently confirmed these results for dutasteride [170].

5ARIs reduce serum PSA concentration by approximately 50% after 6–12 months of treatment [151]. Nevertheless, serum PSA-concentration can still be used for prostate cancer screening if the measurement results are multiplied by 2 [171]. The calculated values of patients with 5ARIs have a similar sensitivity (66%) and specificity (82%) during long-term treatment compared to patients without 5ARIs treatment [172]. However, the speed of serum PSA reduction varies between individual patients and, therefore, the false-positive rate of increased PSA concentration (>4 ng/mL) is slightly higher during the first year of treatment (35%) compared to the time afterwards (25%).

Adverse Event Profile of 5ARIs

The most relevant adverse events of 5ARIs are related to sexual function and include reduced libido, erectile dysfunction and, less frequently, ejaculation disorders, such as retrograde ejaculation, ejaculation failure, or decreased semen volume [75, 81, 151]. The incidence of sexual dysfunction and other adverse events was low in the individual trials and even decreased with trial duration. At least four meta-analyses have been published to evaluate sexual dysfunction associated with 5ARI treatment for LUTS/BPH or androgenetic alopecia [173–176]. The relative risks for sexual dysfunction in general and erectile dysfunction or decreased libido in particular were significantly increased for 5ARI users. The risk was higher in men with LUTS/BPH than with alopecia, most probably due to the lower 5ARI doses used in alopecia patients [176]. Ejaculation disorders were significantly more common with 5ARIs than with placebo (odds ratio 2.73), and both dutasteride (odds ratio 2.81) and finasteride (odds ratio 2.70) increased this risk [175]. Combination treatment of 5ARI + α_1-blocker

significantly increased the risk of ejaculation disorders compared to α_1-blocker alone (odds ratio 3.75) or 5ARI alone (odds ratio 2.76). Meta-analyses calculated a significantly increased risk for hypoactive sexual desire (odds ratio 1.54) and erectile dysfunction (odds ratio 1.47) in patients using 5ARIs [173]. Some patients even reported persisting erectile dysfunction and diminished libido for more than 10 years after cessation of finasteride treatment (post-finasteride syndrome). A causal relationship between 5ARI treatment and prolonged sexual dysfunction is possible but not well understood. EMA and FDA warnings have been published on their homepages accordingly.

Other adverse events are gynecomastia (breast enlargement with breast or nipple tenderness in approximately 1–2% of patients), depression (with suicidal thoughts) and anxiety disorders. The psychiatric adverse events are a matter of EMA and FDA warnings and currently under closer investigation.

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Urologic Endocrinology

9

V. Mirone and R. La Rocca

Definition of Hypogonadism in Elderly

Male hypogonadism is the failure of the testis to produce normal amounts of T, with the presence of symptoms and signs of androgen deficiency, and a normal number of spermatozoa resulting from a disruption of one or more levels of the HPG axis. Maintaining normal T levels is important in sustaining male secondary sexual characteristics, bone mass, muscle mass and strength, erythropoiesis, sexual and cognitive function, and well-being. The significant decrease in androgen action is associated with a syndrome consisting of osteoporosis, weakness, redistribution of body fat, hypoproliferative anemia, decreased libido and sexual function, malaise, and cognitive abnormalities.

Patients with primary hypogonadism often have a decrease in T levels, sperm count, or both, along with an increase in the concentration of pituitary gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Hypogonadotropic hypogonadism is characterized by a reduction of T production, sperm, or both, in the presence of normal or low concentrations of gonadotropins. Combined primary and secondary testicular failure may occur in several conditions, such as hemochromatosis, sickle cell disease, alcoholism, glucocorticoid treatment, and also in older men.

Several longitudinal studies have shown that aging is accompanied by a decrease in T levels. The Baltimore Longitudinal Study showed that the average annual decrease in total T was 3.2 ng/dL in men older than 53 years, representing approximately 1% per year for a normal lower limit of 325 ng/dL. The rate of fall in serum T with age varies among individuals and is affected by chronic diseases and medications. Aging is also accompanied by an increase in the concentration of sex hormone binding globulin (SHBG), whereby the concentration of free T (FT) is further reduced. Age-related androgen deficiency may be exacerbated in the presence of abdominal obesity that results in elevated estrogen levels and SHBG.

In some older men, this fall in T can lead to clinical signs and symptoms such as decreased libido, impotence, decreased growth of body hair, reduced muscle mass, fatigue, and decreased bone mass. This situation has been described as androgen deficiency in the elderly male, andropause, or LOH. The International Society of Andrology and the International Society for the Study of the Aging Male define the LOH as a clinical and biochemical syndrome associated with advanced age and characterized by typical symptoms and a deficiency in serum T levels. It may result in significant detriment in the

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quality of life and adversely affect the function of multiple organ systems. The symptoms most associated with hypogonadism are loss of libido, erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density (BMD) and osteoporosis, decreased vitality, and depressed mood. None of these symptoms are specific of the low androgen state.

Epidemiology

One of the challenges of diagnosing and treating AOH is that its true prevalence is unclear. Epidemiological studies vary in how androgen deficiency (AD) was defined and in whether signs and symptoms were considered. In addition, even when men are categorized as having primary vs. secondary hypogonadism, the designation of secondary hypogonadism does not establish the extent to which the low T level is truly the consequence of inadequate gonadotropinsdsome of these men may well have a primary testicular failure component.

The breakdown of the primary vs. secondary distinction highlights the need for a more accurate definition of these patients (e.g., AOH).

These studies provide useful information, however, given that AOH is conceptualized as a subgroup of men with signs and symptoms who have an inadequate pituitary response to low T levels.

In the EMAS, the prevalence of hypogonadism was 13.8%; of these men, 85.5% were classified as having secondary hypogonadism [1]. The prevalence of hypogonadism in a group of 990 men seeking care for sexual dysfunction was 36% (359); of these men, 83.8% (301 out of 359) had secondary hypogonadism [2]. Similarly, 87.1% (727/835) of men with hypogonadism were classified as having secondary hypogonadism by Maseroli et al. [3] when reporting on a large series of patients presenting at an emergency department clinic (n°3847). Another report on an overlapping cohort from the same clinic noted that approximately 87.5% (724/827) of men with hypogonadism had secondary hypogonadism [4]. Importantly, among men with secondary hypogonadism, only 11% had a specific medical condition (e.g., genetics, surgery, radiotherapy, and trauma) that could account for the hypogonadism; the etiology in the remaining 89% was unknown [5].

Association with Common Comorbidities

Adult-onset hypogonadism more often occurs in men who have chronic disease states that are more common as men age, making it difficult to separate the influence of comorbidities from the influence of aging. High body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared), central adiposity, and the MetS are associated with low serum total T and to a esser extent low free T levels [6]. Low serum total T level predicts the development of central obesity and accumulation of intraabdominal fat [7]. Low total and free T levels are associated with an increased risk of developing MetS, independent of age and obesity. Lowering serum T levels in men with prostate cancer by treatment with GnRH analogs increased body fat mass [8]. These data are derived from observational studies and from meta-analyses of these studies; definitive answers regarding the causal relationship between T levels and obesity and the MetS require properly designed and adequately powered longitudinal studies. Ding et al. reported a meta-analysis of the relationship between diabetes, T, SHBG, and estradiol in cross-sectional and prospective studies [9]. Cross-sectional studies revealed that T levels were significantly lower among men with DM2. Prospective studies indicated that men with higher T levels had a 42% lower risk of DM2. Men with higher SHBG levels had a 52% lower risk of DM2. Estradiol levels were significantly elevated among men with diabetes compared to nondiabetic men. Kupelian et al. [10] analyzed data from the Massachusetts Male Aging Study and reported that low serum SHBG, low total T, and clinical AD were significantly associated with increased risk of developing MetS over time; this relationship was particularly strong among normal-weight,

middle-aged men. Among veterans, men with low T levels had higher BMIs and were more likely to have diabetes than were men with normal T levels [11].

At a mean follow-up of 4.3 years, all-cause mortality was lower (20.1%) among men with normal T levels than among men with low T levels (34.9%).

In the EMAS, BMI was significantly associated with the risk for secondary hypogonadism [1]. In an overlapping population, Maseroli et al. [3] found that most men with secondary hypogonadism had metabolic disease, with BMI of 30 kg/m^2 or more tripling the risk of LOH (defined as low T levels þ sexual symptoms). Among normal-weight men, only 1 of 6 men was diagnosed with LOH in contrast to nearly two-thirds of men with a BMI of more than 35 kg/m^2 who had low T levels and inadequate gonadotropins. Men with other types of comorbidities also may present with AOH. The presence of one or more comorbidities was significantly associated with secondary hypogonadism in the EMAS. In the Hypogonadism in Males study, men were significantly more likely to have hypogonadism if they also had diabetes, hypertension, hyperlipidemia, asthma/chronic obstructive pulmonary disease, and/or prostate disease compared with men without these conditions [12]. The presence of low T level, therefore, may be a marker of poor health and the possible presence of comorbidities.

Diagnosis

It is critical that men presenting with possible signs and symptoms of AOH be systematically evaluated, accurately diagnosed, carefully counseled regarding the risks and benefits of treatment, and followed regularly if testosterone therapy (TT) is initiated.

Patients presenting with possible signs and symptoms of AOH should have a history and physical examination and morning total T level measured by a reliable assay. Men who are acutely or subacutely ill may have a low T level because of illness and their evaluation should be deferred. A low or borderline low total T value should be interpreted in the context of other known causes of low T level (e.g., medication effects). If a low value is found, then a second morning total T level should be measured in conjunction with LH and FSH values to assess for testicular vs. HP components of hypogonadism. The SHBG levels should be measured if there is reason to suspect an SHBG abnormality; in this case, free T or bioavailable T level should be assessed.

If the T level is low and the LH level is elevated, then the patient has primary hypogonadism. If the T (and free/bioavailable T when indicated) level is low and LH þ FSH levels are low or normal and the patient has signs and symptoms of AOH, then the patient may have AOH. If the total T level is extremely low (i.e., <150 ng/dL), then an endocrine pituitary workup including prolactin and a magnetic resonance imaging study is indicated. If no cause is identified, then a trial of TT after exclusion of contraindications and with lifestyle modifications and comorbidity management is appropriate. The panel strongly recommends that TT be combined with lifestyle modifications (e.g., dietary changes, exercise, and stress management) if the patient is overweight or obese, deconditioned, or sedentary, has other comorbidities such as hypertension or dyslipidemia, and/or reports elevated psychosocial stress levels. Patients who report signs or symptoms consistent with sleep apnea should be referred as necessary for the management of this condition. Obesity, DM2, and other comorbidities should be managed medically as necessary to optimize the patient's overall health and to maximize the potential positive impact of TT. Once a man commences a trial of TT, he should be followed regularly for TT effectiveness and for adverse events. The panel endorses the timing and content of the Endocrine Society's guidelines for monitoring of patients on TT.

Testosterone Replacement Therapy and Cardio Vascular Disease

Low Testosterone levels are associated with an increased risk of CVD. Meta-analyses suggest that T level is lower among patients with CVD

but conflict regarding whether low T level is associated with increased CVD related mortality or risks are similar for hypogonadal and eugonadal men.

Several retrospective analyses have raised concern that T treatment may increase CVD risk [13]. Because of these concerns, the Food and Drug Administration recently required manufacturers of prescription T products to change their labeling to clarify the approved uses of these medications and to add information about a possible increased risk of heart attacks and strokes in patients who take T. Definitive evidence, however, regarding the short- and long-term cardiovascular risks of T treatment is not yet available because the published prospective trials were not designed or powered to examine cardiovascular end points. Findings reviewed below from meta-analyses that pooled findings across individual studies with these weaknesses, therefore, must be interpreted with caution.

There are multiple published meta-analyses that evaluated possible CVD risks associated with T treatment. Challenges to interpreting findings across meta-analyses include that these publications varied in study inclusion criteria, outcomes evaluated, and data analytic strategies. In addition, most authors report that the methodological quality of the included trials was poor to moderate.

A meta-analysis of 75 placebo-controlled randomized trials revealed no increase in CVD risk and a protective effect of T in men with metabolic disorders [14]. A meta-analysis of 24 placebo-controlled TT trials revealed no increased risk for major adverse cardiovascular events among men treated with T compared with men treated with placebo. Another meta-analysis of 19 randomized placebocontrolled trials also reported no increased risk for any cardiovascular event among T-treated men compared with placebo-treated men [15]. Fernández-Balsells et al. [16] conducted a meta-analysis of comparative, randomized, and nonrandomized studies and reported no differences between T-treated men and none T-treated men in all-cause mortality, need for coronary bypass surgery, or myocardial infarction. Haddad et al. [17] conducted a meta-analysis of 30 randomized placebo-controlled trials of TT and reported no significantly increased risk of CVD-related adverse events. However, although odds ratios (ORs) for any cardiovascular event (1.82; 95% CI, 0.78–4.23; $P > 0.05$) and for myocardial infarction (2.24; 95% CI, 0.50–10.0; $P > 0.05$), were nonsignificant, the ORs are large enough to call attention to the possibility that there may be CVD risk associated with TT. In this meta-analysis, men randomized to TT had twice the number of CVD-related adverse events as men in the placebo arm. An additional meta-analysis has reported that TT is significantly associated with an increased risk of CVD-related adverse events (OR, 1.54; 95% CI, 1.09–2.18; $P < 0.05$) [18]. These authors also note that CVD risks appear to be higher in trials not funded by the pharmaceutical industry (OR, 2.06; 95% CI, 1.34–3.17).

The need for definitive trials that can yield unambiguous findings is underscored by several recent publications that report possible risks of TT. Specifically, Layton et al. [19] reported findings from a retrospective cohort study using administrative insurance claims data. Men who received T injections had significantly higher rates of CVD events, hospitalizations, and death than did men who used T-containing gels; event rates for men using T-containing patches were similar to rates for gels. These data are potentially important but difficult to interpret because the study did not include assessment of whether men met criteria for TT (e.g., were hypogonadal) or compare event rates to those in none T-using men. Finkle et al. [20] reported that T-treated men had a higher rate of nonfatal myocardial infarction in the 90 days after receiving a T prescription compared with the 12 months before the prescription. These data are also difficult to interpret because of the lack of a control group of untreated men with low T level and the use of a comparison group of men prescribed phosphodiesterase type 5 inhibitors. Furthermore, Vigen et al. [13] reported that T-treated men had a higher rate of CVD adverse events (myocardial infarction, stroke, or death) compared with untreated men. These findings also are difficult to interpret given the statistical limitations of the analytic procedures.

Testosterone Replacement Therapy and Severe LUTS

In aging men lower urinary tract symptoms (LUTS) and benign prostatic hypertrophy (BPH) increase and adult hypogonadism/testosterone deficiency increases as well. Hypogonadism affects approximately 20% of elderly men with LUTS [21]. So, the combination is a common clinical scenario. There is a general, not proven, believe that Testosterone Replacement Therapy (TT) may exacerbate LUTS because of the growth-promoting effect of Testosterone(T) on the prostate during and after puberty. Therefore the question arises if patients with LUTS/BPH and hypogonadism can be treated with testosterone safely.

The EAU-Guidelines on Male Hypogonadism 2016 stated that "severe LUTS due to BPH is a contraindication against TT", but no data are given [22]. The Endocrine Society Guidelines recommended in 2010 "no TT if the IPSS > 19" [23].

A recent systematic review on 14 RCT's revealed only data from patients with mild LUTS and TRT. This review showed no statistically significant difference in IPSS from baseline to follow up after 1 year [24]. In a long term prospective non-randomised study TRT could decrease the IPSS significantly with only a marginal increase in prostate volume [25]. Other authors showed similar results in mild to moderate LUTS-patients on long term TRT [26]. But there are no data on TRT in men with severe LUTS (IPSS > 19).

Therefore, from clinical epidemiological studies, TRT can be given safely to patients with mild to moderate LUTS/BPH without fear of increasing LUTS and prostate volume; for severe LUTS no data are available. Further basic scientific research is necessary and RCT's on TRT in patients with severe LUTS are needed.

Testosterone Replacement Therapy and Prostate Cancer

Historically, TT in the presence of previous or current Pca was contraindicated [27]. However the relationship between PCa and TT is not clear. Recent literature does not link high intrinsic testosterone levels with Pca [28] and low testosterone is associated with higher Gleason score cancers and poor prognosis [29]. Recent data from observational or controlled studies among hypogonadalmen without PCa and treated with TT found no evidence of higher risk of PCa development. The same lack of higher PCa risk is found in studies among men receiving TT after curative treatment for low-risk Pca [30]. The major criticism is the still short follow-up for these trials, which limits the possibility of detecting new-onset or recurrent PCa at a later stage. No trials have evaluated patients treated for high-risk PCa. Reports on TT in men on active surveillance are too scarce to draw meaningful conclusions.

Testosterone Replacement Therapy and Male Fertility

A key pathophysiological feature of hypogonadism is the testicular failure to T, either for a central disorder (hypothalamus or pituitary) or a primary deficiency. The phenotypes of these two clinical entities are very similar; the main difference is that in primary hypogonadism spermatogenesis tends to be impaired to a greater degree than Leydig cell function, whereas both functions are impaired to the same degree in men with secondary hypogonadism [31]. In both conditions, TT can lead to impaired spermatogenesis. Indeed, exogenous T reduces endogenous testosterone production by negative feedback on the hypothalamic-pituitary-gonadal axis and thus can lead to hypospermatogenesis with a severe reduction in sperm production up to azoospermia [32]. Therefore, both EAU guidelines on male infertility and on male hypogonadism highlight that generally TT should not be given to men who are considering fathering in the future or in case of male infertility. In this context, a Cochrane database review detailed that there is not enough evidence to evaluate the use of exogenous T for male subfertility [33]. Conversely, a number of studies discussed the recovery of spermatogenesis after use of exogenous T; overall, success rates of recovering spermatogenesis after exogenous T

use are quite good. Of clinical importance, Liu et al. [34] reported that after TT suspension there were higher rates of sperm recovery with older age, Asian origin, shorter treatment duration, shorter-acting T preparations, higher sperm concentrations at baseline, faster suppression of spermatogenesis, and lower blood concentrations of LH at baseline. However, data outlines that not all men may recover spermatogenesis after TT, even long time after exogenous T discontinuation [35].

European Association of Urology Position Statement on the Role of the Urologist in the Management of Male Hypogonadism and Testosterone Therapy

With the increasing interest in men's health, the EAU has formulated the following statements:

- Testosterone is a crucial sex hormone linked to the physiological development of the male gender across all stages of growth. It leads the integrity and maintains functioning of several systems and organs (including the male sexual and reproductive system, erythropoiesis, and bone, lipid, and glucose metabolism).
- Obesity and poor general health are the main causes of late-onset male hypogonadism. Losing weight and improving lifestyle are important advice points for men with hypogonadism, since these will result in normalization of testosterone and reduce associated health risks.
- Testosterone deficiency is linked to a number of signs and symptoms potentially affecting every man in his complexity and masculinity, and is therefore of close urological interest. For this reason, the urologist should attach importance to the need for knowledge, vocational education, and training in this specific area.
- TT should be given only to symptomatic men in whom the deficiency has been confirmed by laboratory tests. Testosterone levels should be monitored regularly during treatment, along with hemoglobin, hematocrit, PSA and liver function.
- Testosterone has beneficial effects on sexual function; TT may increase the effect of PDE5 inhibitor mono-therapy in men with LOH.
- TT can be given to patients with mild to moderate LUTS. Further research in men with severe LUTS is needed. Caution should be exercised for men with significant prostatic enlargement and significant residual urine in the bladder.
- Men wishing to preserve their fertility should be informed that TT may cause impairment of fertility, ranging from oligozoospermia to even azoospermia. Therefore, TT should not be used by hypogonadal (infertile) men who have an active wish to conceive children or undergo infertility treatment.
- Current evidence does not support an association between TT and higher risk of developing PCa. However, sufficiently powered trials with long-term follow-up are needed to reach definite conclusions. PSA testing and digital rectal examination should be offered to men older than 45 year before commencing TTH, along with a discussion of the potential benefits and harms according to the EAU guidelines on PCa. TTH can be given to hypogonadal patients after curative treatment for low-risk PCa under close observation and after a prudent interval. Active PCa is still considered a contraindication to TTH.
- Mammary carcinoma is an absolute contraindication to TTH.
- Careful monitoring with clinical assessment is warranted during TTH in men with pre-existing CVD. TTH is contraindicated in men with severe chronic cardiac failure (New York Heart Association grade IV).
- In men with elevated hematocrit (>0.54%) TTH is contraindicated; whenever possible the underlying condition should be corrected before TTH.

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Pharmacology of Male Sexual Function

10

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The terms male sexual dysfunction encompass a variety of pathological conditions determining an impaired sexual health and causing the inability to have satisfactory sexual relationships.

Overall, it is possible to distinguish various clinical manifestations, including erection problems and a number of disorders of ejaculation.

Erectile dysfunction refers to a condition characterized by the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance [1].

Premature ejaculation refers to persistent or recurrent occurrence of ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The International Society for Sexual Medicine (ISSM) defines premature ejaculation as an ejaculation that always or nearly always occurs before or within about 1 min of vaginal penetration from the first sexual experience (lifelong premature ejaculation), or a clinically significant reduction in latency time, often to about 3 min or less (acquired premature ejaculation) [2].

Retarded ejaculation is a delay in obtaining ejaculation during sexual activity [3].

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Erectile Dysfunction

Epidemiology

Erectile dysfunction (ED) is a widespread condition among the male population. Historically, the Massachusetts Male Aging Study, a community-based survey of men between 40 and 70 years of age, outlined that 52% of respondents reported some degree of ED: 17% mild, 25% moderate, and 10% complete [4]. Erectile dysfunction has been widely associated with age [5–7]. Population-based studies showed that the prevalence of ED linearly increases with age, reporting rates of 22–30% at 50 years up to 40–80% among men older than 70 years of age [6]. Likewise, a growing amount of data showed that an impairment of erectile function is not uncommon even at younger ages, with worrisome prevalence rates of ED ranging from 2% to nearly 40% in men younger than 40 years old [6, 8]. In this context, recent real-life findings suggested an increasing incidence of ED among young individuals, with a significant proportion of men well below

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40 years of age seeking medical help for bothersome ED over the last decade [9].

Furthermore, recent evidences have reported a decrease in the age at first presentation for ED over the last decade [9], with almost 50% of young men complaining of severe ED, underlining once again the importance of recognizing and treating this clinical condition.

Physiology of Erection

Three main mechanisms determine penile erection: increase of blood flow to the penis, relaxation of cavernous smooth muscle, and restriction of venous outflow from the corpora cavernosa [10]. The vascular events behind penile erection rely on parasympathetic neural input derived from cholinergic preganglionic neurons residing within the sacral (S2–S4) spinal cord. These neurons release neurotransmitters such as nitric oxide (NO), acetylcholine (ACh), and vasoactive intestinal polypeptide (VIP) which can act relaxing the cavernous smooth muscle.

NO is the most important neurotransmitters in this process; indeed, NO activates soluble guanylate cyclase within the cavernous smooth muscle cell, leading to a rise in cyclic guaninosine monophosphate (cGMP). The rise in cGMP produces a fall in cytosolic Ca^{2+} and relaxation of cavernous smooth muscle. In the penis, the effects of cGMP are reduced by phosphodiesterase type 5 (PDE-5) enzyme. For this reason, PDE-5 inhibitors (PDE-5Is) are used in the pharmacological ED therapy. ACh and VIP represent two other fundamental neurotransmitters throughout the erection process; both those molecules are released by efferent fibers within the cavernous nerves. ACh acts on the muscarinic receptors on the endothelium determining the production on NO, which is synthesized by endothelial NOS (eNOS) [11]. VIP acts through adenylate cyclase to trigger a rise in cyclic adenosine monophosphate (cAMP) [12, 13] determining a fall in the cavernous smooth muscle cytosolic Ca^{2+} and, eventually, relaxation of the cavernous smooth muscle itself.

Penile erection also occurs through inhibition of contractile mechanisms [14]. The contraction mechanism of smooth muscle fibers is mediated by the activation of α_{1A}-, α_{1B}-, and α_{2A}-adrenergic receptors which determines the activation of G-protein-coupled receptors, such as membrane-associated phospholipase C with subsequent formation of diacylglycerate (DAG) and inositol triphosphate (IP3). IP3 triggers release of Ca^{2+} from sarcoplasmic reticulum, thereby raising cytosolic Ca^{2+}. The binding of Ca^{2+} to calmodulin mediates smooth muscle contraction through activation of myosin light chain kinase (MLCK). In the penis this ultimately translates into detumescence/flaccidity.

In summary, three general schemes underlie pharmacological strategies to ED: agents that (1) raise cGMP; (2) raise cAMP; and, (3) prevent IP3 formation. These three mechanisms form the basis of the available pharmacological therapeutic strategies [15].

Nonsurgical Treatment of Erectile Dysfunction

According to most of the scientific societies dealing with ED, thus including the European Association of Urology (EAU) guidelines on the treatment of male sexual dysfunction, oral PDE-5 inhibitors represents the first-line treatment for ED [16]. Other approaches are: lifestyle modification, rigorous control of comorbid conditions, hormonal treatments (whenever needed), vacuum devices, and psychotherapy. Recently, low-intensity shock wave treatment (LI-SWT) has been also added among the first level options for ED (EAU 2018, weak recommendation), although it is still considered a research treatment modality. Likewise, because of its non invasiveness combined with the reported effectiveness, the intraurethral injection of alprostadil (Vitaros©) has been also considered as a potential first level approach [16].

Lifestyle Changes

Besides tons of piece of information dealing on the link between ED and the atherosclerotic coronary and peripheral vascular diseases, as well as the metabolic syndrome - character-

ized by obesity, abnormal lipids profile, insulin resistance, and hypertension – numerous scientific evidences have stated the strict correlation between ED and incorrect lifestyles. Indeed, ED has been linked to unhealthy diet, smoking, and excessive alcohol consumption/intake [17–19].

The beneficial effect of lifestyle changes was firstly demonstrated in a randomized, single-blind trial of 110 obese men (body mass index >30) age 35–55 years, without metabolic syndrome but with ED (International Index of Erectile Function – Erectile Function (IIEF-EF) domain score ≤21). The mean IIEF score improved in the intervention group (from 13.9 ± 4.0 to 17 ± 5; $P < 0.001$), but remained stable in the control group [20]. Thereafter, further studies have confirmed similar findings [21].

According to the EAU guidelines, a complete evaluation of the patient seeking medical help for ED must identify reversible risk factors for ED as a first line approach; thereof, lifestyle changes and risk factors modification must precede or accompany any physical or/and any pharmacological treatment [16].

Psychosexual Therapy

This approach is particularly indicated in patients presenting with evidence of psychological problems. Psychosexual therapy alone or in combination with pharmacological treatment, in a specific group of patients, may result in a cure of the problem. In this context, ED in young individuals has been mainly regarded as a psychogenic disorder [16]. In a study conducted on 948 men with an IIEF score below 21, findings showed that 85.2% of those younger than 40 years had psychogenic ED as their primary ED aetiology as compared with 14.8% exhibiting a specific cause for an organic form of ED (i.e., vasculogenic, neurogenic, hormonal, drug-induced, or mixed [22]).

Recent approaches to sex therapy have included cognitive-behavioural interventions focused on challenging or correcting maladaptive cognitions, behavioural techniques, exploration of past developmental experiences on present behaviour, and couples' therapy [3].

However, psychosexual therapy requires ongoing follow-up and has had variable results [16].

Pharmacologic Therapy

Phosphodiesterase type 5 inhibitors—To date, seven molecules (sildenafil, tadalafil, vardenafil, avanafil, lodenafil, mirodenafil, and udenafil) with different dosages and formulations are available with a geographically-inhomogeneous availability [23]; of those, only sildenafil, tadalafil, vardenafil and avanafil are actually available in all continents. Overall, all these drugs have largerly demonstrated to be safe, easy-to-use and highly effective in enhancing erectile function across a wide range of outcome measures, causes of ED and patients subgroups [23]. Efficacy comparisons among PDE-5Is are not feasible because of the differences in the trial designs which had tested the effectiveness of each molecule in the clinical setting; as a whole, they appear to be equivalent in terms of efficacy with minimal side effects and similar warnings [16, 24].

Mechanism of action—As described in the previous paragraphs, sexual stimulation determines the release of NO from the nerve endings of cholinergic preganglionic neurons, which then diffuses into vascular and cavernous smooth muscle cells of the corpus cavernosum [25]. As a result, the levels of cGMP elevate in the smooth muscle cells, lowering the cytoplasmic calcium and resulting in smooth muscle relaxation and subsequent penile erection. PDE-5 physiologically inhibits the cGMP pathway; for this reason, PDE-5Is intake eventually enhances erectile function [25]. Of major relevance, without sexual stimulation and the resultant NO release, however, these inhibitors are ineffective; therefore, the efficacy of these drugs is strictly related to the presence of sexual stimulation [3, 25].

Clinical efficacy—The clinical efficacy and safety of sildenafil, vardenafil, tadalafil and avanafil have been evaluated in many placebo-controlled, double-blind trials, as well as in numerous open label studies [24, 26–28]. Currently, there is no strong evidence supporting the superiority of one molecule toward the other [23]. In a meta-analysis including 118 trials and more than 31,000 patients, Yuan et al. [29]

compared the efficacy of different classes of oral PDE5is; they reported that all investigated compounds were associated with a significant higher improvement in the IIEF-EF domain score as compared with placebo, with a mean difference ranging from 5.6 to 7.4 points among the different molecules. Similar results were achieved in terms of response to the Global Assessment Questionnaire question 1 (GAQ1) and the Sexual Encounter Profile question 2 and 3 (SEP2-3) [29].

Sildenafil was the first PDE-5Is launched on the market in 1998; its efficacy was tested in a study conducted by Goldstein et al. which comprised a first phase of dose response and a second phase of dose escalation test [28] In the dose response phase, 532 men were prescribed with oral sildenafil (25, 50, or 100 mg) or placebo; as a result, increasing doses of sildenafil were associated with significantly improved erectile function. In the dose escalation phase 69% of all attempts at sexual intercourse were successful for those men actually receiving sildenafil, as compared with 22% for those conversely receiving placebo ($P < 0.001$) [28].

A subsequent meta-analysis conducted in 2016 confirmed these results in a wider cohort of 11,364 ED men, using pooled data from 48 randomized, double-blinded, placebo-controlled, parallel-group, flexible-dose trials. The percentage of men reporting improved erections on the global assessment question was statistically significantly higher with sildenafil than after placebo for all age subgroups, although the efficacy of sildenafil tended to decrease for increasing ages (<65 years, 80%; 65–74 years, 69%; ≥75 years, 59%) [30].

Tadalafil was licenced as a ED treatment in February 2003. Its molecule is unique since it has a long elimination half-life of approximately 18 h [31], with the potential advantage that sexual spontaneity may be more easily restored using this compound [27]. The specific pharmacokinetics profile of tadalafil allows the administration of the drug both in on-demand doses of either 10 or 20 mg, and as an once a day dose of 5 mg [23]. The efficacy of tadalafil has been established in almost every subgroup of patients with ED, thus including difficult-to-treat subgroups (e.g. diabetes mellitus) [16]. In a meta-analysis comparing the efficacy of PDE-5Is, tadalafil showed a small advantage in terms of efficacy compared to the other drugs [absolute effect for IIEF-EF: 9.21 (CI: 8.17–10.21)] [29]. Because of its longer half-life and the convenient 5-mg daily dose, tadalafil has been the most widely assessed PDE-5Is also in patients with lower urinary tract symptoms (LUTS) and ED, thus resulting the only drug currently licensed as an on-label treatment for male LUTS. Roehrborn et al. [32] performed a dose-finding trial that enrolled 1058 men with LUTS randomized to either placebo or tadalafil at 2.5, 5, 10 or 20 mg once daily for 12 weeks. All tadalafil doses resulted in a significant improvement of urinary symptoms as compared with placebo, with a clear dose–response effect. The efficacy of tadalafil therapy in patients with LUTS was then confirmed in other well-conducted RCTs and meta-analyses [33, 34].

Vardenafil became commercially available in March 2003. Vardenafil is a potent and selective PDE-5I with a chemical structure which differs from that of both sildenafil and tadalafil, therefore reflecting differing pharmacological properties. In vitro studies have shown that the potency of vardenafil in inhibiting PDE5 purified from human corpus cavernosum tissue was approximately 25-fold greater than that of sildenafil and 48 times greater than that of tadalafil (IC50 values 0.14, 3.5, and 6.74 nmol/L, respectively) [35]. Three different dosages for film-coated oral tablets (5, 10, 20 mg) have been approved and marketed as on demand ED treatments. In a dose-response study, improved erections were reported by 66%, 76% and 80% of a general ED population taking 5, 10 and 20 mg vardenafil, respectively, compared with 30% of men taking placebo [36, 37]. Vardenafil significantly improved patient scores for IIEF, Sexual Encounter Profile (SEP2, SEP3) and GAQs and treatment satisfaction. Moreover, the orodispersible tablet (ODT) formulation of vardenafil 10 mg launched in 2012 was the first available ODT among PDE-5Is. Debruyne et al. [38] published the results of a post-hoc integrated analysis performed on data from two 12-week, double-blind, RCT of vardenafil ODT. They reported

that the mean per-patient SEP3 success rate was 62.5% for study medication compared to 29.4% for placebo within 15 min post-dosing, with corresponding overall SEP3 success rates of 59.8% and 38.2%, respectively.

The latest PDE5-Is that was released on the market and widely approved for the treatment of ED was avanafil. Avanafil is a highly selective and potent second-generation oral inhibitor of the cGMP-specific PDE5 [39]. It was launched in 2013 and the main characteristic is related to its selectivity compared to other PDE-5Is, thus allowing this drug to be effective while lowering to the minimum the rates of treatment-emergent adverse events (TEAEs). Goldstein et al. assessed clinical efficacy and safety of three different dosages of avanafil (50, 100, 200 mg) vs. placebo randomly assigned to 646 subjects [40]. The analysis showed a significant improvement in both SEP2 and 3 and IIEF-EF scores compared to placebo, with a more significant improvement for 100 and 200 mg doses over 50 mg dose. Similar results were reported by other four RCTs [40]. Avanafil was found to have a consistent time course of action across all doses, with the peak response occurring within 15–40 min after avanafil administration. In a recent study evaluating the efficacy of avanafil treatment in the general population with ED, the treatment was associated with higher rates of successful sexual intercourses as compared with placebo, with higher rates of success for higher doses of avanafil (i.e., avanafil 200 mg) [40, 41].

Recently, Chen et al. [42] performed a meta-analysis with a complete assessment of efficacy and side effects across different drugs and direct benchmarking of treatments. The results of this trade-off analysis, including 47,626 patients for the efficacy analysis and 20,325 patients for the TEAEs analysis, confirmed the overall established higher efficacy of all PDE-5Is compared to placebo, and suggested a possible advantage of sildenafil 50 mg in terms of efficacy and tadalafil 10 mg in terms of tolerability; still, the choice of a specific drug should still rely on patient's preferences in relation to the different pharmacokinetics profiles of the molecules themselves [42].

Pharmacokinetic profiles—The rapid onset of action of a PDE-5Is has been observed to have a significant impact in terms of patient's compliance toward a specific drug, either per se or as a perception of lack of efficacy of the compound itself in case of delayed onset of action [43]. However, success rates after 20 min are much less than after 1 h. High-fat meal intake has been shown to delay absorption of vardenafil and sildenafil; conversely, this effect is not seen with tadalafil and avanafil [24]. However, clinically speaking, it has been recommended to take a pill with sufficiently in advance to the attempts of sexual activity, and preferably far from meals to increase the better the chances of therapeutic success.

Tadalafil therapy has the broader therapeutic window, with an half-life of approximately 18 h. Avanafil has a half-life variable between 6 and 17 h, while vardenafil and sildenafil has the lower half-life with approximately 3.7–3.9 h [16].

Adverse events—Overall, the meta-analysis comparing efficacy and safety of PDE-5Is demonstrated their excellent safety profiles [29, 42]. Drugs-related adverse events are generally mild in nature; more specifically, class-specific TEAEs usually include flushing, headache, nasal congestion or rhinitis, musculoskeletal symptoms (myalgia and back pain) and dyspepsia [44]. Chen et al. [42] analysed data from 72 trials, reporting an overall rates of TEAEs for each starting dose of 10.23% for tadalafil 10 mg, 11.42% for udenafil 100 mg, 16.12% for mirodenafil 50 mg, 18.14% for avanafil 100 mg, 18.15% for vardenafil 10 mg, and 18.42% for sildenafil 50 mg, respectively thus suggesting an overall better tolerability for tadalafil 10 mg.

Despite the higher specificity of PDE-5Is for the PDE5 enzyme isoform, each molecule shows a different level of inhibition also for other PDE isozymes, thus possibly resulting in small differences in terms of AEs [44]. Visual disturbances, due to a weak inhibition of PDE6, have been more often associated with sildenafil, followed by vardenafil [22, 23]; similarly, the low selectivity for PDE1 resulted in slightly higher rates of vascular AEs (hypotension, flushing and tachycardia) associated with sildenafil [23];

likewise, higher rates of back pain have been reported with tadalafil possibly because of its effect toward PDE11 [24].

An important aspect to consider while prescribing these drugs is related to cardiac safety. Many post marketing studies for all the approved PDE-5Is have demonstrated no increased risk of myocardial infarction or cardiovascular events in the treated population compared to an age-matched general population, stating the cardiovascular safety of these drugs [16]. However, patients with resting hypotension or hypertension, with an history of myocardial infarction or life-threatening arrhythmias in the last 6 months, unstable angina or congestive heart failure should not be treated with PDE-5Is [16]. Furthermore, an absolute contraindication to PDE-5Is intake is represented by patients who are using any form of organic nitrate (e.g. nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate) or NO donors. The reason for this absolute contraindication is related to the fact that both these drugs act enhancing the levels of cellular cGMP, thus resulting in unpredictable falls in the blood pressure levels [16].

PDE-5Is starting doses—The recommended starting doses are 50 mg for sildenafil, 10 mg for vardenafil and tadalafil and 100 mg for avanafil. For this latter molecule, the usual starting dose in clinical terms has been rapidly moved to 200 mg. The dose should be then adjusted based on the efficacy and the TEAEs profile developed by each single patient.

Intracavernous Injections (ICI)—ICI of vasoactive drugs is considered the second line therapy for ED, once oral agents have eventually failed [16]. However, ICI could be also used as a first line treatment in specific groups of patients, such those previously submitted to pelvic surgery with an extrafascial approach (therefore, without formal neurovascular bundles preservation).

Men who have failed first-line oral pharmacotherapy constitute the largest group of ICI-treated patients, with a significant erectile response rate of >85% demonstrated among PDE-5Is non-responders, indicating that progression to second-line injection therapy is appropriate [3, 23].

Overall, ICI treatment offers several potential advantages, including a rapid onset of action, reduced incidence of systemic complications and drug interactions compared to oral treatments [16].

Papaverine—Papaverine, an alkaloid isolated from the opium poppy, induces relaxation of cavernous smooth muscle and penile vessels via nonspecific inhibition of PDE, elevates cAMP, and impairs calcium influx through blockage of voltage-dependent calcium channels. Advantages of this drug are low cost and stability at room temperature; however, papaverine injection is also associated with higher incidences of priapism (up to 6%), corporal fibrosis (6–30%), and elevation of liver enzymes [45].

Alprostadil (prostaglandin E1)—Alprostadil was the first and only drug approved for intracavernous treatment of ED [46, 47]. Alprostadil causes smooth muscle relaxation, vasodilation, and inhibition of platelet aggregation through elevation of intracellular cAMP. It is metabolized by the enzyme prostaglandin 15-hydroxydehydrogenase.

This drug showed success rates as high as 70–75% in the general ED population, as well as in patient subgroups (e.g. diabetes or CVD), with reported sexual activity of 94% after ICI and satisfaction rates of 87–93.5% in patients and 86–90.3% in patients' partners [46, 47]. Common TEAEs include pain at the injection site or during erection (11–15%), small hematoma or bruising, penile fibrosis (1–3%), and burning sensation at time of injection. Rates of priapism are quite low (1–3%) and systemic side effects are actually rare [45].

Beside prostaglandin E1 (PGE1)-based monotherapy, several combinations of different drugs have been introduced and popularized, counting on the synergistic effects of different compounds on penile vasodilation. Among them, the Tri-Mix preparation with papaverine, phentolamine and PGE1, is currently indicated in poor responders to alprostadil monotherapy, showing higher efficacy rates compared to PGE1 alone in a randomized trial (50 vs. 22%), with overall less reported pain (12.5 vs. 41%) [29]. Finally a Quadri-Mix

preparation, adding atropine to the previous triple combination of drugs has been introduced [23]; the addiction of atropine to this combination should ensure also the block of the anti-erectile arm of the cholinergic pathway in the CC [48]. However, a RCT failed to demonstrate a superiority of Quadri-Mix toward Tri-Mix in terms of penile rigidity (35.1 vs. 39.1%) [49]. It is relevant to outline that, although effective, those reported combinations are still off-label in most countries, deserving galenic preparations.

Patient acceptance—Despite the high rates of success in determining a satisfactory erectile function, patients' acceptance toward ICI is variable and the drop-out rate is quite high. The percentage of men who accept a therapy with ICI ranges from 49 to 84%, and patient's discontinuation rate is between 20 and 60% [46, 47, 50]. Most drop-outs occur within the first 2–3 months of therapy. Reasons for discontinuation have historically included lack of partner (26%), poor response (23%), fear of needles (23%), fear of complications (22%), and lack of spontaneity (21%). Careful counselling of patients during the office-training phase is of major importance in addressing patient withdrawal from an ICI programme [16].

Adverse effects—Priapism and fibrosis are the two more serious side effects associated with ICI therapy. Priapism occurred in 1.3% of 8090 patients in 48 studies with alprostadil, which is about five times lower than with papaverine [51].

Contraindications—Therapy with ICI is contraindicated in patients with sickle cell anemia, schizophrenia or severe psychiatric disorders. In patients with poor manual dexterity, the sexual partner can be instructed to perform the injection.

Other Treatments

Vacuum Erection Devices

Vacuum erection devices (VED) provide passive enlargement of the corpora cavernosa, together with a constrictor ring placed at the base of the penis to retain blood within the corpora [16]. A comprehensive analysis reported a very high patients' satisfaction rates (90%) [52]. However, the use of vacuum erection devices is contraindicated in patients taking anticoagulant or those with coagulation disorders. The most common AEs include pain, inability to ejaculate, petechiae, bruising, and numbness, which occur in <30% of patients [52].

Topical/Intraurethral Alprostadil

Alprostadil can be administered in three different ways: as an intracavernous, as a topical or as a per urethra compound. These last two modalities have been actually described as less invasive, but clinical data are, to date, still limited.

The recently launched topical alprostadil cream (Vitaros®) combines PGE1 (300 μg) with a chemical enhancer to increase skin permeation; this tool showed promising results in two multicentre placebo-controlled trials including 1.732 patients, with a satisfactory erectile response ranging between 74 and 83% of patients [53, 54]. More recently, an update form of administration has been suggested in order to increase drug effectiveness while reducing patients' discomfort [55]. Overall, side effects include penile erythema, penile burning and pain. Systemic side effects are very rare [54, 56].

Lastly, the intraurethral insertion of alprostadil uses a dedicated medicated pellet (MUSE™) [57]. This compound showed higher rate of successful intercourse compared to placebo (64.9 vs. 18.6% in 1511 patients) [53], although in a direct comparison with ICI the erectile efficacy was rated as 43 vs. 70%, respectively [57]. The most common TEAES are local pain (29–41%) and dizziness with possible hypotension (1.9–14%). MUSE™ is not broadly available any longer.

Premature Ejaculation (PE)

Physiology of Ejaculation

Ejaculation is based on two distinct phases, emission and expulsion. Normal antegrade ejaculation is a highly coordinated physiological process with emission and expulsion phases being under the control of autonomic and somatic nervous systems, respectively. Several

organs are involved in the emission phase: epididymis, vas deferens, seminal vesicles, prostate gland, prostatic urethra and bladder neck. The organs participating to the expulsion phase comprise bladder neck and urethra again as well as pelvic striated muscles [58].

Emission is the ejection into the posterior urethra of spermatozoa mixed with products secreted by accessory sexual glands. During the emission phase, both epithelial secretion and smooth muscle cells contraction take place throughout the seminal tract. All organs participating to emission phase receive an autonomic innervation composed of sympathetic and parasympathetic axons mainly coming from the pelvic plexus. Stimuli from the genitalia, essentially those reflecting the degree of activation of sensory receptors mainly located in the penile glans, are integrated at the spinal level and stimulate emission. The emission phase of ejaculation is under considerable cerebral control and may be elicited following visual and physical erotic stimulations [58].

Expulsion represents the ejection of sperm from the urethra at the glans meatus. During expulsion phase, smooth muscle fibres of the bladder neck contract to prevent semen to flow backward into the bladder, and the pelvic floor muscles, with bulbospongiosus and ischiocavernosus muscles playing primary roles, display stereotyped rhythmic contractions to propel semen distally throughout bulbar and penile urethra. Normal antegrade ejaculation also requires the external urinary sphincter to relax. Bladder neck and proximal part of the urethra, both containing abundant smooth muscle fibres, receive a dual sympathetic and parasympathetic innervation. The external urethral sphincter and the pelvic floor striated muscles are solely commanded by the somatic nervous system.

The central command of ejaculation is located at the thoracolumbar and lumbosacral levels of the spinal cord and is activated by stimuli of genital origin, although cerebral descending pathways exert both inhibitory and excitatory regulatory roles. Cerebral structures specifically activated during ejaculation form a tightly interconnected network comprising hypothalamic, diencephalic and pontine areas [58].

Epidemiology

It is difficult to precisely define the prevalence of premature ejaculation (PE) since there is no validated questionnaires specific to epidemiologically address the disease. The prevalence of PE in sexually active men has been reported to vary from 20 to 75% in different studies [59, 60]. Traditionally, PE was considered one of the most common sexual complains among males with a reported prevalence between 20 and 30%. However, considering the number of patients seeking medical help for this disease, this rate may be overrated [16]. According to the DSM-V definition, the prevalence of PE reported by two large observational studies was 2.3–3.2% (lifelong PE), 3.9–4.5% (acquired PE), 8.5–11.4% (natural variable PE) and 5.1–6.4% (premature-like ejaculatory dysfunction) [61, 62]. These reports disagreed with previous findings that showed a prevalence of 20–30%, but were based on self-reported diagnosis of PE and not on IELT time assessments. In fact, with the new ISSM definition of LLPE based on IELT <1 min, the prevalence of PE was dramatically reduced [6]. In a survey of 4997 men of which 816 reported a diagnosis of PE, only 22.6% had an IELT <2 min [63]. Similarly, in a study with 2704 men with PE, the diagnosis was confirmed in only 19.3% of individuals when applying the ISSM criteria [64].

Treatment of Premature Ejaculation

Management of PE usually involves a range of interventions. These include systemic drug treatments (such as selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, PDE-5Is, and analgesics), topical anesthetic creams and sprays, and behavioural approaches.

Psychological/Behavioural Strategies (BT) for PE

In the context of PE patients, psychotherapy has two overlapping goals: (1) to help men developing sexual skills that enable them to delay ejaculation while broadening their sexual scripts,

increasing sexual self-confidence and diminishing performance anxiety; (2) to focus on resolving psychological and interpersonal issues that may have precipitated, maintained or being the consequence of PE symptom for the man, partner or couple.

There is a lack of strong data dealing with BT because, the majority of the psychotherapy treatment outcome studies are uncontrolled, unblinded trials and few meet the requirements for evidence-based studies [65].

The behavioural strategies applied for the treatment of PE are mainly the 'stop-start' technique and the 'squeeze' technique. Both those latter approaches are usually applied with the goal to re-training the man to recognise the feeling of ejaculatory inevitability.

As said, the 'stop-start' technique, developed by Semans, involves the man or his partner stimulating the penis until he feels the urge to ejaculate, then stopping until the sensation passes; this is repeated a few times before allowing ejaculation to occur [66]. The aim is to learn to recognize the feelings of arousal in order to improve control over ejaculation.

In the "squeeze" technique, proposed by Masters and Johnson, the man's partner stimulates the penis until he feels the urge to ejaculate, then squeezes the glans of the penis until the sensation passes; this is repeated before allowing ejaculation to occur [66].

Regarding the sensate focus or sensate focusing [67], the man and his partner begin by focusing on touch, which excludes breasts, genitals, and intercourse, to encourage body awareness while reducing performance anxiety; this is followed by gradual reintroduction of genital touching and then full intercourse [68].

Pelvic floor muscle rehabilitation exercises may also assist with ejaculatory control [69].

Psychological factors may be associated with PE and should be addressed in treatment. These factors mainly relate to anxiety, but could also include relationship factors [70]. The limited studies available suggest that behavioural therapy, as well as functional sexological treatments, lead to improvement in the duration of intercourse and sexual satisfaction [71, 72].

The results regarding the efficacy of these techniques are limited; however, short term success rates have been reported to be around 50–60% [71, 72]. Even if improvements achieved with these techniques are generally not maintained in the long-term [73], behavioural strategies may represent an added value to the pharmacological therapy, which nowdays represents the best treatment option for this condition.

A recent systematic review analysed randomized controlled trials for behavioral therapies in the management of PE [74]. Four trials compared BT against waitlist control, of which two (involving squeeze, stop-start, and sensate focus) reported IELT differences of 7–9 min, whereas two (web-based sensate focus, stimulation device) reported no difference in terms of ejaculatory latency after treatment. Some study reported that BT was superior to waitlist in improving sexual satisfaction, desire, and self-confidence, whereas others were not significant. Combined behavioural and drug treatment was superior than drug treatment alone, with small but significant differences in IELT (0.5–1 min) and significantly better results in terms of other sexual outcomes (e.g., sexual satisfaction, ejaculatory control, and anxiety). Direct comparisons of behavioural therapy vs. drug treatments gave mixed results, mostly either favouring drug treatment or showing no significant differences. In comparison with a pharmacological treatment, most BTs require a willingness of the man and his partner to engage with the therapy and practice the relevant techniques. The suitability of a BT is likely to depend on individual patient (and partner) preference. Combinations of medical and psychological approaches may be useful where there is a clear psychosocial or relationship issue.

Pharmacotherapy

Currently only two drugs have been officially approved as on-label treatments for lifelong PE, e.g. the oral drug dapoxetine and the topical anesthetic Fortacin™ (lidocaine + prilocaine (spray).

Dapoxetine—Dapoxetine hydrochloride is a derivative drug belonging to the class of SSRI, with a short acting pharmacokinetics profile

and without any anti-depressant profile. It has a rapid onset of action and a short half-life [75]. It is approved for on-demand treatment of PE in European countries but not in the USA. The recommended starting dose for all cases is 30 mg, taken approximately 1–3 h prior to sexual activity, with no more than one dose taken every 24 h [76]. A pooled analysis of several randomized control studies showed that oral dapoxetine 30 or 60 mg induced significantly greater improvements from baseline in the geometric mean IELT at all time points measured, as compared with placebo [77].

At 12-week follow up, the geometric mean IELT increased from a baseline of approximately 0.8 min to 2.0 and 2.3 min with dapoxetine 30 and 60 mg, respectively, as compared with 1.3 min for placebo, corresponding to a 2.5-fold and 3.0-fold increase in the geometric mean IELT respectively (vs. a 1.6-fold increase for placebo) [77].

Dapoxetine showed a good safety profile and reasonable TEAEs prevalence, with a dose-dependent profile. Nausea, headache, and vertigo were the most common side effects. Dapoxetine side effects were reported in 47.0% and 60.3% of patients receiving 30 and 60 mg, respectively, with dapoxetine-related discontinuation occurring in 3.5% and 8.8% of these patients [77].

Off-label use of antidepressants: SSRIs and clomipramine—Serotonin pathway is key in regulating ejaculation, specifically 5-hydroxytryptamine exhibit an ejaculation-retarding effects due to the activation of 5-HT1B and 5-HT2C receptors, both spinally and supraspinally [78].

SSRIs are used to treat mood disorders, but can delay ejaculation and are therefore widely used as 'off-label' compounds for PE. As for depression, SSRIs must be given for 1–2 weeks to be effective in PE [78]. Administration of chronic SSRIs causes prolonged increases in synaptic cleft serotonin, which desensitises the 5-HT1A and 5-HT1B receptors [79].

Five different SSRIs have been studied for daily PE treatment: paroxetine 20 mg, sertraline 50 mg, fluoxetine 20 mg, citalopram 20 mg, and fluvoxamine 100 mg.

All these drugs were effective in delaying ejaculation in men with PE [80]. Among them, daily paroxetine 20 mg led to the longest ejaculatory delay. Interestingly, the efficacy of paroxetine seems to be independent of baseline IELT.

These drugs have been reported in several meta-analysis to increase the geometric mean IELT by 2.6–13.2-fold [81].

In clinical practice, two different dose regimens for long-acting SSRIs have been proposed: daily and OD treatments. Ejaculation delay usually starts a few days after intake. However, a clinically relevant effect only gradually occurs within 1–3 weeks.

Common side-effects of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhea and perspiration [82, 83]. Decreased libido, anorgasmia, anejaculation and ED have also been reported.

Patients should be advised not to stop taking the SSRI acutely in order to prevent the occurrence of an SSRI discontinuation syndrome, which is characterized by symptoms like tremor, shock-like sensations when turning the head, nausea, and dizziness.

Few studies explored the efficacy of OD use of SSRIs, administered 3–6 h before expected sexual intercourse [84–86]. OD treatment with citalopram and paroxetine before sexual intercourse were found to be more efficacious than placebo [84–86]. These data were confirmed by Gameel et al. who reported that daily treatment with paroxetine led to significantly longer mean IELT compared to placebo [85].

A clear advantage of on-demand oral drug treatment is that there is no risk of getting TEAEs of long-term drug intake. Another advantage is that one can use the drug only when it is required for a better sexual performance. However a disadvantage is that on-demand oral drug treatment may negatively interfere with the spontaneity of sexual activity.

Phosphodiesterase Type 5 Inhibitors (PDE-5Is)

PDE-5Is represent the gold standard first-line treatment for ED. PDE-5Is were also proposed as potential treatment for PE; of them, the com-

pounds that have been studied in PE include sildenafil, vardenafil, and tadalafil. A systematic review reported that PDE-5Is treatment was significantly more effective than placebo in increasing IELT [80]. However, the method and designs of studies are insufficient, thus hampering a generalized conclusion of their efficacy in terms of ejaculation delay. However, in the case of acquired PE due to erectile difficulties, ED should be treated first with a PDE-5I [16].

Topical anaesthetic agents—The oldest strategy to treat PE was based on the use of topical anaesthetic agents. To date, several trials have demonstrated the efficacy of topical anaesthetics in reducing the sensitivity of the glans penis thereby delaying ejaculatory latency. By diminishing the glans penis sensitivity it is argued that the spinal and cerebral input of sexually arousable impulses is also reduced.

Two recent meta-analyses confirmed the efficacy and low side effect profile of topical anesthetics [87, 88]. Too much application may cause penile hypesthesia, numbness or erectile difficulties. Transfer of the cream to the female partner may lead to vaginal numbness. Topical anaesthetics are contraindicated in patients or partners with an allergy to any ingredient in the product.

Currently, there are three off-label local anesthetics for the treatment of PE: eutectic mixture of local anesthetics (EMLA) cream, Stud-100 spray, and Promescent spray.

Lidocaine-prilocaine spray—Fortacin™ is a metered-dose aerosol spray that delivers topical anesthesia to the glans penis. It contains purely base (uncharged) forms of the local anesthetics lidocaine 150 mg/ mL and prilocaine 50 mg/mL, with no excipients except the spray propellant (norflurane). The active substances block transmission of nerve impulses in the glans penis, reducing its sensitivity, which is then translated into a IELT delaying without adversely affecting the sensation of ejaculation and orgasm. The clinical efficacy of on-demand Fortacin™ in the treatment of lifelong PE has been evaluated in five studies [89].

The first phase III study showed that Fortacin™ produced significant, clinically meaningful improvements in IELT, control, and satisfaction [90]. Fortacin™ lead to a 6.3-fold and 1.7-fold increase in adjusted geometric mean IELT, demonstrating a significant difference between treatments in favour of the active treatment, which was also efficacious in restoring control with significantly greater increases from baseline to month 3 for the IPE domain scores of ejaculatory control, sexual satisfaction, and distress [90].

The incidence of TEAEs was low in both patients (9.6%) and their female partners (6.0%). The most frequent side effects reported in male patients were local effects of genital hypoesthesia (4.5%) and ED (4.4%). The most frequent side effects reported in female partners were vulvovaginal burning sensation (3.9%), and genital hypoesthesia (1.0%).

Tramadol—Tramadol exhibits an effect both on the opioid receptor (activation) acting as an analgesic, and on the re-uptake inhibition of serotonin and noradrenaline; for these reasons in effective in the treatment of PE [16].

Tramadol is readily absorbed after oral administration and has an elimination half-life of 5–7 h.

A randomised, double-blind, placebo-controlled, multicentre 12-week study was carried out to evaluate the efficacy and safety of two doses of tramadol (62 and 89 mg) by ODT in the treatment of PE [91]. In patients with a history of lifelong PE and an IELT <2 min, increases in the median IELT of 0.6 min (1.6-fold), 1.2 min (2.4-fold) and 1.5 min (2.5-fold) were reported for placebo, 62 mg of tramadol ODT, and 89 mg of tramadol ODT, respectively [16, 91]. Other trials showing the efficacy of tramadol vs. placebo have been conducted, but the quality of their design was frequently quite poor to draw definitive conclusions [80].

Overall, pruritus and somnolence were the most common side effects; moreover, tramadol was associated with a negative influence on vigilance. Nausea, vomiting, and dizziness were less frequently complaints.

Tramadol may be an effective option for the treatment of PE. However, it may be considered when other therapies have failed because of the risk of addiction and side effects. It should not be combined with an SSRI because of the risk of

serotonin syndrome, a potentially fatal outcome. Further well-controlled studies are required to assess the efficacy and safety of tramadol in the treatment of PE patients (LOE2).

Peyronie Disease

Definition and Epidemiology

Peyronie's disease (PD) is clinically a fibrotic plaque/nodule at the tunica albuginea of the penis which is mostly associated to an acquired pathological curvature of the penile shaft causing a negative impact toward sexual life due to both psychological distress and difficulties in achieving successful intercourses [92]. The prevalence of PD in the general population has been estimated to range from 0.5 to 13% [6], although it has been frequently under-reported due to patients embarrassment and the lack of a proper assessment by physicians [93]. There are two distinctive phases of PD: an active phase, characterized by painful erections and a progressive worsening of the penile curvature, and a stable chronic phase, which is usually asymptomatic [16]. Patients in the stable phase of the disease may benefit from effective surgical treatments [94]; moreover, intra-lesion injections of collagenase clostridium histolyticum (CCH) have been recently popularized as an effective local treatment to reduce penile curvature for those patients with a stable disease [95].

To date, there are no available and efficacious medical treatments for acute phase of PD.

Medical Treatments

Phosphodiesterase type 5 inhibitors (PDE-5Is) **-** PDE-5Is can have a potential role in slowing down plaque formation in PD since it had been observed in animal model that plaque development is associated with high expression of iNOS, not expressed in normal penile tissues [96]. In this context, PDE-5Is might be perfect candidates since many of the effects of NO are mediated via the stimulation of guanylyl cyclase to produce cGMP [97]; thereof, it could be possible that part of the antifibrotic action of NO may occur through the elevation of cGMP levels in the PD plaque [98].

Research on animal models suggests that continuous and long-term administration of PDE-5Is has anti-fibrotic properties that might help to relieve fibrotic plaques as well as diffuse corpora cavernosa fibrosis [99, 100]. The only clinical data come from a retrospective controlled study, investigating the effect of daily tadalafil (2.5 mg for 6 months) in patients with PD, showing a statistically significant ($p < 0.05$) resolution of septal scar in 69% of patients compared to 10% in the control group (no treatment) [101].

Other oral treatments—Several oral treatments have been investigated for the management of patients in the acute phase of PD (Table 10.1). Studies investigating the efficacy of medical treatments in patients in the acute phase of the disease are controversial and as such, there is currently no general consensus regarding any oral compound to eventually improve patients' symptoms or modifying the course of the disease [16].

Pentoxifylline is a non-selective PDE inhibitor interacting with the transforming growth-factor β1 (TGF-β1). Non-randomised studies have shown an encouraging effect of pentoxifylline 400 mg three times daily for 6 months in terms of penile curvature and plaque improvement [102, 103].

Vitamin E (tocopherol), has been investigated at the dose of 400 UI once or twice daily, showing no significant effect on penile deformity or plaque size in a RCT [104]. Potassium para-aminobenzoate (Potaba) has been shown to exert an antifibrotic effect by increasing the oxygen

Table 10.1 Available oral treatments for Peyronie's disease

Oral treatments
Vitamin E
Potassium Para-aminobenzoate (Potaba)
Tamoxifen
Colchicine
Acetyl esters of carnitine
Pentoxifylline
Phosphodiesterase type 5 inhibitors

uptake at the tissue level, rising the secretion of glycosaminoglycans and enhancing the activity of monoamine oxidases [105]. In a double-blind study the authors showed an improvement of penile pain with Potaba 12 g/day for 1 year, with no effect on curvature and plaque size [106]. Tamoxifen, an oestrogen receptor antagonist, has been investigated in the treatment of penile curvature due to its effect in modulating the fibroblast activity. In a placebo-controlled study, tamoxifen failed to show any improvement in patients with acute PD. Colchicine has been tested in PD patients due to its anti-inflammatory effect. Non-randomized studies have shown some improvement in pain, curvature and plaque size, however this results should be interpreted with caution due to the lack of a placebo arm [107, 108].

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Immunology in Tumor and Transplant

11

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Abbreviations

APC	Antigen presenting cell
CTLA4	Cytotoxic T-lymphocyte-associated antigen 4
HLA	Human leukocyte antigen
MHC	Major histocompatibility complex
PD1	Programmed death 1

In this chapter on the immunology of cancer and transplantation, we successively expose the steps and actors of the immune response, the current concepts of immunotherapy in cancer, and the global principles of the immunosuppressive treatment in transplantation.

Immune System and Immune Response

The function of the immune system is to protect the individual, mainly against infections. This function is indispensable to life, needs: to be able to distinguish antigens from the "self" and the "non-self" (so-called alloantigens), and to have many effectors to start a defensive response. This recognition system is very specific; it has to be able to detect and destroy a wide variety of aggressors (bacteria, virus, tumoral cell ...) but also to prevent an immune response against the cells belonging to its own organism [1, 2]. Thus, a transplanted graft will be recognized as not belonging to the "self" and will therefore be considered as an aggression. An immune reaction, called the allogeneic response, will therefore be started against the graft. The purpose of the immunosuppressive therapy is to avoid the rejection of the graft. The same immune response occurs against the cancer cells, but cancer cells are able to escape the immune system and induce tolerance. The new immunotherapies aim to block these escape ways and allow the immune system to target and destroy cancer cells.

The Allogenic Response

The immune response schematically comprises three steps: recognition of alloantigens, activation of effector T cells and destruction of the "non-self" (Fig. 11.1).

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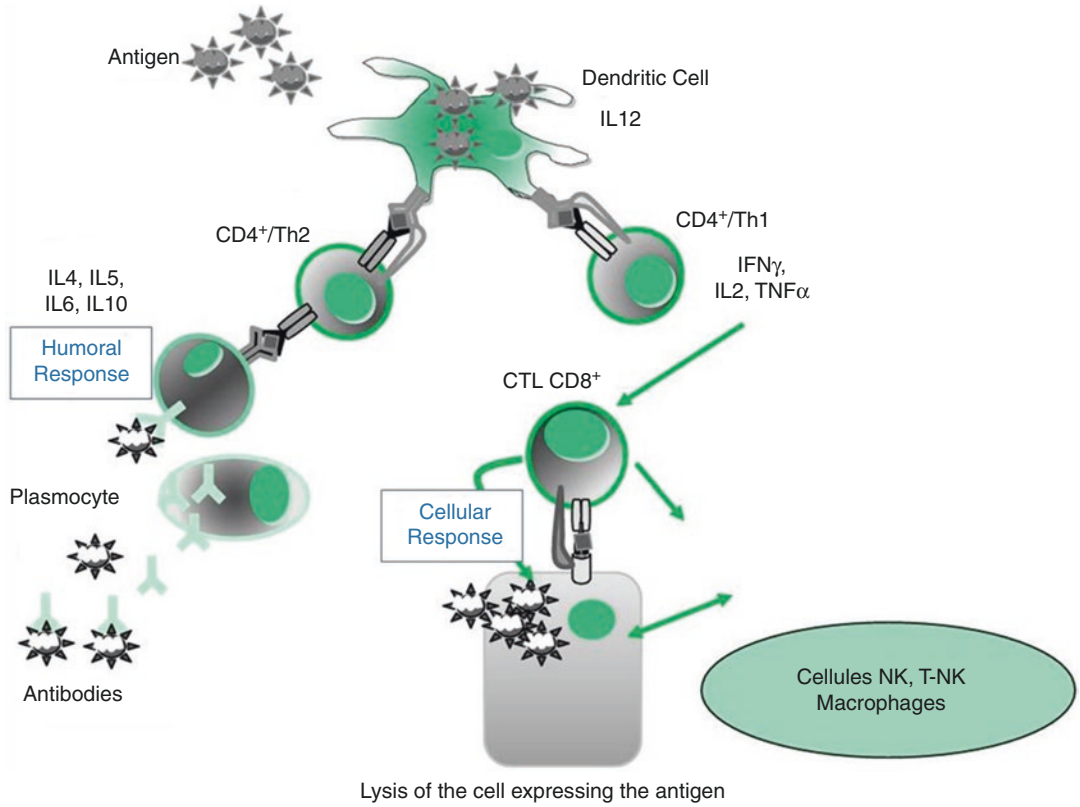

Fig. 11.1 The immune response. The immune response includes: • the alloantigen recognition: the alloantigen is presented by the Major Histocompatibility Complex (MHC) on the surface of the Antigen-Presenting Cell (APC), • the activation of the T lymphocyte, • destruction of the cell expressing the targeted antigen by humoral (antibodies) and/or cellular response (Cytotoxic lymphocyte)

Alloantigen Recognition

The Major Histocompatibility Complex (MHC)

The central element that gives to the immune system the ability to recognize the "non-self", is the Major Histocompatibility Complex (MHC), also called Human Leukocyte Antigen (HLA) system. Its existence and role in the immune response in transplantation was discovered by Jean Dausset who was awarded for this by a Nobel Prize in 1980 [3, 4]. The role of the HLA is to present antigens to the lymphocytes.

The loci coding for the HLA are located on the short arm of the chromosome 6. There are six loci defining two types of HLA: HLA class I which is expressed on the surface of nucleated cells, and HLA class II that is specifically expressed on the surface of Antigen Presenting Cells (APCs). The HLA system has two features. It is codominant, which means each individual expresses the alleles of the two chromosomes for each of the six loci. Thus, the HLA genotype of an individual comprises 12 different HLA molecules: HLA-A, HLA-B and HLA-C coding for the HLA type I, and HLA-DP, HLA-DQ, HLA-DR coding for the HLA type II. HLA is polymorphic, which mean each HLA locus can express many different molecules.

This polymorphism and codominant characters explain the huge variety of HLAs. In transplantation, the major loci involved in the alloimmune response are the HLA-A, HLA-B, HLA-DR and DQ loci. The impact of the HLA-C, HLA-DP loci appears to be lower and they are not taken into account routinely.

Presentation of the Antigen

The two main actors of the allo-antigen recognition are the APCs and the lymphocytes T CD4+. APC expose on their surface the complex antigen + MHC. The lymphocytes T CD4+ screen the APC and detect whether the antigen belongs to the "self" or the "non-self" [5]. The immune response starts with the presentation of an alloantigen to the immune cells. Antigens (from the tumor cell or from the donor in the case of a transplant) are caught by the APCs, mainly the dendritic cells. The dendritic cell binds these antigens to the MHC, exposes the complex MHC-Antigen on their cell surfaces and then migrate to the surrounding lymph node where the lymphocytes are concentrated [1, 2].

Activation of Lymphocytes

The activation of the naive T lymphocyte requires three signals, which are essential for the ongoing of the allogenic response.

First Signal

The first signal arises with the recognition of the antigen (tumor or donor) presented on the MHC on the APCs, by the T Cell Receptor (TCR) of a naive T lymphocyte. The TCR that is expressed on the surface of T lymphocytes, binds to the MHC-antigen complex and induces an intracellular signal that initiates the activation and the proliferation of the antigen-specific lymphocytes [1, 2].

Second Signal

The second signal, also called "co-stimulation signal" consists in reinforcing the link between the lymphocytes and the APC by other surface molecules (CD 40, 154, CD 28 on the lymphocytes, CD 40, CD80, CD86 on the APCs) [6]. This second signal results in the huge synthesis of interleukin-2 (IL-2), the main cytokine involved in the proliferation of lymphocytes, by the lymphocyte itself (Fig. 11.1).

Third Signal

The third signal, also called "proliferative signal" starts with the binding of Interleukin 2 to its receptor (IL-2R), leading to the proliferation of lymphocytes by a clonal expansion and the secretion of other cytokines and chemokines. The binding of IL-2 to its receptor (IL-2R or CD25) results in the activation of the Pi3 K pathway and Akt kinase that activates the mTOR protein involved in mitosis and controls the cell cycle [7]. The activated T cell proliferation will result in the recruitment of immune effector cells, such as T CD8, T NK, B lymphocytess or macrophages which will participate in the immune response (antitumor immunity or graft rejection). The recruitment of leucocytes is triggered by wide range of cytokines. Depending on the type of cytokines that are released, two ways of immune response are activated: the cellular and the humoral immunities. In the cellular immunity profile, Lymphocyte T helper type 1 secrete IL-2, Interferon-g (IFN-g) and tumor necrosis factor (TNF) which lead to the activation and recruitment of cytotoxic T lymphocytes and macrophages [8]. In the humoral immunity profile, Lymphocyte T helper type 2 leads to the secretion of antibodies via the IL-4, IL-5 and IL-10 [7, 8].

Mechanisms of "Non-self" Destruction

Activated T CD4 T are the pivot of the immune response against the "non-self". The activated lymphocyte expresses on its surface molecules of MHC and secretes cytokines, both leading to the recruitment of other immune cells targeting the "non-self" antigen. The activated CD4 T lymphocyte stimulates the proliferation of cytotoxic lymphocyte T CD8 and lymphocyte B. Lymphocytes T CD8 have a direct cytotoxic action on the cell expressing the targeted antigen, by a cytotoxic secretion of perforin and granzyme. T CD8 cells also promote the over-expression of Fas-L (Fas ligand) which induces apoptosis. On the other side, lymphocytes B are also activated by the lymphocyte T CD4 and get differentiated into plasmocytes secreting high affinity antigen antibodies. The accumulation of antibodies on the surface on the targeted cells lead to the activation of the complement and their destruction. Some of

these B-cells, called memory B cells, have a long shelf life and are also able of an immediate proliferation and a permanent secretion of anti-HLA antibodies [1, 2].

Tumor Immunology

Every day in our body, some cells manage to escape the mechanisms of apoptosis and engage in malignant differentiation. The immune system is able to detect and eliminate the cells engaged in the process of malignant differentiation before they multiply and evolve into a tumor. Tumor cells however can develop "escape ways" that are the targets of new immunotherapies.

The Immune Response in Cancer

As any other cell, the tumor cell constantly releases antigens into its environment. In the same way as it was previously described, these tumor antigens are captured by APCs dendritic cells. After capturing these tumor antigens, the dendritic cells expose the antigen on their membrane and migrate to the surrounding lymph nodes where stand the T lymphocytes. The activation signal between the dendritic cell and the T lymphocyte specific for the antigen is mediated by two surface molecules: B7 and CD28 (Fig. 11.2). Once activated, the lymphocytes proliferate, migrate to the tumor and release the antibodies that will lyse the tumor cells.

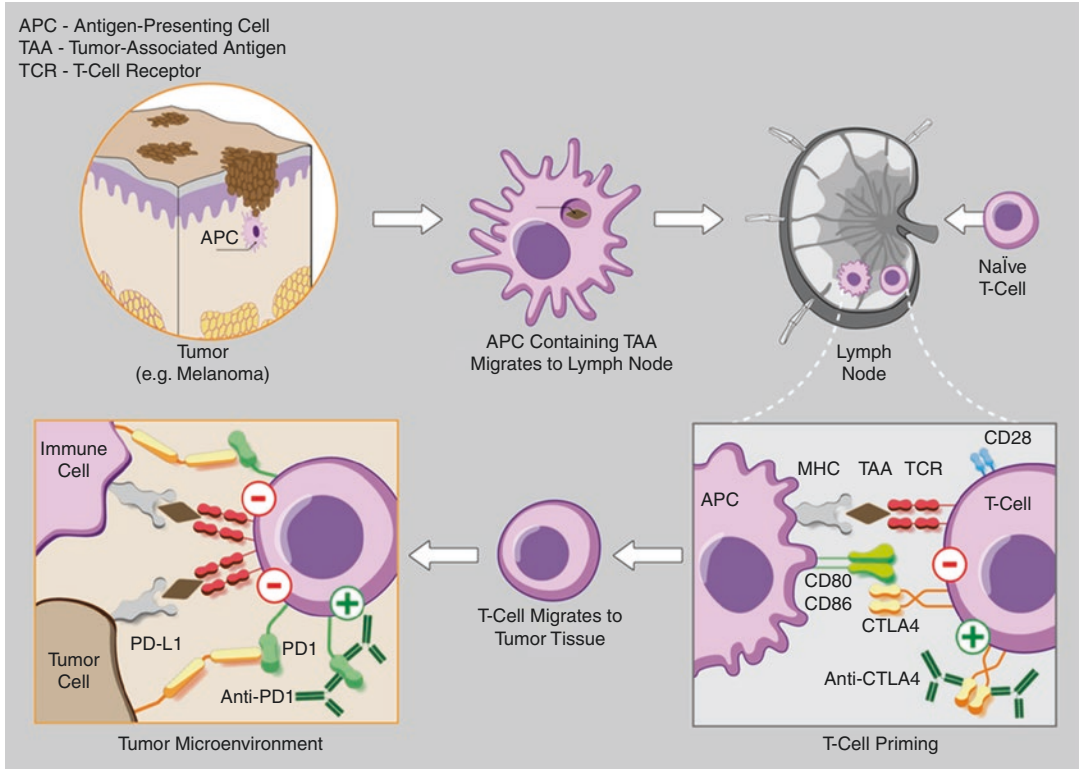

Fig. 11.2 PD1 and CTLA4 echapatory pathways to the antitumoral immune response. The cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) immune checkpoints are negative regulators of T-cell immune function. Inhibition of these targets, result in an increased activation of the immune system. CTLA-4 is thought to regulate T-cell proliferation early in an immune response, primarily in lymph nodes, whereas PD-1 suppresses T cells later in an immune response, primarily in peripheral tissues

In the same way the tumor cell can thwart the physiological mechanisms of apoptosis, it can also develop ways to escape the anti-tumoral immunity. Two pathways capable of "slowing down" the anti-tumor response have been identified:

- Cytotoxic T-Lymphocyte-Associated antigen 4 (CTLA4) which binds B7 and blocks the acceleration phase of the immune reaction in the peritumoral lymph node,
- Programmed Death 1 (PD1) which is expressed by activated T cells. The binding of the PD1 receptor localized on the T lymphocyte to its ligand PDL1, sends an inactivation signal to the lymphocyte and slows down the anti-tumor immune reaction [9, 10] (Fig. 11.2).

These immune checkpoints and their ligands are the targets of the new immunotherapies developped for the treatment of cancer.

Immunotherapy in Urological Oncology

Immunotherapy is not a new concept in oncology [11]. By the mid-1980s, interleukin 2, a cytokine that stimulated T-cell proliferation, was used at high doses in oncology. The principle was to globally stimulate the immune system especially the anti-tumoral immunity [12]. Although the response rate was low, some patients had durable responses. This first immunotherapy found an indication in metastatic melanoma and kidney cancer. Other immunotherapy approaches exist, such as anti-tumor vaccination or endovascular BCG therapy [13].

The principle of "modern" immunotherapy is no longer to stimulate the immune system globally (as was the case with interleukins and interferon alpha), but to block the echapatory mechanisms that the tumor develops to escape the anti-tumoral immune system (PD1, CTLA4 and their ligands).

Compared to the first generation of immunotherapy and classical chemotherapy, the "modern" immunotherapy has several advantages. The CTLA4 and PD1 immune checkpoints are ubiquitous and common to all kind of tumors, so that immunotherapy based on one or the other of its pathways is potentially effective on all types of cancer. This property is all the more interesting for chemo-refractory cancer, such as cancer of the kidney, lung, bladder or melanoma. Immunotherapy can be prescribed in monotherapy, which limits the risk of toxicity and restrict the types of toxicities, while on the opposite several molecules adding their own toxicities are combined in "standard" chemotherapies. The administration of immunotherapy usually consists in a single 60 min intravenous infusion every 2–3 weeks. So far the studies reported show that the side effects of immunotherapy were less severe than conventional chemotherapy, and most importantly, that complete and lasting responses could occur [14].

The predictive factors of response to immune checkpoints inhibitors that have been identified so far are mainly intratumoral factors: the PD1 mutation rate and the T lymphocyte infiltration rate [15, 16]. These three parameters allowed identification of two tumor profiles: the "hot" tumor (high load of PD1 mutation associated with a major intratumoral lymphocytes infiltration) characterized by a high level of antigenicity and a high sensitivity to immunotherapy, and in contrast the so-called "cold" tumors predicting a weak response to immunotherapy. One solution to potentially improve the response rate to the immunotherapy would be to transform "cold" tumors into "hot" tumors by increasing their level of antigenicity with a combination of immunotherapy, chemotherapy, radiotherapy or even oncolytic virus [17, 18].

Immunology of Transplant

The Immune Response in Renal Transplantation

There are two types of immune response: innate immunity and acquired/adaptive immunity [25, 26]. The innate immunity is not specific to any alloantigen, and constitutes the first step in the

immune response. Owing to the surgical stress of the kidney removal/transplantation and ischemia reperfusion, many pro-inflammatory cytokines (IL-1, IL-12) are released into the bloodstream of the recipient resulting in the recruitment of many immune cells (macrophages, polynuclear cells, natural killer cells) to the graft. This mechanism is named "Homing" [27]. Due to ischemia/reperfusion lesions, the endothelial cells of the graft vessels produce numerous adhesion molecules such as LFA-1 (CD11a, leukocyte factor antigen) or ICAM-1 (CD154, intracellular) that catch circulating leukocytes also expressing adhesion ligands. By a process of extravasation, the leucocytes of the recipient leave the vessels, infiltrate the graft following a gradient of chemokines and cytokines. Due to release of pro-inflammatory cytokines, APCs are activated and strongly express on their surface the major histocompatibility complex (MHC) of class I, as well as the co-stimulation molecules (CD80, CD86) essential to the development of the acquired/adaptive immune response. At this step, all the actors of the allogenic response are present in the graft which becomes the target of an adaptive immune response.

Because of the important polymorphism of the MHC, T lymphocytes of the recipient have the ability to recognize the MHC on the APCs of the donor being in the graft and then initiate an immune response with respect to the donor cells carrying this MHC. This mechanism is called direct presentation. This mode of presentation is particularly involved in the mechanism of acute rejection. The recipient's APCs may also present antigens lost by donor cells to the recipient's T-cell. These antigens are lost by the donor cells, are catched by the APCs which expose them on the MHC. This mechanism of antigen recognition, called indirect presentation, is the main activation pathway for T CD4 cells and is particularly involved in the mechanism of chronic rejection [28].

Humoral Hyperacute Rejection

This rejection occurs within minutes or hours after the transplantation. The graft quickly becomes cyanotic, purplish, oedemated and doesn't product any diuresis. Histologically, it consists in a massive intravascular thrombosis of the renal capillaries. Major cell necrosis and complete renal infarction occur within a few hours [29]. Immunologically, the hyper-acute rejection is related to the presence of Donor Specific Antibodies (DSA) in the recipient [8, 30]. These DSA bind to the endothelial cells of the graft and activate the complement cascade resulting in the secretion of coagulation factors leading to intravascular thrombi. The immunohistochemical analysis of the graft shows the presence of immunoglobulin and complement C3 fragments in the capillaries. The hyperacute rejection has now almost disappeared because of the pre-transplant immunological evaluations of the donor and the recipient, particularly by thepre-transplant regular and systematic search for anti-HLA antibodies and by carrying out the "Cross match" test before the transplantation.

Acute Rejection

Acute rejection occurs in the first few weeks of the transplantation. There are two types of acute rejection: the cellular and the humoral acute rejection. The cellular acute rejection is induced by T cells while humoral acute rejection is mediated by B cells, IgG immunoglobulins and complement [30]. Cellular acute rejection is the most common. It is characterized by an infiltration of the graft by leukocytes and monocytes in the tubules and glomeruli. The diagnosis relies on a biopsy of the graft. The histological lesions are evaluated according to the classification of BANFF which combines morphological lesions (inflammatory infiltrate in peri-tubular capillaries, thrombosis of the glomerular capillaries), immunohistological criteria (markings for the C4d fragment positive) and serological criteria (circulating antidonneur antibody) [31].

Chronic Rejection

The term "chronic rejection" is now replaced by "chronic allograft nephropathy" (CAN). CAN is defined by a progressive loss of the graft function resulting in a decrease of the glomerular filtration rate and the occurrence of a proteinuria. It is the first cause of transplant loss, generally leading to

a new transplant or a return to dialysis. Chronic allograft nephropathy is due to immunological factors (chronic rejection) and non-immunological factors (immunosuppressive toxicity). The diagnosis is histological and is based on the biopsy of the transplant: thickening of the intima of the capillaries, proliferation of myofibromatous cells derived from the differentiation of endothelial cells (epithelio-mesenchymal transition) induiced by ischemia reperfusion injury. There are also tubular atrophy lesions associated with interstitial fibrosis, and an infiltration by lymphocytes and plasmocytes [8, 31]. An histological classification, the Chronic Allograft Disease Index (CADI) has been developed and was integrated into various evaluation scores of the renal function on the long-term [32–34].

Immunotherapy in Renal Transplantation

Anti-Lymphocytes T Treatments

Monoclonal Antibodies Anti-Lymphocytes T

Monoclonal anti-Lymphocytes T antibodies (anti-CD3 and anti-CD52) are mainly used in acute rejection. They induce a rapid depletion of lymphocytes populations. Side effects are related to the significant release of inflammatory cytokines called *cytokine release syndrome*, and consist in lymphopenia, fever, sweat and pulmonary edema.

Calcineurin Inhibitor: Ciclosporin and Tacrolimus

Calcineurin Inhibitors (CNIs) revolutionized transplantation in the early 1980s. It is still the main immunosuppressive therapy in renal transplantation despite many side effects: nephrotoxicity, hepatotoxicity, neurotoxicity, infections and increased risk of cancer [35]. Calcineurin inhibitors inhibit the expression of cytokine genes in the lymphocyte T, especially the gene coding for interleukin 2 [5]. The main side effect of CNIs is nephrotoxicity, requiring a regular monitoring of blood rates of anticalcineurin, especially as many treatments may change their absorption and pharmacological characteristics. In the long term, anti-calcineurins are also involved in the occurrence of allograft nephropathy responsible for graft loss.

Other treatments involved in the inhibition of T lymphocytes are:

- Monoclonal antibodies competitively binding to the receptors involved in the CPA-Lymphocyte T interaction (anti-CD80, CD86, CD40)
- The anti-receptor antibodies of interleukin 2.

Anti Lymphocyte B Treatment

The anti-CD20 Monoclonal Antibody (Rituximab) is a CD20-targeted monoclonal antibody which induces a profound depletion of B lymphocytes by induction of apoptosis, complement-dependent cytotoxicity and antibodies [19,63]. Currently its current indications are, the desensitization for immunized recipients in compatible ABO transplantation. In this indication, anti-CD20 are administred in combination with polyvalent immunoglobulins. The second indication is in incompatible ABO transplantation, as an alternative to splenectomy [36, 37, 37–39].

Steroids

Corticosteroids have been used early in the history of kidney transplantation, for their immunomodulation potential. Steroids inhibit the secretion of cytokines, induce a depletion and an apoptosis of T lymphocytes, block the Th1 differentiation and alter the functions of macrophages. However, the numerous side effects related to their long-term use (diabetes, hormonal changes, infections, osteoporosis, behavioral disorders and delayed healing) tend to limit their use in kidney transplantation [40, 41].

Inhibitors of Purine Bases (Azathioprine and Mycophenolate Mofetil)

In the alloimmune response, cell proliferation is an essential step that requires the synthesis of purine nucleotides. Purine bases inhibitors (PBI) are active on the enzymes involved in the synthe-

sis of purine mucleotides during mitosis and therefore have an antiproliferative action. In contrast to CNIs, PBI have no nephrotoxicity and do not induce metabolic disorders. Their main side effects are cytopenia and diarrhea [42].

mTOR Inhibitors

The best-known inhibitor of mTOR is rapamycin, from which mTOR's name derives. mTOR pathway has an important regulatory function in cell growth and proliferation. Rapamycin was originally applied as an immunosuppressant and has been in use since around 2000 to prevent kidney graft rejection [19]. Sirolimus also exhibits immunosuppressive effects via inhibition of B cell and T cell proliferation [19, 43]. The main side effects are hyperlipidemia, thrombocytopenia and arthralgia.

While it is tempting to presume that it can promote tumor development via immunosuppression, actually Sirolimus has been proven to inhibit cancer cell proliferation through the same mechanism that is responsible for immunosuppression; the PI3K/AKT/mTOR pathway being also crucial in the production of the Vascular Endothelial Growth Factor (VEGF) which plays a key role in the growth and neo-angiogenesis of kidney cancer. Both Temsirolimus and Everolimus mTOR inhibitors were approved by the US Food and Drug Administration for metastatic renal cell carcinoma in 2007 and 2008 respectively [20, 21].

Considering the incidence of most cancers increases substantially after kidney transplantation, and cancer is one of the main cause of death for the recipient (after cardiovascular events), the use of mTOR in kidney transplantation for both graft rejection and reducing the risk of malignancy has been explored in several studies [22, 23]. The results are contradictory, although it seems that Sirolimus in kidney transplantation is associated with a reduction in the risk of malignancy and non-melanoma skin cancer [24]. The benefit seems most pronounced when patients are converted from an established immunosuppressive regimen to Sirolimus. Given the increased risk of mortality, however, the use of this drug does not seem warranted for most patients with kidney transplant.

Immunosuppression Strategies and Current Trends

The immunosuppression in renal transplantation consists in an initial "*induction therapy*", that has the objective to prevent the acute rejection. It is then relayed by a *"maintenance therapy"* to contain the allogenic response of the immune system on the long term [5, 7, 44]. The main limits to the maintenance treatment are the risk of nephrotoxicity, de novo neoplasia and cardiovascular events. The conventional maintenance immunosuppression regimen usually combines calcineurin inhibitor, purine bases inhibitor and steroids. Current trends are a growing use of tacrolimus instead of ciclosporin, of mycophenolic acid instead of azathioprine and especially an early withdrawal of steroids [45, 46]. With regard to maintenance treatment, the current challenge is to limit the use of calcineurin inhibitors by replacing them, if possible, by a m-TOR inhibitor to prevent the occurrence of chronic allograft nephropathy.

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Pathophysiology of Renal Obstruction

12

Scott V. Wiener and Marshall L. Stoller

Introduction

Renal obstruction is one of the most commonly managed conditions by urologists, and the pathophysiology of this ailment lies at the intersection of urology and nephrology. In the acute setting, this situation can cause significant pain, places the patient at risk for severe sepsis if associated with infection, and when bilateral (or in a solitary kidney) can result in acute renal failure requiring dialysis. When it becomes chronic, tubular atrophy, inflammatory processes resulting in fibrosis, and an irreversible loss of nephrons and renal function will ultimately occur.

A comprehensive understanding of the disease process is critical for all urologists to appreciate. This chapter will outline the myriad causes of renal obstruction and focus most closely on those aspects of pathophysiology most relevant for the urologist. A brief overview of the management options will be discussed but a comprehensive discussion of these many options is beyond the purview of this chapter.

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Normal Renal Physiology

For the purposes of understanding the pathophysiologic processes occurring with obstruction of the kidney, a brief overview of nephron function and physiology will be essential [1]. The functional unit of the kidney is the nephron, a single filtration unit that acts in concert with hundreds of thousands of other nephrons, varying in length and their exact architecture throughout the kidney. The nephron is composed of several parts (Fig. 12.1)—afferent and efferent blood supply, the glomerulus within Bowman's capsule, the proximal convoluted tubule, the loop of Henle (thick descending limb, thin loop, the thick ascending limb) the distal convoluted tubule, and the collecting duct [1–3].

The glomerulus functions as a biological sieve, separating protein and blood cells from the fluid within Bowman's capsule; it is the site of filtration for the nephron. Blood passes first from the afferent arteriole and filters through the glomerulus into Bowman's capsule where changes in pressure within the kidney (as a result of obstruction) will alter the hydrostatic forces facilitating this initial filtration step [4]. This filtration rate is expressed mathematically as the Glomerular Filtration Rate (GFR), where $GFR = Kf(P_{GC} - P_T - \pi_{GC})$. Kf: Glomerular filtration coefficient, P_{GC}: Glomerular capillary pressure, P_T: Tubular Pressure, and π_{GC}: oncotic pressure of the Glomerular capillary. The filtrate will pass through the aforementioned nephron segments, passing from the outer cortex,

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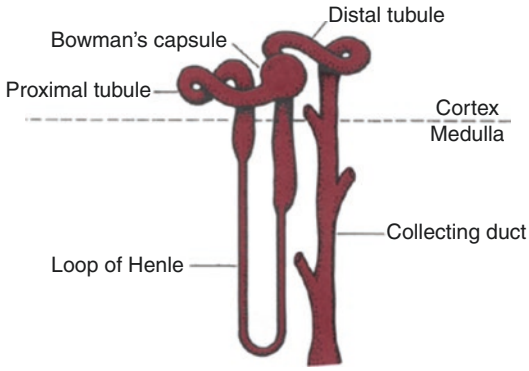

Fig. 12.1 The human nephron is composed of several segments and varies in length depending on its location within the renal papilla. Reproduced with permission from [1]

into the inner medulla and back repeatedly. Active and passive transport mechanisms ensure the exchange of ions and steep concentrations gradient occur—permitting excretion of excess water, urea, and unneeded ions and other solutes. After passing through each segment, the urine eventually exits the duct of Bellini to mix with urine within the calyx, infundibulum and eventually the renal pelvis [5].

A variety of solutes are transported back into the blood prior to leaving the nephron as urine as the fluid is traverses through the nephron. At the glomerulus, large molecules are initially filtered. The filtered solution is rich in glucose, sodium, chloride, potassium, and other ions. In the proximal convoluted tubule, approximately 60% of sodium, potassium, and calcium ions are resorbed along with 80% of phosphate, water, and bicarbonate molecules; nearly 100% of glucose is returned to the systemic circulation during this initial stage. A steep interstitial concentration gradient is produced, up to 1400 mOsm/kg, as the fluid descends down the thick limb of the loop of Henle into the papilla. Within this distal papillary interstitial space, the osmotic gradient is driven largely by urea [1]. This region of the nephron is notoriously poorly perfused and is often subject to ischemic insult during episodes of hypotension or obstructive processes.

Traveling through the distal papilla, the urinierous fluid becomes increasingly hypotonic in comparison to the interstitium. It is here that solutes are transported out of the tubule and into the interstitium, where at the papillary tip the interstitium reaches the highest solute concentration. Ion exchange in the papilla maintains charge neutrality. If the organism becomes dehydrated, this will cause a shift in the generally water-impermeable collecting duct, facilitating reuptake of water through surface expression of aquaporins via antidiuretic hormone action. The steep concentration gradient makes water resorption thermodynamically favorable and helps to re-establish total body fluid homeostasis.

Etiologies, Pathogenesis and Prevalence

Urinary tract obstruction can occur at the level of the kidney, ureter, bladder, or the bladder outlet. At each of these locations, the etiology of the obstruction can be congenital or acquired (malignant or benign). The consequences vary depending if the obstruction is complete or partial and can range from an incidental finding to one which is painful, or from metabolic abnormalities to renal failure, and in severe cases can ultimately result in death. With each etiology, the consequences and permanence of the damage increase with the duration of the obstruction. In this section we will review some cases which may have relevance for the urologist in consideration of obstructive renal pathophysiology.

Bladder Outlet Obstructions

One of the most common causes of bilateral hydronephrosis are bladder outlet obstructions including those originating from benign prostatic hyperplasia, trauma, urethral stricture disease, vesicovaginal prolapse, and obstructing pelvic malignancies. Bladder outlet obstructions can be either intrinsic (benign prostatic hyperplasia or prostatic malignancy, urethral stricture or penile cancer, bladder neck contracture [*de novo* or post-operative]), or extrinsic (i.e. malignancies or mass effect from the colon, rectum, uterus, cervix, etc.).

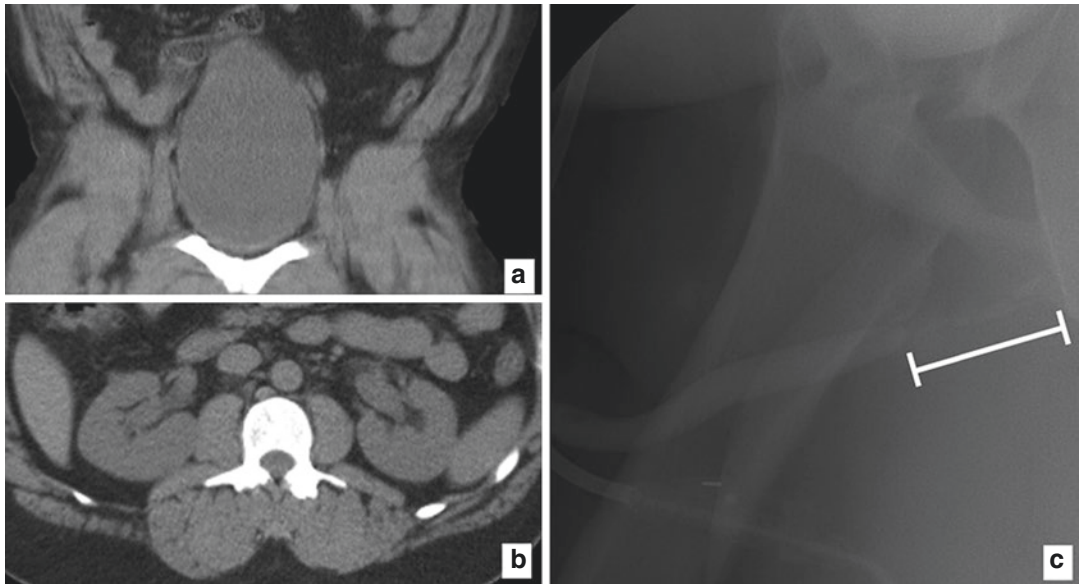

Fig. 12.2 A young man presents with acute urinary retention. (**a**) Computerized Tomogram scan depicting the dilated urinary bladder. (**b**) Same scan, showing the bilateral hydronephrosis due to bladder back pressure and resulting ureteral angulation/reflux. (**c**) Retrograde urethrogram showing the bulbar urethral stricture

Consider the case of a 33-year-old male who presented with acute urinary retention, low abdominal pain and bilateral flank pain (Fig. 12.2). On further evaluation he was found to have a bulbar urethral stricture after a distant straddle injury while riding a bicycle. A computerized tomography (CT) scan revealed bilateral hydroureteronephrosis along with a markedly distended bladder. The patient initially was managed with a suprapubic catheter for bladder decompression, and ultimately required a buccal mucosal graft urethroplasty to eliminate the urethral obstruction, shown in the preoperative retrograde urethrogram. In this case, the hydronephrosis was due to angulation of the ureterovesical junction under high volumes and pressures within the urinary bladder. With prompt bladder decompression, the hydronephrosis resolved and the patient had no untoward long-term effects from his transient renal obstruction.

Ureteral Obstruction

Similarly, the ureters are also subject to both benign and malignant obstructive processes - both intrinsic and extrinsic. The frequency at which these conditions affect one versus both ureters vary.

Non-malignant Extrinsic

Non-malignant extrinsic processes include traumatic obstruction, iatrogenic injury, crossing vessels, retroperitoneal fibrosis, and mass effect—most commonly due to the gravid uterus or similarly enlarged uterus from fibroids.

A 75-year-old woman presented after undergoing an anterior spinal fusion surgery with significant hardware implantation (Fig. 12.3). She developed massive right-sided hydronephrosis as evidenced by axial CT imaging. A nuclear scan revealed that the kidney was nonfunctional. The patient was having significant nausea and vomiting and still recovering from her anterior spinal fusion. She elected for ureteral stent placement. The collecting system was markedly dilated but after stent placement the hydronephrosis improved and her nausea symptoms dissipated. Key here is that even the nonfunctional kidney, when obstructed, can still cause significant symptoms. Relieving the obstructive process can improve the patient's quality of life even without residual renal function to preserve.

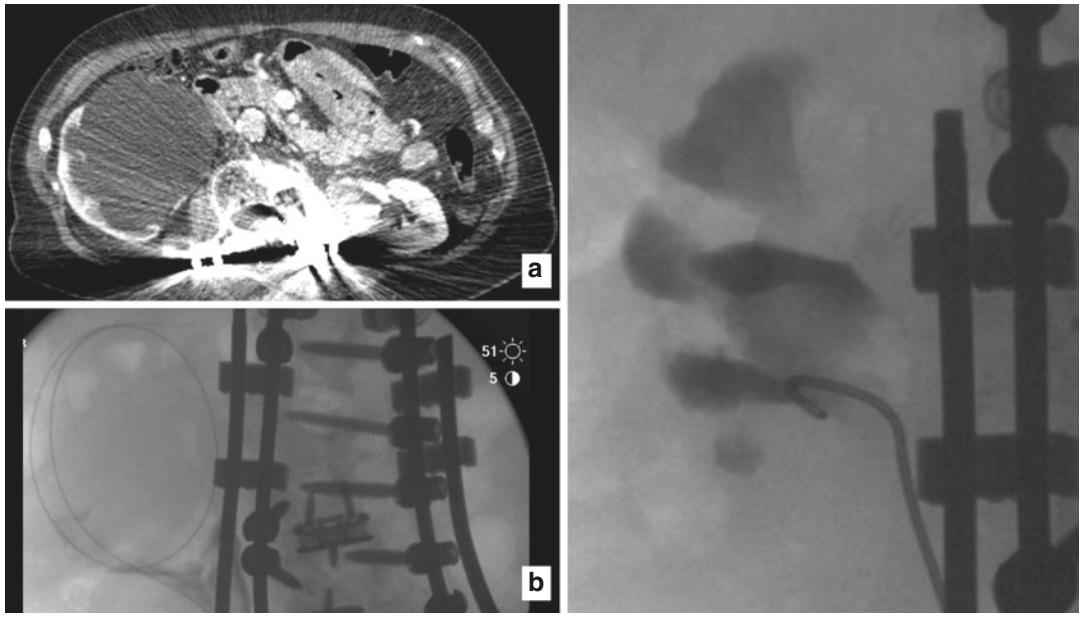

Fig. 12.3 A 75-year-old woman with iatrogenic right ureteral obstruction. (**a**) CT scan showing the thin rim of kidney remaining with massive hydronephrosis. Scatter artifact is from the spinal hardware. (**b**) Intraoperative image showing placement of the wire in the massively dilated pelvis. (**c**) Interval resolution of hydronephrosis at 3-month stent exchange

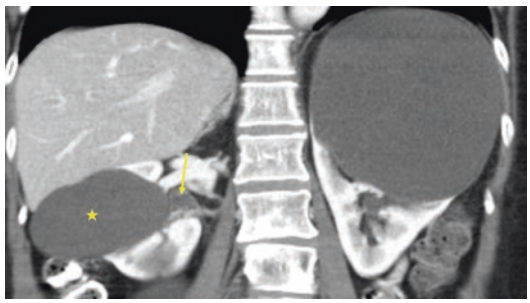

Fig. 12.4 Parapelvic cysts (star) can be easily confused for hydronephrosis. Note the large left upper pole cyst which was causing early satiety. The right sided renal pelvis (arrow) can be seen at the medial aspect of the kidney, inferior to the renal hilum and is decompressed

In some cases, the diagnosis of obstruction is unclear. A 55-year-old woman presented with early satiety. She was found to have an extremely large left upper pole renal cyst compressing the stomach (Fig. 12.4). The patient was told by the referring provider that she had right-sided hydronephrosis as well, but on closer inspection, the hydronephrosis was actually a parapelvic cyst. These cysts can mimic hydronephrosis but are separate and unique from the collecting system which is often decompressed. Parapelvic cysts should be on the differential for hydronephrosis, especially in the asymptomatic patient with contralateral renal cystic disease. Retrograde pyelography or delayed images after intravenous contrast during CT imaging will help establish the diagnosis.

Occasionally ureteral obstruction can be idiopathic. For example, a 63-year-old woman presented with incidentally discovered left hydroureteronephrosis down to the level of the ureterovesical junction (Fig. 12.5). She had adequate bladder capacity on a cystography and retrograde pyelography revealed an extremely tortuous and convoluted ureter which had been chronically obstructed. In situations where the ureters are chronically obstructed, it can develop significant tortuosity and folding, making retrograde access complex. Establishing access is possible through the use of angled-tipped hydrophilic glide catheters as well as careful manipulation of the open-ended ureteral exchange catheter. The exchange catheter was advanced slowly over

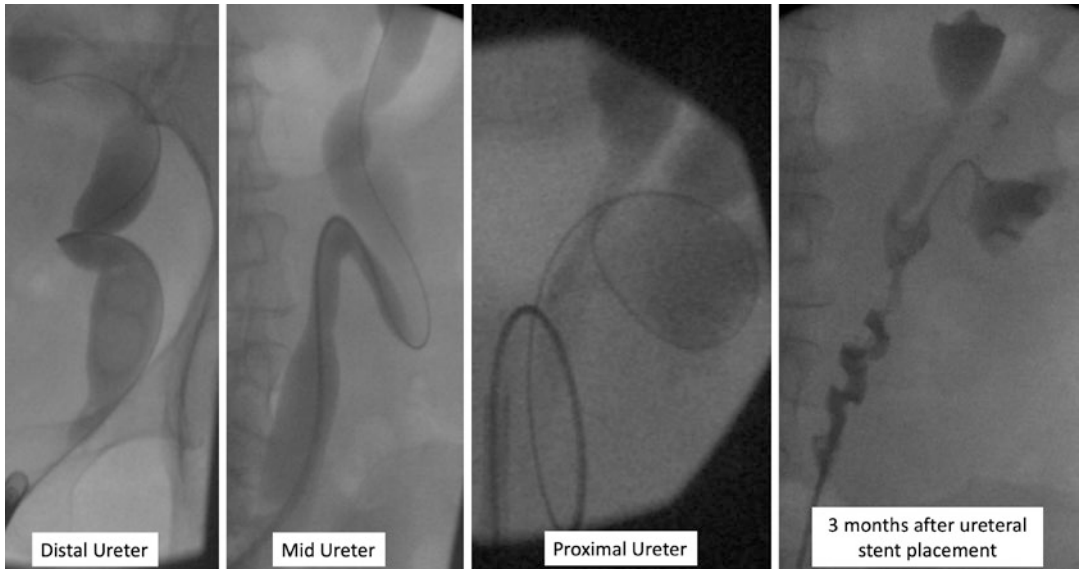

Fig. 12.5 Ureteral Tortuosity. Depicted is a case of idiopathic ureterovesical junction obstruction in an elderly woman. Retrograde pyelogram shows the extreme tortuosity of the distal, mid, and proximal ureter with associated hydroureteronephrosis. Three months after ureteral stent placement, a corkscrew effect has occurred, with the decompressed ureter exhibiting redundancy

the wire until such time as further navigation became difficult and then the hydrophilic catheter is torqued and advanced. The angulated/kinked ureter can be straightened by pulling back gently on both the exchange catheter and wire simultaneously to create friction and countertension. Ultimately, after stent placement and ureteral biopsy (showing benign urothelial cells), the patient elected for laparoscopic ureteral lysis and psoas hitch reimplantation. Negotiating such complex ureters requires the availability and use of a variety of guidewires including hydrophilic, angle-tipped, floppy and stiff/super-stiff varieties.

Similar findings were noted in a patient with right-sided renal tuberculosis and left ureterovesical junction obstruction of unclear etiology (Fig. 12.6). The left ureter was extremely tortuous and dilated while the right ureter showed multiple filling defects consistent with renal tuberculosis. The patient underwent a right laparoscopic nephrectomy for renal tuberculosis and is currently being managed with stent changes for her left hydroureteronephrosis. Chronic stent changes require plastic (to be changed every 3–4 months) versus metal varieties that can be left indwelling for up to 1 year. Such stent changes frequently can be performed under local anesthesia with fluoroscopic guidance.

Ureteropelvic junction obstruction is a common etiology for unilateral (or even bilateral [Fig. 12.7]) renal obstruction. Workup includes functional nuclear imaging and, in some cases, cross sectional arteriography to evaluate for a blood vessel crossing over the anterior aspect of the ureteropelvic junction. A complete description of evaluation and management of ureteropelvic junction obstruction is beyond the scope of this chapter.

Non-malignant Intrinsic

Non-malignant intrinsic causes can include obstructing ureteral stones, ureteral strictures, congenital ureteropelvic junction obstruction, infection and fibroepithelial polyps among others.

A representative case involves a 68-year-old female with a long mid-ureteral stricture which developed after a series of complicated ureteroscopy procedures performed for obstructing cal-

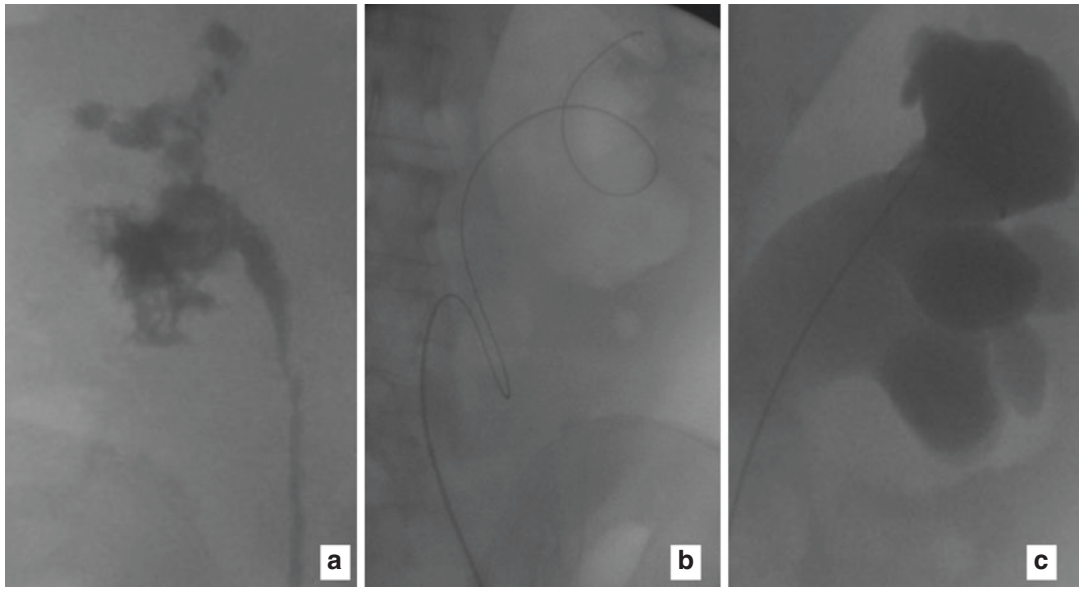

Fig. 12.6 Renal Tuberculosis. (**a**) Typical retrograde pyelogram showing renal infection with mycobacterium tuberculosis. (**b**) Same patient, with associated left ureterovesical junction obstruction, tortuosity of the ureter, and severe hydroureteronephrosis

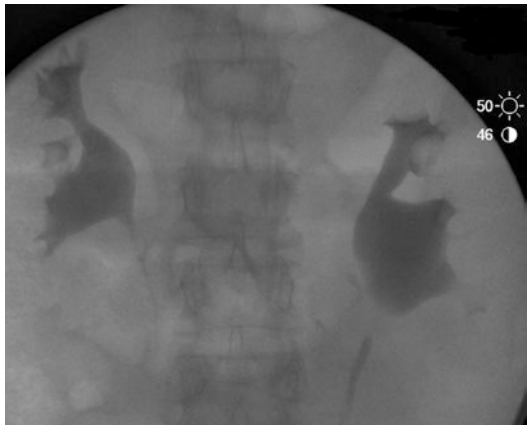

Fig. 12.7 Bilateral Ureteropelvic Junction Obstruction

culi (Fig. 12.8). The patient ultimately developed a complete obstruction; retrograde imaging combined with antegrade nephrostography illustrated that the ureter was obliterated from the entire middle third. The patient's GFR was approximately 28 mL/min and she had 34% split renal function on nuclear imaging on the affected side. This patient elected for management with a laparoscopic donor nephrectomy followed by an auto-transplantation of the left kidney to the left pelvis to avoid potential dialysis. In cases where marginal renal function would preclude an ileal ureteral substitution due to electrolyte abnormalities, long or proximal ureteral defects, and/or preservation of existing renal function is critical to avoid dialysis, laparoscopic donor nephrectomy with auto-transplantation offers an excellent management option.

Next consider the case of a 56-year-old female who presented with an infected ventriculoperitoneal shunt (Fig. 12.9). She was incidentally discovered to have bilateral "obstructing" ureteropelvic junction calculi and severe hydronephrosis on CT imaging. The patient was producing urine, had normal renal function, and had no flank pain. Given the dilation of the collecting system and the impacted appearance of the stones on CT imaging, the patient elected for bilateral simultaneous percutaneous nephrolithotomies. She was rendered stone free after one procedure. Figure 12.9 reveals that the kidneys had excellent initial uptake of contrast on CT images and her normal renal function suggested that even though the kidneys were "obstructed", remarkably they

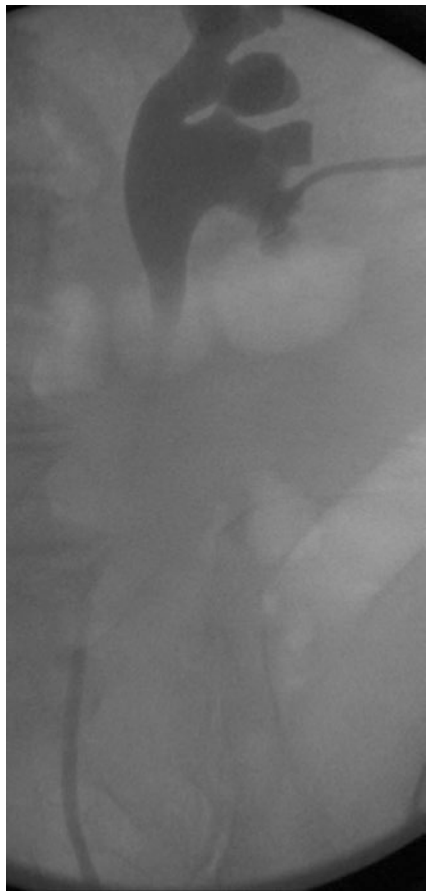

Fig. 12.8 Ureteral Stricture. A simultaneous antegrade nephrostogram and retrograde pyelogram demonstrate a long segment mid-ureteral stricture in a patient with marginal renal function. She elected for auto-transplantation as she was not an ideal candidate for ileal-ureter interposition and wanted to avoid hemodialysis

are still functioning normally. The patient was not having any pain from her "obstructing" stones. Acute urinary obstruction without radiographic evidence of obstruction can result in severe pain while chronic obstruction with slow dilation may be associated with an asymptomatic patient. History along with appropriate imaging will help direct therapy.

Oftentimes multiple etiologies will coexist in a single patient to create a clinical scenario of renal obstruction. Two elderly gentlemen for example, presented with left-sided hydronephrosis (Fig. 12.10). On physical examination and CT imaging they were both noted to have extreme prostatomegaly. In the first gentleman (Fig. 12.10a), hydroureteronephrosis persisted down to the ureterovesical junction where J hooking (where the ureters are acutely angulated superiorly due to mass effect from the prostate) was appreciated. The patient's renal pelvis was severely dilated, and contained a 2 cm ovoid renal calculus. A stent had been placed prior to our encounter for management of this previously impacted stone.

The second gentleman (Fig. 12.10b) however had a distal ureteral calculus which had been lodged at the J hook created by the extremely large prostate. This acute angulation is a common site for impaction of ureteral calculi and presents a unique and difficult clinical scenario for the endourologist. Access to the angulated distal ureter is complex, requiring careful navigation

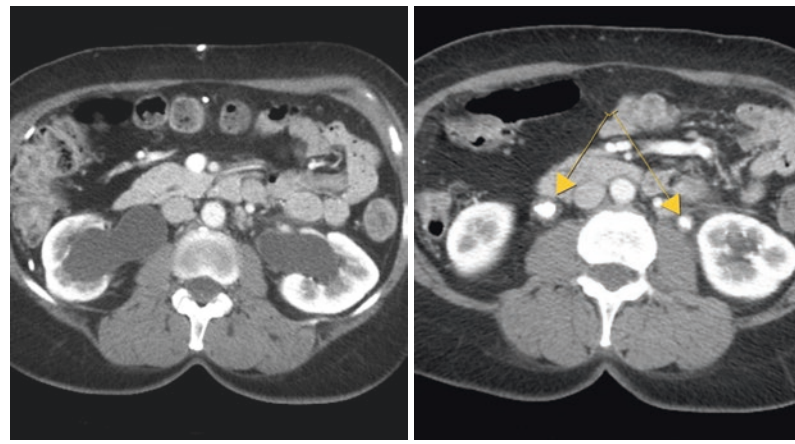

Fig. 12.9 Silent "Obstruction". A patient with bilateral hydronephrosis (left) caused by bilateral impacted ureteropelvic junction stones (right). She had no flank pain and normal renal function on presentation; nephrograms are symmetric and the kidneys have good uptake of contrast on this contrast enhanced CT scan

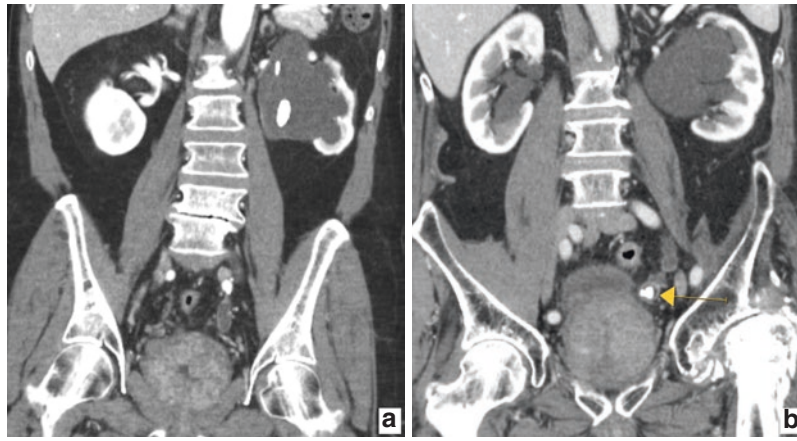

Fig. 12.10 Extreme Prostatomegaly. (**a**) A gentleman with an extremely large prostate who presented with hydroureteronephrosis despite the presence of a ureteral stent placed for a previously obstructing stone seen in the renal pelvis. The large prostate inhibited ready drainage of the renal pelvis due to acute angulation at the ureterovesical junction. (**b**) A different elderly man with a very large prostate who presented with an asymptomatic distal ureteral stone which was lodged at a site where the ureter abruptly angulated superior-medially in a classic "J Hook"

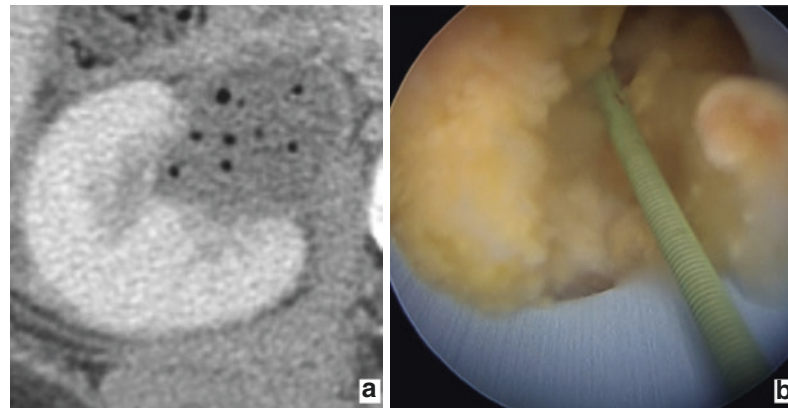

Fig. 12.11 A young woman with poorly controlled type 1 diabetes mellitus was found to have a fungal bezoar in the right renal pelvis on cross sectional CT imaging (**a**). This mucoid material was extracted percutaneously (**b**)

around a friable and enlarged median lobe which obstructed the view of the distal ureter. Furthermore, the ureteral orifice pointed superior-medially, making cannulation difficult. Percutaneous antegrade approaches often prove to be more successful.

Infectious etiologies can cause renal obstruction, as in the case of a 23-year-old woman who struggled with intravenous drug abuse and had brittle, poorly controlled, type 1 diabetes mellitus (Fig. 12.11). She presented with acute abdominal pain and fever and was found to have fungemia on blood culture; CT scan revealed a complex loculated collection within the right kidney. Suspecting a fungal bezoar, percutaneous renal surgery was performed to evacuate the obstructing fungus ball. The patient made a prompt recovery and the evacuated material was sent for culture, growing *Candida Tropicana*.

Malignant Extrinsic

Malignancies of the pelvis and abdomen are common causes of hydronephrosis. Often, this is caused by mass effect as opposed to tightening scar tissue or bands. Consider the case of a 91-year-old female, with a large right adnexal mass causing a right ureteral obstruction (Fig. 12.12). The patient elected for placement of a long-term metallic ureteral stent to manage the compression being exerted upon the right ureter

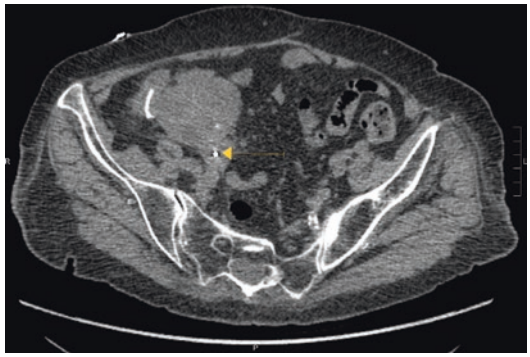

Fig. 12.12 External Compression from a large right adnexal mass in an elderly female. The arrow denotes the metallic ureteral stent that was placed for palliative management

and to preserve renal function. Key to such cases is recognizing the prognosis, goals of care, and values of the patient and their family/caregivers. Often, as the obstruction and malignancy progress, stents will fail necessitating nephrostomy tubes. It is pertinent to consider the patient's goals of care in these situations, as nephrostomy tubes can present a significant loss in quality of life for many of these patients.

Malignant Intrinsic

Urothelial carcinoma, particularly of the ureter or renal pelvis, represents a relatively uncommon cause of unilateral ureteral obstruction. It is most commonly managed with nephroureterectomy but can also be managed by endoscopic means in select situations. Occasionally, invasive bladder cancer can cause ureteral obstruction as well, which is more often bilateral than that of upper tract disease (Fig. 12.13).

Anatomic Changes Due to Obstruction

Depending on the location of the obstructive process, a variety of anatomic changes will take place [2, 3, 6]. In the case of bladder outlet obstruction, compensation will often occur if the process is chronic. The bladder will become stretched and the wall trabeculated as the urothelium herniates between the fibers of the detrusor

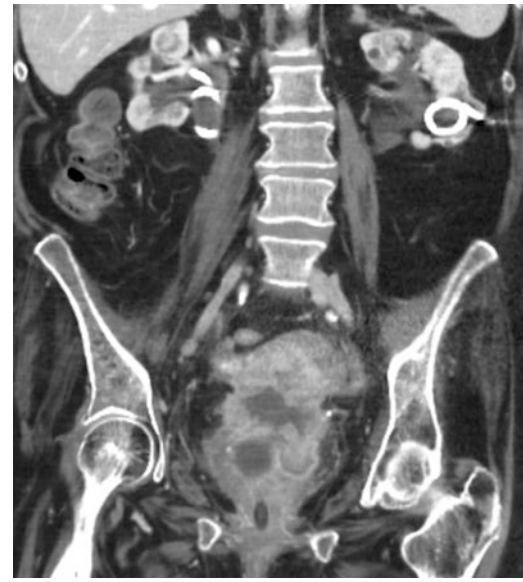

Fig. 12.13 Invasive bladder cancer causing bilateral ureteral obstruction managed with bilateral nephrostomy tubes

muscle and collagen. The elevated pressures within the bladder can facilitate poor emptying of the ureter into the bladder due to a reduced pressure differential as well as, over time, chronic hypertrophy of the bladder trigone. This process will ultimately result in hydronephrosis and ureteral hypertrophy, compounding the effects at the ureterovesical junction as the ureter increasingly angulates and thickens. Ultimately ureteral reflux can compound any hydronephrosis as the valve effect of the ureterovesicular tunnel is lost, exposing the kidney to increased pressures. This phenomenon results in the poor ureteral drainage and "J Hooking" seen in the case study shown in Fig. 12.10.

Should the obstruction be more proximal than the bladder outlet, the effect on the kidney will be similar over time. The mildest forms of obstruction will produce hydroureteronephrosis, or dilation of the ureter and/or renal pelvis (Fig. 12.2). With chronic mild obstruction, we observe blunting of the renal calyces as the papillae that project into them become flattened and attenuated (Fig. 12.7). The convexities normally observed in this area transition to flattened areas. Over time, atrophy within the renal parenchyma is observed

and thought to be principally related to both compressive and ischemic forces (Fig. 12.3). Furthermore, tortuosity of the ureter will develop over time as shown in Fig. 12.5. Typically, such renal unit loss is more commonly observed when the obstruction is unilateral, as the other kidney can compensate for the loss of urine filtration. Such a condition, if bilateral, would manifest with metabolic derangements associated with renal insufficiency much sooner than required for renal atrophy and fibrosis.

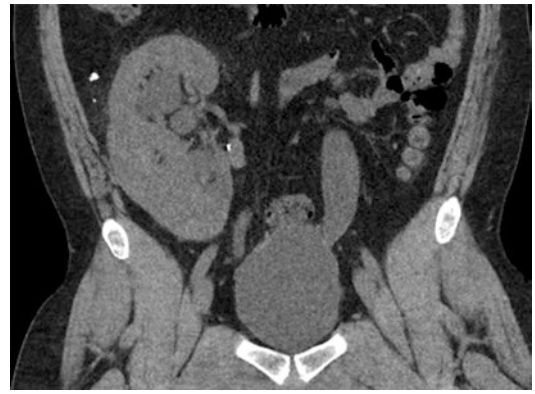

Fig. 12.14 A young man presented with recurrent urinary infections status post Cohen cross trigonal ureteral reimplantation, left nephrectomy, and a right cadaveric renal transplantation. The left ureteral stump (∗) had become dilated and poorly draining. The right native kidney was hydronephrotic. The transplant kidney also had mild hydronephrosis (arrow)

Congenital Obstruction

Congenital obstructive nephropathy has become increasingly recognized since the advent of prenatal ultrasonography, beginning in the 1980s. This clinical condition is the leading cause of renal failure requiring transplantation among children and the most common cause of renal insufficiency in males under 1 year of age [7]. In pediatric populations, renal obstruction can result in hypoplasia of the renal unit, or progressive deterioration in renal function over time should that kidney not involute prior to birth (such as with reflux nephropathy). Occasionally, obstructive hypertension will be found and is often mediated by renin release, especially in cases of unilateral obstruction [8].

Consider the case of a 29-year-old male who presented with recurrent urinary tract infections. He reported a history of having undergone an unknown pediatric urologic procedure as well as undergoing a renal transplant approximately 15 years previously (Fig. 12.14). Axial imaging revealed a right-sided cadaveric renal transplant with mild hydronephrosis and an atrophic native right kidney. The left kidney was surgically absent, however there was a dilated distal left ureteral remnant noted on the CT scan. Cystoscopy and retrograde pyelography revealed that the patient was status post a Cohen cross-trigonal ureteral reimplantation and left laparoscopic nephrectomy with closure of the left ureteral remnant and had no evidence of posterior urethral valves. Selective cultures were performed from the transplant ureter and bilateral native ureters but returned negative for infection. Here, it is important to recognize that ligation of the distal ureteral stump can create an opportunity for a poorly draining reservoir that can be the source for recurrent infections. Furthermore, the atrophic native kidneys can become chronically colonized and infected. Reflux into the transplant ureter can create a nidus for infection.

Congenital obstructive nephropathy represents a distinct entity from a pathophysiologic standpoint compared to that of acquired, adult, obstructive nephropathy (Fig. 12.15). This signifies a failure of development—a dysplasia—as opposed to atrophy of well-formed tissues [9–12]. Throughout the process of embryologic development, stem cell differentiation represents the basis for the formation of the complex network of nephrons the makeup of the kidney. This cellular progression becomes disrupted as obstructive forces are applied to the tubular segments resulting in alterations and expression of genes responsible for kidney growth and development.

The exact determinants of cellular differentiation and dysplasia in congenital obstructive models have not been fully elucidated. In animal models, a complete obstruction prior to 50% of the gestational cycle has been shown to lead to

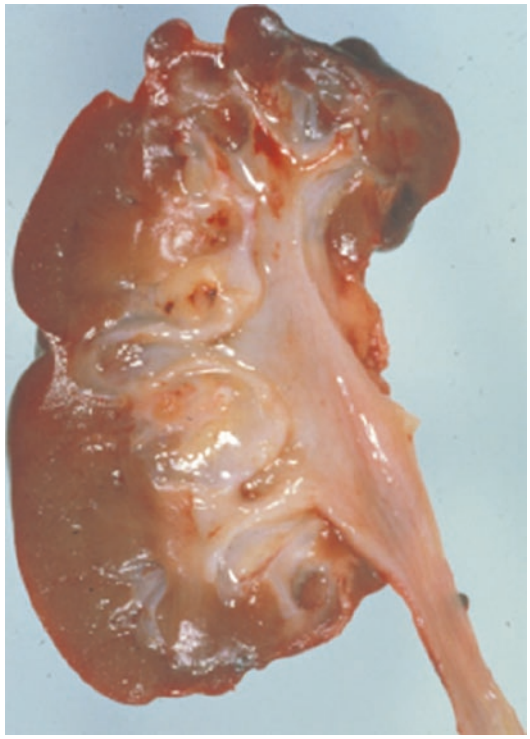

Fig. 12.15 Reflux nephropathy. Reproduced with permission from [3]

dysplastic development in animal fetuses [13]. Histologic findings in renal dysplasia include "fibromuscular collars", which are known as primitive ducts [3]. It is thought that these form as a result of abnormal interaction of the primitive nephrogenic blastema and ureteral bud epithelium. Associations have consistently been made with increased expression of α-smooth muscle actin (α-SMA) and Transforming Growth Factor β (TGF-β) [14–18].

Dysregulated apoptotic mechanisms are also a hallmark feature of renal dysplasia and are mediated by Tumor Necrosis Factor alpha (TNF-α) [19, 20]. In the developing kidney, as cells are growing and differentiating, a small fraction of cells will normally undergo apoptosis in order to create the complex architectures necessary for normal nephron function. In the presence of obstruction, however, those cells will be stimulated by apoptotic cellular signaling to undergo cell death, a process recognized as the primary mechanism for renal mass loss in congenital renal obstruction [21]. A number of molecules have been implicated in this process including, but not limited to, TGF-β1, TNF-α, and p53 caspases. Eventually, the obstructive process becomes intimately linked with a fibrotic process [18] similar to that which occurs in acquired obstructive nephropathy, the details of which are discussed below.

Acquired Obstruction

Hemodynamic Changes

Animal studies have been pivotal in our understanding of the nephrological and hemodynamic changes which occur following urinary obstruction. The most famous studies, by Vaughan, were performed with anesthetized dogs in the 1970s. In the experiments either one or both ureters were ligated in dogs with either one or two kidneys. Renal blood flow was measured, and in subsequent studies so were the various renal vasoactive hormones. Pathophysiologic effects vary with unilateral compared with bilateral (similar to obstructed solitary kidney) obstructions.

Unilateral Obstruction

With unilateral ureteral obstruction (UUO) three phases of renal blood flow are observed [22]. In five awake dogs, continuous monitoring of ipsilateral renal blood flow and ureteral pressure was performed. During the first 90 min, renal blood flow and ureteral pressure rose concomitantly. Next, up to the 5-h mark, renal blood flow was observed to decrease in contrast to a rising ureteral pressure. Over the next 13 h, both the blood flow and ureteral pressure steadily declined. Prostaglandin E2 and nitric oxide act as vasodilators, maintaining afferent arteriolar pressure and GFR in the obstructed kidney [23, 24]. After the ultimate plateau of collecting system pressure, Renal Blood Flow (RBF) begins to decrease (and with it GFR) as a result of afferent vasoconstriction and a decline in P_{GC}. Blood flow becomes redistributed within the kidney, from the cortex to juxtamedullary regions, resulting in reduced glomerular perfusion associated with Angiotensin II (AT-II) release [24]. The third and final phase is

characterized by reduced tubular and collecting system pressures from the contralateral kidney's response to Atrial Naturietic Peptide (ANP), restoring fluid balance and increasing urine excretion. Thromboxane mediated vasoconstriction occurs at the afferent and efferent arterioles on the affected side. Ureteral pressures steadily normalize with decreased urine output on the affected side and renal pelvic/ureteral dilation.

In animal models of acute unilateral ureteral obstruction, an afferent arteriolar constriction occurs in response to thromboxane A2 and AT-II, lowering glomerular hydrostatic pressure and decreasing GFR [4]. In contrast, congenital ureteral obstruction is often a situation of partial ureteral obstruction that occurs over a prolonged period during renal development. Using a rat model of congenital hydronephrosis, one group of researchers sought to elucidate the role of thromboxane A2 and AT-II and the effect of these substances on GFR as measured during micropuncture flowmetry [4]. The researchers found that single nephron GFR and single nephron blood flow were 50% lower in hydronephrotic right kidneys compared to controls. Treatment of affected rats with thromboxane A2 or AT-II receptor antagonists resulted in improvement of renal function. With combined treatment, the filtration coefficient increased above control, suggesting that independent mechanisms for filtration reduction beyond afferent vasoconstriction alone are at play in obstructive nephropathy.

Bilateral Obstruction

In the bilateral or solitary kidney obstructive model (BUO), the first phase of renal blood flow increase is blunted in comparison to the UUO model. There is a more significant vasoconstrictive/hypertensive effect that augments the second phase; glomerular blood flow decline is suppressed due to increased afferent arteriolar pressure. GFR is later decreased with a significant increase in tubular pressures. In the late phase, GFR remains suppressed; ureteral pressures are persistently elevated due in part to continued afferent vasoconstriction and hypertension in response to fluid retention [25] which cannot be offset by the contralateral kidney.

Changes at the Level of the Nephron

Elevated intrarenal pressure caused by obstruction will result in a cascade of cellular and molecular processes, in some cases revisable and in some cases permanent. As the pressures within the collecting system increase, fluid will flow retrograde into the ducts of Bellini causing pressure on the vasa-recta and small capillary beds in an already poorly vascularized region. With increased intra-tubular pressure comes decreased renal blood flow and GFR. Hypoxic signals are released from the renal tubular cells, including AT-II and TNF-α [19, 20]. AT-II will cascade with NF-kβ towards renal fibrosis mediated by inflammatory matrix metalloproteases. Alternatively, TNF-α can cascade towards apoptosis mediated by cytochrome-c caspases. Profibrotic signaling pathways including TGF-β and Notch are critical for the development of fibrosis after ureteral obstruction occurs.

During renal development, Notch molecules (single pass transmembrane receptors involved in cellular differentiation and signaling) are critical for renal development [26]. Notch signaling also has been implicated in chronic kidney disease. In particular, Notch 1 and Notch 2, two molecules active during kidney development but typically inactive in adulthood, have been shown to be expressed in various models of chronic kidney disease. The Notch 3 molecule is also thought to be of importance for the processes of renal fibrosis in kidney disease, having been found to stimulate endothelial proliferation and promote fibroblast migration and pro-inflammatory pathways. It is not clear, however, if Notch 3 receptors exhibit more of a regulatory (or even protective) effect in the setting of renal injury, as homozygous Notch 3 deficient mice experience increased renal injury after the infusion of AT-II [27, 28].

One study examined the role of *notch 3* expression in 18 patients with obstructive nephropathy and compared them to 6 control patients [26]. The researchers observed that *notch 3* was upregulated in patients with obstructive nephropathy compared to controls. They further verified their findings in a rat model, in which unilateral ureteral obstruction was produced. In

these rats, *notch 3* expression steadily increased over time from days 3 to 21, in unison with increases in histologic signs of kidney injury and fibrosis and the expression of α-SMA. Furthermore, the authors found that TGF-β protein expression increased over time in the setting of ureteral obstruction. The administration of TGF-β to cultures of human kidney cells stimulated the expression of *α-SMA* and *notch 3* compared to controls. Lastly, the authors were able to elucidate the role of extracellular signal-regulated kinase (ERK) and Smad family proteins to establish a molecular model wherein TGF-β 1 stimulates α-SMA and notch 3 in parallel through ERK and Smad to produce renal fibrosis in a potential feedback loop.

After approximately 12 h of obstruction and through the first 2 weeks, interstitial inflammatory cell types, and in particular macrophages, will infiltrate into the obstructed kidney in response to upregulated cytokines [29]. Upregulation of TNF-α, and AT-II, a variety of cell adhesion molecules, cytokines, and osteopontin all have been described [21]. Down regulation of AT-II activity has been shown to reduce fibrosis in obstructive nephropathy models.

Mechanical stretch and ischemic injury to tubular cells has been shown to be largely related to apoptosis within models of unilateral ureteral obstruction [29]. This tubular cell depth is first observed only 1 day after unilateral ureteral obstruction, and steadily increases over the first several weeks. Tubular dilation and apoptosis peak at the two-week mark. Cell cycle arrest is also a hallmark of ureteral obstruction in the acute phase. Ultimately, this will progress to fibrosis as large amounts of TGF-β1 proceed to activate fibroblasts.

Tubulointerstitial fibrosis is a progressive process occurring as the acute kidney injury from obstruction proceeds into the chronic phase. Type I and type III collagen are laid down within the interstitium of the renal parenchyma beginning at 2 weeks after obstruction. The accumulation of extracellular matrix is often irreversible and results from the process of fibroblasts becoming activated into myofibroblasts with *de novo* expression of α-SMA, largely stimulated by TGF-β1. With chronic exposure to TGF-β1, the methytransferase Dnmt-1 becomes constitutively activated and allows for *Ras* Gene hyperactivation through the RAS protein activator like 1 (RASAL-1) pathway. Subsequently, fibroblasts activation and proliferation of fibrosis begins.

Role of Mast Cells

Increasingly, infiltrative inflammatory leukocytes have been found to play an important role in the development of renal fibrosis and chronic kidney disease, especially in the setting of obstruction [30, 31]. These inflammatory cells not only include macrophages and T cells but also mast cells, which are granulated cells that release histamine and a variety of cytokines/proteases (10–12). Mast cells include a number of important inflammatory regulators in their granules, one of which is known as tryptase, a potent fibroblast proliferation and collagen deposition promoter. Mast cells also contain a protein known as chymase which, in conjunction with matrix metalloproteinase, works to degrade the extracellular matrix proteins.

In settings of renal obstruction, elevated renin release will trigger the renin angiotensin aldosterone system (RAAS) [30]. This cascade results and AT-II stimulating the production of TGF-β, thereby suppressing the degradation of extracellular matrix and leading to fibrosis. This process has been experimentally demonstrated in a number of models of renal injury including obstructive models, models for glomerulonephritis and diabetic nephropathy. RAAS blockade has been shown to reduce the rate of renal functional decline amongst diabetics. Importantly, mast cells have been shown to release renin during degranulation. Chymase, also produced by mast cells, is able to facilitate the conversion of AT-I to AT-II, thus potentiating the pro-inflammatory, pro-fibrotic, systemic response to renal obstruction.

In a mouse model of unilateral ureteral obstruction, the role of the human analogue to α-chymase, mouse MC protease 4 (mMCP-4), researchers were able to establish that mice deficient in this chymase exhibited increased renal fibrosis and collagen deposition after ureteral

obstruction compared to wild type mice and control mice without obstruction [31]. Furthermore, myofibroblast generation and the inflammatory response (as evidenced by E-cadherin and α-SMA expression) was noted to be significantly increased amongst mMCP-4 deficient mice. mMCP-4 was found to reduce levels of fibronectin expression but had no effect on AT-II levels in obstructed kidneys.

Another study sought to examine the role of mast cells in renal fibrosis in an obstructive model by using mice deficient in mast cells that have mutations in the gene *c-kit*, which is responsible for mass cell differentiation [32]. The authors noted that after a week of unilateral ureteral obstruction, mast cell deficient mice had reduced levels of renal fibrosis compared to controls; mast cells are typically recruited to hydronephrotic kidneys and undergo degranulation, and the expression of *tgf-β, α-sma*, and *matrix metalloproteinase 12 (mmp-12)* are reduced in these mice. Restoration of mast cells to affected mice stimulated fibrotic responses to hydronephrosis. Disodium chromoglycate, which prevents mast cell degranulation, was noted to reduce levels of renal fibrosis in the obstructive mouse model.

Mast cells may not only serve to promote fibrosis within obstructed kidneys, as there is some evidence to suggest that they perform regulatory processes as well by modulating profibrotic mediators [33]. In a study utilizing *WBB6F1–kit* knockout mice which are deficient in mast cells, one group of researchers found that tubular injury scores were lower in the presence of mast cells. When compared to controls, mice with no mast cells showed increased levels of renal tubular damage inflammatory cell infiltrates, and fibrosis. Reconstitution of these mast cell deficient mice with mast cells reduced levels of tubulointerstitial damage and collagen deposition seen on histologic preparation at 3 weeks post obstruction. Levels of TGF-β1 were noted to increase after obstruction in kidneys of uterine mice, but reconstitution with mast cells reduced the levels of TGF-β1 towards control. The authors conclude that mast cells may have a regulatory effect on TGF-β1 release and the infiltration of other inflammatory cell types.

Urinary Concentrating Ability

Urinary concentrating ability will become compromised with renal obstruction. Aquaporin expression becomes dysregulated within the proximal tubules, thin descending loops, and collecting ducts as the hypertonic environment of the distal papilla is lost with papillary ischemia and due in part to chronic antidiuretic hormone (ADH) exposure suppressing aquaporin channel expression [34]. The distal nephron will become deficient in acidification potential with reduced expression of the H^+ATPase, and magnesium excretion will also decrease markedly. Fractional excretion of sodium will increase (more significantly in the BUO model) due to water and salt retention stimulated by reduced renal blood flow and the renin, angiotensin, aldosterone system. ANP will increase [35], and sodium transporter expression will be reduced. If one were to measure the urea to creatinine ratio in the urine of an obstructed UUO kidney, the concentrating power of that kidney would be noted to be lower as measured by a reduced urea to creatinine ratio. The obstructed kidney will continue to produce poorly concentrated urine even while obstructed. The fluid and solutes will tend to be reabsorbed through lymphatic and osmotic processes. Alternatively, forniceal rupture may occur in acute hydronephrosis and cause the pressure to be relieved.

Recovery

Ultimately, in the UUO model compensatory renal growth will compensate for renal functional loss on the contralateral side. The length of the proximal convoluted tubules will tend to increase, while the number of nephrons will remain constant. In those kidneys which have become acutely obstructed, as by stone or similar mechanism, functional decline will tend to be temporary through the first 4 weeks. After such time, renal function will tend to steadily deteriorate, and the contralateral kidney will assume more and more of the functional load. Upon removal of such an obstruction, the presence of a hypertrophied renal unit is thought to reduce the stimulus for the affected kidney to regain significant function.

Management

Decompression of the obstructed urinary system is achieved depending on the level of the obstruction. For that occurring at the bladder outlet, urethral or supra-pubic catheter placement is the mainstay. Ureteral obstruction can be rapidly relieved with ureteral stenting or nephrostomy tube placement. More definitive reconstructive, oncologic, or endourologic procedures are performed on a case by case basis.

Clinical Sequelae

Hypertension

Volume related hypertension is a relatively common complication of BUO. In a UUO, hypertension development would tend to be related to elevated levels of hormones from the renin angiotensin aldosterone system and is more often transient.

Post Obstructive Diuresis

Post-obstructive diuresis is of concern after the relief of bilateral obstruction; most commonly seen in the setting of severe acute urinary retention, after a Foley catheter has been placed. The obstructive process will have precipitated a volume expansion in the individual, as well as the resorption of a significant amount of sodium. The loss of the medullary countercurrent-exchange osmotic gradient, the downregulation of sodium transporters within the ascending limb of the loop of Henle, elevated ANP and a resistance to ADH through aquaporin downregulation will set the stage for post-obstructive diuresis. When renal pressure decreases, GFR will increase and the disrupted tubular concentrating mechanism will produce a pathologic diuresis. Release of bilateral ureteral obstruction permit renal function to resume in the setting of high levels of ANP, stimulating a prompt diuresis [23].

Management of post obstructive diuresis relies on controlling the fluid balance with cautious replacement of intravenous fluids, generally at a 1:2 ratio to urine loss, however the patient should be allowed liberal access to oral fluids. The patient must be monitored and treated for electrolyte abnormalities as they manifest. Recovery can be charted by measurement of urine osmolarity.

Conclusion

The pathophysiology of renal obstruction lies at the intersection of urology and nephrology. This condition when acute often represents a significant cause of pain and suffering for patients, while when chronic can result in significant deterioration in quality of life in the event of renal failure requiring dialysis. Recognizing and treating the condition is of paramount importance for the urologist to prevent renal functional decline. Stratification of renal obstruction into intrinsic and extrinsic etiologies may be helpful in formulating a differential diagnosis and treatment algorithm. An understanding of the long-term sequelae, including renal fibrosis is important for the development of future interventions aimed at renal function preservation and restoration.

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Urologic Imaging

13

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Abbreviations

ADC	Apparent diffusion coefficient
ADPKD	Autosomal dominant polycystic kidney disease
AML	Angiomyolipoma
AS	Active surveillance
AUA	American Urological Association
BCG	Bacillus of Calmette-Guerin
BPH	Benign prostatic hyperplasia
bpMRI	Bi parametric magnetic resonance imaging
BS	Bone scan
BSI	Bone scan index
CDUS	Color Doppler ultrasound
CEUS	Contrast enhanced ultrasound
chRCC	Chromophobe renal cell carcinoma
CIN	Contrast induced nephropathy
cRCC	Clear cell renal cell carcinoma
csPCa	Clinically significant prostate cancer
CT	Computerized tomography
CTU	Computerized tomography urography
DCE	Dynamic contrast enhancement
DECT	Dual energy computerized tomography
DMSA	Dimercaptosuccinic acid
DRE	Digital rectal examination
DTPA	Triamine pentaacetic acid
DWI	Diffusion weighted images
EAU	European Association of Urology
EC	Endorrectal coil
FDA	Food and Drug Administration
FDG	Fludeoxyglucose
GCT	Germ cell tumors
GSUS	Grey scale ultrasound
HU	Hounsfield units
IP	In phase
KUB	Radiographs of the kidneys ureters and bladder
LUTS	Lower urinary tract symptoms
MAG-3	Mecapto acetyl triglycine
MEST	Mixed epithelial stromal tumor
mpMRI	Multi parametric magnetic resonance imaging
mpUS	multi parametric ultrasound

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MRI	Magnetic resonance imaging
MRU	Magnetic resonance urography
NCCN	National Comprehensive Cancer Network
NCCT	Non-contrast computerized tomography
NICE	British National Institute of Health and Care Excellence
NPV	Negative predictive value
NSGCT	Non-seminomatous germ cell tumors.
OOP	Out-of-phase
PCa	Prostate cancer
PDUS	Power Doppler ultrasound
PET	Positron emission tomography
PI-RADS	Prostate imaging reporting and data system
pRCC	Papillary renal cell carcinoma
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
PZ	Peripheral zone
RCC	Renal cell carcinoma
RI	Resistive index
SWE	Shear-wave elastography
T1-WI	T1 weighted images
T2-WI	T2 weighted images
TAUS	Trans abdominal ultrasound
TB	Tuberculosis
TRUS	Trans rectal US
TZ	Transition zone
UPJ	Ureteral pelvic junction
US	Ultrasound
UVJ	Ureteral vesical junction
VNC	Virtual non-contrast
XGP	Xanthogranulomatous pyelonephritis

Introduction

Imaging is an integral part of the evaluation of urologic patients, regardless of the organ site or disease process. Historically, the ability to image the upper tract enabled the identification and management of renal stone disease, urinary obstruction, and eventually, malignancies. In contemporary practice, imaging is a core component of the evaluation of a wide range of common urinary tract symptoms including hematuria, recurrent infection, hypertension, orchalgia, and incontinence. Almost all urologic surgeries, whether reconstructive or extirpative, are preceded by imaging—both for determining indication and planning the operation itself.

The relationship between urologist and radiologist is a critical one, as the urologist's actions are often based upon the judgement of the radiologist. Continual communication, both to understand the image interpretation of the radiologist and to communicate the need of the urologist, is critical for good patient care, quality assurance, and maximizing patient outcomes. It is also incumbent upon the urologist to understand the indications, techniques, and strategies for general interpretation of films. By understanding imaging, and gaining the skills to interpret images in the context of urologic disease, urologists empower themselves to become better clinicians.

Imaging Techniques

Multiple imaging tools are available to assess the urinary tract. Each has its own strengths and weaknesses. Knowing which to use in the correct clinical scenario will help the urologist in management decisions. Imaging tools include ultrasound (US), computerized tomography (CT), magnetic resonance imaging (MRI), radiography, and nuclear medicine studies.

US

US is the usual first line imaging modality as it is one that provides the most information for the least cost, both monetarily and with regard to radiation exposure. The location of the kidneys in the retroperitoneum without overlying bowel lends them well to ultrasound imaging. Ultrasound offers multiple types of imaging techniques. Grey-scale imaging is best in characterizing overall renal anatomy and renal masses to determine whether they are solid or cystic or contain calcifications. Color Doppler imaging can show flow of fluid demonstrating vascularity of a lesion or flow of urine, such as ureteral jets in the bladder. Spectral Doppler imaging investigates

the specific waveforms that are produced in flow, which further investigates vascular flow, thereby confirming whether a mass is truly solid with internal vascularity or cystic, containing hemorrhage or debris [1]. In addition, from waveform analysis, spectral Doppler imaging can elucidate functional information such as increased intrarenal pressure from venous thrombus or ureteral obstruction.

Contrast enhanced ultrasound (CEUS) utilizes microbubble agents which are foci of gas encased in polymers, lipids, or proteins. These molecules measure approximately 1–10 μm. Agents are injected intravenously and images are acquired in regions of interest, typically in dynamic imaging. The ultrasound probe detects the harmonic signals produced by the bubbles expanding and contracting in response to the ultrasound waves. The gas is exhaled and the encasing molecules are excreted, typically by the liver [1].

Limitations of ultrasound include the dependency on the technical ability of the end user and the body habitus of the patient. US also is only able to acquire images in a small field of view.

CT

CT utilizes X-rays to create cross-sectional imaging with high contrast between various soft tissues, especially with the use of intravenous contrast. This is advantageous to urologic imaging as it can separate solid, enhancing lesions versus cystic lesions. It can easily detect, characterize, and localize urinary calculi. In addition, CT is able to visualize a large field of view to evaluate structures adjacent to the kidneys and urinary tract, metastasis, as well as any other abnormality that may mimic urologic pathology. Images are acquired over a few seconds, which decreases motion artifact.

CT is important for evaluation of renal lesions as it allows improved ability to detect lesions, as compared to ultrasound, especially with the administration of intravenous contrast material. Intravenous contrast is excreted through the kidneys and progressively enhances the kidneys in a time dependent predictable pattern. Images acquired 25–80 s after contrast administration are considered the corticomedullary phase in which the cortex appears hyperdense while medullary pyramids are hypodense [2]. The nephrographic phase acquired 85–120 s after contrast administration, demonstrates homogeneous enhancement of the cortex and medullary pyramids [2]. Finally, the urographic phase acquired 3–10 min after contrast administration images the kidneys after excretion of contrast into the collection system and bladder [2].

A relatively new CT technology is dual-energy CT (DECT), which utilizes or detects specific low and high kilo-voltages to discriminate between materials of different atomic numbers [3]. Post-processing algorithms utilizing material decomposition principles have been developed to subtract iodine in contrast enhanced images to create virtual non-contrast image [4]. This potentially allows one to gain information of a non-contrast examination without a separate CT acquisition, which significantly decreases radiation exposure to patients [5]. The greatest downside to CT is the high radiation exposure, especially of repeated scans performed for follow-up [6]. Iodinated intravenous contrast may also cause contrast induced nephropathy (CIN), especially in patients with renal insufficiency [7].

Multiparametric MRI

MRI utilizes a strong magnetic field and radiofrequency pulses to organize and flip protons of hydrogen atoms within the complex molecules of the human body. Different sets of pulses elicit various responses of protons and give rise to the signals which in turn translate to tissue contrast greater than CT or US. Each sequence is designed to highlight distinct attributes of the tissue under evaluation. Multiparametric MRI (mpMRI) is a combination of sequences performed in a set for in-depth characterization [8]. The most commonly performed sequences are described below.

T2-Weighted Sequence

T2-weighted images (T2-WI) are fluid sensitive sequences in which fluid is high signal including

free fluid, fluid in structures of the body such as the urinary bladder, spinal canal and gallbladder. Fluid in edema also increases signal in tissues. In addition, neoplasms are typically T2 bright, with some exceptions. Thus, T2-WI are generally anatomic sequences useful as an initial overall view of the overall condition of the patient [8].

T1-Weighted Sequence

Fat, blood and proteinaceous products appear bright on T1-weighted images (T1-WI). Fluid has low-signal on T1-WI. In addition, gadolinium, the intravenous contrast agent used, is also high signal on T1-WI. Thus, all contrast-enhanced images are T1-WI. Typically pre-contrast images are acquired in addition to post-contrast images so that subtraction images can then be obtained to determine which tissues are truly enhancing [8].

Fat Suppressed Sequences

Fat demonstrates high signal intensity on T1-WI and turbo T2-WI. A common option is the suppression of fat from these sequences in order for more problem-solving technique. Fat is suppressed on T2-WI to highlight features of fluid or malignancy. On T1-WI, fat is suppressed on contrast enhanced sequences in order to minimize signals that may confound enhancing structures, which are also T1 hyperintense.

In and Out-of-Phase

In-phase (IP) and out-of-phase (OOP) sequences take advantage of the chemical differences of water and fat molecules. The hydrogen protons in each rotate at different frequencies and align at certain times to become additive (IP) and align at other times to cancel each other (OOP). OOP images can be distinguished from IP images as all the organs are outlined in a thick black line, an artifact called "India ink." These sequences are used together to ascertain whether lesions have fat and water in the same imaging unit, or voxel, called microscopic fat, such as in clear cell renal cell carcinoma. Lesions with fat and fluid in the same cell will be at least 10% decreased in signal intensity on OOP when compared to IP [9].

Diffusion-Weighted Sequence

Free flowing water molecules typically move in random patterns called Brownian motion. Water molecules can become trapped in some clinical situations such as in highly cellular neoplasms or abscesses. Diffusion-weighted images (DWI) are acquired at specific "b-values." Increasing b-values increases the weight of diffusion on imaging, thus DWI with high b-values only show signal of those trapped water molecules while freely diffusing water molecules lose signal. Apparent Diffusion Coefficient (ADC) maps are acquired by calculating the change of signal with multiple b-value sequences. Thus, those regions that maintain signal from low to high b-value will have low change and have low signal on ADC maps. Regions with restricted diffusion will have high signal on high b-value DWI sequences and low value on ADC maps [8].

Contrast-Enhanced Sequences

Similar to CT, intravenous contrast can be administered to increase conspicuity of renal masses, infectious process, or inflammation. Because there is no radiation exposure, images of multiple different time points may be acquired after contrast administration to assess dynamic contrast enhancement. Due to angiogenesis and increased vascularity of tumors, neoplasms tend to enhance earlier. Thus, dynamic contrast enhancement can differentiate lesions from other enhancing structures. Contrast is excreted through the kidneys and delayed urogram can be acquired to evaluated the collecting system, ureters, and bladder [10].

MRI utilizes gadolinium based intravenous contrast. The newer, macrocyclic contrast agents have not been proven to cause nephrogenic sclerosing fibrosis, even in the setting of renal insufficiency and thus can be administered in patients with renal failure. This is advantageous compared to CT intravenous contrast, which increases risk of CIN if administered in patients with renal insufficiency. In addition, gadolinium based contrast agents have not been shown to cause contrast induced nephropathy [11–15]. However, older linear gadolinium based agents have a rare risk of causing nephrogenic systemic fibrosis in patients

with renal insufficiency. If such agents are used, renal function should be assessed prior to contrast administration, Gadolinium based contrast administration is however contraindicated in pregnant patients.

Limitation

For the best images, patients must be able to be still during the duration of the examination, which may last up to one hour long. They must also be comfortable within an enclosed space for long periods of time. Care must be taken to ensure any devices and implants of patients are MRI compatible.

Radiographs

Plain film radiographs of the kidneys ureters and bladder (KUB) utilize x-rays and have high resolution but low tissue contrast. Radiographs can identify urinary calculi however the sensitivity is not as high as CT and is better used for follow up rather than initial diagnosis. Radiographs have less of a role in urologic imaging when compared to other modalities.

Nuclear Medicine Examinations

Nuclear medicine examinations utilize radioactive particles which are attached to specific ligands. The ligands bind to molecules in the body giving specificity in assessing function and presence of certain tumors. Nuclear medicine studies such as dimercaptosuccinic acid (DMSA) evaluate renal tissue while diethylene triamine pentaacetic acid (DTPA) or mecapto acetyl triglycine (MAG-3) renal studies are excreted from the kidneys and offer information about functionality and obstruction. Positron emission tomography (PET)/CT is not typically used for renal or urinary tumors as most radiotracers are excreted into the urine, obscuring masses. There have been promising results on the use of more prostate cancer-specific radiotracers which may improve sensitivity in detecting recurrence and metastasis [16, 17].

Renal Masses

Renal masses can be broadly divided into cystic and solid. Differentiating the two is important as solid renal masses tend to have a higher malignant potential and are typically resected while cystic masses tend to be bening (although some may have maignant potential) and can, in some cases, be managed more conservatively [1]. Ultrasound is the first line of imaging and is important for characterizing a renal lesion. On grey-scale imaging, simple cysts are anechoic, while more complex cysts can have internal echoes, however, all cysts, including those with internal echoes, have posterior acoustic enhancement which may separate complex cysts from solid masses. Spectral imaging and dynamic CEUS imaging can also assess the interval vascularity of masses.

CT and MRI renal mass imaging require a non-contrast phase and a nephrographic phase, which is especially important as masses can occur both in the cortex and medulla. If the image is acquired too early in the corticomedullary phase, masses can be easily missed within the hypoenhancing medulla. Non-contrast imaging is important to assess true enhancement of renal masses which categorizes them into cysts and solid masses [1, 10].

The addition of a non-contrast acquisition increases the radiation exposure to patients. DECT has the ability to subtract iodine from contrast-enhanced images to create virtual non-contrast (VNC) images. There have been promising studies which have shown that Hounsfield (HU) measurements of various abdominopelvic viscera are statistically the same between acquired non-contrast CT and VNC [18, 19]. Others studies have demonstrated accurate detection of enhancing renal lesions with the use of VNC [20]. However, not all studies support the use of VNC [5]. One study demonstrated strong agreement between HU of renal masses measured on VNC and non-contrast images for renal lesions, especially low attenuation lesions; however, there was more discrepancy on higher attenuated lesions [21]. Because there is no standardization of technique, and results are highly affected by technique, each institution must verify the validity of

their equipment and acquisition technique in order to adopt VNC and forego a non-contrast acquisition [22].

Renal Cysts

Bosniak Classification

Renal cysts are fluid filled masses contained within a thin layer of epithelium, often incidentally identified on imaging. Management depends on their malignant potential which is typically assessed first utilizing ultrasound and then with cross-sectional imaging such as CT and MRI. Morton Bosniak developed a five point grading system (Bosniak categories I, II, IIF, III, and IV) which correlates imaging features with management recommendations [23] (Table 13.1). Malignant features include peripheral wall thickening, thickened septations, solid nodules, calcifications, internal enhancement.

The Bosniak classification was initially developed for the CT with intravenous contrast. Contrast enhancement is a major criterion in assessing malignant potential of masses. Application of the classification can be used on MRI studies with intravenous contrast however should not be applied to studies without contrast (including US).

Bosniak I lesions are simple cysts with close to 0% malignant potential. They have thin peripheral walls, no septations, calcifications, or enhancing nodules. The internal density measures fluid density on CT (0–20 HU) and are simple fluid intensity on MRI. These cysts are considered benign and require no follow up (Fig. 13.1) [10].

Bosniak II cysts are slightly increased in complexity with thin, non-enhancing septations or minimal thin calcifications, measuring less than 1 mm in thickness. Hemorrhagic cysts measuring less than 3 cm in diameter are also considered Bosniak II cysts [23, 24]. These lesions are also close to 0% in malignant potential and do not require follow up (Fig. 13.2) [23, 25].

Bosniak IIF ("F" for "follow-up") cysts are of intermediate complexity and have increased malignant potential, previously reported to be ~5% although more recent studies have demonstrated malignancy rates of 25% in resected

Fig. 13.1 Simple cyst (Bosniak I) on coronal T2 weighted image. The cyst is thin-walled with no internal complexities

Table 13.1 Bosniak classification and management

Bosniak category	Morphology	Prevalence of malignancy (%)	Management
Bosniak I	Simple cyst, fluid attenuation (0–29 HU)	~0	No follow up
Bosniak II	Minimally complex cyst. A few thin non-enhancing septations. A few thin calcifications.	~0	No follow up.
Bosniak IIF	Mildly thickened nodular calcifications. Slight increased number of septations with perceived enhancement, <1 mm in thickness.	~5	6 month imaging follow-up
Bosniak III	Complicated cyst with multiple thickened, enhancing septations. Nodular, thickened calcifications.	30–100	Resection
Bosniak IV	Clear, solid nodular components	100	Resection

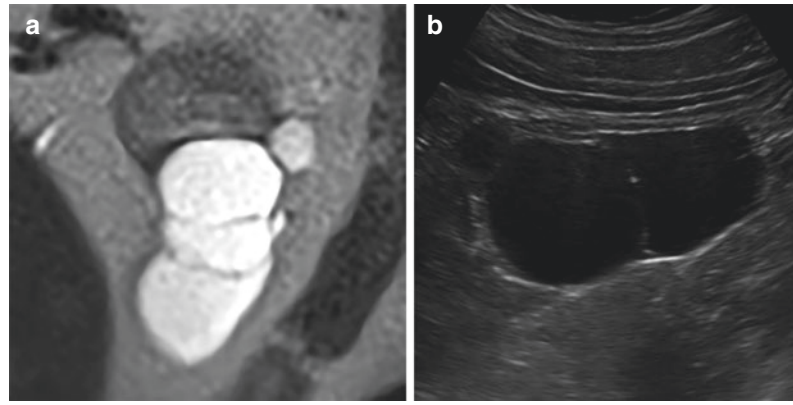

Fig. 13.2 Ultrasound (**a**) and axial T2 weighted image (**b**) shows a Bosniak II lesion with a few thin septations. No solid nodularity

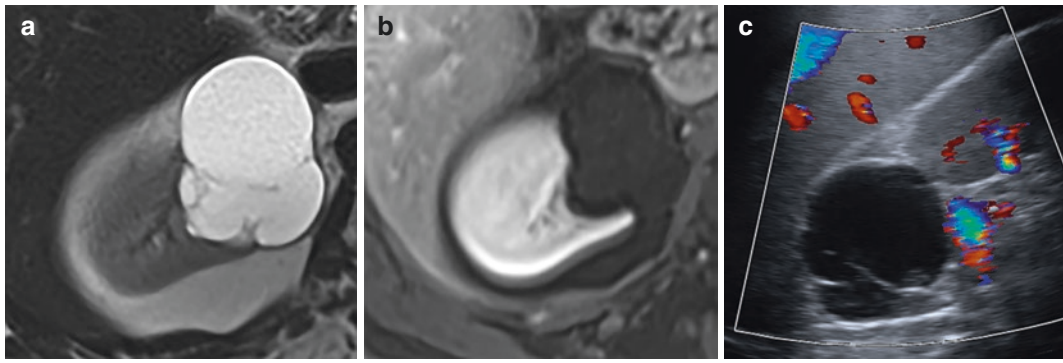

Fig. 13.3 Bosniak IIF cyst on axial T2 weighted image (**a**) shows mildly thickened and complex septations without measureable enhancement on post contrast MRI (**b**) and no internal vascularity on ultrasound (**c**)

Bosniak IIF lesions (~5%) [10, 26]. They have increased number of septations, which may have perceived, though not measurable enhancement (Fig. 13.3). Nodular and thickened calcifications may also be present. Hemorrhagic cysts measuring greater than 3 cm are included in this category [26]. The increased complexity of these cysts necessitates follow-up imaging to ensure stability, typically after 6 months with ultrasound, CT, or MRI [26–28]. Cysts in this category are generally followed with serial imaging, initially every 6 months, and then annually, for 5 years in order to demonstrate stability.

Bosniak III cysts are complex cysts, which demonstrate worrisome findings such as irregular walls, increased number and thickness of septations which may have measurable enhancement. There may be thickened nodular calcifications. Bosniak III cysts have 30–100% malignancy rate [10]. Differential considerations for lesions in this category also include mixed epithelial stromal tumors, renal abscesses, benign multilocular cysts, or benign hemorrhagic cysts (Fig. 13.4). However, due to the inability to confidently distinguish between these entities, resection is generally recommended [24].

Bosniak IV cysts are nearly 100% malignant. They demonstrate solid nodular enhancement and possibly necrotic components (Fig. 13.5). These masses are generally resected if patient condition allows [10, 24, 26].

Benign Renal Cysts

Mixed Epithelial Stromal Tumor

Mixed epithelial stromal tumor (MEST) is a rare cystic tumor characterized by complex cystic and sometimes solid mass. Histologically, the mass resembles ovarian stroma with epithelial components composing the cystic walls. MEST's are

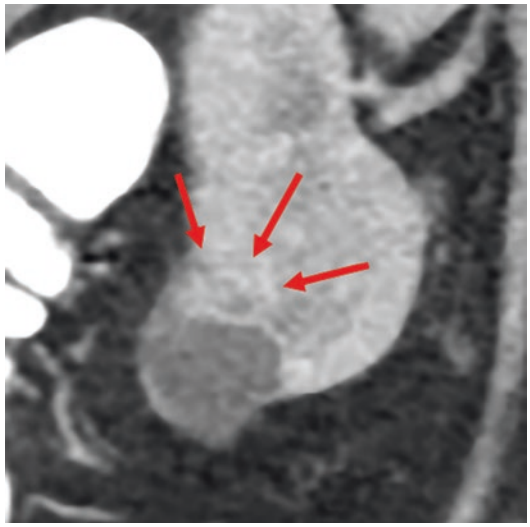

Fig. 13.4 Coronal CT shows a cyst with solid nodule along the superior aspect of the cyst (red arrows) compatible with a Bosniak III cyst

more common in females (11:1 female to male ratio) presenting at an average age of 56 years (range of 17–84 years) [29, 30]. On imaging, they are multiloculated cysts. One feature of MEST that differentiates it from malignant renal cystic masses is that it invaginates into the renal pelvis and the septations have delayed enhancement. MESTs can have internal hemorrhage seen as hyperintensity on T1-WI (Fig. 13.6). MESTs cannot be clearly distinguished from malignant cystic neoplasms and thus are most often surgically resected [29].

Multicystic Nephroma

Another benign multiloculated cyst is the cystic nephroma. The lesion is bimodal in age of presentation, which manifest in boys less than 4 years old and women between 40 and 60 years old [31]. Cystic nephromas have similar histological

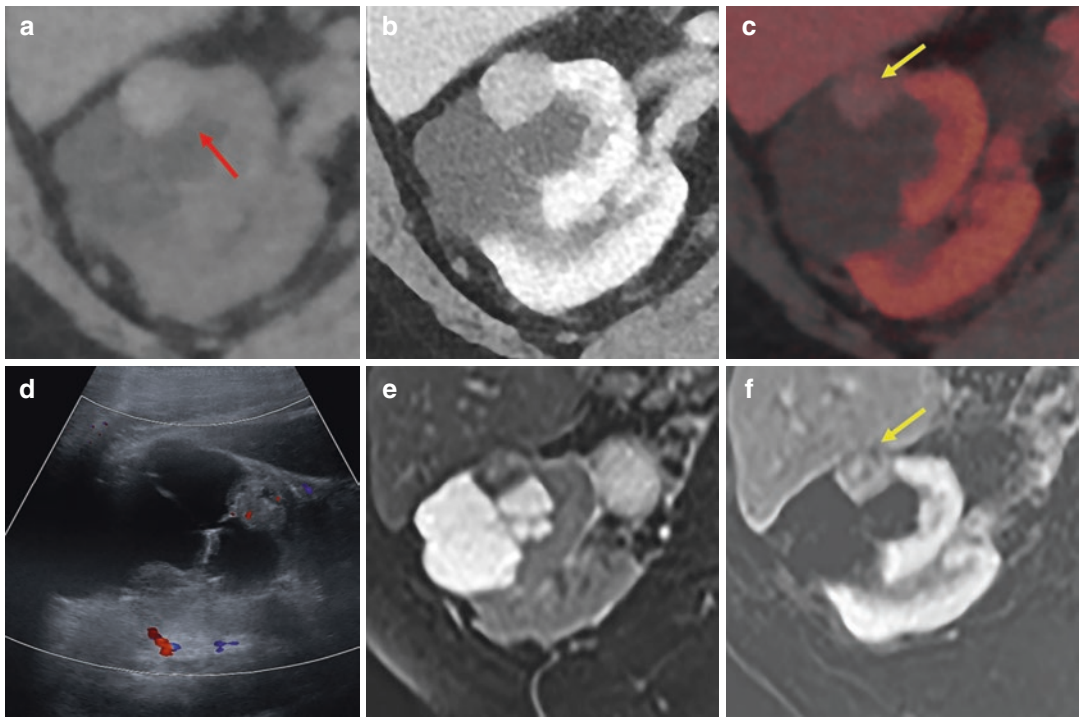

Fig. 13.5 Virtual non-contrast (**a**), Contrast enhanced (**b**), and iodine map (**c**) of a dual energy CT of Bosniak IV cyst with solid nodule. Focus of hyperattenuation on virtual non-contrast (**a**, red arrow) indicates hemorrhagic material, which also shows subtle enhancement centrally more apparent on iodine map (**c**, yellow arrow). Ultrasound (**d**) shows complex cyst with soft tissue nodule with internal vasulcarity. T2 weighted image with fat suppression (**e**) and post-contrast with subtraction (**f**) demonstrates complex, thickened, and enhancing septations with hemorrhagic enhancing solid nodule (**f**, yellow arrow)

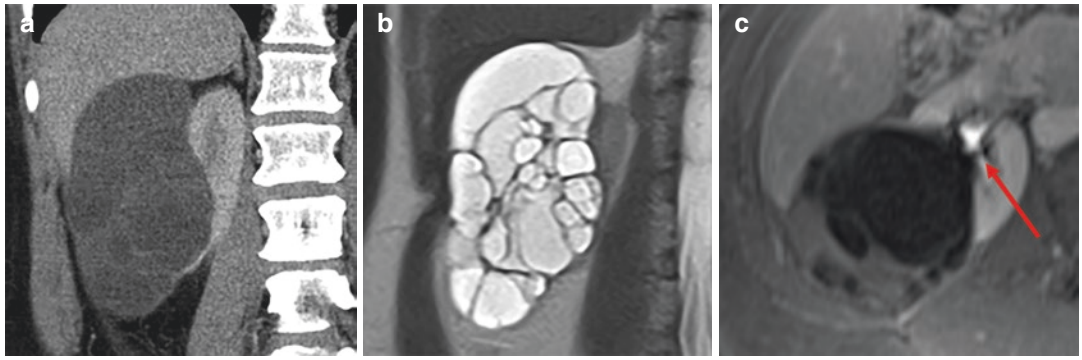

Fig. 13.6 Pathologically proven mixed epithelial stromal tumor presents as a complex cyst with thickened septations on coronal CT (**a**), coronal T2 weighted imaging (**b**), and axial post-contrast enhancement (**c**). The cyst invaginates into the collecting system (**c**, red arrow), typical for mixed epithelial stromal tumor

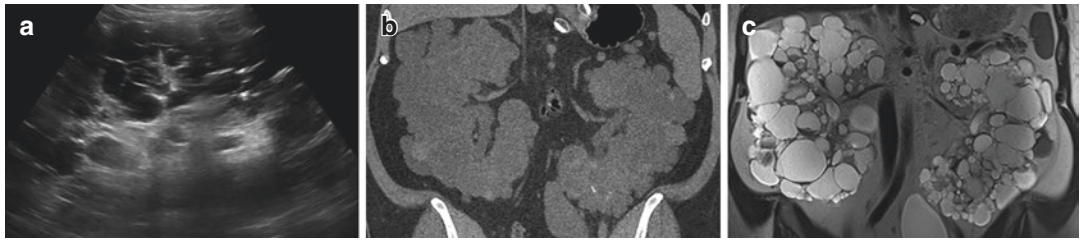

Fig. 13.7 Enlarged kidneys with numerous cysts on ultrasound (**a**), non-contrast coronal CT (**b**), and T2 weighted image CT (**c**). Some cysts contain hemorrhagic material seen as hyperattenuation on non-contrast CT (**b**) and hypointensity

appearances to MEST and have been suspected to be on a similar spectrum of stromal tumor. They present as encapsulated multiloculated cystic masses, at times with hemorrhagic or proteinaceous contents. Multicystic nephromas can also invaginate into the renal pelvis and have delayed enhancement of septations, which likely reflects the fibrous content of the lesion [31, 32]. There is no imaging criteria which can definitively distinguish a cystic nephroma from a cystic malignancy, and for this reason, most are resected.

Renal Cystic Disease

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) present as cysts in both kidneys, which are enlarged. Cysts are of all sizes, small and large, and can be simple or hemorrhagic (Fig. 13.7). There is no increased risk of renal malignancy unless patient is on dialysis [33]. Extra-renal manifestations include cysts in the liver and pancreas. The disease progresses by progressively increasing number of cysts. Approximately 50% of patients with ADPKD develop renal failure from replaced renal parenchyma [33].

Imaging is important in screening first-degree relatives of people with ADPKD as genetic testing only identifies 70% of those with the disease [34]. Criteria for diagnosing ADPKD is age dependent. For high-risk patients between the age of 15 and 39 years, three cysts are required for diagnosis, for high-risk patients between the age of 40 and 59 years, two cysts are required for diagnosis, and for high-risk patients 60 years or greater, four cysts are required for diagnosis [35].

Localized Cystic Renal Disease

Localized cystic renal disease is a rare benign entity which may be mistaken for a mass of

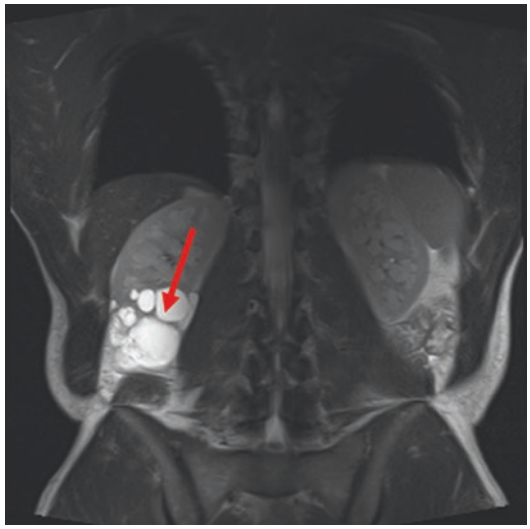

Fig. 13.8 Localized cystic renal disease. Multiple cysts in the lower pole of the right kidney on a T2 weighted image shows compressed normal parenchyma between cyst (red arrow), which mimics the malignant feature of thickened septations in Bosniak 3 cysts

malignant potential. The disease manifests as cysts in one kidney, unilaterally. Cysts are separated by normal renal parenchyma with no capsule, distinguishing it from a cystic nephroma (Fig. 13.8) [36]. Trauma may cause bleeding and hemorrhagic product within the cysts. There are typically no cysts in other organs. Increased number of cysts may compress the intervening normal renal parenchyma which may give a more malignant appearance, thus imaging follow-up may be warranted if clear diagnosis cannot be confidently made (Fig. 13.8) [37].

Acquired Renal Cystic Disease

Patients with end-stage renal disease without an inheritable renal disease may develop acquired renal cystic disease, which is defined as at least three cysts in each kidney [33]. The cysts are usually cortically based and small in size (<3 cm). 8–13% of patients with end-stage renal failure develop acquired renal cystic disease, which increases to 13% after 2 years of dialysis, 50% after 6 years of dialysis, 87% after 9 years of dialysis, and close to 100% after 10 years of dialysis. Patients with acquired renal cystic disease have increased risk of ureteral stones and renal cell carcinoma, particularly clear cell type (3–7% of patients develop renal malignancy) [33]. Even after renal transplant, cysts may regress, however, risk for renal malignancy is persistently elevated. On ultrasound, kidneys are small with echogenic renal parenchyma and small cysts. CT and MRI also demonstrate similar findings. There are no consensus recommendations for screening of patients with acquired cystic kidney disease, however imaging should be considered.

Lithium-Induced Nephrotoxicity

Patients with long-term lithium use may develop nephrotoxicity manifested by acute intoxication, nephrogenic diabetes insipidus (most common and reversible), and chronic renal disease [38–40]. Imaging appearance of lithium associated chronic renal disease include normal sized kidneys with many uniformly distributed microcysts (1–2 mm in size) which are located in the cortex and medulla. On US, the microcysts may paradoxically appear as hyperechoic foci as the cysts are so small that ultrasound resolution can only detect the closely apposed walls of the cysts which reflect sound waves. The cysts are best visualized on MRI with T2-WI as the cysts are T2 hyperintense foci (Fig. 13.9) [41].

Solid Renal Masses

Solid renal masses are most worrisome for renal cell carcinoma (RCC). Not all solid masses are malignant, though, and imaging can help differentiate between the two in a non-invasive fashion. Ultrasound maintains to be the first-line imaging tool, however, it does not have the soft tissue contrast to truly differentiate between solid tumors. CT offers an overall view of the lesion and surrounding structures and can detect macroscopic features of renal masses. These features are helpful for staging and detecting metastasis. mpMRI remains the best tool for distinguishing solid renal masses due to the high tissue contrast. With mpMRI, masses can be potentially categorized as benign and malignant, and even subdivided into specific types of RCC. However, even

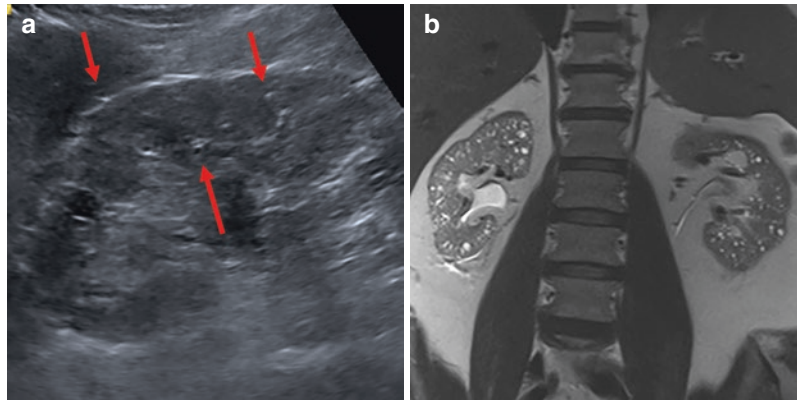

Fig. 13.9 Ultrasound of the kidney (**a**) shows multiple punctate echogenicities predominantly in the cortex which correlates with T2 hyperintense microcysts seen on the T2 WI of the same patient (**b**). Microcysts are paradoxically hyperechoic on ultrasound as the cysts are so small the echoes reflect the cyst walls which are nearly apposed together

with these advanced tools, overlapping imaging features challenge diagnosis [42].

Malignant

RCC

RCC are one of the most common adult cancers, about 2–3% of all adult neoplasms [43]. Amongst RCCs, there are major histologic subtypes including clear cell RCC (ccRCC), papillary RCC (pRCC), and chromophobe RCC (chRCC). Some of the histologic features translate into distinguishable imaging features (Table 13.2). On ultrasound, RCC's are hyperechoic compared to renal parenchyma, though less echogenic than renal sinus. Further characterization is reserved for mpMRI which can tease out secondary manifestations of histologic features. In the following section, discussion will emphasize MRI features of solid renal tumors.

Table 13.2 Image characteristics of benign and malignant solid renal tumors

Subtype	Unique imaging
Clear Cell RCC	Heterogeneous, T2 bright, Hypervascular, Intravoxel fat, Necrosis
Papillary RCC	Homogeneous, T2 dark, Hypovascular, Hemosiderin
Chromophobe RCC	Heterogeneous T2 signal, Heterogeneous enhancement
Lymphoma	Infiltrative T2 intermediate to dark, strong restricted diffusion
Urothelial Renal Mass	Centered in the renal pelvis, Infiltrative
Angiomyolipoma (AML)	Bulk fat, vascular
Lipid Poor AML	T2 dark, hypervascular
Oncocytoma	Heterogeneous T2 signal, Stellate scar, Segmental enhancement

ccRCC

ccRCC subtype is the most common RCC representing 65–80% of all RCC [44]. It is typically sporadic, but is associated with many syndromes such as von Hippel Lindau syndrome and tuberous sclerosis. Because of its potentially aggressive nature, management is also often aggressive and thus early diagnosis is important.

On histology, ccRCC are composed of cells that have cytoplasm which appear "clear" because of accumulation of cholesterol and lipids [45]. On a more macroscopic level, ccRCC are vascular tumors. MR features reflect the histology. Masses are typically T2 hyperintense, T1 hypointense and heterogeneous. Increased vascularity of ccRCC translates into avid enhancement on imaging, greater than adjacent parenchyma and also greater than other types of RCC (Fig. 13.10) [46, 47]. ccRCC tumors may bleed, seen as irregular T1 hyperintensity. The intracellular fat is reflected in IP and OOP sequences which demonstrate intravoxel fat (signal drop on OOP when

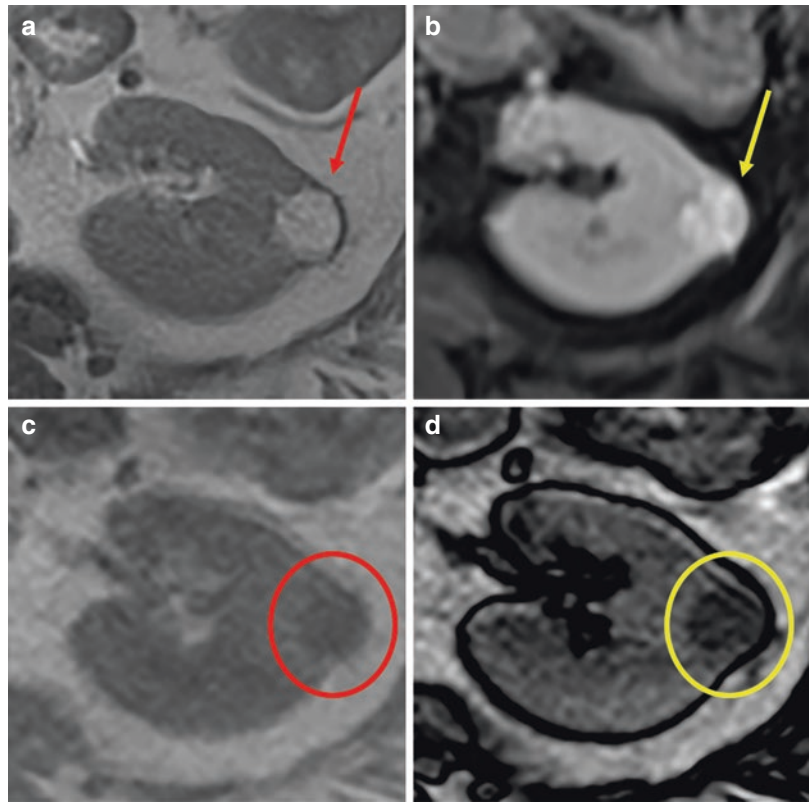

Fig. 13.10 A clear cell renal cell carcinoma (ccRCC) is typically heterogenously hyperintense on axial T2 WI (**a**, red arrow) and heterogeneously enhances on post contrast MRI (**b**, yellow arrow). Comparison of the lesion on in-phase (**c**, red circle) and out of phase (**d**, yellow circle) T1 weighted sequences show slightly decreased signal on the out-of-phase image indicating some intra-voxel fat within the lesion, typically for ccRCC. On out-of-phase sequence, the thick black line outlining the margins between organs and fat is typical and can be used to distinguish the sequence

compared to IP). ccRCC also restrict diffusion due to increased cellularity [47]. Because of ccRCC's aggressive nature, larger lesions often out-grow vascular supply and have necrotic centers [46]. ccRCC's also often contain calcifications, which indicates malignancy and may help differentiate benign and malignant masses in otherwise ambiguous lesions.

pRCC

The second most common subtype of RCC is pRCC comprising 10–15% of RCC cases [44]. There are two types (I and II). Type I is usually less aggressive than ccRCC, whereas type II pRCC are more aggresive. Pathologically, pRCC's often contain necrosis and hemorrhage product [48]. Histologically, they have papillae which are covered by thin layer of uniform cells with scant cytoplasm, hemosiderin, and foamy macrophages [49].

Again, imaging correlates with pathologic findings. The masses are typically well-defined and homogenous and less than 3 cm in size. pRCC's are T1 and T2 hypointense, likely from low cytoplasm content of cells. Larger lesions may contain hemorrhagic product (T1 hyperintense). Hemosiderin causes loss of signal on IP imaging compared to OOP. Rarely, intracellular lipids from foamy macrophages, translate to intravoxel fat and loss of signal on OOP compared to IP. DWI is somewhat confounding with the presence of hemosiderin and hemorrhage. On contrast enhanced images, pRCC are hypovascular and demonstrate progressive enhancement through dynamic imaging. More rarely, pRCC present as complex cysts. Lipid poor angiomyolipomas (AML) may have similar appearance to pRCC, however, they enhance avidly rather than the progressive enhancement of pRCC (Fig. 13.11) [50].

chRCC

chRCC is less prevalent compared to pRCC (4–11% of all RCC). Similar to type I pRCC, chRCC have better prognosis than ccRCC with

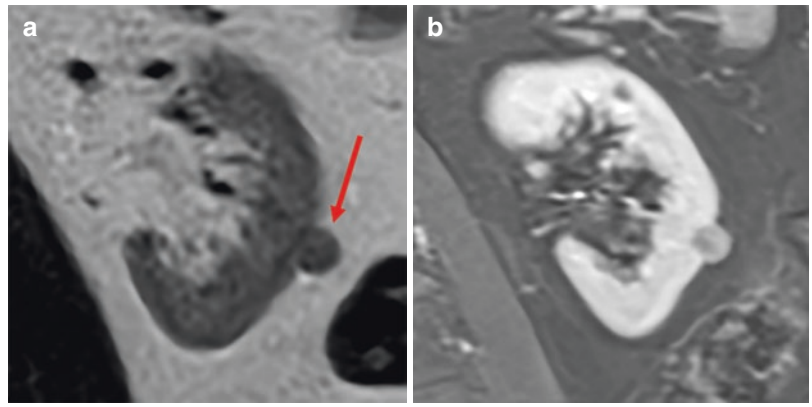

Fig. 13.11 In contrast to clear cell renal cell carcinoma (ccRCC), papillary type renal cell carcinoma (pRCC) is homogeneusly hypointense on T2 weighted sequence (**a**, red arrow) and enhances homogeneously on post contrast MRI (**b**)

5-year survival rate reported to be 78–93% [51]. chRCC arise from the intercalated cells of the kidneys, much like oncocytomas. Pathologically, chRCC are well-defined lesions which present larger than other RCCs, average mass size of 7.2 cm [52].

Imaging features of chRCC are varied and less specific than other RCCs. They are peripherally located, homogeneous, typically demonstrate T2 intermediate to low intensity signal. They restrict diffusion and also enhance, although demonstrate intermediate enhancement, between pRCC and ccRCC. Calcifications are also often seen, which occur in 38% of such lesions. Sometimes, chRCC have a "tail" which extends towards the renal pelvis. Very rarely, chRCC may demonstrate segmental enhancement inversion, which is heterogeneous enhancement with some portions enhancing earlier and other portions demonstrating progressive enhancement [53]. Since chRCC's are histologically similar to oncocytomas, imaging features are similar as well. chRCC's may exhibit an enhancing spoke wheel central scar, approximately 30–40% of time, which can also be seen in oncocytomas [54].

Lymphoma

Distribution of lymphoma is wide spread and the genitourinary systems is the second most commonly affected site [55]. Within the genitourinary system, kidneys are involved the most. Detection is typically via imaging. CT and MRI are both sensitive in diagnosis. US is likely the first line imaging technique and may be used for follow-up, however is less specific in initial diagnosis.

On imaging, lymphoma has multiple patterns of presentation. The most common presentation is multiple tumors, seen 50–60% of the time. Other presentations include single tumors, centralized to perinephric regions, and infiltrative tumors. Lymphoma may also extend into the kidney from primary retroperitoneal location [56].

Lymphoma of the kidney is slightly greater density than renal parenchyma on non-contrast CT but enhance less than renal parenchyma thus appear as homogeneous hypodense lesion to parenchyma on contrast enhanced images. Masses can occur in both cortical and medullary regions, thus nephrogenic phase is important to acquire to not miss lymphomatous tumor [56]. On MRI, lymphoma masses are T1 and T2 hypointense. Due to the closely packed cells in lymphoma, they show avid restricted diffusion (Fig. 13.12). Similar to CT, tumors are hypoenhancing compared to renal parenchyma. On US, lymphoma is typically hypoechoic and homogeneous. Color Doppler imaging shows lesions displace normal renal vessels. Little vascularity is seen within the lesion itself [57, 58].

Several secondary signs can help distinguish lymphoma from other renal malignancies. Lymphadenopathy is a systemic disease and often presents simultaneously with retroperitioneal lymphadenopathy. In addition, lymphoma is rarely associated with renal thrombus [55].

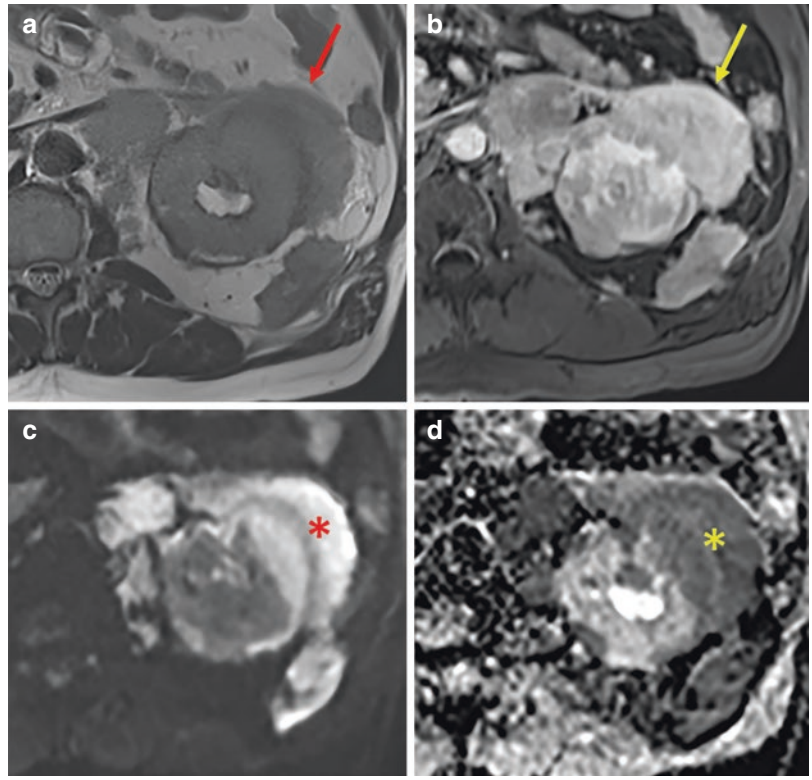

Fig. 13.12 On T2 weighted image (**a**), renal lymphoma is a homogeneous iso or hypointense infiltrative tumor (red arrow) in contrast to more distinct renal cell carcinomas. It homogeneously enhances less than renal parenchyma on post contrast MR images (**b**). Lymphoma is avidly diffusion restricting because of the tightly packed cells and is demonstrated by marked hyperintense signal on diffusion weighted image (**c**, red star) and hypointense signal on ADC map (**d**, yellow star)

Intrarenal Urothelial Carcinoma

Urothelial carcinoma most commonly occurs in the bladder, less commonly in the ureters, and even more rarely the renal pelvis. When in the renal pelvis, urothelial cancers tend to grow centripetally into the renal parenchyma [59]. These lesions can be confused with central RCC [60, 61]. It is clinically important to distinguish these two entities as management is drastically different.

CT and MRI are the best imaging tools for diagnosis as both morphology of tumors and intrinsic lesion characteristics that identify one from the other. Six useful morphologic features that preferentially indicate urothelial carcinoma over RCC include central location of tumor within the collecting system, focal filling in renal pelvis, preservation of renal shape, absence of cystic or necrotic, homogeneous enhancement of tumor, and extension of tumor toward ureteropelvic junction (Fig. 13.13) [59]. Of those six features, preservation of renal shape was the most reproducible sign indicating urothelial tumor [59]. Homogeneity on T2-WI and hypovascularity on all phases of dynamic sequences have also been shown to indicate urothelial origin of tumor over RCC [62].

Benign Solid Masses

Angiomyolipoma

AML are benign solid renal tumors which contain three elements: dysmorphic blood vessels, smooth muscle, and bulk adipose tissue. The amount of each component varies in each tumor, determining the appearance of the lesion on imaging. The presence of fat is pathognomonic. On US, the typical AML is hyperechoic. Hyperechoic masses less than 1 cm have been shown to be clinically insignificant [63], and may not need follow-up, especially if patients are low risk for RCC. On CT, AMLs are hypodense or have hypodense foci with HU comparable to bulk fat. MRI also demonstrates bulk fat which can be seen on OOP sequences separating AMLs and

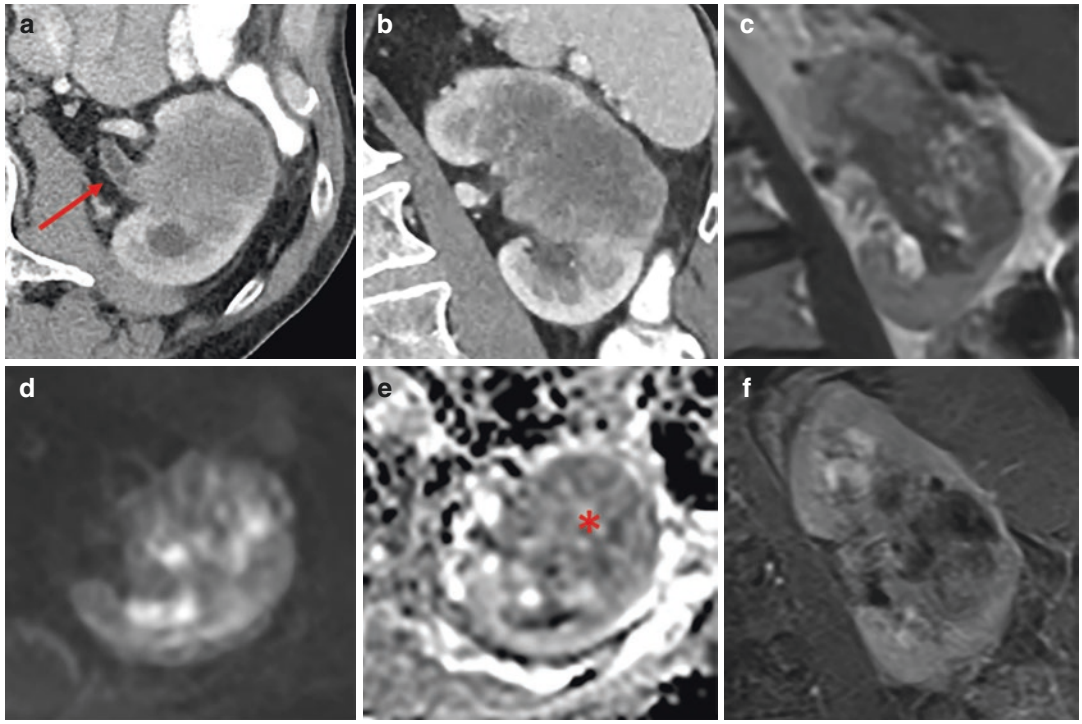

Fig. 13.13 Urothelial carcinoma of the kidney is an infiltrative mass as seen on axial (**a**) and coronal (**b**) CT with intravenous contrast and coronal T2 weighted image (**c**). The mass is typically centered in the renal pelvis as can be seen in this patient (**a**, red arrow). The kidney preserves its reniform shape unlike central RCC. Diffusion weighted image (DWI) (**d**) and ADC map (**e**) show restricted diffusion (red star), though less than lymphoma. On contrast enhanced images, the mass is hypoenhancing compared to the renal parenchyma, especially prominent on post contrast MRI (**f**)

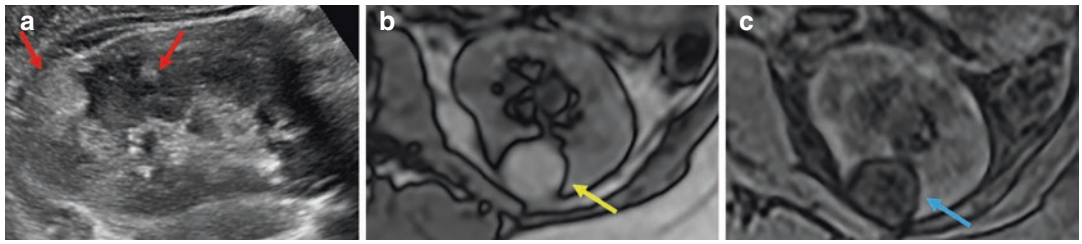

Fig. 13.14 Ultrasound (**a**) of a patient with tuberous sclerosis with multiple hyperechoic masses (red arrows) compatible with angiomyolipomas (AML) containing fat. On out-of-phase imaging (**b**), the fat containing AMLs are outlined with the India Ink artifact which mark the margins of fat and fluid (yellow arrow). AML on Fat suppressed axial T1 weighted image (**c**) are hypointense as the fat signal is suppressed (blue arrow)

renal parenchyma by the India ink artifact and with signal drop out on fat suppressed imaging (Fig. 13.14).

Lipid poor AMLs, defined histologically as less than 25% fat content per high-power field, present a diagnostic dilemma as RCCs have similar appearances, especially for small masses (<3 cm) [64, 65]. On ultrasound, lipid poor AMLs are isoechoic to renal parenchyma, limiting detection and evaluation. Without fat, lipid poor AMLs have increased components of blood vessels and smooth muscle, which are both hyperattenuating

compared to normal renal parenchema on CT without intravenous contrast and thus lipid poor AMLs are typically heterogeneously hyperattenuating compared to renal parenchyma, however this is not consistently true [65]. MRI features of AML may include homogeneous T2 signal compared to renal cortex and the lack of cystic degeneration or necrosis [64, 66]. These findings are similar to that of pRCC, however AMLs tend to be more vascular. Image diagnosis of lipid poor AMLs may be difficult however should be considered as a differential, especially in patients whose demographic is atypical of RCC [64]. If there is strong suspicion of a lipid poor AML, on the basis of genetic risk or patient age, needle biopsy with HMB45 staining can by quite diagnostic. In the absence of heightened suspicion of AML, larger solid renal masses are generally resected.

Oncocytoma

Oncocytomas, the second most common benign renal neoplasms, are histologically similar to chromophobe RCC and are thought to arise from intercalated cells [51]. They are well-defined and hypovascular on enhancement compared to renal cortex. On MRI, oncocytomas also share characteristics with chRCC including heterogeneous T2 signal and enhancement, and hemorrhage or microscopic lipid [54]. Oncocytomas are often characterized by a central "scar," a central stellate region of T2 hyperintensity which does not enhance (Fig. 13.15) [54, 67]. Segmental enhancement, as described in the chRCC section, is typically a feature of oncocytoma, although rarely, chRCCs can enhance in a similar fashion. The overlapping imaging features between oncocytoma and malignant RCC are many, thus suspected oncocytomas are typically treated as malignant masses [68].

Renal Infections

Infections in the kidneys have unique appearances. US is often the first line imaging for urinary processes, however, CT is most effective at imaging for renal infections. MRI plays less of a role in imaging as many of the secondary findings such as air and calculi are not well-visualized.

Bacterial Pyelonephritis

Although US is often used as first line imaging, bacterial pyelonephritis is not well characterized on grey-scale imaging and thus produces many false negative results, demonstrating abnormalities in only 24% of patients [69]. Some findings include changes in echogenicity, decreased in the setting of edema, or increased in the setting of hemorrhage. There may be loss of corticomedullary differentiation or foci of hypoperfusion on color Doppler imaging [70]. Use of harmonics imaging highlights patchy hypoechoic foci. Abscesses can also be seen on ultrasound as fluid collections with peripheral hyperemia which demonstrate mass effect on adjacent structures. Source for possible obstruction should be investigated, especially in the bladder (e.g. enlarged prostate).

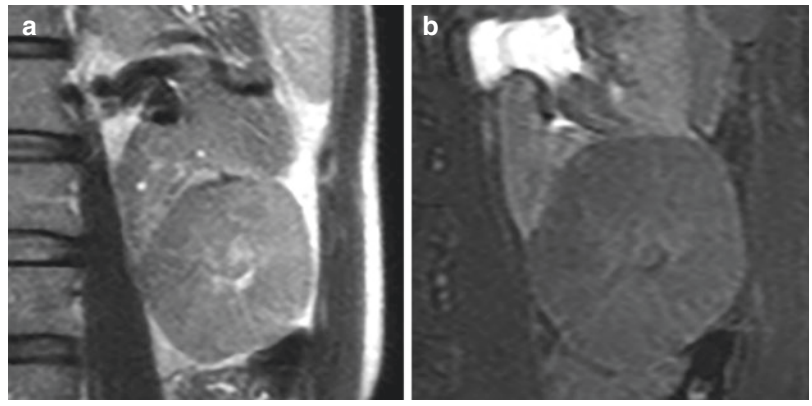

Fig. 13.15 Oncocytomas are benign soft tissue masses often mimicking malignant neoplasm. On T2 weighted imaging, they have characteristically hyperintense central stellate scars (**a**), which do not enhance on post contrast imaging (**b**)

CT with intravenous contrast in the nephrographic phase is the best to evaluate bacterial pyelonephritis. In acute pyelonephritis, renal enhancement is often patchy with wedge shaped hypo-enhancement to the papilla reflecting regions of edema, tubular obstruction and vasoconstriction (Fig. 13.16) [71]. With time, the hypo-enhancement will gradually decrease and may result in scarring or cortical thinning. Secondary signs of infection are also apparent on CT with easily visualized perinephric fat stranding or asymmetric enlargement of the kidney. Abscess are readily visible and are seen as peripherally enhancing fluid collections [72]. With the larger field of view, the full extent of abscess can be assessed.

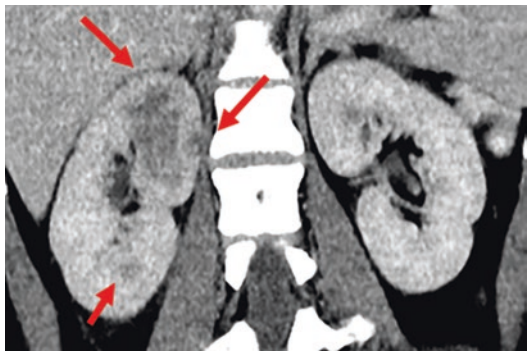

Fig. 13.16 Coronal CT of a patient with fever and right flank pain shows patchy hypoattenuation in the right kidney, predominantly in the upper pole compatible with acute pyelonephritis

MRI plays a smaller role in imaging bacterial pyelonephritis compared to CT as it is more expensive and time consuming without increased diagnostic benefits. Patchy edema and tubular obstruction can be seen as patchy restricted diffusion on DWI. In addition, abscesses are especially accentuated on DWI and as abscess markedly restrict diffusion. Enhancement patterns on MRI appear similar to that of CT [73].

Emphysematous Pyelonephritis and Pyleitis

Emphysematous pyelonephritis is a necrotizing form of infection, typically in diabetic or immunocompromised patients, resulting from obstruction by urinary calculi, neoplasm, or sloughed papilla. The disease is life-threatening with a high mortality rate, thus early diagnosis is imperative [74].

On radiographs, foci of radiolucency may be seen overlying and outlining the kidneys, which are ominous findings. Ultrasound demonstrates enlarged, hypoechoic kidneys with multiple shadowing hyperechoic foci of gas reflecting sound waves. Shadowing renal calculi may have similar appearances, but gas tends to produce "dirty" shadowing as opposed to clear crisp shadowing of stones (Fig. 13.17) [75]. The kidney is also typically hypervascular on color Doppler imaging.

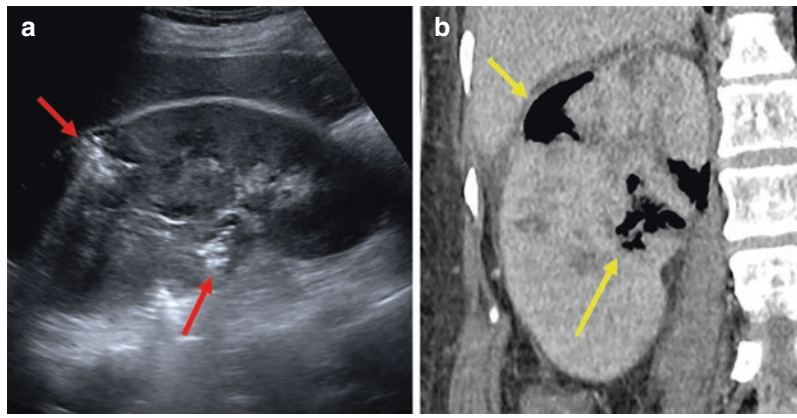

Fig. 13.17 Emphysematous pyelonephritis is a necrotizing form of infection producing gas, which appears as ill-defined echogenicities on ultrasound (**a**, red arrows) with posterior shadowing. Coronal CT demonstrates gas within the renal parenchyma extending to the perinephric space (Type 2) and collecting system (**b**, yellow arrows) and patchy hypoenhancement of the renal parenchyma

CT provides the most complete evaluation. The kidneys are low attenuation and may contain foci of gas in a linear pattern. Fluid from necrosis and abscesses within the kidney or in perinephric spaces are readily visible. Infection can be centered around the renal parenchyma (type 1) or more extensive connecting perinephric fluid collections with the collecting system (type 2) (Fig. 13.17) [76]. Obstructive etiologies may also be evaluated at the same time.

Gas only within the collecting system is termed emphysematous pyelitis, and is less ominous than emphysematous pyelonephritis. On CT and ultrasound, gas can be seen layering in the renal pelvis. Care must be taken to exclude other causes of gas such as recent procedures [77, 78]. MRI is less favorable than CT as gas is not well seen on the modality; however, MRI may be used in circumstances to minimize radiation exposure or for patients with renal insufficiency.

Pyonephrosis

Infection can be centered around the collecting system and is referred to as pyonephrosis. On ultrasound, there is prominence of the renal pelvis which often contains debris. On CT, a prominent renal pelvis can also be seen, and also demonstrates thickened walls (>2 mm) with adjacent fat stranding. Exclusion of obstructive etiology must be performed. Urine versus pyogenic fluid often have similar HU and may be difficult to differentiate. MRI findings are similar to CT however is able to detect debris within the collecting system [79].

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis (XGP) is a rare chronic destructive granulomatous infection of the kidney caused by lipid-laden (foamy) macrophages. This typically occurs in women and patients with diabetes. Patients also often have obstructive renal calculi such as staghorn calculi. The most common causative organism includes *Proteus mirabilis* and *Escherichia coli* [80].

Radiographs are non-specific and only demonstrates renal calculi. On ultrasound, the affected kidney is enlarged often with a large central echogenic shadowing calculus in the renal pelvis. The kidney is often distorted with loss of normal renal architecture. CT also demonstrates an enlarged kidney with central calculus, contracted renal pelvis, and caliectasis with thinning of the cortex, or the "bear claw" sign, which is pathognomonic for XGP (Fig. 13.18). Although it may appear to be simple hydronephrosis, often, the caliectasis contains a thick inflammatory infiltrate [81]. Secondary signs of inflammation are visible as perinephric fat stranding and thickening of the renal pelvis. Delayed phase of a contrast enhanced CT often shows decreased renal function and delayed excretion of contrast. In many cases, an associated heterogenous renal mass can be confused with renal cancer. In the absence of urinary infection or associated

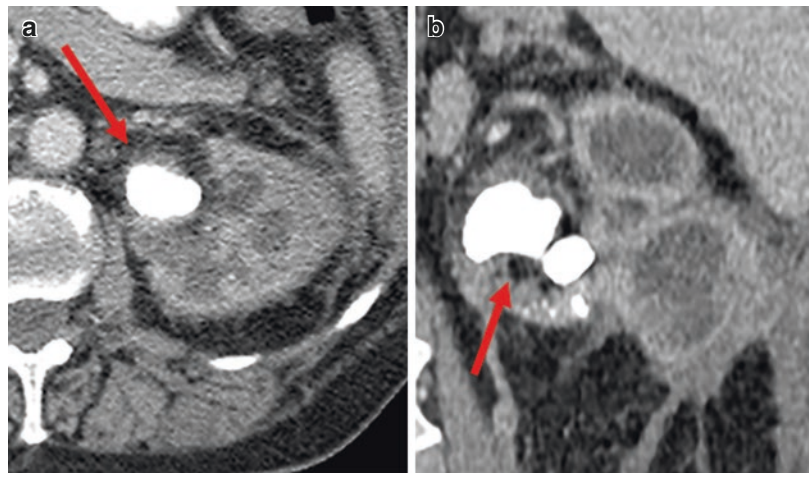

Fig. 13.18 Staghorn calculus (red arrows) on axial (**a**) and coronal (**b**) CT with intravenous contrast. The kidneys are enlarged with caliectasis, referred to as the "bear claw" sign

obstruction, resection is often required to rule out malignancy.

Tuberculosis

CT and MRI are the best modalities to evaluate urinary tuberculosis (TB). The imaging findings of tuberculosis depends on the stage of the disease. The disease typically progresses from kidneys to bladder such that disease of the lower urinary tract does not occur without disease of the upper urinary tract. TB of the renal parenchyma manifests as patchy hypo-enhancement similar to bacterial pyelonephritis. The collecting system is the most common site of urinary TB. There is uneven progressive caliectasis with papillary necrosis and cortical thinning, which has a similar appearance to XGP as both are granulomatous processes, however, unlike XGP, the kidney in the setting of TB atrophies as there is increased fibrosis. The renal parenchyma atrophies completely and multiple thin-walled cysts are formed. Eventually dense calcification replaces the atrophied kidney, resulting in the so called "putty kidney" (Fig. 13.19) [82, 83].

TB in the ureters present as multifocal strictures with ureteral wall thickening and hyperenhancement which causes hydronephrosis [84]. The urinary bladder with TB appears with wall thickening. After time, there is increased fibrosis and shrinkage of the bladder and eventually dystrophic calcification [83, 85].

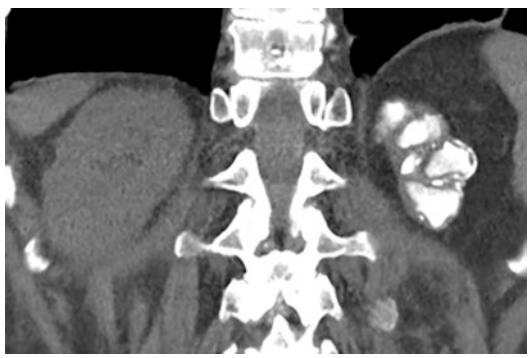

Fig. 13.19 CT without intravenous contrast shows characteristic chronic tuberculosis infection with small left kidney with diffuse dense calcification nearly overtaking the kidney known as "putty kidney"

Upper Tract and Bladder Imaging

Disease of the upper urinary tract vary from urinary obstruction to urothelial cancers to infectious processes. Due to the broad nature of upper urinary tract disease, imaging plays an important role in assessment of the upper tracts in order to diagnose and treat patients as well as to follow disease progression. Multiple modalities are available to clinicians, each with their own strengths and weaknesses. Thus, understanding imaging is important to maximize the information gained while minimizing the inherent risks.

Urinary Obstruction

Urinary obstruction is a common entity with multiple different etiologies. Many modalities exist to assess for obstruction and cause of obstruction including various protocols of CT, MRI, US, radiography, and nuclear medicine studies. Clinical signs and symptoms are likely to point to specific causes initially, which will direct urologists to choose the highest yielding imaging study.

Urolithiasis

Urinary calculi is a common entity affecting 6% of women and 12% of men in the United States [86, 87] with incidence increasing up to the age of 60 [88]. Urinary calculi are formed by excretion and precipitation of salts including calcium, struvite, uric acid, and cysteine into the urine. These salts may become lodged throughout the urinary tract causing pain and urinary obstruction.

The composition of urinary calculi is reflected in imaging characteristics and also have treatment implications. Calcium based calculi is the most common, representing 70–80% of calculi in the US [89]. Within the category of calcium based calculi, calcium-based oxalate calculi are the most common, representing 60% of all calculi [90]. When imaged with CT, calcium based urinary calculi have the highest HU measuring up to 1700 HU [91].

Struvite calculi, 15–20% of urinary calculi, are formed by urease-producing bacteria (e.g. Proteus, Pseudomonas, Klebsiella, and enterococci). Escherichia coli, the most common organism causing urinary tract infections, however, does not produce urease [89, 92]. Urea is broken down into carbon dioxide and ammonia which raises the pH level of urine allowing carbonate to precipitate with struvite forming calculi. These calculi typically involve at least two calyces of the renal pelvis giving the appearance of antlers reflected of its namesake staghorn calculi [93]. HU of struvite are varied depending on percentage of struvite in the calculi and can range from 200 to greater than 1300 [94].

Less common calculi include uric acid calculi, which occur in the setting of gout, chronic diarrhea, or in acidic urine such as with increased body mass index and diabetes. Uric acid calculi are radiolucent on radiography but are visualized on CT with HU of <500 (Fig. 13.20) [95–97]. Cysteine calculi are also low in HU and have a ground glass appearance and may also be radiolucent but visualized on CT. Some medications, such as protease inhibitors used in HIV treatment (e.g. Indinavir) and herbal supplements can induce renal calculi formation. Indinavir related renal calculi are unique in that they are radiolucent, even on CT [98].

Calculi can be present throughout the entire urinary tract. Calculi within the calyces are typically non-obstructing and asymptomatic, although some non-obstructing calyceal calculi can present with renal colic and gross or microscopic hematuria. Stones that migrate into the ureteral pelvic junction (UPJ) which can cause obstruction and flank pain. Once through the UPJ, there are three anatomic locations of ureteral narrowing which calculi may lodge: just distal to the UPJ, at the crossing of the iliac vessels, and at the ureteral vesical junction (UVJ). The UVJ is quite narrow, resulting in obstruction of tiny 1–5 mm stones [99].

Imaging indications can be broadly divided into suspicion of stone disease versus recurrent stone disease, which are optimized with different imaging protocols. Multiple modalities are available to use including non-contrast computed tomography (NCCT), KUB, US, and MRI.

Acute Flank Pain/Suspicion of Ureteral Stone

US

The European Association of Urology (EAU) recommends initial evaluation with US before other diagnostic imaging as it can visualize the kidneys, collecting systems, parts of the ureters, and bladder to determine presence of calculi or urinary obstruction. US has 45% sensitivity and 94% specificity for ureteric stones and 45% sensitivity and 88% specificity for renal stones and increases to sensitivity of 77% and specificity of 93% in patients with acute flank pain [100–103]. With the utilization of US prior to CT, there was no significant difference in outcomes compared to the initial utilization of CT, however, radiation exposure was decreased [101].

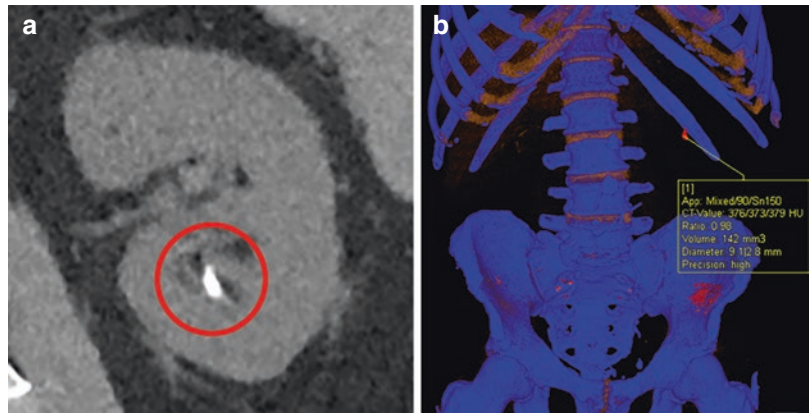

Fig. 13.20 CT without intravenous contrast (**a**) with dense calculus in the lower pole of the left kidney. Further evaluation with dual energy CT (**b**) showed 376 HU with dual energy ratio of 0.98, the characteristics of a uric acid calculus

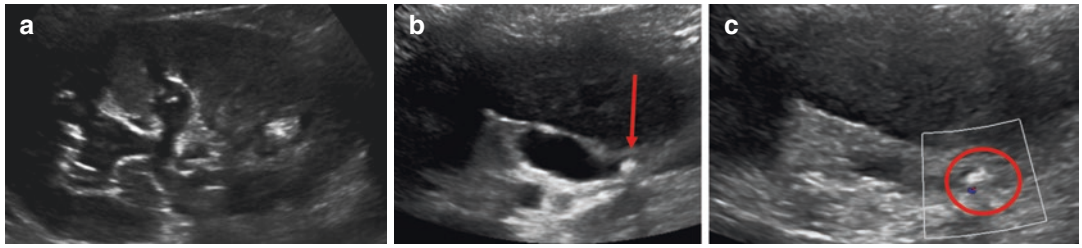

Fig. 13.21 Ultrasound shows kidney with hydronephrosis (**a**). Hyperechoic focus with sharp posterior shadowing is lodged at the ureteropelvic junction (**b**, red arrow). On Doppler (**c**), there is posterior twinkling artifact (red circle)

Renal calculi appear as hyperechoic foci with sharp distinct posterior shadowing. Due to the variability of posterior shadowing of calculi and the abundance of obscuring adjacent hilar fat and peri-ureteral fat, identification of urinary on ultrasound may prove to be difficult. Utilization of color Doppler imaging can assist by demonstrating a "twinkle" artifact secondary to sonographic waves reflecting off the rough surface of the calculi (Fig. 13.21). Sensitivity for detecting calculi ranges from 61 to 90% and is heavily dependent on user.

Direct visualization of ureteral calculi is more difficult due to overlying bowel gas and retroperitoneal fat. Similar to renal calculi, ureteral calculi are seen as hyperechoic foci within the ureteral lumen and demonstrate distinct posterior shadowing (Fig. 13.21). There may also be associated ureteral wall thickening and edema. If transabdominal approach does not reveal a ureteral calculus, transvaginal or transperineal approach may be attempted to evaluate for distal ureteral calculi [104, 105].

Aside from direct visualization of calculi, US is sensitive for evaluating presence of obstructive uropathy demonstrated by hydronephrosis, hydroureter, and perinephric edema. Visualization of ureteral jets in the bladder can also confirm patency of the ureters. This may be seen on grey scale imaging as a stream of low-level echoes or as color jets on color Doppler imaging. The degree of hydration of the patient can affect the visibility of the ureteral jets and can range from less than one jet per minute to continuous flow in a healthy patient. Healthy patients can also have asymmetric jets, thus visualization of decreased jets on affected side should only be used as an adjunct tool for increased sensitivity of stone detection [106, 107].

There have been some promising studies utilizing spectral Doppler imaging and intrarenal resistive index (RI) ((peak systolic velocity-end diastolic velocity)/peak systolic velocity) to assess the hemodynamics of acute obstruction. Both absolute intrarenal RI of ≥0.70 and a difference of RI between kidneys (Δ_{RI}) of ≥0.08 have been shown to in acute obstructive uropathy [108–110]. This is controversial, as some studies have also demonstrated less promising results in the use of RI to predict obstruction [111–113]. This accentuates the complexity of renal obstruction and renal tissue and vascular compliance and pulse pressures, which determines RI.

There are several limitations to US. The largest is that it is operator dependent [114, 115]. Evaluation can also be limited by the patient's body habitus, decreased mobility of patients, or inability of patients to follow directions. In addition, renal vascular calcification, calcified sloughed papilla, calcified tumor, or calcified ureteral stents may be mistaken for urolithiasis. Secondary obstructive signs such as hydronephrosis can also be misdiagnosed in the setting of parapelvic cysts. Thus, confirmation of findings with other diagnostic exams such as non-contrast CT is recommended.

NCCT

The advent of helical (spiral) NCCT for the evaluation of flank pain, has shown to be the exam yielding the highest sensitivity (>95%) and specificity for detecting urolithiasis [116]. Although radiographs have higher resolution, the high contrast between tissue types in NCCT allows several

facets of urolithiasis to be assessed including detection of the presence of nearly all types of calculi, size and location of calculi, and signs of obstruction. Coronal reformatted images are also available, which increase rate of detection of stones and accurate assessment of stone size [117, 118]. In addition, NCCT is a fast exam requiring only seconds to acquire a scan. Thus, NCCT is recommended after the initial evaluation with ultrasound in order to determine the extent and location of urolithiasis.

NCCT is preferred over contrast-enhanced CT because there is increased conspicuity of urothelial calculi without the obscuration by intravenous contrast, especially in more delayed phases as contrast is excreted into the collecting system and ureters. Intravenous contrast, however, can be helpful in unique situations by defining anatomy and differentiating pelvic phleboliths versus urinary calculi.

Patients should be scanned in the prone position. This allows the posteriorly located UVJ to be in a non-dependent location which can differentiate the location of calculi lodged in the UVJ versus layering calculi in the urinary bladder.

Evaluation of NCCT should include focus on the urinary collecting system, ureters, and bladder for evaluation of presence of calculi. First, location of urinary calculi should be determined, which can change prognosis. Calculi located more proximally are associated with higher need of intervention [119]. Measurement in both axial and coronal plane should be performed to ensure maximal diameter is assessed. HU of the calculus should also be measured as this provides additional information on type of calculus as mentioned previously. Finally, investigation for signs of obstruction is important. These include hydronephrosis, perinephric fat stranding, and peri-ureteral fat stranding. Other causes of flank pain should also be assessed, especially if no calculus or findings of urinary obstruction are visible. Other causes of flank pain may include acute diverticulitis, appendicitis, rib fracture, or metastatic osseous lesions.

Conventional helical (spiral) CT uses broad range of X-ray energies. DECT is a relatively new technology which is able to assess two specific different energies of X-rays. This technology has been preliminarily shown to determine the composition of calculi by measuring the HU ratio of one energy to the other as substances absorb X-ray energies to variable degrees (Fig. 13.20) [120]. More studies are needed to optimize this technique [121, 122].

One major concern of CT is the radiation exposure to the patient, especially to younger patients. Low dose CT has been shown to have high sensitivity (97%) and specificity (95%) in detecting urolithiasis [123]. In addition, it has been shown that there is no significant difference in measurement of stone size on low-dose CT versus standard dose [124]. Effort to limit scan exposure to only necessary organs is an additional method to decrease radiation exposure.

Radiography

KUB can identify renal calculi, however is less sensitive (72%) than CT for calculi greater than 5 mm [122, 123]. Radiographs are better used for follow up than the evaluation for source of acute flank pain. Radiodensity overlying the region of the kidney, ureters, and bladder may indicate renal calculi. Limitations of radiography include the inability to locate the calculus in the anteroposterior plane unless lateral view is obtained. Not all types of urinary calculi can be seen on radiographs. Quality of radiographs is heavily dependent on overlying bowel contents, patient body habitus, size, location, and composition of stone. Thus, comparing to NCCT, it has been shown that radiography has decreased sensitivity (72%) for stones greater than 5 mm in diameter and less affective in the acute setting [125, 126].

Radiography exposes patients to radiation, however at a much lower dose than NCCT. The radiation exposure from multiple KUBs obtained are additive and may eventually equal that of NCCT if a large number are taken.

MRI

Although not the first line of imaging, MR urography can be helpful in assessing for secondary signs of obstruction. Hydronephrosis is readily visible on T2-WI as it is highly sensitive to fluid. The ureters are well-assessed throughout their entire course, especially if dilated. Calculi are diagmagnetic material and do not produce signal on MRI, thus are seen as signal voids on T1, T2, and gradient sequence, called "blooming," within the urinary tract, which is

at times difficult to visualize. MRI is beneficial as it provides abundant information on tissue without exposing patients to radiation, which may be more beneficial in pregnant or pediatric patients.

Urolthiasis Follow Up Imaging

Patients with a history of urolithiasis often have recurrent flank pain and stone disease. Repeat NCCTs increase patient exposure [127, 128]. If NCCT is clinically necessary, low-dose protocols should be used. Stones that are seen on the scout image of NCCT can be followed with KUB, which expose patients to less radiation [129]. Stones that are not visualized on scout image may not be visible on KUB. Finally, ultrasound remains a radiation free and comparatively inexpensive method for imaging follow up.

Urothelial Neoplasm

Urothelial neoplasm affects the upper urothelial tract including the renal pelvis and ureters, as well as the lower tract including the urinary bladder, urachus, and urethra. The most common histological subtype of urothelial neoplasms is urothelial carcinoma, which accounts for 90% of bladder tumors [130] and 10–15% of renal tumors [131]. Only 4% of urothelial carcinomas occur in the ureters [132]. Squamous cell carcinoma is the second most common histologic type associated with recurrent urinary tract infection followed by adenocarcinoma often in the urachal remnant, both occur mostly in the bladder [133, 134].

Urothelial carcinoma is unique in that it is often multifocal and metachronous with frequent recurrence. 2–4% of people with bladder cancer will develop renal pelvis or ureteral urothelial carcinoma and 40% of those with renal pelvis or ureteral disease will develop bladder tumors [135]. Because urothelial carcinoma can occur anywhere along the urinary tract, it is important to image the entire urinary tract for initial assessment and staging of disease and for follow-up. As such, CT and MR urography are the mainstays of imaging of urothelial carcinoma. PET/CT with fludeoxyglucose (FDG)—^{18}F and ^{11}C choline may also be used to assess lymph node metastases in patients with urothelial carcinoma.

CT

CT Urography (CTU) utilizes intravenous contrast to assess the urinary tract during multiple time points after contrast administration and has been demonstrated to have sensitivity greater than 90% in detection of urothelial/bladder lesions in patients with hematuria [136]. Multiple differing protocols are available. In a single bolus study, several acquisitions are obtained: pre-contrast, parenchymal phase (80–90 s after injection), and urographic phase (7–9 min after injection). Urothelial carcinoma is typically hyperenhancing on earlier post-contrast phase, lending itself to be more accentuated on parenchymal phase against the walls of renal pelvis, ureters, and bladder (Fig. 13.22). The urographic phase is a delayed phase in which contrast is

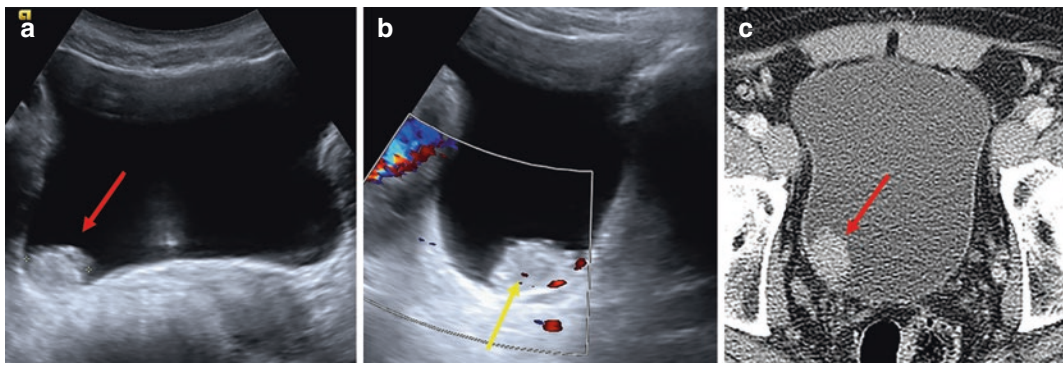

Fig. 13.22 Papillary projection on transverse ultrasound (**a**, red arrow) and axial CT with intravenous contrast (**c**, red arrow) compatible with bladder urothelial carcinoma. The mass showed internal vascularity on sagittal color Doppler imaging (**b**, yellow arrow)

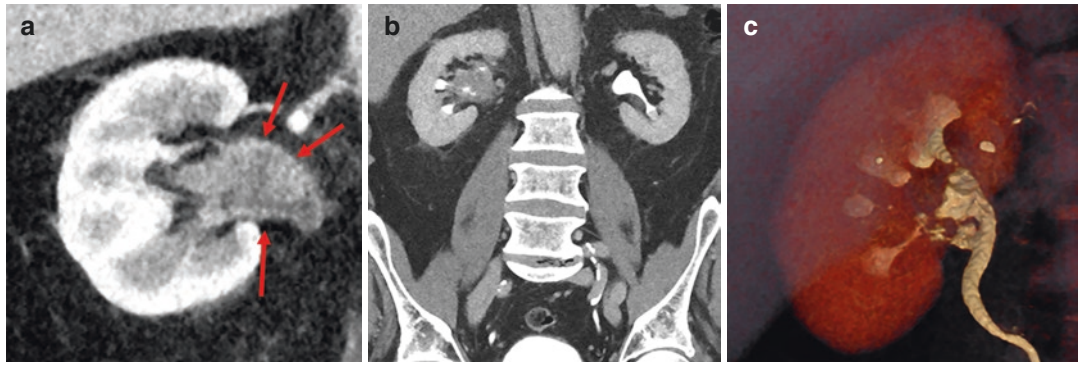

Fig. 13.23 CT urogram of an upper tract urothelial tumor. Corticomedullary phase of CT with intravenous contrast (**a**) shows enhancing upper tract urothelial tumor within the renal pelvis. On the urographic phase (**b**), the urothelial mass presents as a filling defect which is also seen on the 3D reconstruction derived from the urographic phase of the CT (**c**)

already excreted in the collecting systems, ureters, and bladder. Lesions will appear as filling defects during the urographic phase. Furosemide can be administered during the examination in order to increase contrast excretion and distention of the ureters for better visualization.

Single bolus requires three different CT acquisitions, which exposes patients to much radiation. The split bolus technique decreases radiation exposure by splitting the contrast bolus into two, injecting only a portion initially and the second portion 7–8 min after initial contrast administration. CT image acquisition occurs 80–90 s after the second portion is administered. This allows for simultaneous visualization of the parenchymal and urographic phase [137, 138]. If performed on a dual energy CT scanner, a virtual non-contrast CT scan can also be obtained, thus forgoing the need for pre-contrast scan. The split bolus technique decreases radiation exposure however may obscure some subtle lesions.

On imaging, urothelial carcinoma have different morphologies including papillary, sessile, and invasive. Papillary lesions, which are the most common, are frond-like and extend into the lumen of the urinary tract [139]. In the renal pelvis, tumors appear invasive which differentiates urothelial carcinoma from other renal neoplasm such as RCC. In the ureter, tumors appear as focal thickening and enhancement. CTU can also readily visualize secondary signs of urothelial tumors such as obstruction (hydronephrosis) (Fig. 13.23).

Staging is often performed with CTU, which can readily detect detects metastatic disease and local invasiveness of tumor. CTU is less effective at assessing the degree of muscle invasion of lesions due to the lack of imaging contrast between muscle layers, which hinders staging of T1 versus T2 disease [140]. However, one study showed sensitivity of 89% and specificity of 95% of detection of locally invasive disease, increasing ability to distinguish T2 versus T3 disease [137]. Extravesical and extra-ureteral extension appear as fat stranding adjacent to the tumor. This may be confused with inflammatory or infectious changes, which have a similar appearance, though is typically more diffuse rather than focal. CTU can also detect distant metastasis in the abdomen and pelvis, such as pathologic lymphadenopathy and invasive disease into the adjacent pelvic organs [139].

Annual follow up with CTU for non-muscle invasive high-risk bladder tumors is recommend by the EAU [141]. Follow up after treatment for muscle-invasive and metastatic bladder tumors are controversial and not specifically established, although regular imaging may help identify recurrent disease in a timely manner [142].

Follow up imaging after treatment of upper tract disease is recommended by the EAU based on invasiveness of primary disease. After radical

nephroureterectomy, noninvasive tumors should be followed by CTU annually afterwards for a total of greater than 5 years. For invasive tumors, CTU should be performed every 6 months for 2 years, then annually for a total of greater than 5 years. If patients undergo kidney-sparing management, CTU should be performed at 3 months, 6 months, and then annually after resection [143].

MRI

MRI urography (MRU) takes advantage of its high soft tissue contrast and ability to acquire multiplanar and multiparametric sequences to serve as a powerful tool in detecting urothelial cancers. Unlike CTU, MRU does not expose patients to radiation. Thus, multiple phases of imaging after intravenous contrast administration can be obtained without harmful consequences, so single bolus technique is typically used to image urothelial tumors. The use of DWI can also further increase contrast between benign and malignant tissue [144]. Urothelial neoplasms have similar appearance on CTU as they do on MRU; however, with the higher degree of soft tissue contrast, there is increased efficacy of staging, especially with the increased distinction of fat, which can clearly identify invasion of adjacent organs [145]. Follow-up utilizing MRI is also useful as DWI can differentiate between recurrence and post-operative inflammation or fibrosis. Both recurrence and inflammation/fibrosis can enhance avidly, however, recurrence has been shown to restrict diffusion more [146]. Follow up imaging after treatment may be performed with MRU in place of CTU if patients have renal failure.

US

Transabdominal imaging can be used to visualize larger tumors and secondary signs of obstruction such as hydronephrosis or hydroureter. The resolution of transabdominal ultrasound is not great enough to determine staging between T1 and T2 diseases. Transvesical sonography provides increased accuracy in local staging of bladder neoplasm compared to transabdominal ultrasound, however has a limited field of view and cannot assess extravesical disease effectively [147, 148]. Visualization and evaluation of the ureters is limited due to the lack of penetration of sound waves through retroperitoneal fat even on transabdominal ultrasound, thus cross-sectional imaging is needed for full assessment of urothelial carcinoma.

PET/CT

For evaluation of metastatic lymphadenopathy, PET/CT can be used. Detection of disease within the urinary tract is limited as it is obscured by radiotracer excreted by the kidneys, thus nuclear medicine findings must be correlated with CT findings [149]. ^{18}F-FDG radiotracer is typically used and can be used to evaluate for distant metastatic nodal disease, especially when renal insufficiency of a patient prevents imaging with intravenous iodinated contrast. Preliminary studies with ^{11}C-choline and ^{11}C-acetate, which has minimal renal excretion, has shown some promising results in identifying primary and metastatic urothelial carcinoma, although continued validation is needed [150].

Prostate Imaging

US

US is a crucial image modality for evaluating all benign and malignant conditions of the prostate. That is because the prostate is a solid organ that has good permeability to sonographic waves, and its anatomical location provides it with good windows to be evaluated in a transabdominal and, especially, a transrectal fashion. The other advantages of US over other image modalities are lower costs, less invasiveness, good tolerance, and capability to evaluate the prostate in real time. The most frequent indications for prostate US are [151]:

- Guidance for biopsy in the presence of an abnormal digital rectal examination or elevated PSA or a suspicious prostatic lesion detected on MRI. This includes use of Trans rectal US (TRUS) biopsy as part of the TRUS/MRI fusion technique.

- Assessment of prostate volume before medical, surgical, or radiation therapy and to calculate PSA density.
- Real-time guidance for the placement of brachytherapy seeds, and the planning and execution of all ablative techniques.
- Assessment of lower urinary tract symptoms.
- Assessment of congenital anomalies.
- Assessment of Infertility.
- Assessment of Hematospermia.
- Assessment of Suspected recurrence in the prostatectomy bed

Trans Abdominal US (TAUS)

TAUS of the prostate should be performed with linear, sector or convex transducers with frequencies ranging from 2 to 5 MHz or wideband transducers with the frequency range from 2 to 5 MHz [152]. The patient should be positioned supine, and in a relaxed and comfortable state. It is important to note that patients must have a relatively filled bladder (at least 100cc), as it plays the part of an "acoustic window", allowing for a more defined appreciation of the gland.

TAUS (as well as TRUS), allows for an estimation of the prostate volume. Since the prostate is considered to have an ellipsoid shape, its volume can be calculated the same way: $1/6\pi \times \text{height} \times \text{width} \times \text{length} = \text{prostate volume}$ (cc). The description of a TAUS examination of the prostate gland should include: the dimensions of the gland, the evaluation of its shape and symmetry, the description of its boundaries and the volume of residual urine after voiding.

TRUS

Even though TRUS is used primarily for guidance of prostate biopsies (either transrectal or transperineal), it can also be indicated for a more thorough appreciation of the prostate gland on men with bothersome lower urinary tract symptoms (LUTS) or pelvic pain; or for a more accurate measurement of the prostate size if the patient is being considered for a surgical intervention. Even though the formula for the calculation of prostate volume with TRUS is the same used for TAUS, TRUS estimates the prostate volume on a more accurate way than TAUS [153, 154].

TRUS should be performed on a higher frequency than TAUS (no less than 8 mHz) to allow for adequate resolution [152], and the procedures and techniques vary according to the type of transducer used. The models that are used the most are the curved array and the biplanar transducer, which are the preferred choices to do transrectal and transperineal biopsies respectively. A curved array crystal is usually aligned to the end of the probe, allowing for sagittal, oblique, or axial image through rotation of the probe. A biplanar probe allows for sagittal or axial image through alternating between planar transducer crystals.

When doing a TRUS with a curved transducer, the examination should be performed with the patient lying on his left side, with legs bent in the knees and pulled to the chest. A rubber protective cap should be placed on the transducer with gel before every examination [152]. A needle guide is typically attached to or through the probe to allow for transrectal sampling. On the other hand, if a transperineal biopsy using a biplanar transducer is to be performed, the patient should be placed on a dorsal lithotomy position, with a clear exposure of the perineum for biopsy sampling [155].

Clinical Applications of Prostate US

Benign Prostatic Hyperplasia (BPH)

US has an important role on the diagnostic evaluation of men with LUTS. Both the EAU and the American Urological Association (AUA) guidelines recommend the routine use of either TAUS and/or TRUS for the evaluation of men with suspected BPH [156, 157].

Prostate ultrasonography in the context of BPH evaluation provides information regarding:

- Assessment of post-void residual volume of the bladder.
- Size and configuration of the prostate. TRUS provides a more accurate information, however, the measurements obtained by TAUS are often enough when considering a patient for surgical intervention.
- Appraisal of the upper urinary tract. Especially presence of hydronephrosis, and kidney cortex abnormalities.

Inflammatory Processes

The role of US in the context of prostatitis is less significant, but it can add relevant information. The diagnosis of acute prostatitis is mostly clinical. The presence of typical symptoms of prostatitis (i.e.: fevers, dysuria, pelvic pain) in addition to the finding of an edematous and tender prostate on digital rectal examination (DRE) usually establishes the diagnosis of acute bacterial prostatitis. US should be used judiciously in men with suspected acute prostatitis given the risk of bacteremia and sepsis upon excessive manipulation of the prostate. TRUS, in particular, may be ill-advised given the need to compress the prostate for establishing an interface with the US transducer.

On US, acute prostatitis can be seen as an hypoechoic rim around the prostate accompanied by increased flow on Doppler [158]. Acute bacterial prostatitis can be complicated by a prostate abscess, which can be seen under US as a walled-off hypoechogenic fluid collection. In some cases, where the abscess grows to a significant size or it doesn't regress after proper antibiotic therapy, drainage of the collection may be warranted. In these cases (depending on the location of said abscesses), the drainage can be performed under TAUS or TRUS guidance. US findings for chronic prostatitis are diffuse and non-characteristic, so neither TAUS nor TRUS possess a significant role on the diagnosis or management of chronic prostatitis.

Prostate Cancer Diagnosis

The diagnosis of Prostate cancer (PCa) is done through biopsy of the gland, which can be done either transrectal or transperineally. Since the late 1980s US, typically TRUS, has become the standard method for guidance for tissue sampling. Whichever route or template is chosen, TRUS guidance ensures a proper sampling of the prostate rather than surrounding tissues, and allows for sampling of visually abnormal regions, as regions containing cancerous cells may be seen as hypoechogenic patches within the prostate [159].

The reported sensitivity for gray-scale TRUS in diagnosing PCa ranges between 11 and 35%, with some series reporting up to 60% whereas the positive predictive value is reported to be between 27 and 57% [160, 161]. These wide ranges of specificity and positive predictive value can be attributed to the high operator variability (a usual limitation for US) as well as the high rate of false positives produced by benign entities such as prostatitis or nodular BPH.

There have been numerous US modalities aimed at improving the sensitivity and specificity of US in PCa detection. These include CEUS; shear-wave elastography (SWE); power Doppler US (PDUS); and color Doppler US (CDUS). In a similar fashion that different MRI parameters combine into a mpMRI, the addition of these different US modalities to a grey-scale US (GSUS) can produce a multi-parametric US (mpUS).

The basis of CEUS have been previously described on this present chapter. The rationale behind the role of CEUS on PCa is that cancerous tissue within the prostate would have an abnormal flow pattern with more dense tissue and less vascularity. The rapid inflow of this gas contrast is interpreted as "enhancement". Different patterns of enhancement are associated with malignancy: increased focal enhancement, asymmetrical rapid inflow, and asymmetric intraprostatic vessels [162].

SWE is a relatively new technique that uses a focal US beam that produces shear waves as it traverses tissues with different densities. It relays on the measurement of tissue stiffness when subjected to external pressure. Cancerous foci have less elasticity (are stiffer) than benign ones due to the high rate of cell proliferation, so based on Young's model (shear waves propagate faster on firmer tissues) they would create a faster dispersion of the shear waves. Each wave is then coded according to their velocity and overlaid on the GSUS creating a dynamic color map of the tissue elasticity.

SWE is an evolution from traditional elastography where the pressure was applied by movements made by the operator. This process lends itself to a considerable amount of subjectivity and has a steep learning curve, whereas SWE is performed in an automated fashion and the information is processed by a computer.

The rationale behind the increase in US performance when using PDUS and CDUS is that, as many other solid tumors, PCa cells grow by increasing its surrounding vascularity. There is also evidence suggesting that the amount of neovascularity correlates with tumor aggressiveness [163]. Both PDUS and CDUS find areas suspicious for PCa by highlighting those zones with increased vascular density. The main difference between PDUS and CDUS is that PDUS has increased sensitivity (as it can pick up smaller vessels), although it is not able to distinguish the direction of the blood flow. One large series that employed PDUS on the preoperative setting for patients who then underwent radical prostatectomy estimated that adding PDUS to GSUS can increase its sensitivity to 74% in the detection of PCa [164].

Although many studies are on ongoing [165, 166], to date there is no direct study comparing of the accuracy of mpUS to mpMRI. The lack of strong evidence in addition to the fact that there is no standardized interpretation language or scoring system (like the Prostate imaging reporting and data system (PI-RADS) is for mpMRI), do not allow for the recommendation of mpUS as a standard diagnostic tool for PCa detection as for now.

US has also been proposed as a tool for local staging of PCa. The most important aspect when staging a prostate tumor is to assess whether it extends beyond the prostate or not. In other words, to describe whether or not it is a T3 tumor. The sensitivity and specificity of TRUS to assess this is very low, therefore, it is not recommended as a staging study [167].

CT

The only role CT has on imaging of the prostate is on the initial staging of PCa. Iodine IV contrast CT scan of the abdomen and pelvis should be done in that setting. CT holds no value on local tumor extension assessment, as it is unable to distinguish extracapsular extension or seminal vesicle invasion. In detecting pelvic lymph node metastases, CT carries a low sensitivity with relatively few false positive rate [168]. A multicenter study was carried out that included patients with newly diagnosed PCa that underwent staging CT and bone scan (BS) prior to pelvic lymph node dissection. CT had a sensitivity of 8.8% and a specificity of 98% [169]. The low sensitivity relates to the fact that CT relies entirely on node size (8–10 mm), and to a lesser extent morphology, in identifying lymph node metastasis, thereby limiting detection to grossly abnormal nodes. This can explain the low sensitivity of the CT scan on the context of the initial staging of PCa because most patients with occult nodal metastasis harbor micrometastases below the threshold of detection. That is why it is not a useful diagnostic tool for patients with low or intermediate risk PCa. These patients have a low incidence of lymph node involvement, therefore the low sensitivity the CT scan presents, adds no additional information. For these reasons, most guidelines only recommend using CT for staging only in patients that are recently diagnosed with high-risk PCa (Fig. 13.24) [170–172].

Pelvic CT can also be useful during workup of a patient under suspicion for a prostate abscess. As mentioned above, the diagnosis of prostate abscess is usually clinical. However, the use of complementary studies like TRUS or CT can aid in management. The total extension of the infectious process can be assessed properly with a CT scan, as well as its extension towards neighboring structures (like the ischiorectal fossa or the perineal floor).

mpMRI

The first case series reporting the use of MRI on the prostate dates from 1982 [173]. The MRI field has substantially advanced since then and newer techniques (the implementation of endorectal coil (EC); the development of a standardized imaging data system) and technologies (the implementation of gadolinium, 3 Tesla (T) magnets, the development of mpMRI) have increased the clinical utility of this tool exponentially over the last years, as well as the enthusiasm of the urological community towards its use.

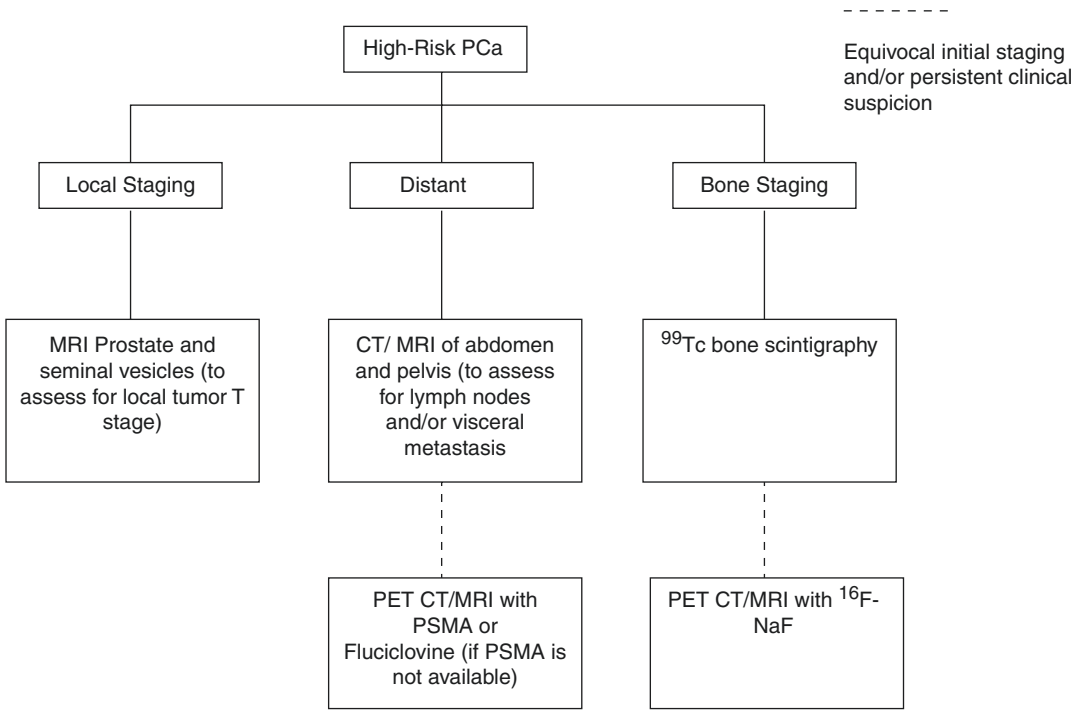

Fig. 13.24 An algorithm illustrating the pathways for imaging patients with high-risk prostate cancer. Adapted from Bjurlin et al. [214]

Technique

The increased utility and demand for mpMRI, brought with it a diversified and heterogeneous interpretation of its findings. To address this issue, the first version of the PI-RADS was developed in 2012, and updated to the second and current version (v2) in 2015 [174]. The objectives of the PI-RADS v2 system are:

- Establish minimum acceptable technical parameters for prostate mpMRI.
- Simplify and standardize the terminology and content of radiology reports.
- Facilitate the use of MRI data for targeted biopsy.
- Develop assessment categories that summarize levels of suspicion or risk and can be used to select patients for biopsies and management.
- Enable data collection and outcome monitoring.
- Educate radiologists on prostate MRI reporting and reduce variability in imaging interpretation.
- Enhance interdisciplinary communications with referring clinicians.

Equipment Standards

A satisfactory result useful for clinical application can be obtained with either a 1.5 T or a 3 T magnet. There is no randomized clinical trial comparing these technologies, and the PI-RADS is validated on both platforms. The utility of an EC is controversial. On one hand its use may provide improved spatial resolution and reduce local motion of the prostate during imaging. But on the other hand, the good results obtained when using externally applied phased array coils in both 1.5 and 3 T machines, along with the increased cost and patient discomfort caused by the EC have significantly reduced its employment in the last years. Therefore, the PI-RADSv2 document states that the use of an EC is left at the discretion of the radiologist. The EC could be particularly useful when an older 1.5 T is employed, or if a newer 1.5 T system will be used for local staging on high risk patients [175].

Parameters

The MRI used for PCa detection and staging is called multi-parametric, as it uses diverse combination of anatomic and functional pulse sequences called "parameters".

The parameters used on the mpMRI are: T1-WI and T2-WI; DWI with ADC; and dynamic contrast enhancement (DCE). The radiologic principles of each parameter have been previously described on this present chapter.

T1-WI

It's utility for cancer detection is very limited. This imaging is acquired primarily to differentiate biopsy-related changes (i.e. hemorrhage) from true enhancement upon contrast administration. On prostate mpMRI, a T1-WI acquisition in the transverse plane is sufficient. T1-WI is also useful for detecting osseous metastasis. Of course, this utility is limited only to the bones of the pelvis as they are the only ones included in the window that the PI-RADS v2 protocol recommends.

T2-WI

It is the parameter that provides the most information regarding normal prostate anatomy, and provides important information regarding tumor location and extension. It can clearly define the borders between the peripheral zone (PZ) and the transition zone (TZ).

Malignancy appears as an isolated region of decreased signal intensity, typically within the PZ, typically with poorly marginated borders. Even though T2-WI can localize tumors in the PZ, their findings on this region are non- specific and it cannot distinguish primary neoplastic foci from other benign conditions such as prostatitis, hemorrhage, glandular atrophy, benign hyperplasia, biopsy related scars, and after therapy changes. Associated findings such as adjacent capsular bulge or irregularity, may increase the suspicion for cancer. Within the TZ, regions of PCa are defined both by decreased attenuation and morphology, and as such, the specificity is improved. Nonetheless, detection in the TZ is difficult owing to the heterogenous architecture and the presence of nodular BPH which typically demonstrates decreased signal intensity with rounded architecture.

DWI-ADC

PCa foci are usually cell-dense, therefore, resulting in restricted water movement. Moreover DWI-ADC values are inversely associated with Gleason scores and clinically correlated with the likelihood of upgrading at the time of prostatectomy [176, 177].

Even though DWI is an essential parameter for mpMRI staging, it has its limitations. One of them is that encapsulated BPH nodules are typically dense with restriction of water movement, so they appear as hypointense on DWI and have low ADC values. Fibrous septae within the central zone and extraprostatic structures such as the neurovascular bundles can also mimic tumor on DWI [178]. Nonetheless, DWI carries the critical role of improving specificity in the detection of clinically significant cancer and serves as the primary parameter for suspicion scoring in the PZ, and the secondary parameter in the TZ within the PIRADS scoring system.

DCE

Like many other malignancies, PCa foci develop local angiogenesis that results in increased blood flow, resulting in earlier wash-in and earlier wash-out of contrast, as compared to normal prostate tissues. That is the basic principle on which DCE relies upon. DCE consists on T1-WI gradient echo images obtained in rapid succession before, during and after injection of gadolinium-based contrast agents. While image resolution is lost, a DCE finding is considered as "positive" when the enhancement is focal, earlier or contemporaneous with enhancement of adjacent normal prostatic tissues, and corresponds to a finding on T2-WI and/or DWI [174].

The role of DCE within mpMRI of the prostate is to offer further refinement of suspicion scoring among lesions equivocal on T2-WI or DWI. Isolated perfusion abnormalities, in the absence of DWI or T2-WI abnormality, are often associated with inflammation or prostatitis and should be considered false positives. DCE is also useful for prioritizing different lesions on a same

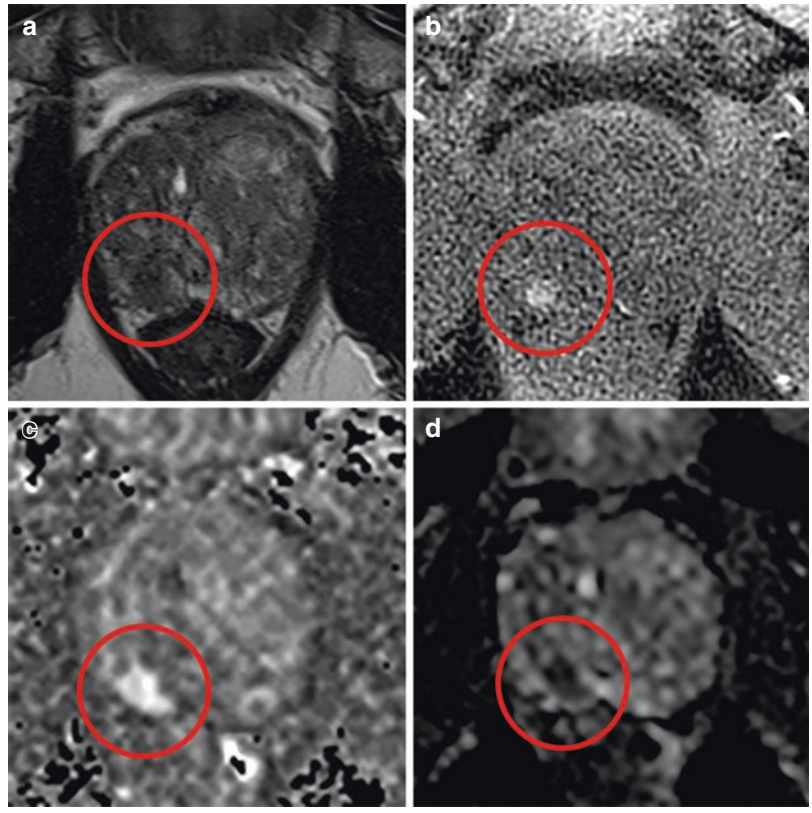

Fig. 13.25 PI-RADS 4 lesion in the right midgland posteromedial peripheral zone (red circle) is hypointense on axial T2 weighted imaging (**a**), enhances early on post contrast sequence before the rest of the prostate (**b**), and markedly restrict diffusion on diffusion weighted image seen on high b-value (**c**), and ADC map (**d**)

patient, as the lesions that have more intense perfusion abnormality can be called "dominant foci" (Fig. 13.25).

Tables 13.3 and 13.4 summarize the scoring system used by PI-RADS v2 [174].

Table 13.3 PI-RADS v2 scoring system in PZ foci

DWI	T2 W	DCE	PI-RADS
1	Any	Any	1
2	Any	Any	2
3	Any	–	3
	Any	+	4
4	Any	Any	4
5	Any	Any	5

Table 13.4 PI-RADS v2 scoring system in TZ foci

T2 W	DCE	DWI	PI-RADS
1	Any	Any	1
2	Any	Any	2
3	Any	≤4	3
	Any	5	4
4	Any	Any	4
5	Any	Any	5

Bi-parametric MRI

Even though it is a very useful tool, mpMRI has several limitations: the study takes up a prolonged time to be carried out and it requires the use of IV contrast. These two limitations add to the cost of the study measured in dollars and convenience. In an era that many studies are aiming towards the use of MRI to distinguish those patients that require a first prostate biopsy in a population-based analysis, the cost is a paramount limitation. That is why biparametric MRI (bpMRI), using only two parameters: T2-WI and DWI, has gained more interest over the past years. The rationale for this procedure is not only that it is less costly, it is mainly because both the PI-RADS v2 and other studies have recognized the limited role of the DCE [174, 179, 180]. Even though the results of bpMRI are promising [179, 181–183], its protocol is not yet validated for the detection of PCa, and even though several scor-

ing protocols have been suggested, there is no standardization available for the moment. It is important to state that the current PI-RADS v2 does not apply to this modality.

Clinical Applications of mpMRI

In clinical applications, prostate MRI has slowly evolved from a study intended to stage prostate cancer, to a tool for identifying missed cancers in men previously biopsied, to a tool for identifying cancer in all men at suspicion, and most recently, to a study intended to determine the risk of clinically significant prostate cancer (csPCa) and the need for biopsy. This evolution has been fueled by a desire to reduce the over-detection of prostate cancer while maintaining the detection of csPCa, typically defined as Gleason score $\geq 3 + 4$. Early single institution studies demonstrated the ability to increase the detection of csPCa, and reduce the detection of indolent cancer, thereby potentially lowering the risk of over-treatment without compromising the noted reductions in mortality over the years.

The clinical implementation of pre-biopsy MRI has been critically linked to the development of techniques for MRI-targeted biopsy [184]. MRI abnormalities can be targeted directly in the MRI gantry (MRI-guided) [185] or in the urologist's office under ultrasonic guidance through visual estimation. More recently, software image co-registration has been linked to spatial tracking systems to allow for MRI-fusion targeted biopsy techniques [186, 187]. Such techniques are not clearly better than visual estimation MRI-targeted biopsy alone [188, 189].

Patients with Prior Negative Biopsies

Much of the early work in clinically validating mpMRI in the pre-biopsy setting was done among men with previous negative biopsy in whom there remains clinical suspicion for cancer on the basis of continued rise in PSA or PSA level. Among these men, mpMRI has been shown to identify the location of missed cancers with great accuracy, and the likelihood of such cancer is well predicted by the suspicion score [190–192]. It is in this setting that mpMRI has the strongest rationale to support its use [193–195]. These cancers typically lie in the anterior gland or extreme base/apex regions, not typically sampled by conventional templated biopsies. In a consensus statement of the AUA and the Society of Abdominal Radiology, mpMRI prior to biopsy was recommended for men with previous negative biopsy, and it was suggested that biopsy may be avoided in men with low suspicion mpMRI as long as quality assurance measures are in place with regard to the MRI reading [196]. More recently, the EAU recommended pre-biopsy MRI be prior to a repeat biopsy in patients for high suspicion for csPCa [197].

Patients with High Suspicion of PCa and No Prior Biopsies

There remains more controversy within the urologic community regarding the routine use of pre-biopsy mpMRI in men presenting with suspicion for prostate cancer, on the basis of elevated PSA level or abnormal digital exam, and no previous biopsy. In these men, the cost implications of routine biopsy are substantial, unless the MRI is utilized to avoid biopsy in a subset of men, thereby reducing over-detection of indolent cancer and reducing downstream costs of care.

A number of large single institution studies demonstrated that when utilizing mpMRI prior to first biopsy, MRI-targeted sampling results in greater detection of csPCa and lower detection of low grade cancer as compared to the associated systematic sample in the same patient [190, 198–200]. It was also noted in these early studies that the suspicion score correlated well with the risk of indolent cancer, and that a low suspicion MRI carried a relatively high negative predicting value (NPV) for csPCa detection on systematic biopsy [201]. The PROMIS study directly compared systematic 12 core biopsy with mpMRI in the prediction of csPCa using a transperineal template biopsy as the referent standard. It was demonstrated that the mpMRI was more predictive of csPCa with a NPV of 76–89%, depending upon the definition of csPCa [202]. These observations led to the PRECISION trial, a randomized comparison of systematic biopsy or MRI-targeted biopsy in men with PIRADS scores of 3–5 designed to demonstrated non-inferiority in the

detection of Gleason score ≥3 + 4 cancer [203]. In men randomized to the MRI-targeted biopsy arm, no systematic sampling was done in men with PIRADS 3–5, and no biopsy was indicated in men with PIRADS 1–2. Twenty-eight percent of biopsies were avoided in the MRI-targeted sample and more csPCa, and less low grade PCa, was identified.

The PRECISION trial has created controversy, in that there remains concern that avoidance of biopsy in men with normal or low suspicion MRI may lead to missed csPCa. The MRI-FIRST study demonstrated that such an approach may miss csPCa in 7.6% of patients [204]. The EAU guidelines have recently been modified to include pre-biopsy MRI among men with elevated PSA [197]. The British National Institute of Health and Care Excellence (NICE) has more recently recommended consideration of mpMRI on all patients before undergoing a first prostate biopsy.

Patients on Active Surveillance

Active surveillance (AS) has proven to be safe management option for men with low risk PCa, demonstrating similar risk of metastasis and disease-specific mortality to radical prostatectomy or external beam radio therapy over 10–15 years of follow-up. Nevertheless, concerns remain regarding the risk of understaging or undergrading during patient selection, and the need for several repeat invasive biopsies in follow-up. Given the increasing utilization of AS globally, there is a desire to improve baseline selection of candidates in order to reduce the rate of progression on surveillance and the need for repetitive biopsy.

MRI-targeted biopsy has been shown to be more likely to find occult higher grade tumors, thus aiding on the selection for patients who may benefit from a more aggressive form of treatment [199]. Most investigators have demonstrated that the NPV of MRI in the normal prostate is lower in men on AS than men with no previous history of cancer, likely due to the increased prevalence of disease in the cohort. As such, both MRI-targeted and systematic sampling is recommended for accurate baseline sampling [198, 205]. There is also increasing evidence that MRI (along periodic PSA and DRE) can be useful in follow up, and determination of when a repeat biopsy is warranted [206]. While MRI is not clearly demonstrated to serve as an adequate measure of progression in follow-up, it may allow for reduced frequency of surveillance biopsy, owing to greater confidence in the accuracy of the biopsy.

Local Staging

While mpMRI has been shown to improve the accuracy of local staging when compared to T2-WI imaging alone [207, 208], the overall sensitivity of MRI remains poor since most extracapsular extension is focal (<2 mm) and poorly delineating on imaging. Gross extracapsular extension is noted in few patients but is demonstrated as evidence of infiltrative extension of decreased T2-WI signal into the peri-prostatic space. Seminal vesical invasion may be demonstrated as a mass-like region of decreased T2-WI signal intensity in the seminal vesicle, or as extension from a large tumor in the gland base. While the demonstration of gross extracapusular extension or seminal vesical invasion can be quite specific, with very few false positives, for the majority of patients, the use of MRI for staging has limited value [209, 210]. Indicators of an increased likelihood of extracapsular extension include >10 mm linear length of capsular contact, capsular bulge, or capsular irregularity [174]. When MRI is added to existing clinical nomograms, the sensitivity improves to 92–94% for prediction of extraprostatic extension [211]. When used for treatment planning, mpMRI is useful to determine if nerve sparing can be safely implemented when performing a radical prostatectomy and this may be the best rationale for its use prior to surgery [212]. This image modality has also been proven to be the most accurate way to estimate prostate volume, with fairly little experience [213].

Inflammatory Processes

The utility of MRI for inflammatory processes has not been thoroughly validated. As mentioned above, although not perfect, mpMRI can distinguish between areas suspicious for PCa and foci

of chronic prostatitis. Prostate abscesses are seen on MRI as a clearly demarcated fluid collection with circumferential enhancement. Bacillus of Calmette-Guerin (BCG) induced granulomatosis of the prostate can mimic areas suspicious for PCa on the mpMRI, and the radiologic distinction can be very challenging. A history of previous intravesical BCG for bladder cancer can help in the differential diagnosis. However, often times a biopsy is necessary to provide the final diagnosis.

Nuclear Imaging

These modalities include BS (or scintigraphy) and PET.

The role of molecular imaging on PCa is in current redevelopment. Ordinarily, PET is only approved for evaluation of patients with elevated PSA after treatment (biochemical recurrence) [214]. However, recent data suggests that PET with ^{68}Ga labelled Prostate Specific Membrane Antigen (PSMA) can have a potential role on the initial workup of patients with high suspicion of PCa, as it demonstrates a higher tumor contrast than mpMRI [215, 216].

BS

Despite being used since the mid 1970s [217], bone scan with Technetium 99m (^{99}T)-labeled diphosphonate is the most widely used method for evaluating extra-nodal metastasis in PCa, due to its high sensitivity and relatively low cost. These radiotracers have increased avidity for bone tissue with enhanced osteoblastic induced osteogenic activity. Another advantage of the BS is that it offers a fast whole-body overview that can also be used for quantification (BS index (BSI) [218]). The ^{99}Tc BS is recommended as a primary staging tool in the initial evaluation of men with high risk prostate cancer, and in the evaluation of recurrence following primary therapy. It is not recommended for use in the primary staging of men with low and intermediate risk cancers, given the low yield and associated costs [219, 220]. Among men with recurrence, the diagnostic yield is quite poor for men in whom the serum is PSA <10 ng/mL. Newer modalities such as ^{18}F-choline PET/CT and ^{16}F Sodium fluoride (^{16}F-NaF) PET/CT carry higher sensitivity for detection of disease in early recurrence [221]. Nonetheless, baseline bone imaging with ^{99}Tc BS remains within the standard of care, though its use may be limited to ruling out occult metastatic disease in patients for whom local salvage is planned, or in evaluating men with PSA levels >10 ng/ml/

PET

Historically, PET has had little utility in the evaluation of PCa. In recent years, several new PET ligands have shown selectivity in the demonstration of prostate cancer metastasis, both in lymph nodes and bone. Newer ligands have demonstrated very high levels of sensitivity for detection of recurrence in men with low PSA levels [222–224], allowing for a potential shift in the therapeutic paradigm towards resection, or focal radiation, of metastatic sites [225, 226]. A number of radiotracer ligands have been evaluated in prostate cancer (Table 13.5) we will proceed to further detail the most widely used ones.

FDG-PET

This radiotracer is the most widely used across different clinical scenarios, but it performs poorly in PCa. This is primarily due to its fast kidney excretion rate, which makes it accumulate on the urinary tract, therefore obstructing the finding of high metabolic uptake by an eventual recurrence on the prostate (or prostate bed), or pelvic lymph nodes.

^{16}F-NaF-PET

The rationale for this tracer is that it uses the high avidity for bone by the sodium to detect areas of fast bone turnover. It is not specific for malignancy; however, the combination of the PET scan with CT or MRI allows for differentiation between benign and malignant lesions, as the underlying anatomy can be better assessed with the latter modalities. When compared to ^{99}Tc BS, ^{16}F-NaF PET/CT has twice the bone uptake, a faster blood clearance, and a higher target/background ratio [227]. ^{16}F-NaF-PET has improved sensitivity on a per lesion basis as compared to ^{99}Tc BS, but it is not clear that it is greatly superior on a per patient

Table 13.5 Summary of radiotracers currently used in the PCa setting

Molecular imaging agent	Biologic process—target	FDA approved	Availability in the USA	Strengths	Weaknesses
^{18}F-NaF	Bone metabolism	Yes	May not be available in all practices	• Shows both lytic and blastic lesions • Well-validated • Better sensitivity compared with conventional bone scan • Higher spatial resolution of PET compared with bone scan, may improve lesion evaluation	Not incorporated into bone staging guidelines
Ferumoxtran-10 or ferumoxytol	Iron oxide contrast agent in macrophages of lymphatic tissue	Yes	Limited US availability	Increased accuracy for detection of small lymph node metastases	Still under investigation, limited studies
m-Tc-nano-colloid or sulfur-colloid	Filtered colloid of human serum albumin	Yes	Currently limited to academic centers	May have potential to identify sentinel lymph node	• Exposure of the patient and surgeon to radiation • Requires gamma probe during surgery • Poor spatial resolution and possible false positives related to improper orientation of the gamma probe during surgery • Still under investigation, limited studies
Indocyanine green	Intravascular dye, binds to plasma proteins	Yes	Readily available	May possibly guide intraoperative lymph node dissection	• Limited use in preoperative staging
^{18}F-fluorodeoxyglucose	Glucose metabolism	Yes	May not be available in all practices	May detect inexplicably high glucose-dependent prostate cancer	• Very limited use in prostate cancer staging
^{11}C-choline	Synthesis of cell membrane phospholipid-choline kinase activity	Yes	Requires on-site cyclotron	• An abundance of clinical evidence, in different setting of disease (initial staging, restaging, and RT planning) • Minimal bladder excretion • Early acquisition time	• Variable sensitivity and specificity for BCR

(continued)

Table 13.5 (continued)

Molecular imaging agent	Biologic process—target	FDA approved	Availability in the USA	Strengths	Weaknesses
^{18}F-choline	Synthesis of cell membrane phospholipid-choline kinase activity	No	Limited availability in the United States	• Minimal bladder excretion minimizes obscuring the prostate • An abundance clinical evidence, in different setting of disease (initial staging, restaging, and RT planning) • Long half-life (120 min) prostate	• Variable sensitivity and specificity for BCR
^{11}C-acetate	Fatty acid metabolism	No	Requires on-site cyclotron • Only few centers in the United States are producing it	• Minimal bladder excretion minimizes obscuring the prostate	• Short half-life
^{18}F-FACBC (or Fluciclovine)	Amino acid transport	Yes	Currently limited to academic centers	• Minimal bladder excretion minimizes obscuring the prostate • High sensitivity for recurrence	• Moderate specificity; only moderate performance at lower PSA levels
^{68}Ga-PSMA	PSMA analog	No	Currently limited to academic centers	• High sensitivity and specificity even at low PSA levels	• Relatively new radiotracer, still under investigation
^{18}F-DCFBC	PSMA inhibitor or antibodies	No	Currently limited to academic centers	• ^{18}F is a superior positron emitter compared with 68 Ga with longer half-life	• Significant blood pool activity • Still under investigation, will need further validation in larger studies
^{18}F-DCFPyl	PSMA inhibitor or antibodies	No	Currently limited to academic centers	• May be able to differentiate between indolent and aggressive disease in the prostate gland • May be more sensitive than 68Ga in detecting BCR	• New radiotracer that needs further validation in larger studies

Adapted from Bjurlin et al. [214]

basis [221]. Despite this, the use of ^{16}F-NaF PET has been shown to influence patient management in more than half of patients [228]. Nevertheless, due to its relatively high cost and limited availability, ^{16}F-NaF PET is not currently approved as a first line image modality, but it has gained its place as an adjunct to an equivocal BS, when bone metastasis are suspected, or in determining if noted bone metastases are truly oligometastatic.

^{11}C/^{18}F-Choline PET

Several preclinical and metabolomic studies have shown augmented choline synthesis in PCa cells when compared to normal prostate cells [229, 230]. This can be explained because tissues with high proliferation rate need more choline to serve as a precursor in the de novo synthesis of phosphatidylcholine, which is an essential component of the cell membrane. These studies prompted the use of choline as a biomarker for PCa, and ^{18}F/^{11}C-choline was developed as a radiotracer. Early studies showed ^{18}F/^{11}C-choline PET has more sensitivity for detection of primary lesions, regional lymph node involvement and bone metastasis than FDG PET [231–233]. Choline PET demonstrates relatively poor detection rates at low PSA levels, with strongest performance in PSA levels >5 ng/ml [234]. Comparative studies demonstrate that PSMA PET has a higher detection rate, and a higher specificity, especially in patients with serum PSA <1 ng/mL [235, 236]. The main difference between ^{11}C and ^{18}F labeled choline is that while ^{11}C has a half life of 20 min, the half life of ^{18}F is 110 min, making it a more practical radiotracer for central production and distribution. Centers that wish to offer ^{11}C labeled choline must have an in-facility cyclotron [237].

^{18}F-fluciclovine

This radiotracer is a nuclear labeled synthetic amino acid which is accumulated in cells that express specialized membrane amino acid transporters called ASCT2 and LAT-1, which are overexpressed in gliomas and PCa cells where they play an important role in the provision of glutamine. However, ^{18}F-fluciclovine does not metabolize in these cells, thereby accumulating [238, 239].

^{18}F-fluciclovine (trade name Axumin) was approved by the Food and Drug Administration (FDA) in 2016. The tracer is primarily useful in detecting extra-prostatic recurrences, but its sensitivity varies by the PSA level. In a post-prostatectomy cohort, detection rates for extraprostatic disease were found to be 72.0%, 83.3%, and 100% at PSA levels of less than 1, of 1–2, and of 2 or more ng/mL respectively, [240] (Fig. 13.26). Other studies on post-prostatectomy cohorts have reported a very high specificity for extraprostatic disease detection, but a much lower one when analyzing recurrences on the prostate bed [224, 241, 242].

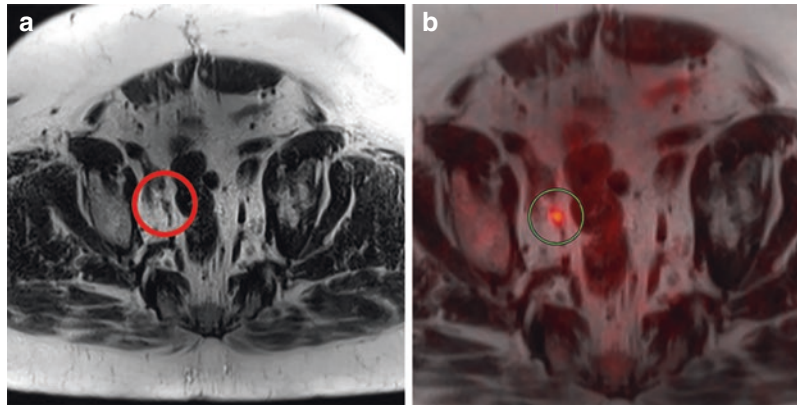

Fig. 13.26 Patient with prostate cancer status post radical prostatectomy presents with rising PSA. Small borderline sized lymph node without suspicious features is seen in the right pelvis on axial T2 weighted imaging (**a**) but demonstrates avid radiotracer uptake on PET/MRI with fluciclovine study (**b**). There was no other uptake in the body including the prostatectomy bed. The lymph node was later resected and proven to be metastatic prostate cancer

On a prospective trial by Nanni et al. [243] Fluciclovine PET outperformed ^{11}C-choline PET/CT on recurrence detection rate, on post-prostatectomy setting, but there are no studies to date comparing ^{18}F-fluciclovine to PSMA PET.

^{68}Ga-PSMA

The rationale behind this image modality is based on radiolabeling of a transmembrane glycoprotein (PSMA) that is transferred from the cytoplasmic side of the membrane to the luminal surface of the prostatic ducts upon malignant transformation [238]. PSMA expression has been correlated with increasing histologic grade and castration-resistance [244], and radiolabeled PSMA has been found to have proportional increased uptake on primary tumors, regional lymph nodes and bone metastasis, as the aggressiveness of the tumor increases [245].

There are currently two radioisotopes available: ^{68}Ga and ^{18}F. While the gallium isotope is the most widely investigated and available for the moment, it also has a half life of only 58 min, thus creating difficulty in the logistics of its implementation. Fluoride based isotopes, have a much longer half life, but remain to be validated clinically. To date, the FDA has not approved the commercial use of PSMA in the United States, though it is widely used for clinical purposes on many other countries around the world.

Maurere et al. studied 130 patients with intermediate to high risk PCa before radical prostatectomy and pelvic lymph node dissection to assess lymph node involvement detection. Preoperative lymph node staging with PSMA PET proved to be superior to standard imaging with CT or MRI. PSMA PET had an 89% accuracy while CT or MRI imaging alone had a 72% [246]. A recent meta-analysis by Perera et al. determined that when analysed on a per-patient basis, ^{68}Ga-PSMA PET has a sensitivity and specificity of 86%, and when analysed on a per-lesion basis, it has a sensitivity of 80% and a specificity of 97%, for nodal involvement detection. Importantly, as compared to other ligands, PSMA carries the greatest sensitivity for detection of recurrence at very low PSA levels with a 48–50% detection rate in men with PSA <0.5 ng/ml [247].

Testis Imaging

US

US is the most used imaging modality for scrotal evaluation, both for suspected testicular or extra-testicular processes. This is because of its wide availability, diminished costs, and paucity of risk to patients, as well as its high resolution and the added availability of Doppler evaluation. Also, the fact that the testis are extra-abdominal organs makes them easily approachable with a standard US device.

Technique

Scrotal US should be performed with the patient on dorsal decubitus and the scrotum held with a towel placed between his thighs [248]. High frequency linear-array devices are advised (14–18 MHz) given the desired depth of penetration. Transverse and longitudinal images of each testis should be obtained and compared with the contralateral side. Color Doppler parameters must be obtained for a proper evaluation of most testicular conditions. Doppler characteristics of each condition will be thoroughly described on their respective subsection.

When sonographically examining the testis, a thorough description of size, echogenicity, blood flow, epididymis, scrotal wall, and spermatic cord has to be made, and compared to the contralateral side. It is also of good clinical practice to perform a Doppler evaluation of the testicular blood flow. Patient positioning variation and other maneuvers (such as Valsalva) can be used in the evaluation of different findings, such as varicocele. When performing a scrotal US due to testicular pain, the examination should start on the asymptomatic side.

Both testes lie on the scrotal sac, and are divided from each other by the scrotal septum. The normal post-pubertal testicular parenchyma is found to be homogenous and granular, with an intermediate grade echogenicity (prepubertal testis tends to be less hypoechoic).

A separate paragraph has to be made regarding intratesticular microcalcifications or microlithiasis. These are found in US as diffuse hyperechogenic foci, usually bilateral, and their

real clinical significance remains a matter of controversy. A large meta-analysis found that microlithiasis is significantly associated with presence of germ cell tumors (GCT) [249]. However, the mere presence of microlithiasis on an US, without a clear mass does not necessarily provide an additional risk factor, because the global prevalence of testicular microlithiasis in healthy young men exceeds the prevalence of GCT in around 1000-fold [250].

US in Scrotal Masses

US has a 100% sensitivity on the detection of scrotal masses [251, 252], and in the hands of a properly trained sonographer it also has a near perfect capacity to delineate extra from intra testicular masses.

When evaluating a patient for a scrotal mass, the assumption should be that intratesticular masses are malignant until proven otherwise. That is not only because most of them truly are, but also because testis cancer can be lethal, and has a high cure rate if treated early [253]. The opposite concept applies for extratesticular scrotal masses of which the vast majority are benign [254].

Intratesticular Scrotal Masses

GCT comprise the majority of intratesticular masses and they can be divided as seminomatous or non-seminomatous tumors (NSGCT). No US finding is specific enough to differentiate them, and the final diagnosis has to be made histologically. However, some findings can be highly suggestive of some subtypes [255]. For example, seminomas are usually hypoechoic homogeneous lesions which can vary in size from small, to considerably large, but are often confined to the tunica albuginea (Fig. 13.27). On the contrary, NSGCT are usually heterogeneous (specially mixed NSGCT), have ill-defined margins, and can invade the tunica albuginea.

Other malignant non-GCT intratesticular masses can be found (such as lymphoma, or metastasis from another organ) on routine ultrasonography. Even though the majority of intratesticular masses are malignant, there are some that are not (Table 13.6). Some even have distinctive features that might increase the suspicion for

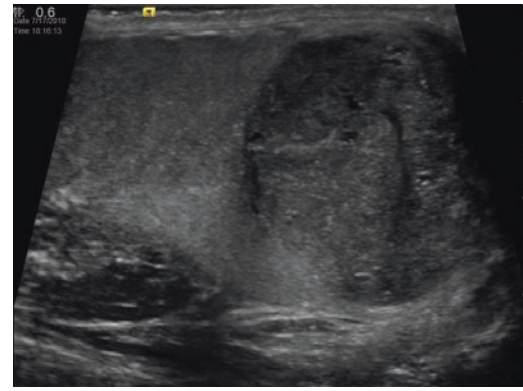

Fig. 13.27 Grey scale ultrasound of a left intratesticular mass with very well delineated margins and fairly homogenic structure, highly suggestive of a germ cell tumor. Patient underwent a radical orchiectomy revealing a classic seminoma

Table 13.6 The most common benign intratesticular masses [255, 257]

• Intratesticular or albugineal simple cysts	Finding of solid or thick mural components has to sway the suspicion for a cystic teratoma.
• Epidermoid cyst	They are benign lesions with no malignant potential. Their sonographic appearance is characteristic (well circumscribed, poorly vascularized masses with an "onion-skin" laminated pattern), but not pathognomonic, as mature teratomas can mimic these findings as well (Fig. 13.28).
• Hemangiomas	
• Tubular ectasia of the rete testis	Dilation of these tubules may occur secondary to obstruction by another mass, sequela of chronic epididymitis, or as normal post-vasectomy changes. It can be seen as avascular tubular structures near the mediastinum.
• Adrenal rests	Traces of adrenal tissue that end up trapped within fetal testis and do not regress. They are associated with congenital adrenal hyperplasia and are usually bilateral hypervascular hypoechoic small masses near the mediastinum.
• Intratesticular hematomas	Usually preceded with a history of trauma, and they tend to regress over time.

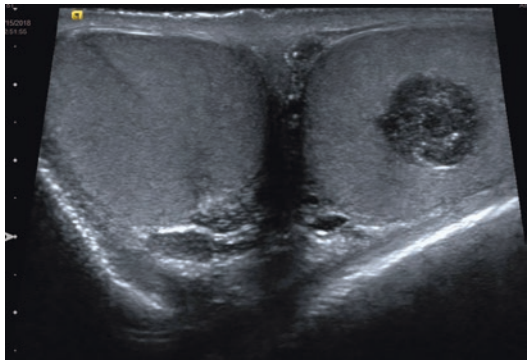

Fig. 13.28 Incidental finding of a right intratesticular mass during a varicocele workup. The image is well circumscribed, poorly vascularized masses with an "onion-skin" laminated pattern highly suggestive of an epidermoid cyst, which was confirmed after a partial orchiectomy was performed

a benign tumor. For example, the finding of a clearly demarcated small hypoechoic mass with intrinsic and peripheral hypervascularity on Doppler is highly suggestive of Leydig cell tumor [256]. Unfortunately, US (even with color Doppler) is not a sufficiently reliable modality to rule out a malignancy in most cases, so patients with a clear hypoechoic mass in the testis should still undergo an inguinal testicular exploration with eventual tissue biopsy.

Extratesticular Scrotal Masses

Hydroceles are the leading cause of painless scrotal swelling [255]. They are easily identifiable on US (as an anechoic fluid collection surrounding the testis) and on clinical evaluation. They can be primary or congenital (seen in children) or secondary (usually seen on adults) and they are the result of fluid accumulation within the tunica vaginalis. Even though usually a homogeneous anechoic collection, it's not rare to find diffuse echogenic specks, representing protein or cholesterol precipitations, floating inside the collection [258]. Other entities that result in fluid accumulation within the tunica vaginalis are hematocele, pyocele, or the very rare development of a tunical mesothelioma. Hematoceles are often more complex and heterogeneous than hydroceles, and can have septations and debris [255]. Pyocele represents an accumulation of pus usually seen after a complex epididymo-orchitis.

Indirect inguinal hernias can protrude through the external inguinal ring onto the scrotum. Their sonographic appearance varies according to their content. Omentum containing hernias are difficult to differentiate from lipomas on US. The key difference is the change in position with Valsalva, which would not produce movement on cord lipomas, and should accentuate the hernia.

Epididymal cysts and spermatoceles are sonographically indistinguishable from each other, but it is very easy to differentiate them from other scrotal masses with more concerning clinical consequences. They are both seen as well-defined, rounded fluid collections arising from the epididymis (usually from the head). Other epididymal masses that can be found are [255]: adenomatoid tumors (benign small tumors that usually arise from the tail of the epididymis); papillary cystadenoma (strongly associated with Von Hippel Lindau disease); malignant tumors (metastasis from other organs, sarcomas or adenocarcinomas). The latter are extremely rare.

Scrotal masses can also be found on the spermatic cord with lipomas being the most common of these. Other (more rare) spermatic cord masses that can be found are leiomyomas; dermoid cysts; lymphangiomas; or adrenal rests. Other possibilities to be considered when evaluating a spermatic cord mass include varicocele and an indirect inguinal hernia.

The most common spermatic cord mass is the varicocele. It is the dilation of the veins that form the pampiniform plexus (the main venous drainage from the testis). It is a very common finding, occurring in 15–20% of the postpubertal men. It is usually left sided (due to the longer length of the left gonadal vein, and the fact that it drains in a 90° angle into the left renal vein, whereas the right gonadal vein is shorter and drains in a less steep angle on to the inferior vena cava). It is seen sonographically as dilated structures over 2 mm in diameter located on adjacent to the testis on its superior/posterior aspect. A characteristic of the varicocele is that it increases in size upon performing Valsalva due to increase on the retrograde flow.

US in the Evaluation of Acute Scrotum

Acute scrotum refers broadly to a clinical presentation of severe, acute scrotal pain, with or with or without an inciting event. US serves as the mainstay in evaluation of the acute scrotum as it allows for accurate assessment of the of potential etiology of pain. The first goal of evaluating acute severe testicular pain is to rule out testicular torsion, as the window to "save" an ischemic testis is relatively narrow. Torsion of the testicular cord can be partial or complete and typically occurs in the setting of an enlarged testicle (due to tumor, trauma, or pubertal growth) relative to the mesotestis. Doppler ultrasound can be a useful tool for diagnosing torsion, and distinguishing partial from complete. In a partial torsion, there is asymmetric flow within the testis and spectral arterial waveforms are abnormal, often demonstrating absent or reversed diastolic flow (Fig. 13.29). In complete torsion there is total absence of flow in the testis and the resistive index is high. Progressive enlargement and heterogeneity of the testicle is seen in later phases due to edematous changes and arterial obstruction [257]. It is important to add that as the heterogeneity of the testicular parenchyma increases, the viability of the testis decreases [259]. The "whirlpool" sign can sometimes be found, which is the representation of the spermatic cord wrapped around itself.

Testicular appendage torsion arises when there is a torsion of a remnant of embryonic tissue on the surface of the testis (which is also called Morgagni appendix). It is usually easy to distinguish from a complete testicular torsion, as the pain is less severe and frequently localized on the superior aspect of the testis. It also usually affects younger boys and sometimes the typical "blue dot" sign, indicated an ischemic appendage, can be identified though the overlying skin. However, it can be clinically challenging to distinguish appendicular torsion from partial testis torsion. Sonographically, the testis is intact as to its echogenicity and vascularity, but extra-testicular avascular nodules can be identified, and reactive hydrocele is also a common finding [260] (Fig. 13.30).

Epididymo-orchitis is a frequent cause of acute testicular pain. It is usually the result of a retrograde bacterial infection, but it can also have viral and other non-infectious etiologies (such as autoimmune diseases). The infection usually starts at the tail of the epididymis and then extends towards the rest of the organ and may extend to the testis in around 20–40% of cases. Orchitis without extension to the epididymis is a rare finding and obliges the clinician to rule out mumps. Sonographically, the affected epididymis and/or testis is seen enlarged, hypervascularized and with a more heterogeneous and hypoechogenic appearance [257]. The inflammation produces increased blood flow to the epididymis (and testis if there is also orchitis), thus

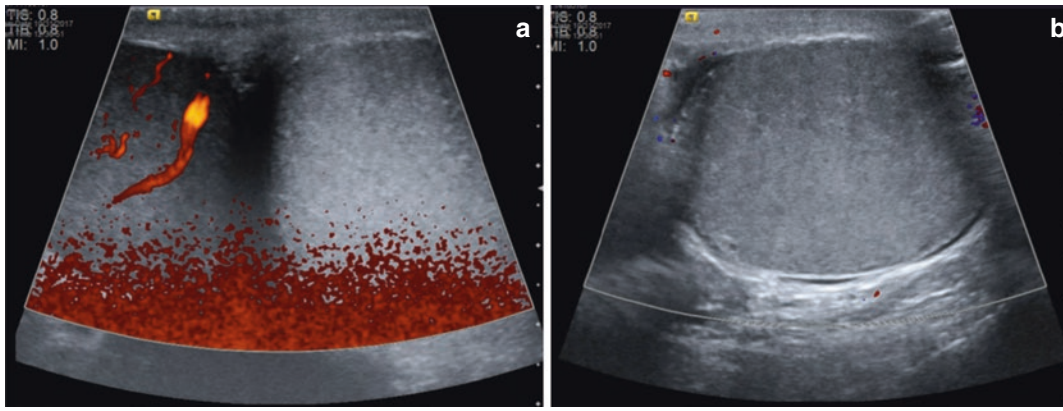

Fig. 13.29 Color Doppler ultrasound of a patient with a left testicular torsion. The axial plane (**a**) shows both testicles and normal flow can be seen on the right testicle, where the left one shows no flow at all. Sagital plane (**b**) showing complete Doppler silence, which indicates complete active torsion of the left testis

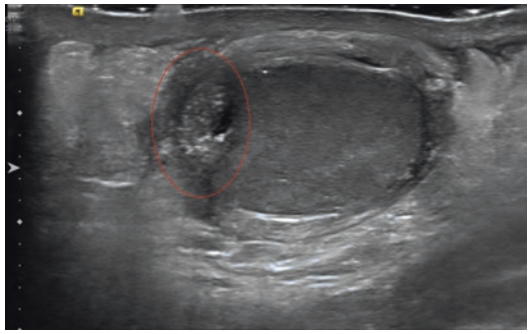

Fig. 13.30 Grey scale ultrasound showing an active testis appendage torsion. The testis is intact as to its echogenicity and vascularity, but an extra testicular nodule is seen (red circle)

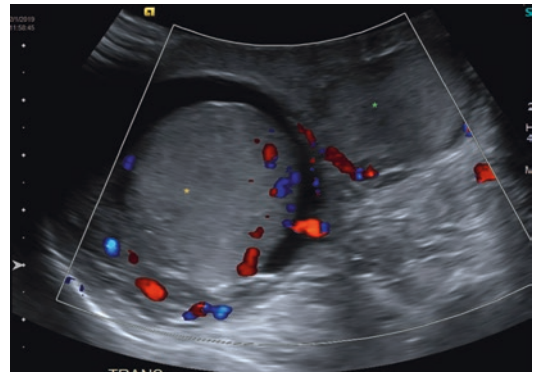

Fig. 13.31 Color Doppler ultrasound of an acute epididymo-orchitis. The affected testis is seen enlarged, hypervascularized and with a more heterogeneous and hypoechogenic appearance. Increased Doppler signal is visualized on the testis (yellow ∗) and specially on the epididymis (green ∗), where all Doppler signal has to be interpreted as abnormal

producing homogeneous increase in Doppler signal throughout the organ. It is important to state that the normal epididymis does not provide Doppler signal as its vascularity is scarce, so any Doppler signal within the epididymis (with correlating clinical features) should be interpreted as hyperemia (Fig. 13.31). More complicated infections may result in scrotal abscesses, pyocele or fistulae formation.

Testicular trauma is also a cause for acute scrotum. The history of recent trauma is good enough for raising clinical suspicion, however US is useful in distinguishing the potential sequelae of the trauma including testicular rupture, intratesticular hematoma, torsion, and extratesticular hematoma. Intratesticular hematomas, as previously described, are seen as non-vascularized hyperechoic foci within the testis and tend to regress over time. Testicular rupture is an emergency that usually requires surgical intervention. It is characterized by a loss of continuity on the tunica albuginea resulting in a loss of contexture of the testis. The finding of extruded seminiferous tubules is not uncommon.

CT

CT is not the imaging modality of choice for evaluation of any scrotal process, as US has a higher yield and lower cost, MRI offers higher resolution, and neither of them expose the patient to ionizing radiation. Even though some scrotal entities may have certain CT findings [261], its use in everyday practice is limited so they will not be described on the present chapter. However, abdominal and chest CT scans do have a significant role on the staging and follow up of men with testicular cancer, and that will be the focus of this subsection.

Role of CT in Testis Cancer Staging

Abdominopelvic CT scan (with intravenous contrast) offer a near 80% sensitivity for detection of enlarged retroperitoneal nodes [262] and is warranted upon diagnosis of testis cancer [263, 264]. It is important to add that the negative predictive value is lower for men with normal sized retroperitoneal lymph nodes (stage I and IIa NSGCT), and that is why primary retroperitoneal lymph node dissections is often considered in this setting.

Chest CT is also useful for detection of mediastinal and supraclavicular nodes, and for lung metastases as it offers a high sensitivity (but low specificity) [265]. All guidelines agree that chest staging is crucial upon diagnosis of NSGCT, however the National Comprehensive Cancer Network (NCCN) guidelines suggest that for seminomas it should only be ordered upon finding an abnormal abdominal CT scan.

Role of CT in Testis Cancer Follow-up

Close follow up for patients treated for testicular cancer is a norm. However, the advised protocol

varies according to the histology of the primary tumor as well as the highest stage reached. CT and MRI scans have similar yield for early recurrence detection, and given the increasing concern over the accumulation of ionizing radiation over time, protocols have been shifting towards pure MRI, or alternating CT and MRI for abdominopelvic follow up. As per chest follow up, certain protocols allow for follow up with chest radiopgraphs in certain cases.

MRI

MRI of the testis offers high sensitivity and specificity for testicular masses [266], but due to its high cost it is not the method of choice for initial evaluation of a patient with a scrotal mass. Nevertheless it is a cost effective tool for patients who present with masses that are equivocal upon clinical and sonographic evaluation [267]. MRI can be useful in over 80% of cases in which the US findings are equivocal, for discerning benign from malignant intratesticular masses, as well as determining whether a mass is located within the testis, or outside from it [266, 268]. Gadolinium enhanced MRI is not essential, but it can help in certain cases [269].

As for the role of abdominal MRI on staging and follow up for testicular cancer, we have mentioned before that it has a similar yield to CT scan on experienced centers, and can be used as an alternative. The benefit is the absence of ionizing radiation exposure, but also, the higher cost implies a significant disadvantage when trying to implement it as a first line on a population-based scale.

Nuclear Imaging

Unlike prostate, there is not a specific radiotracer for testis cancer, so PET imaging on this clinical setting is limited to ^{18}F-FDG PET. There is not a role for PET imaging on the workup of a recently found scrotal mass, and the uses of FDG PET on testis cancer fall on the detection of distant metastases. Although FDG PET has a better detection rate than CT scan on the staging setting, the benefit is slightly increased, and there is not enough evidence to recommend it for this purpose neither on seminomatous nor on NSGCT [270, 271].

Both the EAU and the NCCN guidelines recommend the use of FDG PET only in the setting of post-chemotherapy residual masses of >3 cm among patients treated for pure seminoma. There is strong evidence that FDG PET has a high negative predictive value for determining the viability of those masses, and therefore aiding on the decision making as to whether they have to be removed [272].

Conclusion

The applications of imaging in urologic disease are quite broad, ranging from diagnostic evaluation of urologic symptoms, to staging of urologic tumors, to risk assessment in malignant and benign urologic diseases. A comprehensive understanding of the indications, application and interpretation of imaging studies is essential for the urologist in order to allow proper patient management, selection of therapy, and surgical planning. Urologists should also recognize the rapid evolution of imaging techniques in the context of urologic disease to allow for continual innovation in clinical approach.

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Urologic Instrumentation: Endoscopes and Lasers

14

Robert B. Lurvey and Noah Canvasser

Introduction

The impact of endoscopic access on the field of urology cannot be overstated. In an increasing number of urologic pathology, endoscopic techniques have replaced morbid open procedures such as open pyelolithotomy, open simple prostatectomy, and stricture repair [1]. This increasing effectiveness is due in large part to ever improving endoscopic visualization and miniaturization of instruments. This chapter covers the fundamental principles of lower and upper urologic endoscopy. In addition, we discuss laser energy sources which have revolutionized the capabilities for endoscopic management. We also review new advances and the future potential of endoscopic intervention. It is our hope that upon reading this chapter one will not only have a firm grasp of the fundamentals of urologic endoscopy and manipulation, but a command sufficient to handle any situation.

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Lower Urinary Tract: Cystourethroscopy

Cystourethroscopy is the sine qua non of evaluation of lower urinary tract disorders. It is mandatory in the workup of hematuria and invaluable in assessment of lower urinary tract symptoms. In the most abstract sense, all cystoscopy involves a means of (1) generating an image and (2) a light source.

The first cystoscopes utilized poor light sources and did not magnify their images. In 1805, during the Napoleonic Wars, German army surgeon Philip Bozzini created the first known cystoscope. The image generator was a "viewing funnel" projecting to a sharkskin covered box and the light source was a candle within the box. By 1853, after further incremental improvements, Antoine Desmormeaux performed the first urologic endoscopic manipulation when he excised a urethral papilloma using his device, a endoscope with the light source in the handle. In 1877, Maximillian Carl-Friedrich Nitze and Joseph Leiter teamed up to produce a cystoscope where the light source was located at the tip of the instrument. By 1930, Physicist Harold Hopkins developed glass fibers capable of carrying images and light. As glass is better at transmitting light than air, Hopkins replaced the tube of air with a tube of glass and by 1959, with Karl Storz, developed the first fiberoptic cold-light source. This improved both light source and image generation [2].

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With further development of fiber optic bundles we reached today's cystoscopes. Cystoscopes come in two forms, flexible and rigid. The diversity of options for manipulation and models are too numerous to adequately enumerate, so we will heel to the basic abstraction of the components of a modern cystoscope: (1) a means to create an image (2) a light source and (3) in modern cystoscopes there is also a means to provide irrigation and sometimes drainage.

Fig. 14.1 Richard Wolf 4.5/6.5 fr pediatric cystoscope, note shorter length

Rigid Cystoscopy

The rigid cystoscope consists of a telescope and sheath which acts as a flow channel for irrigation. Within or connected to the sheath one can place a working bridge, obturator, or working element. Traditionally, an obturator is used to reduce trauma associated with insertion and blunt the sharp edges of the sheath on insertion to prevent shearing. Once inside the bladder, the obturator is removed and a working bridge is inserted to allow passage of treatment implements or a working element is attached to allow for manipulation of tissue with instrumentation.

The traditional cystoscope is a "rod and lens" construction, with a single fiber optic or lens. This allows for a higher resolution image than the "fiber bundle" of a flexible cystoscope. Semi-rigid ureteroscopes utilize a bundled fiber approach, as do some smaller cystoscopes. Understanding if an endoscope is a fiber based or rod and lens scope allows the surgeon to adjust focus and expected manipulation; a fiber bundle scope will have a honeycomb appearance but allows for some deflection of the scope without distortion of the image.

All cystoscope and ureteroscope sizes are measured in the French gauge, which is essentially equivalent to the circumference of the instrument in millimeters. Therefore, the diameter can be calculated by dividing the number in the French gauge by 3. The standard size for adult cystoscopes is between 16 and 25 fr, while pediatric is between 8 and 12 fr. Resectoscopes are designed between 22 and 28 fr due to the need for an additional channel for drainage and continuous flow. Modern resectoscopes separate the inflow sheath from the outer drainage sheath allowing the surgeon to choose a smaller sheath, though compromising the ability for continuous flow. Both Richard Wolf (Vernon Hills, IL) and Olympus (Center Valley, PA) manufacture pediatric cystoscopes down to ~6 fr, with a 4.5 fr channel for irrigation or wires. Of note, in addition to the small width, the pediatric cystoscopes are also much shorter and therefore not appropriate for use in adult examinations (Fig. 14.1).

Within the sheath sits the telescope. Universally, the light source for cystoscopes remain either within the handle (for digital scopes) or a separate light box. The light is then transmitted through a fiber cable. This allows for the production of more lumens than a light within the tip of the scope. The rigid lens then comes in multiple angles. The 0° lens allows the best view of the urethra and is used primarily for urethral manipulation such as direct visualized internal urethrotomy. The 30° lens provides visualization of the base and anterolateral aspect of the bladder and is the standard for most endoscopic bladder manipulation in urology. Most endoscopic working elements are designed such that the active element is always within view of a 30° lens. A 70° lens allows for improved visualization of the dome and anterior bladder neck, though makes visualization of instruments difficult. The angled lens and light source fiber represent "blind spots" in the scope that the surgeon must remember during the procedure. Through these blind spots a surgeon can create trauma to or impact tissue without visualizing its presence.

In general, the surgeon should pick the sheath size that is the smallest to perform the desired task. This is a function of the costs and benefits of

a particular size. For example, as discussed above, the light source is transmitted through a fiber conduit in the cystoscope. Therefore, smaller scopes will accommodate smaller light conduits, decreasing lighting and therefore visualization. Additionally, smaller scopes tend to have less robust irrigation also leading to worse visualization. This can lead to increased operative time for which there is evidence of increasing risk of stricture [3]. Conversely, it is a clinical principle that manipulation with larger instruments through a urethra increases the risk for urethral or fossa navicularis stricture. There is some data to support this principle, though limited [4]. Gunes et al. performed a retrospective study of 61 men undergoing transurethral resection of prostate using either a 24 or 26 fr resectoscope. The rate of bulbar stricture was 3% versus 11%, respectively, and statistically significant on univariate analysis [5]. Ultimately, we recommend the largest sheath that remains comfortable while providing adequate visualization and manipulation.

Flexible Cystoscopy

In comparison, flexible cystoscopes do not have the option for continuous irrigation. Yet, they present significant advantages for patient tolerance and visibility with their ability to deflect up to 220°. They are also better tolerated by patients, particularly male patients where the flexion of the flexible cystoscope can more easily overcome the bladder neck and prostatic urethral curves. In a flexible cystoscope, the irrigation connection and working port are on the instrument's shaft and typically connect to a single common rubber-lined working channel within the scope. Functionally, this puts the cystoscope at risk for damage if instrumentation is passed with the scope in the deflected position; the instrument can perforate the inner channel.

Traditional analog flexible cystoscopes utilize a bundled fiber approach leading to an eyepiece. This is then connected to a light cord and camera or can be viewed directly. Increasingly, flexible cystoscopes utilize digital image generation. The digital cystoscope operates by a "chip on stick" approach where a video sensor is placed on the working tip of the cystoscope. The first digital cystoscopes were present in the 1970s and reached full commercial viability around 2005 [6]. The digital cystoscope allows for a higher resolution image and avoids the honeycomb effect of an analog bundled fiber. Using an early version of ACMI digital cystoscopes against analog cystoscopes, Quayle et al. performed a simple in-vitro study of resolution. The cystoscopes were placed a fixed position inside a cell culture plate with a set of numbers printed in a size 4 font in the back. Participants were asked to use the cystoscopes to identify the numbers. As the solution concentration increased, the digital cystoscope had visualization of 100% even as the best analog scope had 60% visualization [6]. The other relative merits, including price and durability are discussed in the ureteroscope section.

Despite the improved quality, a consideration should be kept for portability. Digital cystoscopes generally require large towers and, at the least, a reliable external power source. However, technology advances in consumer electronics, especially in the era of smart phones, has allowed analog cystoscopes to gain new portability. Multiple teams have developed attachments that allow for an analog cystoscope to be attached to a smartphone either to provide a standalone video platform or to connect with a larger screen. For example, the Endockscope is an attachment developed at the University of California Irvine that allows pairing between a standard analog cystoscope and an iPhone [7]. The quality is equivalent to that of a standard digital cystoscope [8]. Though, a formal adapter is not always necessary as Robinson et al. demonstrated the use of the smartphone camera light as a light source in the absence of an external power source [9].

Enhanced Cystoscopy

Enhanced cystoscopy adds an additional layer to the fundamental image generation and lighting of cystoscopy. Enhanced cystoscopy is performed using either narrow band imaging or fluorescent cystoscopy.

Narrow band imaging filters white light into two discrete bands, one blue at 415 nm wavelength and one green at 540 nm. Both bands are absorbed by hemoglobin. The shorter band penetrates the superficial mucosa and is absorbed by the superficial capillary vessels, giving a brown color. The longer band penetrates deeper into the bladder wall and is absorbed by deeper vasculature and gives a green color. Therefore, under the filtered light the superficial vessels will be dark brown and the deeper vessels appear green. Concentrated enhancement of vasculature would suggest a malignant growth. For example, flat lesions such as carcinoma in situ are very dense in vasculature but may have relatively normal appearing mucosa. Under the filter, the increased vasculature would be seen as a brown collection. Papillary lesions with deep vasculature would have a green plexus [10]. It has a role in the surveillance of non-muscle invasive bladder cancer as it has been shown to decrease recurrence in lower risk lesions [11, 12].

Fluorescent cystoscopy, also called photodynamic cystoscopy, involves the instillation of either 5-aminolaevulinic acid (ALA) or hexaminolevulinate (HAL) into the bladder. HAL and ALA are photosensitizers which result in preferential accumulation of protoporphyrins in rapidly proliferating cells such as malignant bladder tumors. They are subsequently converted to photoactive porphyrins, which emit a red fluorescence under blue light (360–450 nm). For example, the HAL solution is typically made up of 100 mg of HAL with 50 ml of diluent. It is allowed to dwell in the bladder for 1–3 h prior to performing cystoscopy with a specially designed cystoscope and processing system, such as the KARL STORZ D-Light C Photodynamic Diagnostic (PDD) system which enables both WLC and BLC (wavelength 360–450 nm) fluorescence cystoscopy. Under cystoscopic examination using this system the entire bladder is evaluated under both white and blue light. Under blue light, abnormalities are defined by the detection of red, homogeneous fluorescence [13]. In a phase III trial of patients with a history of non-muscle invasive bladder cancer, using a rigid cystoscope version of the system, about 20% of high grade non-muscle invasive were seen only with blue light [14]. Interestingly, in one subanalysis of 246 patients in the United States within the phase III trial for blue light fluorescent cystoscopy, patients did not report any increase in pain from the catheterization procedure required for instillation of HAL. Additionally, just over half the patients were willing to pay $100 or more for the perceived improvement in surveillance, while 30% prefered to pay no additional for the blue light [15].

The improved detection has made fluorescent cystoscopy part of the American Urologic Association/Society of Urologic Oncology guidelines. In patients with non-muscle invasive bladder cancer undergoing TURBT, the clinician should offer blue light. Additionally, blue light now has a role in patients who have normal cystoscopy but positive cytology as part of enhanced evaluation [12].

Disposable Cystoscopes

With concerns over infection control and cost increasing, multiple companies have worked towards the development of disposable and semi-disposable cystoscope and ureteroscope equipment. For endoscopy, the difficulty in sterilization and decontamination is in the flow channels and working sheaths. The CST-5000 is a flexible cystoscope manufactured by Cogentix (Orangeburg, NY) that contains a single scope with a disposable cover sheath. The sheath contains a flow and working channel. Theoretically, eliminating the need for scope downtime in decontamination will increase speed of analysis. However, in one randomized trial of an earlier version of the cystoscope in 100 patients head-to-head with the standard 16 fr cystoscope, there was marginal though statistically significant poorer optical quality, handling, and ease of insertion. The turnover time was reduced between 4 and 30 min and there was a similar cost per procedure with standard cystoscopes. Although, potentially significantly decreased repair costs due to the less complicated permanent mechanisms [16]. An alternative model is use specific cystoscopes, such as the Isiris by Coloplast (*Humlebæk*,

Denmark). The Isiris has a built in stent grasper and is adequate for stent retrieval, though due to flow limitations associated with its design would not be adequate for routine cystoscopic surveillance and has no working channel for other instrumentation [17].

Future Technologies

To review, we have added light, better image generation, more portability, and increased image processing. Further development remains adding even more information to the options available. Potential future directions include improved means of data storage from endoscopy, such that the creation of 3D reconstruction of the bladder with white light cystoscopy [18]. Future directions also include the use of more off the shelf technology, therefore improving portability and decreasing cost. One of the most exciting future developments in our view may come from increasing computing power and machine learning allowing for improved image processing and interpretation beyond the capabilities of the surgeon's eye. Such technologies may include optical coherence tomography (OCT). OCT allows for a non-invasive real time high resolution imaging of tissue in cross section to a depth of 2 mm through the analysis of the backscatter and absorption properties of near-infra-red light (890–1300 nm) It has been demonstrated in concept in bladder lesions and has been shown in other fields for a number of years [19, 20]. Further very early clinical trials have demonstrated that OCT is also very good at distinguishing Ta from T1 to T3 lesions with nearly 100% sensitivity and over 90% specificity [21]. A similar technology confocal laser endomicroscopy has been utilized in gastroenterology and is finding a place in urology [21].

Upper Urinary Tract: Ureteroscopy

Flexible Ureteroscopes

The field of ureteroscopy has grown immensely since the first flexible ureteroscope was described in 1964 [22]. Advancements in maneuverability, optics, and miniaturization, has allowed surgeons to access what was previously inaccessible. In 1971, Takayasu and colleagues published their use of a 2.5 mm flexible ureteroscope that was advanced into the ureter and kidney [23]. Although impressive in its own right, this scope only had 30° of passive deflection. Further improvements allowed the development of actively deflectable ureteroscopes with working channels that could maintain irrigation as well as instrumentation for treatment of upper urinary tract pathology [24]. Fuchs and Fuchs published one of the early large series of flexible ureteroscopy to treat stone disease in 208 patients utilizing a 10.4F flexible ureteroscope. Although this scope had a contemporary 3.7F working channel, the 160° of flexion was limited to one plane (70° in the second plane) [25]. Regardless, the technology was ripe for expansion.

Contemporary flexible ureteroscopes all have similar properties, although there are some notable differences (Table 14.1). Most flexible ureteroscopes have a 3.6F working channel, which allows the passage of guidewires, stone baskets, laser fibers, and irrigation. The Richard Wolf Cobra vision ureteroscope is the only dual-channel ureteroscope with both a 3.6F and 2.4F working channel, which allows the simultaneous use of any combination of the previously mentioned instruments. Alternatively, irrigation can be maintained nicely by leaving one of the working channels empty.

An important optical advancement over the past 10 years in flexible ureteroscopy was the development of digital flexible ureteroscopes, which use complementary metal-oxide semiconductor (CMOS) and charge-coupled device (CCD) technology (Fig. 14.2). Although to a small degree, the improved vision has translated into significantly faster operative times, and improvements in durability [26] compared to fiberoptic flexible ureteroscopes scopes [27]. However, the improved optics does equate to a larger size. The tip size of the digital reusable ureteroscopes ranges from 5.2F to 8.4F, but the more important shaft size ranges from 8.5 to 8.9F for the single channel scopes, and up to the 9.9F for the dual-channel flexible ureteroscope. Both

Table 14.1 Selection of currently available flexible ureteroscopes

Manufacturer	Model	Working channel	Tip size	Shaft size	Optics	Deflection (up°/down°)
Richard Wolf	Cobra vision	3.6F and 2.4F	5.2F	9.9F	Digital	270/270
Richard Wolf	Boa vision	3.6F	6.6F	8.9F	Digital	270/270
Karl Storz	Flex-xc	3.6F	[a]	8.5F	Digital	270/270
Karl Storz	Flex-X2	3.6F	[a]	7.5F	Fiberoptic	270/270
Olympus	V2	3.6F	8.4F	8.6F	Digital	285/285
Olympus	P6	3.6F	4.9F	7.95F	Fiberoptic	270/270
Boston Scientific	Lithovue™ (single-use)	3.6F	7.7F	9.5F	Digital	270/270
Pusen	Uscope (single use)	3.6F	9.0F	9.5F	Digital	270/270

[a]Not published

Fig. 14.2 Karl Storz Flex-Xc digital flexible ureteroscope (©2018 courtesy of KARL STORZ SE & Co. KG, Tuttlingen, Germany)

Fig. 14.3 Olympus P6 fiberoptic flexible ureteroscope (©2018 courtesy of Olympus Corporation, Tokyo, Japan)

digital single-use ureteroscopes currently available have a shaft size of 9.5F. Fiberoptic flexible ureteroscopes are notably smaller with shaft size from 7.5F to 7.95F, which warrants their use in narrowed ureters and infundibula (Fig. 14.3).

Flexible ureteroscope deflection has improved significantly, allowing consistent access to lower pole calyces. Almost all scopes have deflection of 270° in both directions, while the Olympus V2 has slightly more at 285°. However, the digital flexible ureteroscopes, owing to their increased size, do have some slightly reduced maneuverability in practice [28].

Concerns about scope durability, reprocessing time and cost, and infection control, has pushed the development of single-use flexible ureteroscopes. The first device on the market was LithoVue™ from Boston Scientific (Marlborough, MA) (Fig. 14.4). Although larger in shaft size compared to the comparable reusable digital scope (9.5F versus 8.5/8.6F), Lithovue™ has shown similar technical abilities [29]. In addition, single institution micro-costing analysis has

Fig. 14.4 Boston Scientific Lithovue™ single-use digital ureteroscope (©2018 courtesy of Boston Scientific, Marlborough, MA)

demonstrated comparable per-case cost when accounting for labor, consumables, and repairs [30]. Other companies have followed suit, with the Pusen Uscope (Clarion Medical, Cambridge, ON) coming to market in 2017. This will likely be a significant area of growth in the coming years.

Semi-Rigid Ureteroscopes

Although Hugh Hampton Young is credited with the first rigid ureteroscopy in 1912 using a cystoscope in a child megaureter, it was not until almost 80 years later when semi-rigid ureteroscopy became commonplace. Dretler and Cho described using a 7.2F semi-rigid ureteroscope, more successfully in women than men, which allowed for broader management of ureteral pathology including stones and strictures [31]. Transition to fiberoptic imaging bundles allowed for larger working and irrigation channels while maintaining a similar size, as noted by Abdel-Razzak and Bagley in 1993 [32].

Most major endoscopic companies produce semi-rigid ureteroscopes, including Karl Storz (Tuttlingen, Germany), Olympus, Schölly Fiberoptics (Denzlingen, Germany), and Richard Wolf. Sizes of the scopes range from 6.0 to 8.4F, and most maintain an irrigation channel and a separate working channel (Fig. 14.5). Lengths can vary between scopes, as shorter scopes (approximately 35 cm) are often reserved for females, and longer scopes (45 cm) for males, although these can clearly be interchanged if needed. These scopes allow the diagnosis and management of ureteral pathology, especially in the mid and distal ureter; the ability to advance into the proximal ureter is often based on patient gender and ureteral tortuosity.

Nephroscopes

Along with the first percutaneous nephrolithotomy (PCNL) described in 1976 by Fernstrom and Johansson [33] the development of dedicated telescopes to handle such procedures became

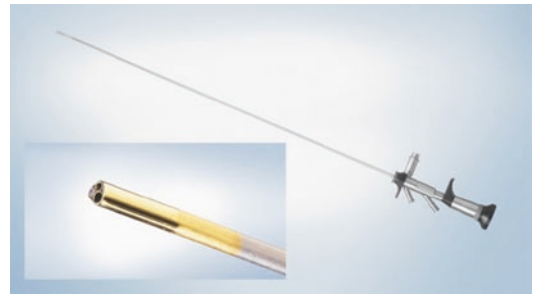

Fig. 14.5 Olympus semi-rigid ureteroscope (©2018 courtesy of Olympus Corporation, Tokyo, Japan)

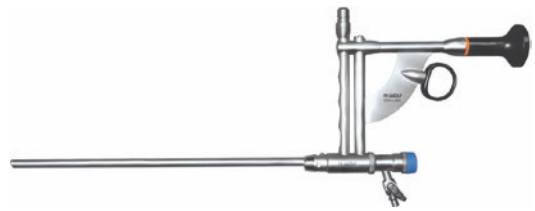

Fig. 14.6 Richard Wolf nephroscope (©2018 courtesy of Richard Wolf Medical Instruments, Vernon Hills, IL)

imperative. Rigid nephroscopes are now produced by most major endoscopic companies, including Karl Storz, Olympus, and Richard Wolf, with sizes ranging from 20F to 27F depending on the configuration. These scopes have an offset lens, which allows for a straight working channel to accept the large lithotrites required to fragment and extract large stone burdens (Fig. 14.6). They also typically have an irrigation channel and an optional sheath that can provide additional irrigation or outflow.

As many major operations have moved towards smaller incisions and instrumentation, so too has PCNL and rigid nephroscopes. Standard PCNL now describes using a tract size from 24 to 30F. A mini-PCNL includes tract sizes from 15F to 23F. And ultra-mini PCNL uses a tract size of 10–14F.

Although the 24F sheath is a significant decrease compared to standard 30F, surgeons can often use their standard nephroscopes by removing the outer sheath [34]. This can be useful in calyces with narrowed infundibulum, but still allow for efficient stone removal using standard PCNL lithotrites.

Table 14.2 Commercially available mini-PCNL and ultra-mini-PCNL sets

Manufacturer	Model	Type	Scope size	Sheath sizes	Working channel
Karl Storz	MIP M	Mini	12F	16F, 17.5F, 22F	6.7F
Schölly fiberoptics	Mini	Mini	13.5F	[a]	5F
Richard Wolf	Miniature nephroscope	Mini	12F	15F, 18F	6F
Karl Storz	MIP S/XS	Ultra-mini	7.5F	9.5F, 12F	2F
Schölly fiberoptics	Ultra-mini	Ultra-mini	6F	11F, 13F	[a]

PCNL percutaneous nephrolithtomy
[a]Not published

Fig. 14.7 Karl Storz MIP M mini-PCNL set (©2018 courtesy of KARL STORZ SE & Co. KG, Tuttlingen, Germany)

The potential benefit of mini-PCNL is less bleeding, [35] improved pain, [36] and decreased length of stay, [37] with the potential to treat moderate sized stones that would have been difficult with a flexible ureteroscope. Since the first description of mini-PCNL in 1998, [38] we have seen development of specific mini-PCNL sets (Table 14.2) (Fig. 14.7). The nephroscopes range in size from 12F to 13.5F, with working channels of 5.0–6.7F. Although some lithotrites can fit, laser lithotripsy tends to be the most common instrument for stone fragmentation. Flushing with irrigation will often result in extrusion of fragments out the working sheath.

On the extreme end of miniaturization is ultra-mini-PCNL, first described by Desai and Solanki in 2013 [39]. The first series involved a 6F nephroscope through a 13F tract. Such small instrumentation can only be used with a laser fiber to fragment stones. Currently, Schölly Fiberoptics and Karl Storz produce a commercially available ultra-mini PCNL set (Table 14.2).

Lasers

Light amplified by the stimulated emission of radiation or "LASER", has taken a prominent role in multiple areas of medicine. In urology specifically, the development of laser technology has greatly changed endoscopic management of benign prostatic hyperplasia (BPH) and stone disease, along with strictures and urothelial tumors.

The various properties and differences between lasers are dependent on the medium utilized and the resultant wavelength. The first laser utilized for endoscopic management was a pulsed dye laser [40]. Although effective for some stones, it proved ineffective for hard stones like calcium oxalate monohydrate. In addition, it was costly and required replacement of the coumarin dye. Utilization of neodynium: yttrium-aluminum-garnet (Nd:YAG) for BPH management was effective [41] but caused deep coagulation, coagulative necrosis, and resultant severe irritative lower urinary tract symptoms in some patients [42].

Continued advancements in laser technology eventually made the previously described laser mediums essentially obsolete in most urology practices. Currently, the two most commonly utilized laser mediums in urology are holmium: yttrium-aluminum-garnet (Ho:YAG) and potassium titanyl phosphate (KTP).

Holmium: Yttrium-Aluminum-Garnet

With the development of a laser medium that maintained a wavelength (2140 nm) close to the absorption of water, Ho:YAG lasers minimized energy dispersion and the potential for surrounding tissue damage. It quickly became a universal energy source to treat stones, BPH, tumors, and strictures, and was therefore the most cost-effective laser to own [43].

Early experience with Ho:YAG laser was in BPH, [44] while later investigations looked at the

Table 14.3 Comparison of various laser generator models

Manufacturer	Model	Watts	Pulse energy	Rate	Variable pulse width	Dual pedal	Pulse modulation
Lumenis	Pulse 120	120 W	0.2–6 J	5–80 Hz	Yes	Yes	MOSES
Lumenis	Pulse 100	100 W	0.2–3.5 J	Max 53 Hz	Yes	Yes	None
Lumenis	Pulse 50	50 W	0.2–3.5 J	Max 25 Hz	Yes	Yes	None
Quanta System	Cyber Ho 100	105 W	Max ×5 J	Max 80 Hz	Yes	Yes	MasterPULSE/ vapor tunnel
Quanta System	Cyber Ho 60	60 W	Max 5 J	Max 60 Hz	Yes	Yes	MasterPULSE/ vapor tunnel
Quanta System	Litho DK30	30 W	Max 4 J	Max 25 Hz	Yes	No	None
Cook	Rhapsody H-30	30 W	0.5–3.5 J	5–20 Hz	Yes	No	None
Olympus	Empower 65	65 W	0.2–5 J	3–60 Hz	Yes	Yes	Stabilization mode
Olympus	Empower 35	35 W	0.1–5 J	3–30 Hz	Yes	No	None
Cogentix	MH01	30 W	0.2–4 J	3–25 Hz	Yes	No	None
Jena Surgical	MultiPulse HoPLUS	140 W	0.25–6 J	5–100 Hz	Yes	No	None
Richard Wolf	Megapulse 70	70 W	Max 5 J	Max 60 Hz	Yes	Yes	None

utility in stone disease [45]. As it demonstrated superiority to prior lasers in the ability to treat any stone regardless of type or density, the market for Ho:YAG lasers grew. Initial Ho:YAG lasers allowed the user to set the pulse energy (joules, J) and rate (hertz, Hz), but as laser technology expanded so did the options. Therefore, it is important to understand the functionality of each laser. (Table 14.3 highlights a selection of lasers with contemporary technology).

Laser generators are defined by the watts they produced, which is based on the maximal pulse energy and the maximal rate. For stone disease, pulse energy determines the efficiency of fragmentation [46]. Higher pulse energy fragments stones faster, with the potential downside of larger stone fragments and more stone retropulsion. Lower pulse energy gives the opposite effect of smaller stone fragments and less retropulsion. The pulse rate determines how fast the stone will be fragmented, with higher rates also causing more retropulsion and lower rates causing less [47]. Most contemporary lasers have pulse energies that cover a standard range for stone treatment (0.2–2.0 J); the real difference is seen in the maximal rate that the laser can achieve. While 20 or 30 W laser will go to 20–30 Hz, higher wattage lasers can reach 80–100 Hz.

For BPH management with Ho:YAG laser, treatment with either holmium laser ablation of the prostate (HOLAP) or holmium laser enucleation of the prostate (HOLEP) typically requires a high-watt laser (at least 100 W) to maintain a pulse energy (2.0 J) and rate (20–50 Hz) for efficient treatment [48].

Contemporary lasers have incorporated the ability to vary the individual pulse width: a short-pulse width puts each pulse energy in a short period of time, while a long-pulse width spreads the pulse energy out. The benefit of a short-pulse is better stone fragmentation, with the potential downside of more retropulsion and fracturing of the laser fiber [49]. A long-pulse width causes a stone disintegration or "dusting" effect, with less retropulsion and less laser fracturing [50]. The decision to use one pulse width over another is often based on the stone density.

A few lasers also allow pulse modulation, which changes the way each laser pulse is delivered. MOSES technology was developed to improve stone ablation, but also demonstrated reduced stone retropulsion [51]. This is currently only available in the Lumenis Pulse™ 120 (Yokneam, Israel). Quanta Systems (Samarate, Italy) has also incorporated similar technology (MasterPULSE/Vapor Tunnel) into some of their lasers (Cyber Ho 60 and 100), and the Olympus Empower H65 has a Stabilization Mode.

Another benefit of many contemporary lasers is the dual-pedal functionality. This allows the surgeon to pre-set two different treatment settings, which improves the efficiency of switching back and forth between settings based on stone or tissue properties.

Potassium Titanyl Phosphate

Expanding on the initial BPH surgical investigations performed with the Nd:YAG laser, passing the beam through a KTP crystal doubled the frequency and halved the wavelength to 532 nm (visible green light, hence GreenLight™ Laser). This decreased the depth of tissue penetration to 3 mm to improve on the irritative urinary symptoms. This wavelength is also highly absorbed by hemoglobin, [43] which significantly improved bleeding from well-vascularized prostate tissue and allows the surgery to potentially be performed on anticoagulation [52].

Early studies demonstrated good success although the machines were underpowered so procedures were limited to smaller prostate glands [53]. Newer GreenLight™ lasers have the same wavelength, although now obtained by passing the Nd:YAG laser through a lithium triborate laser instead of KTP crystal, resulting in higher power (GreenLight™ HPS 120 W or XPS 180 W) [54]. These are produced by Boston Scientific (Marlborough, MA) and demonstrate improved efficiency with the potential to treat larger glands.

Conclusion

In the first edition of this book in 2006, laser therapy and endoscopy had become firmly entrenched in the armamentarium of the urologist. Since then, continued miniaturization has made laser and endoscopic technology indispensable. Further development will see the introduction of and improvement of software in the management of endoscopic images and laser energy. The urologist armamentarium now includes not only the equipment hardware, but also software the leads to more elegant treatment choices.

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Wound Healing and Plastic Surgery Principles

15

Hunter Wessells

Introduction

Successful surgery relies on proper wound healing and tissue repair. When these processes do not follow their normal pattern, urological surgeons may be faced with complications including skin separation, wound dehiscence, tissue necrosis, and breakdown of vascular, urinary and parenchymal structures. Determinants of proper surgical healing include preservation of critical anatomical structures; restoration of tissue integrity and homeostasis; and the regenerative potential of tissues. In addition, the surgeon must have a detailed knowledge of previous surgical, traumatic, infectious, and radiation related perturbations to normal anatomy and physiology, along with an understanding of the time course and vulnerability of tissues after injury in order to properly plan for successful primary repair or tissue transfer to achieve restoration of function.

Five essential domains of knowledge are required to carry out successful surgery:

- gross anatomy with particular emphasis on the vascular supply of skin, subcutaneous tissue, fascia, muscle and individual organs.
- understanding of the microvasculature of skin and epithelia, which support the primary barrier functions of the body.
- cellular and tissue events in restoring tissue integrity.
- proper harvesting of free grafts and the process and timeline of tissue engraftment, for cases when tissue transfer cannot be accomplished with a vascularized flap.
- flap creation, which relies on the intrinsic vascular anatomy of the tissue, propensity for collateral formation, and in cases of replantation or free flaps, the timeline for perfusion and reperfusion.

Gross and Vascular Anatomy

Genitourinary tract organs vary in their response to injury and "success" in wound healing in proportion to the density and/or redundancy of their blood supply. In any organ, matched arterial inflow and venous outflow are required for wound healing, and congestion of the venous outflow can just as certainly, although more slowly, doom the success of a tissue transfer or surgical procedure as arterial occlusion. In this section, we will work from cephalad to caudad to review how anatomical knowledge informs surgical principles and patient care.

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The kidney is well extremely perfused, and its segmental arterial blood supply [1] underpins successful selective embolization, partial nephrectomy and renorraphy by allowing different portions of the kidney to be occluded, excised, or repaired with confidence (Fig. 15.1). However, being served by a single artery, complete occlusion or accidental ligation of the renal artery leads to irreversible damage within hours and cannot be recovered. Minor additional circulation from accessory renal or capsular arteries generally does not reliably perfuse the remainder of the kidney in cases of main renal artery occlusion. The renal venous system has analogous considerations [2], with the caveat that the right and left sides differ in drainage. Thus, acute ligation or occlusion of the right renal vein is invariably devastating whereas on the left side, gonadal and adrenal veins allow potential for venous collateral development, which in certain circumstances mitigate the complications of occlusion. The testicular vasculature originates near the renal arteries on the abdominal aorta, but the testis gains additional supporting blood supply through the arteries of the vas deferens and cremaster muscle. The testis becomes ischemic with torsion because all three of its supporting arteries become occluded in the spermatic cord. In contrast, knowledgeable surgeons can successfully manipulate and preserve some or all of these vascular components during the course of orchidopexy, varicocelectomy, and other testicular surgery.

Ureteral surgery depends on the vascular network within the ureteral wall for its safe mobilization and effective use in reconstruction (Fig. 15.1) [3]. An adventitial vascular plexus receives arterial supply from a number of points along the ureteral course including the renal artery, the aorta, iliac artery and its pelvic branches. These perforate through the muscular layers to reach the mucosal vascular plexus. The ureter thus has a variable propensity for ischemia

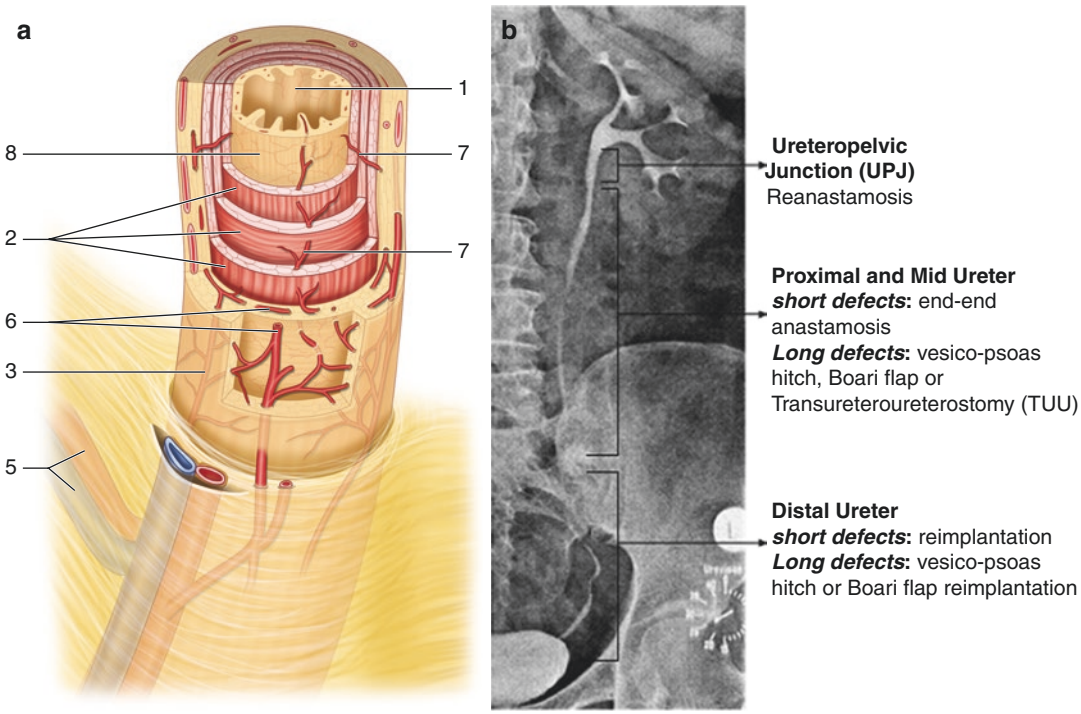

Fig. 15.1 Ureteral vascular architecture. (**a**) schematic drawing of vascular plexus (drawn from Ref. [3]) demonstrating adventitial vascular plexus; perforators; and mucosal vascular plexus. 1- urothelium, 2 - muscular wall, 3 - adventitia, 5 - segmental arterial and venous supply, 6 - adventitial vascular plexus, 7 - perforating arteries, 8 - mucosal vascular plexus. (**b**) ureteral vascular regions and impact on reconstruction

like any flap; ureteral healing depending on the amount of mobilization, the distance from its next perforating arterial branch, and preexisting or intraoperative damage to its vascularity from fibrosis, radiation or improper manipulation. These considerations greatly influence the choice of ureteral reconstructive strategy, from pyeloplasty and ureteroureterostomy when both ends are healthy, to reimplantation or substitution. Figure 15.1 provides the divisions of ureteral vascular zones and appropriate reconstructive strategies. The portion of the ureter crossing the iliac vessels and more distal is considered in a watershed area, and less reliably supports ureteroureterostomy; reimplantation is preferred whenever possible in the lower 1/3 of its course.

The bladder and prostate are resistant to ischemic complications, in part because of redundant blood supply (see chapter on anatomy of the pelvic organs), a relatively low metabolic demand compared to other organs (such as the kidney or testis) and the robust interconnected intrinsic vasculature which allows for collateral flow beneath the epithelium. Bladder ischemic damage results from longstanding outlet obstruction, chronic inflammation or pelvic irradiation. Its usual manifestation is in a loss of compliance and elasticity, making it difficult to reconfigure for reconstructive purposes such as a Psoas hitch, Boari flap, Y–V plasty or bladder tube formation. Circumstances in which prostatic ischemia are relevant to wound healing predominantly relate to prior radiation therapy [4, 5], in which obliterative endarteritis leads to inadequate reepithelialization of the prostatic fossa and development of fibrosis, heterotopic calcifications and refractory stenoses. Rarely, severe ischemic complications of pelvic fracture including vascular injury or embolization may lead to prostatic or membranous urethral necrosis.

The male external genitalia and urethra benefit from a highly redundant vascular supply possibly reflecting the evolutionary importance of reproductive success [6]. The posterior urethra receives inflow through branches of the inferior vesical artery perforating through the bladder neck and prostate, while the anterior urethra is served by multiple branches of the internal pudendal artery. These include bilateral direct flow from the bulbourethral, with important collateral supply from the dorsal arteries (via anastomoses in the glans) as well the deep or cavernosal artery (via perforators from the corpora cavernosa to the spongiosum). Importantly, the watershed between posterior and anterior urethra is the membranous urethra, which explains why radiotherapy related strictures fall predominantly in this location. Urethral vascular anatomy informs reconstructive strategies in pediatric and adult urological surgery such as division of the urethral plate during anastomotic urethroplasty or chordee correction, reconstruction of failed hypospadias, staged and one stage substitution procedures, as well as microsurgical revascularization for urethral or erectile problems–beyond the scope of this chapter [7]. Analogously, the penile erectile bodies and glans can be split, separately mobilized, and even transected and reattached yet be expected to heal reliably in the absence of all but the most severe vascular disorders (such as Monckeberg's calciphylaxis). The ultimate demonstration of the robustness of the penile and urethral vasculature is penile disassembly advocated in selected cases of complete bladder exstrophy and epispadias.

The skin of the external genitalia has a similar redundant blood supply. Penile shaft skin receives primary vascular support from the superficial external pudendal arteries with collateral flow from the bulbourethral and dorsal arteries via the glans. The scrotum receives arterial input from the named arteries off of deep external pudendal arteries as well as anastomoses with the perineal arteries posteriorly. Thus lacerations, burns, surgical incisions, and a variety of random flaps can reliably heal when based on genital skin. An exception to this rule of thumb is the perineum. If the skin is lost through necrotizing soft tissue infection, the underlying perineal soft tissue and fat poorly support skin grafts and often must be left to close by secondary intention or with the support of vascularized tissue transfer.

Tissue Healing Responses

With rare exception of certain organs and fetal tissue, the healing response replaces damaged

tissue through the deposition of collagenous connective tissue. Fibrosis to temporarily stabilize newly formed or newly connected tissues is important for healing, but may be perturbed by excessive fibrosis which ultimately impairs tissue function and leads to patient discomfort, loss of function, and even mortality.

Recent investigations in the processes involved in skin injury provide a significantly enhanced understanding of the cellular networks involved in wound healing [8]. Skin healing is an organized process of overlapping immune responses associated with migration and proliferation of different cell types, extracellular matrix deposition, and tissue remodeling (Fig. 15.2). Fibroblasts are the first wave of cells to enter into a healing wound, being transformed into myofibroblasts that produce collagen and alpha smooth muscle actin,

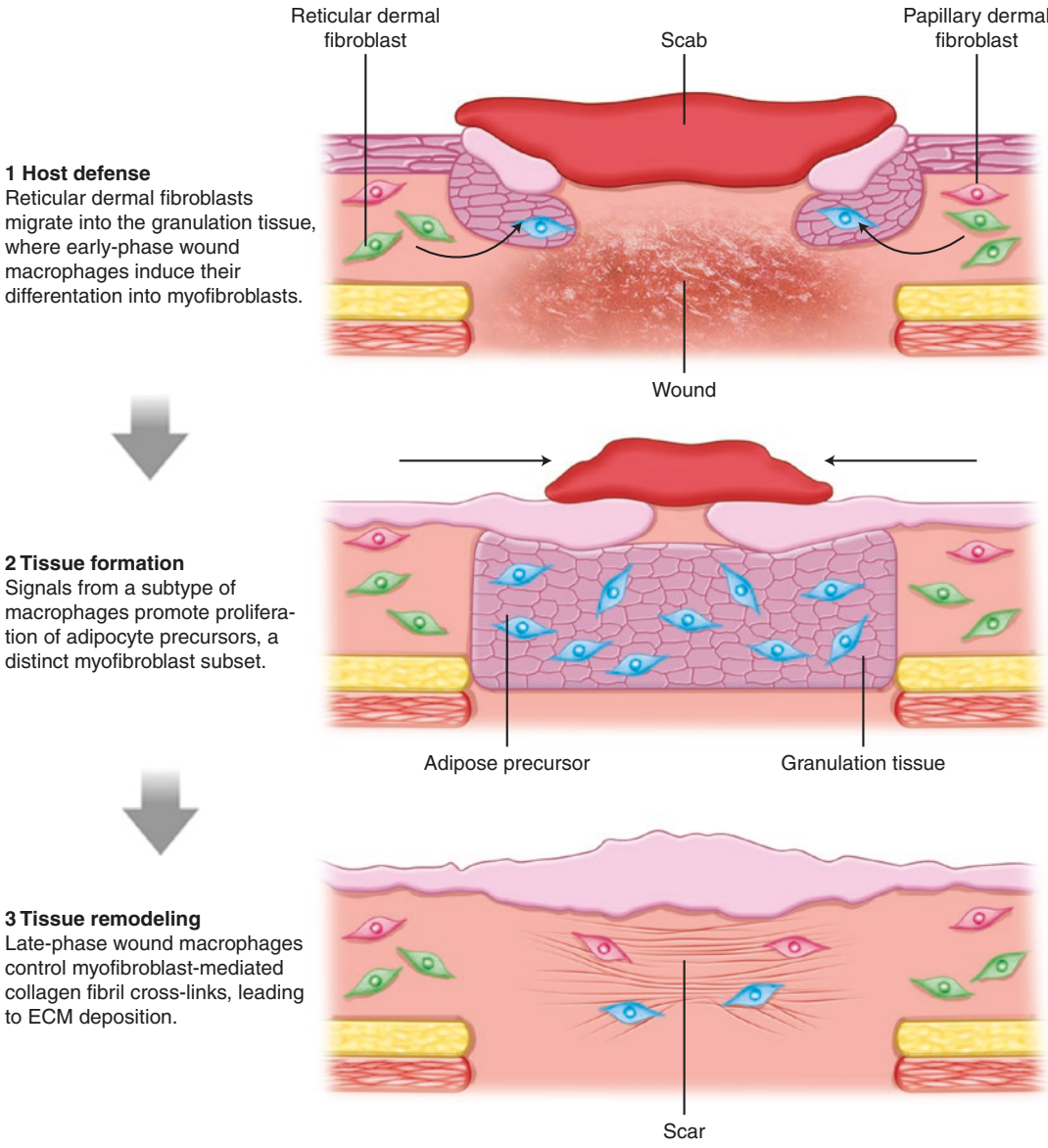

Fig. 15.2 Skin wound healing schematic (drawn from Ref. [8]) showing role of dermal fibroblasts and adipocytes in mechanisms of wound healing and scar contraction

thus leading to the process of wound contracture and scar formation. It is likely, though unproven, that interaction between specific macrophage and myofibroblast populations determines the outcome of the repair response. Surgeons would not be surprised to learn that profibrotic programs such as collagen cross-linking pathways, that usually only occur in hard connective tissue such as bone and cartilage, become activated during wound healing and can lead to scarring and heterotopic ossification. Underlying healing responses in most tissues is a complex network of cytokines and mediators which facilitate communication between the key cellular players. TGF-beta and type 2 immune responses have been identified as drivers of the process. Interestingly, the adipocyte might be an important additional related cell in tissue repair, and its dysfunction in certain disease states might contribute to impaired wound healing. Advances in the scientific understanding of this process will undoubtedly lead to potential anti-fibrotic therapies, the development of which are currently slow.

Epithelial Microarchitecture and Determinants of Graft Take

The microarchitecture of skin and other epithelia provides insight into how tissues heal, why they fail to heal, and different strategies used in reconstructive surgery such as skin grafting of male genital organs, neovaginal reconstruction, as well as one stage and staged urethral reconstruction [6]. Epithelia are comprised of an epidermis or epidermis-like multicellular covering barrier and supporting connective tissue and vasculature, the latter two referred to as the dermis in the skin and the lamina propria in the urinary tract. Attention has been paid to the thickness of the lamina propria vis a vis its overlying epithelium. This has led to significant debates as to the benefits of different grafts for genital and urethral reconstruction. Buccal mucosa with its thick, many layered epithelium, and relatively thin lamina propria compared to skin with its reverse proportions are shown in Fig. 15.3. Compared to these two donor sites, bladder epithelium has the least adequate of all combinations of epithelium and lamina propria.

The "take" and ultimate survival of free grafts requires assessment of the properties of the donor site, recipient bed, and general principles of engraftment. Equally important are more subtle factors that bear more on the long-term functionality of the intended graft such as elasticity, thickness, collateral formation and tolerance for tubularization.

Donor site concerns include the above-mentioned discussion of thickness of the lamina propria; the absence of infectious or inflammatory conditions (such as an acute fungal infection or lichen sclerosus); ease of harvesting and availability; cosmetic concerns such as pigmentation matching; and the ability to close the donor site. Recipient bed considerations overwhelmingly relate to the ability to support and vascularize the graft. When a graft is placed on a newly created wound, the inherent characteristics of the recipient bed define the likelihood of successful graft take. Thus, a graft affixed to the normal corporal body, the testis or tunica vaginalis, or a healthy muscle, will have a high chance of take. Conversely, when a recipient site is compromised, such as in complex open wounds from trauma and infection [9], the surgeon must decide whether a period of wound care will clear contamination and allow granulation tissue to form, or instead the patient needs adjunctive measures involving flaps to cover the wound or create a better recipient site.

The steps in revascularization of an epithelial graft have direct influence on patient care decisions [6]. Successful "take" of a free graft requires survival of the epithelium, initially through direct absorption of oxygen and micronutrients from the underlying recipient site. This process of imbibition is thought to last 24–48 h until neovascularization proceeding from the graft bed meets up with the still-living vascular network of the donor tissue. Once inosculation occurs, stable perfusion is generally achieved within another 48 h. Thus, the first 4 days after grafting have the most impact on ultimate graft take. Importantly, certain comorbid conditions including poorly controlled diabetes, cigarette

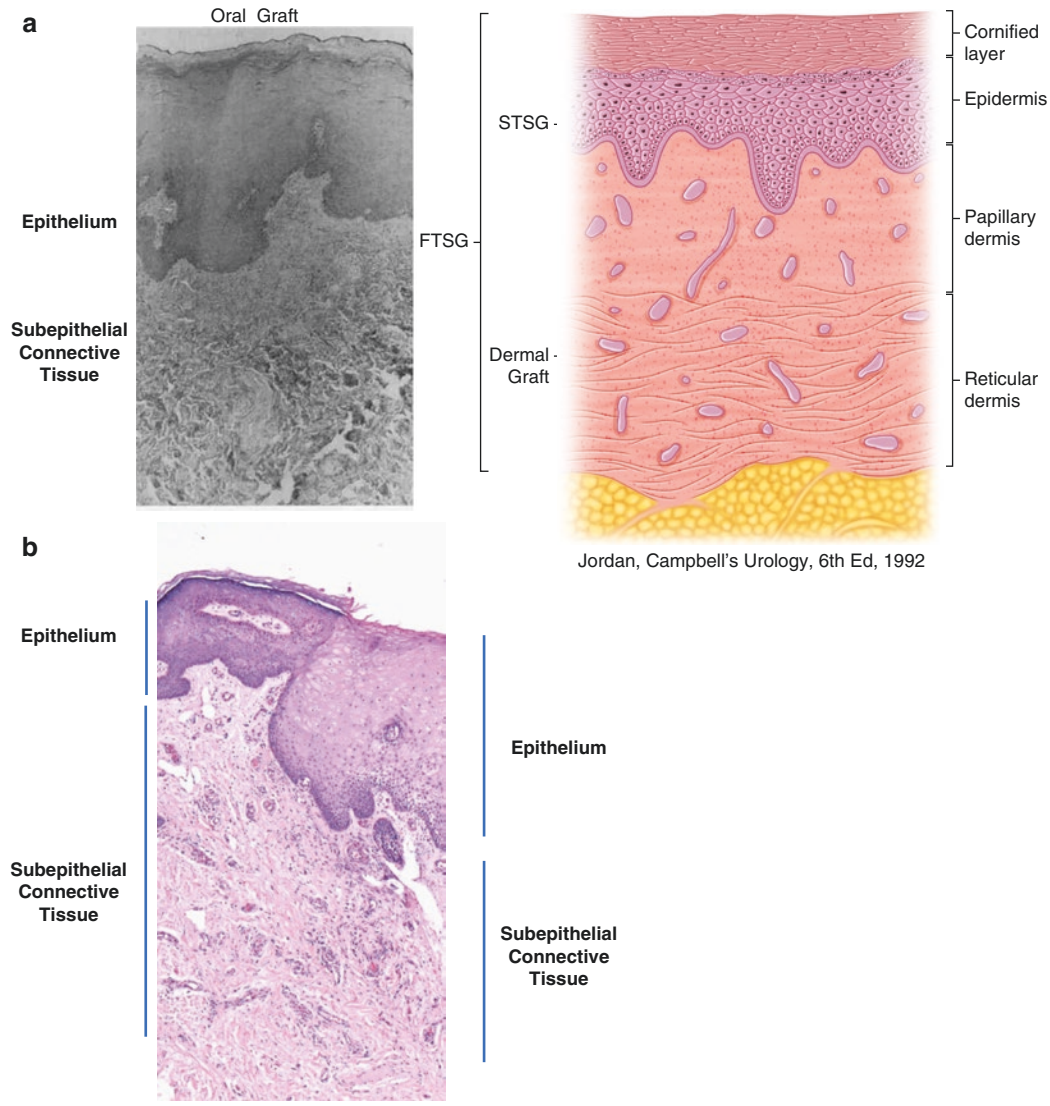

Fig. 15.3 Comparison of microanatomy of skin and buccal mucosa grafts. (**a**) Schematic showing the epithelial and subepithelial layers of normal skin, along with the layers used in full thickness (FTSG) and split thickness (STSG) skin grafts as well as dermal grafts (redrawn from Ref. [6]). (**b**) Histological section showing interface of adjacent skin (left) and oral mucosa (right) after a staged urethroplasty. Note the cornified surface, thinner epithelium, and deeper subepithelial layer of the skin versus the adjacent oral mucosa which is not cornified

smoking, and severe peripheral vascular disease may influence graft take and must be factored into decision making.

Immobilization of the graft to its recipient site, whether through quilting sutures, dressings, or a combination of both, are beyond the scope of this chapter but must be considered in detail. On a practical note, steps to prevent lifting of the graft off of the recipient site during this critical period are important and may include "pie crusting" or meshing of the graft [10]; fixation as mentioned above, and in certain circumstances, visualization of the graft and de-blebbing.

Additional considerations in graft creation relate to the ultimate functionality required of the grafted tissue. Each surgery must strike a balance between "take", contracture and elasticity. Autologous grafts, harvested and placed without

any treatment or preservation, maintain their elasticity and impart it to the recipient site. Full thickness grafts will undergo minimal shrinkage *unless there is graft loss,* in which case wound contraction and fibrosis replaces normal epithelium. Conversely, the split thickness skin graft, with its thinner subepithelial connective tissue (see Figure 15.3a) allows better imbibition and inosculation, although the price paid is in the fragility of the skin and higher degree of contraction, stiffness of the tissue, and lesser functionality. Furthermore, how the tissue is laid out and fixed to the recipient bed will influence its later functionality. For example, in a staged urethroplasty an oral mucosa graft may be harvested in a 6 × 3 cm size. However, if the elasticity of the graft is used to achieve greater *length*, the consequence will be neourethra with less than 3 cm *width*. Meshing of STSG's will influence contraction, ranging from a ratio of 1:1 (e.g. no expansion and lesser contraction) up to 1:3 (significant expansion and greater contraction). Grafts also have less supporting soft tissue and may therefore lack bulk or cushioning which may make them less desirable without adjunctive use of underlying muscle or other soft tissue flaps.

A consideration related to grafts is whether skin that has not been adequately prepared (e.g. defatted) can serve as a graft, Skin flaps, if cut off from their blood supply, generally will not survive as a free graft because the underlying or adjacent pedicle provides too thick of a barrier to events during revascularization, and as a result leads to ischemic loss. Analogously, genital shaft skin which has been avulsed in an injury may have suffered damage to its dermal network of arteries and veins. Thus, the classic "power takeoff injury" in which the entire penile and scrotal skin is avulsed in rotating machinery, likely has suffered shearing injury to its intrinsic vasculature and should only be used as a free graft with caution.

Vascularized Flaps and Genitourinary Tissue Transfer

All flaps are vascularized. The author nevertheless prefers the redundant term to emphasize the essential difference between flaps and free grafts. When free grafts are not appropriate, either due to limited tissue availability, depth of defect, or inadequate recipient site vascularity to support engraftment, flaps offer solutions for the care of patients with severe injury, cancer, surgical complications, and necrotizing soft tissue infection. Vascularized flaps can fill a defect in an organ, cover vulnerable structures, or in certain circumstances support a graft in an area of poor vascular supply.

Conceptual understanding of the blood supply of flaps is essential. Jordan and associates have summarized the key issues in a definitive chapter [6], which we have summarized in Fig. 15.4.

Random flaps are used frequently in urology, whether by taking a spiral renal pelvic flap; creating a bladder flap to bridge a defect, stricture or a fistula; use of a Boari flap for ureteral reimplantation; or any number of penile and scrotal skin advancements used to cover defects related to hypospadias, injury, necrotizing skin loss, and the like. In these cases, the most important principle is creating proper length-to-width ratio, in which a given length of a flap survives based on the proportional width of pedicle. Generally, a random flap should be no longer than 3 times its width. Whether to create a flap as a rectangle, U, or triangular, depends on the expected robustness of the intrinsic blood supply of the tissue to be transferred. Axial flaps have a known and reliable underlying arterial pattern, which allows for predictable vascularization of the leading edge of the flap and a different length-to-width ratio. Finally, pedicle flaps, whether supported by a very robust arcade of vessels or a single blood vessel, can be moved greater distances because they do not rely on connection of the overlying skin or epithelial structure. Taken to its extreme form, this is the essence of a free flap with microvascular anastomosis: when the pedicle is not long enough to reach the intended recipient site, division and anastomosis to new arterial and venous structures is required at a new location.

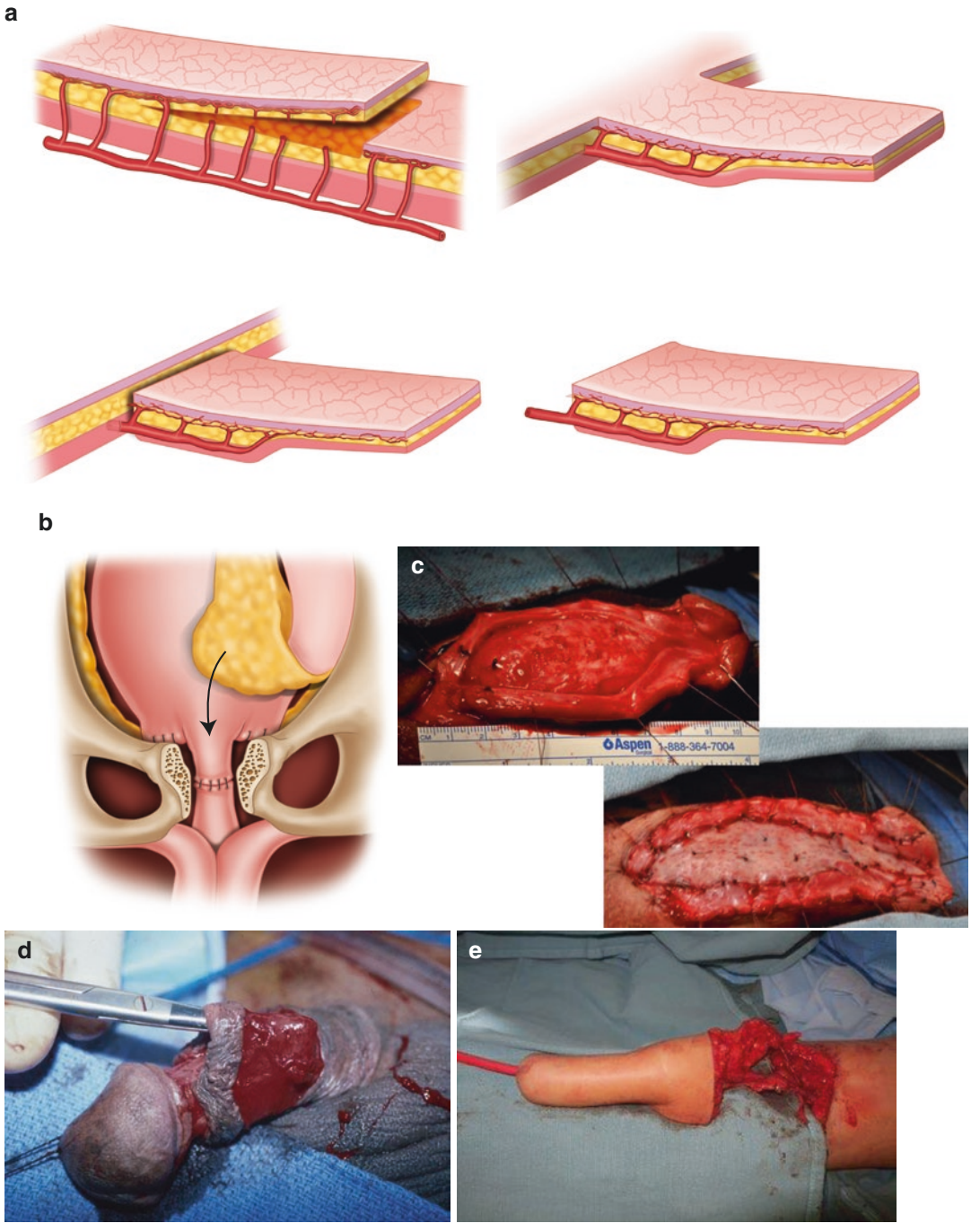

Fig. 15.4 Principles of flaps. (**a**) Classification of random, axial, pedicle and free flaps (drawn from Ref. [6]). Illustrative examples: (**b**) Random flap—anterior bladder tube; (**c**) Axial flap—longitudinally split and lateralized corpus spongiosum/urethral plate, upper and lower images before and after placement of oral mucosa grafts respectively; (**d**) Pedicle flap—penile fasciocutaneous flap; (**e**) Free flap—radial forearm phallic construct

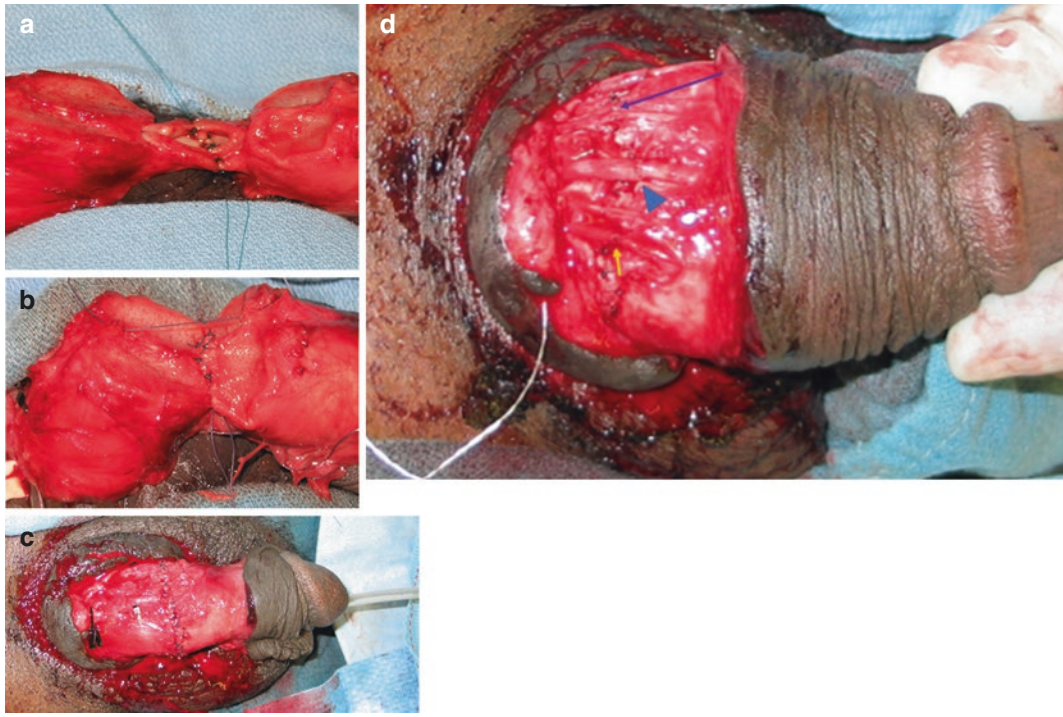

Fig. 15.5 Microvascular penile replantation. (**a**) Urethral anastomosis, after placement of ventral wall sutures. (**b**) Corporal reapproximation in progress. (**c**) Completed corporal reanastomosis. (**d**) Microvascular anastomoses of vein (arrowhead), artery (arrow), and nerve (long arrow)

Synthesis

Urologists acquire a range of surgical skills to manage tissue loss from cancer surgery, trauma, infection, iatrogenic and congenital causes, although a formal plastic surgery curriculum has not been introduced. Reconstructive urological principles offer the chance for addressing some of the most complex problems using a multidisciplinary team approach. In such cases, the presence of a knowledgeable urologist to guide other specialists provides the best chance for success. Penile amputation provides a relevant synthesis (Fig. 15.5). Success begins with proper preservation of the amputated phallus and preparation of the recipient stump; understanding of the ischemic tolerance of the organ; indications for reconnection of urethral and corporal structures; microvascular arterial and venous anastomosis to ensure skin survival and corporal tissue reperfusion; nerve reanastomosis for long term functional sensation; management of venous engorgement after replantation; and secondary surgeries to manage complications. Other cases in which anatomical knowledge, tissue rearrangement, flap and graft use are all integrated include bladder exstrophy, disorders of sexual differentiation, and gender affirming surgery.

Summary

The genitourinary system consists of specialized epithelial and stromal aggregations that carry out vital excretory and reproductive functions. When disrupted, function of these organs can be successfully restored applying principles of tissue transfer in the context of anatomical knowledge and an understanding of the processes of wound healing. Unfortunately, no current technology provides readily available robust means of assessing the vascular status of a recipient bed, mobilized flap, or adjacent tissue edge. Emerging technology such as vital imaging during robotic

surgery with fluorescence dyes [11, 12] represents one advance, which if validated, and shown to improve outcomes, may diffuse to a wider set of users. For the time being, close adherence to the principles outlined in this chapter will provide the reader with a framework from which to make surgical decisions in the face of uncertainty. The ensuing chapters in this textbook show the application of these concepts across the full range of urological surgery.

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Part II

Clinical Urologic Practice

Haematuria: Evaluation and Management

16

Karl H. Pang and James W. F. Catto

Introduction

It is estimated that 2.5% of the population have non-visible haematuria (NVH) if tested and consequently haematuria accounts for approximately 20% of urological referrals [1]. Around 40% of patients investigated for haematuria have an underlying pathology, with around half attributed to urological malignancy [2]. The nature, severity and potential causes need careful assessment during consultation and investigated and managed appropriately. Most cases are investigated and managed in the out-patient setting, however, in extreme cases, admission and acute management with blood transfusion, catheterisation of the bladder, washout and irrigation may be required.

Definition and Classification of Haematuria

Haematuria occurs when there are red blood cells (RBC) in the urine. This can be classified into Visible Haematuria (VH: previously termed frank, gross or macroscopic haematuria) or NVH (detected by microscopic examination of urine or dipstick analysis) [3]. In addition, haematuria can be symptomatic or asymptomatic. The dipstick method to detect haematuria is based on the oxidation of a chromogen by the presence of haemoglobin, producing a degree of indicator colour change proportional to the degree of haematuria. The dipstick method has a sensitivity of 95% and a specificity of 75% and positive tests need to be confirmed with microscopy. Microscopic haematuria is commonly defined as ≥3 RBC per high powered field (HPF) on one sample (American Urological Association (AUA) guidelines) or on two samples (Canadian Urological Association (CUA) guidelines). None of the European guidelines comment on the degree of haematuria on microscopy [4]. Dipstick specificity is limited due to other peroxidases or oxidizing agents such as myoglobin and Vitamin C (these lead to false positive tests).

Aetiology of Haematuria

Bleeding into urine may occur from intrinsic renal pathologies (affecting filtration in the glomerular or damage to the tubules) or from benign and malignant pathologies in the post-renal urinary tract (renal pelvis to the urethra, Fig. 16.1):

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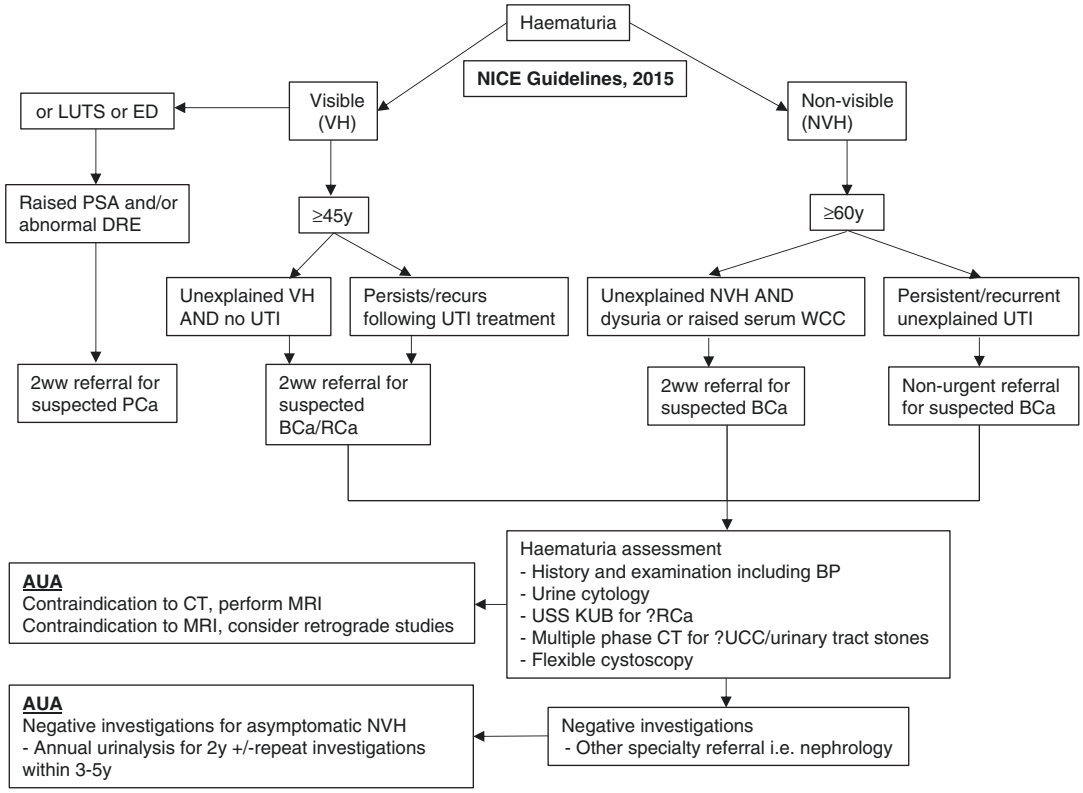

Fig. 16.1 NICE referral criteria and subsequent urological evaluation of haematuria. *NICE* National Institute for Health and Care Excellence, *LUTS* lower urinary tract symptoms, *ED* erectile dysfunction, *DRE* digital rectal examination, *UTI* urinary tract infection, *PCa* prostate cancer, *BCa* bladder cancer, *RCa* renal cancer, *UCC* urothelial cell carcinoma, *AUA* American Urological Association

Urological Malignancy

Haematuria is an important symptom of renal cancer (RCa), upper tract urothelial cell carcinoma (UCC) and bladder cancer (BCa) [4, 5]. Painless haematuria is considered the cardinal symptom of bladder cancer. Advanced prostate cancer (PCa) may cause VH but is usually detected through other symptoms. The risks of cancer vary with extent of haematuria, patient age and sex. Around 14% of patients with VH have cancer, compared to 3.1% with NVH [2]. The risks are lower in younger populations. For example, in patients under 45 years old, the risk of cancer with VH is 3.5% versus 0.5–1.1% for NVH [2].

Infection and Inflammation

Urinary tract infections (UTIs) usually present with local symptoms (cystitis or pyelonephritis) but often have NVH or even VH. It is uncommon for men to have ascending UTI of the upper tracts, but prostatitis can occur as a primary infection or as a complication of prostate biopsy. In younger patients with infection, potential underlying sexually-transmitted infections (STI) need to be explored.

Non-infective inflammatory conditions such as interstitial cystitis can cause haematuria and require cystoscopic evaluation with hydrodistension (glomerulation and Hunner's ulcers) and biopsy (mast cells) for a definitive diagnosis.

Haemorrhagic cystitis secondary to radiotherapy and chemotherapy will result in haematuria. Benign prostate hyperplasia (BPH) and post-transurethral resection of the prostate (TURP) regrowth/inflammation of the prostate cavity is a common cause of haematuria in older men.

Urolithiasis

Urinary tract stones can be asymptomatic or present acutely with painful ureteric colic. Most patients will have NVH if tested. Exceptions include upper tracts obstructed by ureteric stones, this could be complicated by infection and urosepsis.

Non-urological Causes of Haematuria

Patients under the age of 45 years with asymptomatic NVH are more likely to have intrinsic renal pathology such as IgA nephropathy (Berger's disease), thin glomerular basement membrane disease or hereditary nephritis (Alport's syndrome). Hypertension, urinary red cell casts, dysmorphic RBC and significant proteinuria is suggestive of a glomerular cause of haematuria.

Other potential non-urological causes of haematuria include haematological pathologies such as thrombocytopenia purpura. Bleeding from the gynaecological system resulting in contamination of the urine can occur, this could be benign in origin, such as normal menstruation, or secondary to gynaecological malignancy. Intensive exercise with or without trauma can cause haematuria [6]. Other spurious causes of haematuria include foods (beetroot and blackberries), drugs (rifampicin and chloroquine) and rhabdomyolysis.

Evaluation of Haematuria

Various international guidelines suggest pathways to investigate haematuria, including the National Institute for Health and Care Excellence (NICE), British Association of Urological Surgeons (BAUS), AUA, CUA and European Association of Urology (EAU) guidelines [4].

Guidelines on Investigating Haematuria

The 2015 NICE guidelines (adopted by BAUS 2016) recommend referring patients with a suspicion of renal/bladder malignancy on a suspected cancer pathway referral (appointment within 2 weeks) if they are aged 45 years and over and have unexplained VH without UTI or VH that persists or recurs after successful treatment of UTI (Fig. 16.2). NICE also recommends referring those who are aged 60 years and over and have unexplained NVH and either dysuria or a raised serum WCC. Patients aged 60 years and over with recurrent or persistent unexplained UTI suspicious for BCa can be referred on a non-urgent basis [5, 7]. In contrast, the 2012 AUA (reviewed 2016) and 2015 CUA recommend cystoscopy for asymptomatic NVH in patients aged 35 years and older [8, 9]. Whilst the Dutch guidelines recommends investigating asymptomatic NVH in older patients aged 50 years and over [4].

History and Examination

A focused history is important in assessing the severity of haematuria, identifying risk factors for urological malignancy and allowing the derivation of a list of differential diagnoses. The presence, location and nature of pain (colicky in stones), urinary symptoms (dysuria, frequency, urgency or urethral discharge) and other associated symptoms such as weight loss and menstrual history should be noted. BCa usually presents with painless haematuria. Men with voiding with or without secondary storage lower urinary tract symptoms (LUTS) may have BPH as the underlying cause of haematuria. It is also important to identify risk factors for malignancy such as tobacco smoking, occupational exposures (aromatic amines, aniline dyes) and relevant pre-existing medical history (e.g. prior TURP, medication with anticoagulants or cyclophosphamide).

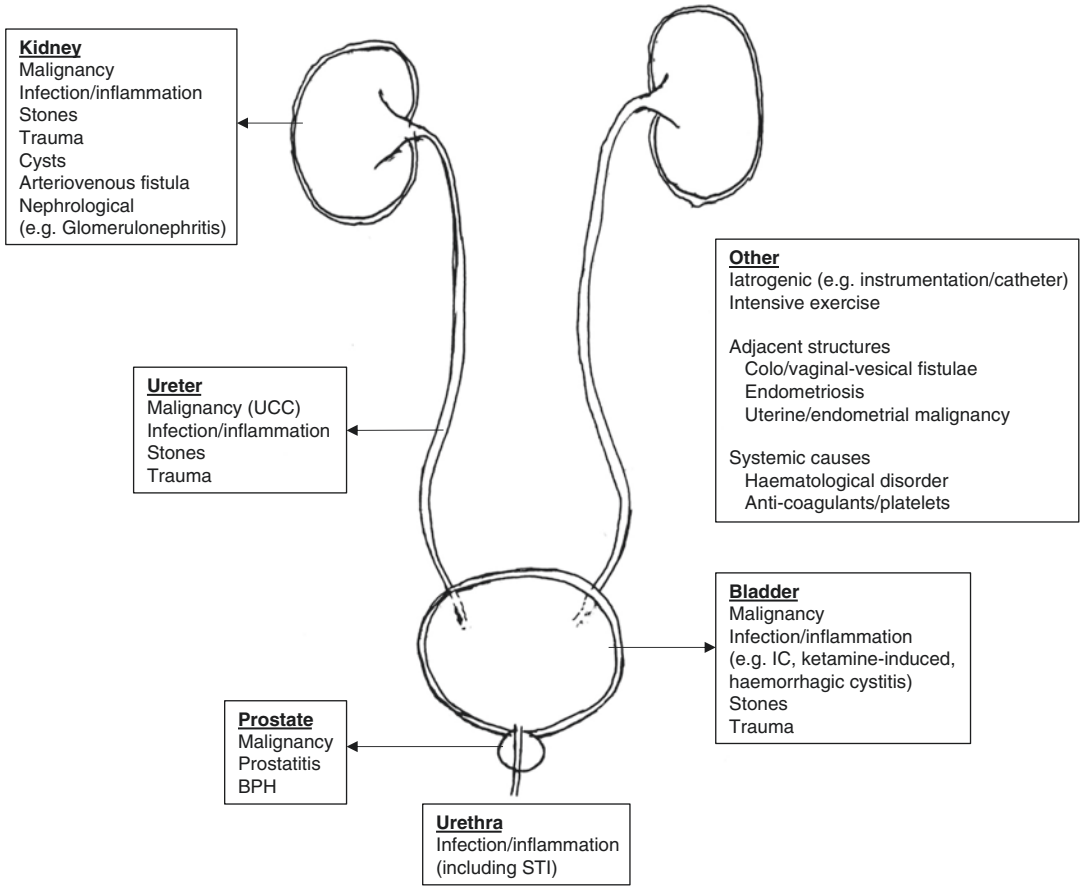

Fig. 16.2 Causes of haematuria. *IC* interstitial cystitis, *BPH* benign prostate hyperplasia, *STI* sexually-transmitted infection

Physical examination of the abdomen, pelvis, rectum, prostate and genitalia may elicit masses and other localising signs. Blood pressure should be measured and may be elevated in renal pathologies. Less than 10% of patients with renal cell carcinoma (RCC) present with the classic triad of haematuria, pain and loin mass. Digital rectal examination (DRE) is mandatory as BPH or advanced PCa can cause haematuria.

Laboratory Evaluation

Blood tests including urea and electrolytes (with eGFR) and full blood count (for haemoglobin, platelets and WBC) are important. A coagulation profile screen could be performed if the history suggests this is a likely problem. Urinalysis with or without MC&S is important in detecting NVH and potential infective (nitrites, leucocytes) and nephrological (proteinuria) causes of haematuria. A Prostate-specific antigen (PSA) blood test is indicated if PCa is suspected.

Diagnostic Cystoscopy

Flexible cystoscopy allows the visualisation of the urethra, (prostate in men) and bladder. Inspection will identify stones, BCa, carcinoma in-situ (CIS) and inflammatory changes secondary to benign causes such as infection, trauma (catheter), recreational drugs (Ketamine) and interstitial cystitis. The role of fluorescence/blue-light cystoscopy in

identify non-muscle invasive BCa (NMIBC) and CIS in patients with NVH is controversial [4].

Radiological Evaluation

Upper tract imaging in patients with VH is supported by all guidelines. The preferred imaging method varies taking into account the risks of radiation and contrast. For benign causes such as urinary tract stones a non-contrast CT (NCCT) is the imaging of choice. Ultrasound scan of the kidney, ureter and bladder (USS-KUB) and abdominal-pelvis is useful in detecting renal masses, renal stones and non-urological abdominal-pelvic causes such as gynaecological pathologies. A CT urogram (CTU) is more useful in identifying filling defects and detecting malignancy along the urinary tract. Patients with contraindication to CTU such as renal insufficiency, contrast allergy and pregnancy, AUA recommend MRI with or without retrograde pyelograms (RPG) as an alternative to evaluate the entire urinary tract. If both CTU and MRI (metal in the body) are contraindicated, the combination of NCCT or USS-KUB with RPG provides alternative assessment of the urinary tract [8].

Urine Cytology and Molecular Markers

Urine cytology can detect atypical and malignant cells and so some guidelines recommend cytology is used together with cystoscopy (especially to detect CIS) [10]. The sensitivity of urine cytology in detecting high-grade tumours is around 84%. Urinary biomarkers such as FGFR3, BTA-stat, NMP22 or UroVysion in BCa screening in high-risk populations have been reported, however, none of the current available tests can replace cystoscopy.

Management of Haematuria

The management of haematuria depends upon its cause [11]. Active VH with clot retention require hospital admission with insertion of a 3-way catheter with or without bladder irrigation. Blood counts, clotting and renal profile should be checked. Red cells, platelets and fresh frozen plasma may be necessary, depending on the blood results. Nephrological and haematological causes of haematuria must be recognised and referred to the appropriate specialty for further management.

Infection

For uncomplicated UTI, oral antibiotics are usually sufficient and the choice could be changed based on sensitives. Complicated UTI associated with sepsis require hospital admission, full resuscitation and administration of intravenous antibiotics. An USS is useful in assessing for hydronephrosis or stones. A nephrostomy may be indicated in septic patients with hydronephrosis.

Urolithiasis

The management of urinary tract stones depends on the size, location of the stone and whether there's any associated acute renal failure and urosepsis. In cases of acute renal failure and sepsis, a nephrostomy or ureteric stent may be indicated. Definitive stone clearance can be achieved by extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotripsy (PCNL) or ureteroscopy with laser lithotripsy.

Benign Prostate Hyperplasia

The management of prostatic bleeding following a TURP of from benign enlargement includes pharmacological treatment with alpha-5 reductase inhibitors (e.g. Finasteride or Dutasteride), surgical treatment (redo/primary TURP) or prostatic embolization.

Urological Malignancy

The management of each urological malignancy is beyond the remit of this chapter and

depends on the grade and stage of cancer, taking into account the patient's wishes and performance status (see relevant chapters in this book). Heavy haematuria may arise from advanced, incurable urological cancers. This can be problematic and often requires multimodal treatment. Options include radiologically guided embolization, pro-coagulant medication and palliative radiotherapy. For BCa, intravesical irrigation with Alum (Aluminium ammonium/potassium sulphate) or Mitomycin C can help reduce VH.

Follow-up After Negative Evaluation

Patients with NVH should be followed in the community to look for nephrological causes or diseases missed by initial screening [4]. Typical regimens include measuring blood pressure and proteinuria (dipstick) annually (to look for IgA nephropathy). Re-investigation is needed if the symptoms change (NVH becomes VH, or asymptomatic becomes symptomatic), if the treating clinician is concerned or if initial tests were inconclusive.

Conclusions

The risk of cancer or renal disease varies with the extent of haematuria, the patients age and the presence of symptoms. Patients with VH often have urological malignancy and so they should be investigated promptly. Few patients with asymptomatic NVH have a detectable disease and so their management is less clear.

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Chronic Prostatitis/Chronic Pelvic Pain Syndrome

17

R. Christopher Doiron and J. Curtis Nickel

Understanding an Enigmatic Urologic Pain Syndrome

Urologic chronic pain is a real condition with at times a debilitating impact on patients, a significant burden on society, and it will be us as Urologists that these challenging patients seek out for diagnosis and management. And it is a common affliction—up to 10% of men will experience pelvic or genitourinary (GU) pain (chronic prostatitits/chronic pelvic pain syndrome or CP/CPPS) over the course of 1 year. It is a fact that numerous excellent studies examining the etiology, diagnosis and management of CP/CPPS have been published resulting in textbook chapters (and even whole books), comprehensive reviews, meta-analyses, and guidelines dedicated to outlining diagnostic and management strategies. Despite this, chronic urologic pain in men remains an enigmatic condition with elusive treatments and the practitioner is often left frustrated and confused, the patients even more so.

It is the goal of this chapter to explore one of the most common urologic chronic pain conditions—chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)—Category III of the prostatitis syndromes (see section "Definition and Classification"). It is without a doubt the most prevalent of the prostatitis syndromes, responsible for 90–95% of prostatitis diagnoses [8]. We aim to provide an up to date review of the etiology, diagnosis and treatment options, arming those tasked with treating this condition with a realistic, practical approach driven by current evidence and extensive clinical experience in treating the disease.

Definition and Classification

In reference to a diagnosis of "prostatitis" it is generally accepted that one is referring to any one of a collection of syndromes, defined on a spectrum of involvement of three main contributors: (1) bacterial infection of the prostate, (2) GU pain, and/or (3) involvement of lower urinary tract symptoms (LUTS). Prostatitis is a clinical diagnosis, relying on thorough history, physical examination and although there is no single diagnostic laboratory test, several investigations can help contribute to arriving at an appropriate diagnosis (see section "Evaluation").

Following their pioneering work, studying the urine cytology and bacterial localization of the urinary tract which culminated in their classic four-glass test of the urine [1], Meares and Stamey first recognized that a definition of "prostatitis" was far too simple and suggested a more nuanced classification of the disease based on

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findings from their research: acute and chronic bacterial prostatitis, nonbacterial prostatitis and prostatodynia [2]. This was the first "official" acknowledgement in the literature of a group of patients with symptoms reminiscent of bacterial prostatic infection, but where no identifiable infection could be found.

The Meares and Stamey classification system laid the groundwork for our current classification system [3], published by the National Institutes of Health's (NIH) International Prostatitis Collaborative Network (see Table 17.1). This research collaborative's effort split bacterial-related infection of the prostate into Categories I and II: acute and chronic bacterial prostatitis respectively. Nonbacterial prostatitis was rolled into Category III, which also introduced the new term, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

This possibly noninfectious category acknowledged that most symptomatic "prostatitis" patients—up to 95%—ultimately have a diagnosis of CP/CPPS, and recognized that their pain may be complex and related to structures in the pelvis other than the prostate. They further sub-classified Category III into Category IIIA—known as the inflammatory subtype—and Category IIIB—the noninflammatory subtype—based on the presence or absence of leukocytes in the expressed prostatic secretion (EPS) or post-prostate massage urine (VB3) specimens of the four-glass test (see section "Urine Studies") or leukocytes in the semen. Finally, Category IV—representing those who were asymptomatic but with findings suggestive of prostate inflammation on investigation—was introduced and not previously described in the in the Meares-Stamey classification system.

Table 17.1 NIH classification system for prostatitis syndromes [3]

NIH category	Clinical presentation
I: Acute Bacterial Prostatitis	Acute symptoms of UTI, general malaise, fever. bacteriuria, pyuria
II: Chronic Bacterial Prostatitis	Recurrent episodes of bacterial UTIs; C&S reveals infection with same organism; evidence of bacterial infection of prostate between symptomatic episodes
III: Chronic Prostatitis/Chronic Pelvic Pain Syndrome	Primary complaint of pain in GU tract with no identifiable bacterial infection
(a) Inflammatory	Leukocytes present in expressed prostatic secretions, post-prostate massage urine, or semen
(b) Noninflammatory	No leukocytes present in expressed prostatic secretion, post-prostate massage urine, or semen
IV: Asymptomatic Inflammatory Prostatitis	No history of GU symptoms; but with leukocytes present in expressed prostatic secretion, post-prostate massafe urine, or semen; incidental diagnosis

Epidemiology

Kreiger et al. [4] proposed a collection of epidemiological study characteristics they suggested would act as a desirable set of criteria for including a specific study in any review evaluating the epidemiology of chronic prostatitis. These characteristics included: (1) population-based studies. The authors point out that population-based studies are preferable to case series and studies based on referral to tertiary care centers, as population-based studies are more likely to be representative of the population as whole. Secondly, the authors suggest a (2) clear case definition for chronic prostatitis should be apparent in the study. Furthermore, they go on to intimate that ideally, this case definition would bear a relationship to those patients seen in routine clinical practice. Thirdly, a (3) survey strategy to ensure an adequate sample of the population was acquired while employing methods of ensuring identified cases met the case definition of the study. Ideally, a (4) standardized instrument—the authors favour the NIH-Chronic Prostatitis Symptom Index (NIH-CPSI; see section "Chronic Prostatitis Symptom Index")—should be employed to identify cases in a reliable, consistent manner. Another desirable study characteristic is (5) that the population studied would be large to have an acceptable statistical power for any subsequent analyses. Finally, (6) the study ideally would be published in a peer-reviewed journal.

There are a number of reviews of epidemiologic studies analyzing the prevalence of prostatitis—the first by Kreiger et al. [4] was performed in 2003, where the Kreiger criteria was first introduced, and later updated in 2008 [5]. The 2008 study by Krieger et al. identified 10 studies that met their inclusion criteria—7 from North America, 2 Asian and 1 European study. Of the studies where prevalence could be determined, 873 men met criteria for symptoms of prostatitis out of 10,617 men surveyed, yielding a prevalence rate of 8.3%—this varied from 2.2 to 9.7% amongst the included studies.

More recently, Nickel et al. [6] used the Krieger criteria and identified 24 studies for inclusion in a epidemiologic review of prostatitis. Their analysis yielded 13 North American studies, six studies from Asia, two European, two African and one Australian study. The results represented a much larger patient population of 336,846 participants with a prevalence of prostatitis of 7.1%, ranging from 2.2 to 16% amongst the individual studies.

Clearly there are limitations to considering an accurate prevalence of prostatitis by collating studies as in the above, described manner: the baseline characteristics are not well-described in many of these studies, definitions of prostatitis varied amongst the studies and importantly, the methods of determining a diagnosis of prostatitis varied from physician diagnosis—both by urologist and general practitioner—to self-reported diagnosis, to determination from survey responses. Despite these limitations, the studies do suggest that prostatitis is a commonly encountered patient problem. Though most studies do not distinguish categories of prostatitis diagnosis, Clemens et al. [7] used an administrative health care database and determined that Category III CP/CPPS made up the majority of prostatitis diagnoses using the NIH-CPSI definitions of prostatitis diagnosis.

Health-Related Quality of Life

There has been increased interest in patient-centered care in medicine in general, in recent years and contingent upon this has been an uptake in research of patient-reported outcomes (PROMs). When evaluating health in general, several PROMs tools exist. The Sickness Impact Profile (SIP), which evaluates sickness-related dysfunction in 12 different life areas—eating, work, sleep and rest, household management, recreation, pastimes, ambulation, mobility, body care and movement, social interaction, emotional behavior, alertness behavior, and communication—has been used to study PROMs in CP/CPPS patients: Wenninger et al. [9], using the SIP total score, found that chronic prostatitis patients suffer to a similar degree in terms of quality of life (QOL) as patients with myocardial infarction, angina and Crohn's disease.

Another common PROMs tool used to measure health in general is the Short Form 12 (SF-12). This tool evaluates a variety of QOL domains including bodily pain, general health, physical functioning, vitality, mental health and emotional problems, role limitations, and social functioning. McNaughton Collins et al. [10], in their NIH-supported Chronic Prostatitis Cohort Study, described SF-12 scores of CP/CPPS patients and revealed they suffer in both the physical and mental subscales of the SF-12, on a severity worse than similar patients suffering from other chronic diseases including diabetes mellitus and congestive heart failure.

Urology has seen an abundance of PROMs tools introduced specific to various urologic diseases [15] and CP/CPPS has a validated PROM tool of its own—the NIH-CPSI (see section "Chronic Prostatitis Symptom Index")—which includes questions specific to QOL. Though helpful for purposes of stratifying disease severity and following response to treatment over time, it should not be relied upon solely as a diagnostic tool. The questions specific to QOL again, although helpful in following CP/CPPS symptoms and QOL impact over time, is not overly thorough in this domain.

Several studies have evaluated the QOL of CP/CPPS patients in more depth, including comprehensive assessments of mental health, disability and coping strategies amongst this patient

population. Patients with CP/CPPS have been shown to exhibit worse depression [11] symptoms and diagnoses than their healthy peers. Those CP/CPPS patients who exhibit worse catastrophizing behaviors have been shown to have worse prostatitis-related pain [12], highlighting the importance of biopsychosocial factors in this disease process.

Krsmanovic et al. [13] have furthermore shown that both catastrophizing and illness-focused coping fully mediated the relationship between pain and mental QOL in CP/CPPS patients. These findings again highlight the importance of patients' perceptions of self and that their cognitive strategies for managing their disabilities are not simply secondary to their disease, but inherent in it and even associated with the severity of their physical pelvic disease in some instances.

Not only are the patient's QOL negatively impacted by their disease, but their spouses' QOL measures have been shown to similarly be affected. In a study following CP/CPPS patients and their spouses over a 2-year period, both patients' and their spouses' depression, disability, pain and catastrophizing behavior remained stable over a 2-year FU period [14] regardless of the type of treatment they received. These QOL studies have demonstrated the crucial attention to biopsychosocial factors that must be paid in these patients.

Etiology

The etiology and pathogenesis of CP/CPPS is not well understood. Perhaps the most broadly accepted working hypothesis is that it is a disease process that is most likely multifactorial, involving several bodily systems including genetic, immunologic, endocrine, neurologic, musculoskeletal, and psychological pathways [6]. Though investigators have failed to discover the smoking gun for a diagnosis of CP/CPPS, it has not been due to a lack of trying. Much research has been devoted to understanding the etiology of this enigmatic disease and below follows an exploration through some of what we know about the etiology of CP/CPPS.

Microbiome

Though by definition, Category III Chronic Prostatitis/Chronic Pelvic Pain Syndrome does not have an identified bacterial causative agent, many have believed that we are simply limited by our current culture-based microbiology techniques—it is not that CP/CPPS lacks a bacterial cause, but that we have not been able find it.

More recently, investigations into the microbiome of the lower urinary tract inspired by this theory have provided additional insights into our understanding of a possible role of bacterial pathogenicity in CP/CPPS. We know the majority of bacteria species, resistant to current culture methods, exist in a "biofilm" mode of growth [16] within the urinary tract and prostate—an area that was previously thought of as a sterile tract. Though this finding of bacteria previously undiscovered in these areas to this degree has been a breakthrough, it remains to be known which of these culture-resistant bacteria are actual pathogens.

Leading the way in this concept of the GU microbiome and its role in CP/CPPS pathogenicity has been the Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. In their 2015 publication [17] where they used a novel, state-of-the-art culture independent method of characterizing GU bacteria in CP/CPPS patients and healthy male controls, Nickel et al. showed that CP/CPPS patients exhibit a GU microbiota distinct from healthy controls. Specifically, they found higher concentrations of Burkholderia cenocepaciaens in CP/CPPS patients compared to their matched asymptomatic male controls.

Later in 2016, Shoskes et al. [18]—using the 16S rRNA-gene amplification method to detect bacteria in urine specimens—performed an analysis of 25 CP/CPPS patients and compared their urinary microbiomes to healthy controls. They similarly found a unique GU microbiome in the CP/CPPS group: higher phylogenetic diversity and higher counts of Clostridia species in CP/CPPS patients compared to healthy male controls. Using similar methods in a subsequent study [19], the same research group demonstrated that the microbiome uniqueness of CP/CPPS

patient was not limited to the GU tract—they showed significantly less microbiome diversity and decreased prevalence of Prevotella species in the gut microbiota amongst CP/CPPS patients compared to controls. Though all these findings are hypothesis-generating, their clinical significance remains unclear and further research is required. It will likely turn out that there will not be a single causative organism but rather a dysbiosis or ecological disruption of the microbiome that impacts symptoms of some patients with CP/CPPS.

Dysfunctional Voiding/Pelvic Floor Dysfunction

Dysfunctional voiding involving abnormalities of the pelvic floor, where there is some degree of neural-motor dysregulation may suggest an underlying abnormality of pelvic neural-sensory pathways. Intuitively, this could lead to a dysfunctional state, manifested as chronic pain. Indeed, investigators have demonstrated these mechanisms. Blacklock [20, 21] showed that abnormal prostate anatomy, urethral and bladder neck abnormalities, leading to high-pressure voiding may have a role in the pathogenesis of prostatitis syndromes.

Furthermore, pelvic floor tenderness has emerged as an important target in CP/CPPS patients. Chronic prostatitis/chronic pelvic pain syndrome patients presenting with the tenderness domain through evaluation using the UPOINT phenotyping tool (see section "UPOINT Phenotyping") is common, reported by Doiron et al. [22] as being present in close to 50% of patients in a large cohort of CP/CPPS patients followed for over 15 years. It remains unclear whether the pelvic floor abnormalities lead to pelvic floor tenderness and then the chronic pain syndrome or vice versa, but it represents an important acknowledgement by those assessing CP/CPPS patients, as targeting the pelvic floor with interventions has been shown to be beneficial (see section "Management").

Immunologic Alterations

It has been well-established that CP/CPPS patients have markers of heightened immune sensitivity [23, 24]. The clinical correlation, though has not been established and a causal linkage is still lacking. The observation by various investigators [25–27] that in those with bacterial infection of the prostate who receive adequate treatment, the immunologic cascade remains activated despite eradication of the bacteria has focused research efforts in this domain.

Neural Sensitization

Men with CP/CPPS have been shown to have altered autonomic nervous system responses [28, 29], which may suggest a role of the central nervous system in the development of chronic pelvic pain. Furthermore, neural cross-sensitization continues to be investigated [30–32] as a possible mechanism for neural dysfunction and sensitization as an etiology of the establishment of chronic pain in these patients. Though a relatively recent concept and its research has mostly been in animal models to date, this concept of neural cross-sensitization represents an active area of investigation.

Psychosocial Associations

It has been well established that patients with CP/CPPS suffer from an inordinate level of psychological stress and poor mental health. What remains unclear is the causal relationship. Investigators have shown that those CP/CPPS patients who suffer worse from psychosocial perspective often suffer worse in terms of their physical symptoms and have worse quality of life. Furthermore, psychosocial factors have been shown to modulate the experience and perception of the disease. So although a causal link has yet to be established, recognizing the importance of this domain of the disease in terms of outcomes make it a desirable area to continue investigation and develop interventions.

Evaluation

As Urologists, we are first clinicians, and it is those clinical skills on which we must draw to appropriately evaluate a patient being considered with a diagnosis of prostatitis. Though the task of

evaluating a patient for a possible diagnosis of a chronic pain condition may seem daunting at times, we have the skill set as clinicians and tools necessary available to us in the outpatient clinic to evaluate and diagnose CP/CPPS.

The evaluation should begin with a thorough history. The history should be directed in a way so as to rule out other confusable diseases in the differential diagnosis. In considering a diagnosis of CP/CPPS, most patients will present with some sort of pain, localized to GU tract—perineal, penile, scrotal, suprapubic—and the onset and duration of their pain should be determined. For those with more acute symptoms, one might be considering a diagnosis of acute bacterial prostatitis, as CP/CPPS is by definition, chronic in nature.

Chronic Prostatitis Symptom Index

The National Institute of Health Chronic Prostatitis Collaborative Research Network—the same collaboration that lead to the current classification system of prostatitis—introduced a symptom index tool in 1999 [33] to aide in the evaluation of CP/CPPS patients. The Chronic Prostatitis Symptom Index (NIH-CPSI), later validated amongst a large cohort of CP/CPPS patients using a placebo-controlled randomized study [34], quantified a patient's symptom experience through a series of 9 questions, addressing 3 domains: physical symptoms of pain and urinary function are covered in the first 6 questions, while the final 3 questions inquire about QOL and the impact of the patient's symptoms more broadly.

The tool has proven useful in clinical evaluation of patients, as it can be administered within minutes to a patient in the waiting room. Though it should not be considered a stand-alone diagnostic tool, it can useful as an adjunct to an otherwise thorough history and physical, and the quantification of a patient's symptoms—pain severity categories were recently developed for the pain domain [35] with a score of 0–7 considered as mild, 8–13 moderate, and 14–21 is considered severe pain—can assess severity of symptoms and allow for patients to be followed over time. This can be helpful to assess response to treatments—the NIH-CPSI represents the most commonly used outcome measure in CP/CPPS clinical trials.

Physical Examination

Physical examination is instrumental in the evaluation of a patient being considered with a diagnosis of CP/CPPS. A focused physical examination including a pelvic exam and digital rectal exam (DRE), should be considered mandatory in their assessment. The authors prefer to perform the pelvic exam prior to DRE as those with significant prostate tenderness, a common finding amongst CP/CPPS patients, may refuse further physical examination following palpation of an exquisitely tender gland. Furthermore, it is important that prior to DRE or any manipulation of the GU tract, midstream urine specimens be collected for culture and sensitivity so as not to interfere with any attempts at bacterial localization (see section "Urine Studies").

In terms of the pelvic examination, it has been the authors' experience that pelvic examination in lithotomy position allows for a more thorough exam (but examination in the left decubitus position is acceptable) inspecting for pelvic floor muscle tenderness, spasticity and trigger points. Digital rectal exam should follow careful pelvic exam. Investigators with the Multidisciplinary Approach to the study of Chronic Pelvic Pain (MAPP) have recently described an extended GU exam [36] that may be useful in those with a confirmed CP/CPPS diagnosis to further subcategorize and phenotype CP/CPPS patients in terms of physical exam findings. Their extended exam includes a thorough assessment for tenderness of the pelvic floor, including palpation of the perineal body, levator, obturator and urogenital diaphragm muscles, an examination of extrapelvic regions including abdomen, flank and back, as well as sensory and motor function examination of the pudendal nerve. Clearly this extended exam is not practical as an assessment for all patients presenting with symptoms of CP/CPPS, but may prove useful for a patient who screens positive for pelvic floor tenderness.

Urine Studies

The goal of urine studies as part of an evaluation of patients with symptoms of CP/CPPS is to identify bacterial infection in the case of Category II patients, while the presence or absence of WBCs from prostate specific specimens can differentiate between the inflammatory (IIIA) and non-inflammatory subtype (IIIB) of Category III patients. For practical purposes, the differentiation of patients into these two subcategories has not proven helpful—that may change with the introduction of better inflammatory biomarkers.

The gold standard for bacterial localization and cytologic examination of the urine in prostatitis patients remains the classic four-glass test developed by Meares and Stamey [1]. Though the test is practically challenging for many clinicians to perform in an outpatient setting [37], and some have questioned the clinical usefulness of the finding of leukocytes in urine specimens [38, 39], the authors feel the findings may still prove helpful in selected cases and the potential role of molecularly phenotyping our patients is under study.

The first specimen in the four-glass test—voided bladder 1 (VB1)—is the initial 10 cc of urine from a collection, corresponding to the urethra. The second specimen—VB2 or midstream collection—represents urine in the bladder. The expressed prostatic secretion specimen (EPS) is collected during prostate massage while the VB3 or post prostatic massage specimen is the first 10 cc of urine collected immediately following prostatic massage and represents an alternative prostate-specific specimen. The results provide a ctyologic and bacteriologic roadmap of the lower urinary tract.

Given the practical challenges of the four-glass test, a more practical screening test introduced in 1985 [40], is a two-glass screening test, which consists of a pre- and post-prostatic massage urinary specimen. Investigators have shown the two-glass test to be as diagnostically robust as the four-glass test in terms of diagnosis, when in a study of 353 patients enrolled in the NIH Chronic Prostatitis Cohort study comparing the two-glass test to the four, the same diagnosis was achieved regardless of what urine test was used over 95% of the time [41].

Imaging and Cystoscopy

Current clinical practice guidelines do not recommend any routine imaging studies in the evaluation of a patient suspected of a diagnosis of CP/CPPS [42, 43]. Imaging's primary role in the evaluation of these patients lies in ruling out confusable disease and should be employed on a case-by-case basis.

Ultrasound can be helpful in evaluation of the prostate, determining post-void residuals in those men with obstructive voiding symptoms, and can rule out a host of confusable diseases, such as obstructed seminal vesicles, prostatic abscess, and prostatic calculi. However, it has little role in diagnosing CP/CPPS directly. Although the role of MRI in prostate cancer has grown significantly in recent years, its role in the evaluation of patients with symptoms of CP/CPPS is limited and should be considered only when specific indications are present.

Cystoscopy should similarly be reserved for those patients with specific indications—microscopic or macroscopic hematuria, treatment refractory storage or voiding symptoms, abnormal urine cytology, or for those in whom malignancy is suspected. There is currently no role for routine cystoscopy in the evaluation of CP/CPPS patients. See Fig. 17.1 for a summary of the authors' approach to evaluation of patients presenting with symptoms of CP/CPPS.

UPOINT Phenotyping

The UPOINT phenotyping tool was described in 2009 [44, 45] as a novel approach to the evaluation and management of pelvic pain patients. The tool recognized the heterogeneity of chronic pain patients and employed a more sophisticated approach, breaking patients' symptoms down into six distinct domains: *u*rinary, *p*sycho-social, *o*rgan-specific, *i*nfectious, *n*eurologic and *t*ender-

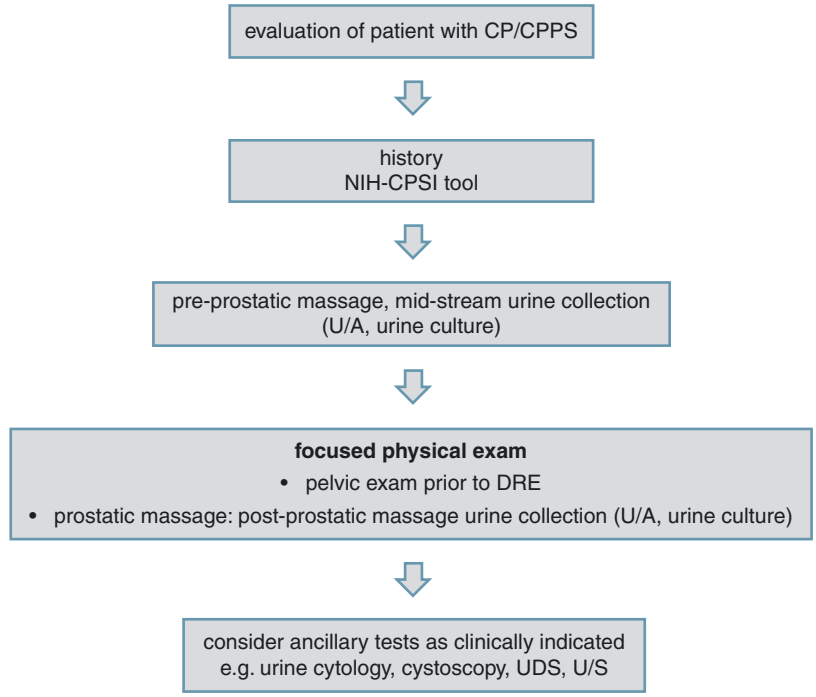

Fig. 17.1 Evaluation algorithm for patients presenting with symptoms of CP/CPPS (Adapted with permission from: *Doiron RC, Nickel JC: Evaluation of the male with chronic prostatitis/chronic pelvic pain syndrome. Can Urol Assoc J 2018: 12(6Suppl3): S152-S154*)

ness (pelvic floor tenderness). Patients may present with symptoms in only one or multiple domains. With a more nuanced approach, the tool empowered practitioners to move away from more traditional rigid disease-treatment paradigms, allowing more patient-centered evaluation and management plans based on these more personalized assessments [46].

The tool was first validated amongst female patients with interstitial cystitis/bladder pain syndrome (IC/BPS) [45] and later in male CP/CPPS patients [47]. Investigators have shown that UPOINT approaches improves patient outcomes [49] and current European [48], Canadian [43] and International [6] guidelines have endorsed a phenotypic approach to the evaluation and management of CP/CPPS patients.

Biomarkers

The search for a diagnostic or prognostic biomarker in chronic pelvic pain syndrome patients has been ongoing since the late 1990s and into the 2000s. A host of inflammatory markers have been explored including IL-1α, TNF-α, IL-6, IL-8 in men with CP/CPPS [50–52]. More recently the MAPP Research Network—a research collaborative effort from the NIH aimed at investigating the basic science and epidemiology of chronic pelvic pain in both men and women—have identified a promising panel of biomarkers for investigation in pelvic pain patients. The panel includes the following markers: matrix metalloproteinase-2 (MMP2), MMP9, neutrophil gelatinase-associated lipocalin (NGAL), the MMP9–NGAL complex, and vascular endothelial growth factor (VEGF) and VEGF receptor 1 (VEGFR1) [53].

They reported significantly higher levels of VEGF, VEGFR1, and MMP-9 in men compared to healthy controls [54], though the ability to differentiate CP/CPPS patients from healthy controls using these alterations was questionable. Meanwhile, symptom severity was shown to be associated with increased levels of biomarkers MMP-9, MMP-9/NGAL complex and VEGF-R1 [54]. Although these and previous findings suggest promise, further research will be necessary to establish thresholds for reasonable sensitivity and specificity as a diagnostic or prognostic tool and further, the clinical utility of such an approach would need to be evaluated.

Management

Though cure remains elusive, several randomized controlled trials (RCTs) and prospective studies have reported favourable results evaluating treatments for CP/CPPS. Several systematic reviews and meta-analyses have described these studies and we can use these analyses to better manage this condition [55–58]. After a long history relying on anecdotal and dogmatic treatments with poor quality evidence, the current body of literature provides a comprehensive, evidence-based guide to management.

Although the results from the clinical studies appears encouraging, major challenges remain. Many of the positive studies show modest improvements in NIH-CPSI symptoms at best, and given CP/CPPS patients represent a diverse, heterogeneous group, applying treatment algorithms to the individual in an outpatient setting can be cumbersome and frustrating. Furthermore, the quality of evidence investigating several treatment modalities is poor and requires further study. What has become clear is that success relies on thorough and comprehensive evaluation and a multimodal, multidisciplinary approach to treatment will provide the highest likelihood of success. Both practitioners and patients should focus their outcome expectations on improvement of symptoms and functioning while recognizing that cure is not always possible.

Pharmacologic Therapy

Antimicrobials

The role of antibiotic therapy for treatment of CP/CPPS remains poorly understood, given that the existing data are of low quality and are underpowered. Only two randomized studies have been completed [59, 60], both of which investigated fluoroquinolones, showing no statistical difference between the treated and untreated groups in terms of symptoms. Obviously antimicrobial therapy is the mainstay of treatment for bacterial prostatitis, but in this non-bacterial category of the syndrome, the evidence is weak. However, for antibiotic-naïve patients, the authors suggest a trial of antibiotics is reasonable particularly for those in whom a diagnosis is less clear.

α-adrenergic Blocker Therapy

Treatment of CP/CPPS with α-blockers in randomized studies has shown conflicting results. Though two large RCTs [60, 61] failed to show symptom improvement amongst CP/CPPS patients in the treatment arm, these studies may have been underpowered (particularly with respect to enrolment criteria) to show a clinical improvement. Subsequently, multiple meta-analyses [55–57] of the RCTs did in fact show improved symptoms in the treated arms.

A possible explanation for the negative result in the individual RCTs was that patients were not enrolled based on symptoms, but rather a general diagnosis of CP/CPPS. We would expect those CP/CPPS patients with significant LUTS to be the group most likely impacted by treatment with α-blocker therapy. Patients with CP/CPPS without voiding LUTS may indeed not derive benefit from a therapy aimed at relaxing pelvic floor and prostate smooth muscle—the main rationale for treatment of chronic pain patients with α-blockers in the first place.

Anti-Inflammatories

Various anti-inflammatory medications, including corticosteroids [62], COX-2 inhibitors [63, 64] pentosan polyphosphate (PPS) [65], tanezumab [66] and zafirlukast [67] have been studied in the treatment of CP/CPPS. Aside from the trials examining the COX-2 inhibitors, all trials have failed to show a significant improvement in symptoms. The COX-2 inhibitors and subsequent meta-analyses have shown modest overall symptom improvement while the clinical significance of their demonstrated improvement remains questionable.

5-α Reductase Inhibitors

Results from three prospective studies [68–70] have investigated the effect of the 5-ARI, finasteride, on treatment of CP/CPPS. Only modest improvements have been observed in the trials. However the authors will consider treatment with 5-ARIs, particularly in elderly patients with

concurrent diagnosis of benign prostatic hyperplasia (BPH).

Neuromodulators

Only one RCT [71] has investigated the role of neuromodulatory medication (pregabalin) in the treatment of CP/CPPS. Although there was no observed statistically significant improvement in the *a priori* outcome, treated patients exhibited modest improvement in pain-related symptoms. The authors' real-world observations suggest that in selected patients with more widespread pain, employing neuromodulatory medication as an option in a multimodal approach can be helpful.

Intraprostatic Botulinum Neurotoxin Type-A

There are few studies evaluating intraprostatic injection of botulinum neurotoxin type-A in the treatment of CP/CPPS. Given its ability to modulate pain and sensory pathways as well as its anti-inflammatory properties [72], there is rationale in looking at the neurotoxin as treatment for men with CP/CPPS. Indeed, it was proposed as a possible therapeutic in 2006 [73], and eventually investigators heeded the call, executing a randomized pilot study in 2015 in 60 patients with a diagnosis of CP/CPPS [74]. The study showed a significant benefit in terms of voiding symptoms and overall CPSI scores. Though encouraging, this pilot study requires confirmation in a larger randomized study, while targets of the drug beyond the prostate should be considered, including pelvic muscle trigger points.

Trigger Point Injection

As part of the physical exam (*see* section "Physical Examination") a thorough assessment of the pelvic floor, including an evaluation for trigger points is an important part of the evaluation of CP/CPPS patients. In those with identified trigger points (or pudendal nerve involvement), injection therapy directed at these areas can be helpful. Though there are few studies to support this approach [75] one retrospective study [76] did report significant improvement in overall CPSI scores in a cohort of CP/CPPS patients undergoing trigger point injection therapy. The specific technique and anesthetic cocktail was not reported in the study. Given the success of this study and anecdotal experience of the authors in this setting, further study with a rigorous exploration of technique and injection medication is warranted.

Other: Cannabis, Phytotherapies

Cannabis as a therapy for chronic pain is poorly studied in general, and indeed studies are lacking of its use the CP/CPPS population. In a survey of outpatient CP/CPPS patients, Tripp et al. reported [77] that use of the drug as therapy was common amongst patients, but benefit in terms of pain amelioration was not universally endorsed by the users. Despite this, based on personal experience with his patient population, Nickel [78] has described cannabis as important in the armamentarium for treatment of patients with CP/CPPS. In his review of cannabis use in CP/CPPS patients [78], he pointed out the non-analgesic benefits in patients experiencing difficulty with coping with their chronic pain disorder. It is important to recognize those at risk for misuse, but with appropriate follow-up and an approach to dosing, it can be a helpful adjunctive treatment [78].

Nutraceuticals cernilton [79] and quercetin [80] are phytotherpies with anti-inflammatory properties that have been investigated as treatment in CP/CPPS patients. The therapies have shown symptomatic benefit amongst CP/CPPS patients. Given the minimal side effect profile and despite the modesty of the observed benefit in these small clinical trials, the authors consider these medications reasonable options in CP/CPPS patients in the organ-specific domain of UPOINT.

Non-pharmacologic Therapy

Lifestyle Modification and Other Conservative Therapies

Treatment of all patients diagnosed with CP/CPPS should begin with conservative measures. Though there are few studies aimed at investigating lifestyle approaches [81], the authors experience has been that addressing lifestyle issues and

introducing conservative approaches to management can be an important first step in establishing a therapeutic relationship with CP/CPPS patients and many will glean at least some benefit. The first step in this process should include education about their condition—several helpful online resources exist [82]—and establishing expectations. Crucial in this initial understanding of their diagnosis is there may be no cure and their goal of treatment should not be complete resolution of their pain (although this does occur in lucky patients). Instead, the focus should be aimed at symptom management and improving their functional status.

Beyond education, simple lifestyle interventions can be addressed including heat therapy, donut cushions to avoid perineal compression, local heat treatment (heating pad applied to perineum), improving bike seats for cyclists and consideration of testicular support for those with testicular or scrotal pain as part of their pain syndrome [82]. Further conservative management includes low impact exercise such as tai-chi, walking, swimming, elliptical, etc. There is evidence of exercise as intervention in CP/CPPS from an RCT [83] of 231 patients showing significantly improved CPSI scores in the group randomized to low-impact aerobic exercise.

Pelvic Floor Physiotherapy

The importance of the pelvic floor assessment has been explored (see section "Physical Examination") while injection therapy for identified trigger points has been discussed (see section "Trigger Point Injection"). For patients suspected of pelvic floor dysfunction as a contributor of their pain syndrome, pelvic floor physiotherapy (PFPT) has emerged as a useful tool in their treatment. A PFPT protocol as treatment of men with CP/CPPS was first published by Anderson et al. [84] in their study of 138 patients, where up to 72% were moderately or markedly improved following at least 1 month of treatment protocol.

Pelvic floor physiotherapy relies on a physiotherapist experienced in PFPT methods, which may not be available to all practitioners. Furthermore, physiotherapy as a treatment may exist outside current funding mechanisms or insurance plans, thus cost can be prohibitive for some patients. Despite this, PFPT has become an important therapy as part of our multimodal treatment strategy. It may only be appropriate for men with clinically defined pelvic floor dysfunction, highlighting the importance of careful clinical evaluation of the pelvic floor in our evaluation of CP/CPPS patients.

Acupuncture

Acupuncture has shown modest improvement in CP/CPPS patient symptoms compared to sham treatment arms in several clinical trials [85–88]. Though the therapy has been shown to result in robust responses in a recent study with follow-up out to 56 weeks [88], the therapy relies on acupuncturist expertise, a factor difficult to control for in clinical trials. Furthermore, the therapy requires buy-in from the patient and is clearly not an appropriate therapy for all CP/CPPS patients. As with many CP/CPPS treatments, proper patient selection is key.

Extracorporeal Shock Wave Lithotripsy

Therapy with ESWL has been investigated as treatment for CP/CPPS patients. Though reported trials are of low quality, they consistently report improvement with significantly reduced CPSI scores in treatment arms [89–92]. Further research investigating patient phenotype most likely to benefit would be helpful in applying this therapy more broadly.

Psychological Interventions

It is now well understood that psychiatric factors play an important role in CP/CPPS patients and can significantly impact on QOL [93]. Introduction of UPOINT as a phenotyping tool helped establish psychosocial evaluation as a pillar of assessment in patients with CP/CPPS and chronic urologic pain syndromes in general. And although UPOINT phenotyping has made strides to highlight the biopsychosocial impact on CP/CPPS patients, a recent systemic review evaluating psychological factors and comorbidities in CP/CPPS has suggested it may not be enough [94].

In terms of interventions, there is a paucity of literature investigating psychological interventions for this patient group. Tripp—an experienced pain psychologist—describes an approach for the practitioner evaluating CP/CPPS patients from a psychosocial perspective in his review psychosocial correlates in urologic chronic pain patients [95]. He highlights the importance of communication and simply asking about some of the psychosocial issues patients are faced with—depression, anxiety, pain catastrophizing, the spousal relationship—as a first step to addressing this often times neglected or ignored domain [95].

A CP/CPPS-specific CBT program has been introduced [96] and its clinical impact appears to be favourable for men with treatment refractory CP/CPPS [97]. The authors' continued experience with CBT in both men and women with urologic chronic pain syndromes has revealed that these psychological strategies and interventions are less successful in male CP/CPPS patients compared with their female counterparts. They still should be considered as an option though and are most likely met with success in educated and committed patients who exhibit a positive attitude for health and well-being.

Transrectal Thermotherapy

Minimally invasive therapies such as transrectal thermotherapy and other minimally invasive thermotherapy approaches have been employed in the past [98, 99]. These approaches have largely been abandoned in current practice and are not included in treatment algorithms of current guidelines on the treatment of CP/CPPS [42, 43]. Rather, more simple, conservative, local heat therapy such as heating pads have been recommended with similar benefits.

Surgery

Surgery should only be considered for specific indications such as urethral strictures, large prostatic cysts, ejaculatory duct obstruction, symptomatic bladder neck obstruction (proven with cystoscopy and urodynamic evaluation) or other anatomical abnormalities that may be involved in the pain and urinary symptoms. Transurethral resection of the prostate (TURP) should be approached with much caution and is never indicated for a diagnosis of CP/CPPS only. TURP can be considered for older men with treatment

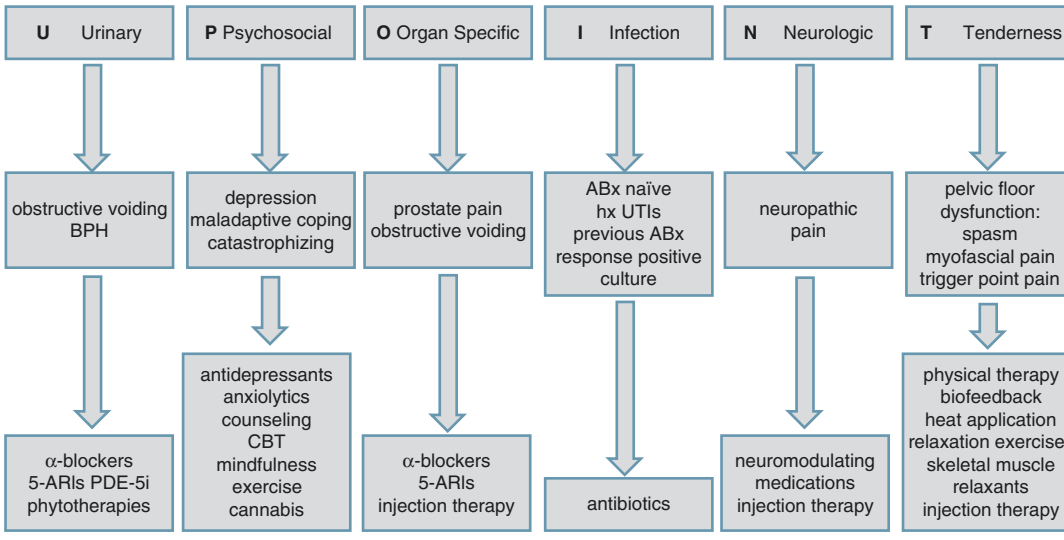

Fig. 17.2 UPOINT domain phenotyping of CP/CPPS patients and associated treatment modalities. Adapted with permission from: *Doiron RC, Nickel JC: Management of chronic prostatitis/chronic pelvic pain syndrome. Can Urol Assoc J 2018: 12(6Suppl3): S161-S163*

refractory BPH who have co-existing CP/CPPS symptoms. Radical prostatectomy (open or robotic), in the authors' opinion, should not be considered to treat the prostate and/or pelvic pain associated with CP/CPPS.

Phenotypic-Directed Approach

A personalized, multi-modal approach to treatment of patients with urologic chronic pelvic pain syndromes has, in the authors' personal and published [45–47] experience, the most beneficial for patients (see Fig. 17.2). The authors use the UPOINT clinical phenotyping tool to carefully assign clinical phenotypes to CP/CPPS patients, determining their "clinical picture." Practitioners' ability to communicate their rationale for one of the several treatment modalities that exist for CP/CPPS provides for increased patient understanding and importantly, buy-in to their treatment plan, empowering patients to involve themselves in the treatment of their own condition.

Conclusion

Management of men with CP/CPPS should not be a frustrating or discouraging experience now that we have some understanding of what is causing this condition, how to properly evaluate and categorize patients and an improved ability to employ a best-evidence approach to treatment. Applying the approach outlined in this chapter will improve patients' outcomes in terms of ameliorating the pain and urinary symptoms and quality of life.

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18 Disorders of the Scrotal Contents: Epididymoorchitis, Testicular Torsion, and Fournier's Gangrene

Sarah C. Krzastek, Parviz K. Kavoussi, and Raymond A. Costabile

Epididymoorchitis

Definition and Etiology

Orchitis is defined as inflammation of the testicle, [1] and may be due to infectious or non-infectious causes. Infectious etiologies can be bacterial or viral, and the most common offending organism varies based on patient age. In 20–40% of cases of infectious orchitis, infection spreads contiguously from the epididymis to the testis [2]. In men younger than 35 years old, the most common organisms are the sexually transmitted pathogens *C. trachomatis* and *N. gonorrhea*, whereas in prepubertal boys and men older than 35, causative bacterial organisms are more frequently derived from urinary sources including *E. coli* and *P. mirabilis* [3, 4]. Other organisms include atypical pathogens such as brucellosis (*B. melitensis*), Cryptococcus (*C. neoformans*), and tuberculosis (*M. tuberculosis*) which may originate in the upper genitourinary tract. Orchitis has also been reported in men who have been treated with intravesicular bacillus Calmette-Guerin (BCG) therapy for bladder cancer, which may present with subacute symptoms and hypoechoic lesions on ultrasound [5].

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Viral orchitis is disseminated by hematogenous route or may represent a direct viral infection via the epididymis [6]. The mumps virus is the most common viral etiology of orchitis, involves both testicles in 15–30% of cases, and can lead to oligospermia and male factor infertility if contracted after the onset of puberty [7]. Childhood vaccination is the best way to prevent mumps orchitis and its sequelae [8]. Enteroviruses and adenoviruses have been implicated in culture-negative epididymoorchitis, [9] and most recently the Zika virus has been associated with orchitis and testis damage leading to infertility in animal models [10].

Non-infectious causes of orchitis may be autoimmune, drug-induced, or ischemic. Autoimmune orchitis is associated with the presence of antisperm antibodies, and may be associated with male factor infertility. Primary autoimmune orchitis is typically asymptomatic and associated with isolated infertility, whereas secondary autoimmune orchitis usually presents with acute symptomatic orchitis and may be associated with other autoimmune diseases including rheumatoid arthritis, ulcerative colitis, systemic lupus erythematosus, and others [11]. Drug-induced orchitis has also been reported with immune checkpoint inhibitors [12]. A rare etiology of non-infectious orchitis is segmental testicular infarction. Cases of segmental testicular infarction have been reported in the setting of embolus, drug-induced or autoimmune vasculitis, sickle cell disease, polycythemia, intimal fibroplasia

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of the spermatic artery, trauma, and intermittent testicular torsion, though the majority of cases are idiopathic [13–17].

Similar to orchitis, epididymitis is defined as an inflammation of the epididymis [1] and can be caused by a variety of conditions including infection, autoimmunity, trauma, vasculitis, and other idiopathic inflammation. Acute epididymitis is thought to be due at least in part to retrograde flow of urine into the ejaculatory ducts, through the vas deferens and to the epididymis. This theory is supported by the fact that 56% of older men diagnosed with acute bacterial epididymitis have concomitant benign prostatic hyperplasia with bladder outlet obstruction, urethral stricture disease, or prostate cancer. Dysfunctional voiding has been identified in 10% of patients with non-infectious epididymitis. However, reflux of urine cannot be the isolated etiology of epididymitis, as patients who have undergone vasectomy can also present with epididymitis. This is thought to be due to congestion and inflammation from obstruction and formation of sperm granulomas which results in a local reaction surrounding nerves and vasculature [18]. Epididymitis in children is often an inflammatory process following an acute viral infection [9].

The infectious etiologies of epididymitis are similar to those of orchitis. In sexually active men younger than 35, *C. trachomatis* and *N. gonorrhoeae* are the most frequent causative organisms in acute epididymitis, whereas *E. coli* is the most common infectious pathogen in men older than 35 [19]. Other bacterial pathogens less commonly seen include *U. urealyticum*, Corynebacteria species, Mycoplasma species, and *M. polymorpha* [20], as well as *B. melitensis*, *M. tuberculosis*, and *C. neoformans* [2]. *M. tuberculosis* can cause a chronic infectious epididymitis, thought to be due to hematogenous spread [21].

Non-infectious etiologies of epididymitis may include sarcoidosis, Behcet's disease, or certain drugs. Behcet's disease is an idiopathic multiorgan vasculitis, which may result in chronic vasculitis and subsequent chronic epididymitis with periodic exacerbations [22]. Men undergoing treatment with intravesical BCG for bladder cancer may develop tuberculous epididymitis. Amiodarone has been shown to cause a drug-induced epididymitis in 11% of patients on high-dose amiodarone, due to anti-amiodarone HCL antibodies which attack the epididymal lining [22–24].

Chronic epididymitis presents with varying degrees of chronic epididymal discomfort lasting longer than 3 months, which may or may not be associated with other clinical signs of infection or inflammation [25]. It may be classified into one of three categories, including inflammatory epididymitis, obstructive epididymitis, or chronic epididymalgia. Inflammatory chronic epididymitis is defined as pain and discomfort associated with swelling, induration, or other physical exam findings consistent with inflammation, due to infectious, granulomatous, drug-induced, or idiopathic etiologies. Obstructive chronic epididymitis results from obstruction of the epididymis or vas deferens due to congenital, acquired, or iatrogenic causes. Chronic epididymalgia is defined as pain or discomfort with a normal physical exam and no identifiable etiology [25].

In the pediatric population, epididymoorchitis is a rare presentation of the acute scrotum. There are several theories for the etiology of this condition in children, including reflux of infected urine into the ejaculatory duct, chemical irritation from reflux of sterile urine, as well as direct infection or hematogenous spread of infection. Dysfunctional voiding has been identified in children with acute epididymoorchitis, with common findings including elevated post-void residuals and meatal stenosis. Epididymitis in children may also be caused by posterior urethral valves, or direct insertion of an ectopic ureter into the urethra adjacent to the ejaculatory ducts or into the seminal vesicle, resulting in reflux of urine and recurrent acute epididymitis. An ectopic ureter may also cause external compression and obstruction of the epididymis [26–29]. Evaluation of urinary tract anomalies in children with recurrent epididymoorchitis should be considered [6, 30].

Clinical Signs and Symptoms

The typical symptoms of orchitis include scrotal pain, swelling, tenderness, and skin fixation over the testicle. Relief of pain with elevation of the

testicle, or Prehn's sign, has been described in epididymoorchitis [31]. However, this is nonspecific and nondiagnostic and cannot reliably distinguish epididymoorchitis from testicular torsion.

In addition to causing pain, orchitis can cause an irreversible effect on spermatogenesis, impacting the quality and number of spermatozoa. In the acute setting, sperm concentration can decrease for 3–6 months and typically recovers spontaneously. However, some studies have shown that azoospermia may persist in 10% of patients, and oligospermia with alterations in sperm quality persists in 30% of men following an episode of orchitis [32]. In cases of chronic orchitis, lymphocytic infiltration and seminiferous tubule damage can be seen on testicular biopsies of subfertile men [33].

Symptoms of acute epididymitis can be similar to those of orchitis, and usually include pain and swelling which develops over several days. A patient may also have a positive urine culture, fever, skin erythema, leukocytosis, a reactive hydrocele, or involvement of the ipsilateral testis [18]. Patients who undergo urinary tract instrumentation or intermittent catheterization are at higher risk of developing infectious epididymitis, especially if the urine is infected at the time of instrumentation [34, 35]. As discussed above, patients with chronic epididymitis can have epididymal tenderness with or without palpable abnormalities or abnormalities on scrotal ultrasound [36]. Chronic epididymitis may be associated with erectile dysfunction, neurological diseases, and musculoskeletal complaints [18]. These men have been shown to have a greater number of sexual partners, a more frequent history of sexually transmitted disease, and have more frequent unprotected intercourse when compared to controls [25]. Children with epididymitis often present with an acute scrotum and sonographic hyperemia on Doppler, with or without leukocytosis, fever, positive urine culture, or pyuria [37].

Chronic epididymitis has been associated with male factor infertility. This has been associated with oligoasthenospermia and alterations in spermatozoa DNA integrity [38]. A recent study evaluated antisperm antibodies using the mixed antiglobulin reaction test and found significant antisperm antibodies in patients with clinical and ultrasound features suggestive of chronic epididymitis. This data further supports epididymitis as a potential underlying etiology of male factor infertility [39]. Other etiologies of epididymitis, such as sarcoidosis and tuberculosis, can lead to obstructive azoospermia via granulomatous epididymal deposits or extrinsic compression of epididymal ducts [40, 41].

Diagnostic Evaluation

A thorough history and physical examination are the most valuable aspects of the diagnostic evaluation of men with acute scrotal pain and swelling. Microscopic examination of a first-void urine specimen should be obtained. Patients younger than 35 years of age should undergo gram stain of urethral secretions and if ≥2 white blood cells (WBCs) per oil-immersion field are visualized, or if they are found to have ≥10 WBCs per high-powered field (HPF) or a positive leukocyte esterase test on microscopic examination of a first voided urine specimen, further evaluation for an infectious etiology should be pursued. To confirm the presence of *N. gonorrhea* or *C. trachomatis*, nucleic acid amplification or urine PCR may be performed. In patients older than 35 years of age, presence of leukocyte esterase or ≥10 WBCs/HPF on a first voided urine should prompt a urine gram stain and culture [42]. Children, adolescents who are not sexually active, and patients older than 35 years of age, should provide a midstream urine specimen. Patients with indwelling ureteral stents, recent anal intercourse, or recent urinary tract instrumentation should undergo urine culture. Patients found to have *N. gonorrhea* or *C. trachomatis* should undergo testing for other sexually transmitted infections including HIV and syphilis [42].

Ultrasound is utilized primarily to evaluate the acute scrotum with the intent to rule out testicular torsion, and should be reserved for patients in whom the diagnosis of epididymoorchitis is unclear. Ultrasound is not needed to make the

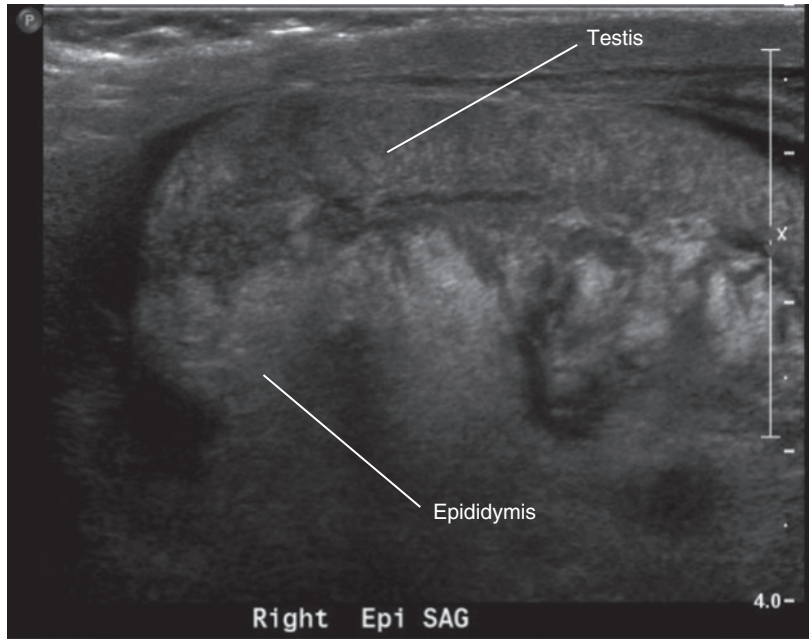

Fig. 18.1 Ultrasound image of acute epididymoorchitis. (Reprinted from Kavoussi PK, Costabile RA. Disorders of scrotal contents: orchitis, epididymitis, testicular torsion, torsion of the appendages, and Fournier's gangrene. In: Chapple CR, Steers WD, editors. Practical urology: essential principles and practice. London: Springer-Verlag; 2011)

diagnosis of epididymitis or to direct therapy [42]. In men with epididymoorchitis, ultrasound typically reveals an enlarged, hypoechoic, heterogeneous epididymis, or the epididymis may appear hyperechoic in the presence of hemorrhage. Scrotal wall thickening, reactive hydrocele, or pyocele may also be seen. Color Doppler may show increased blood flow, or hyperemia, to the epididymis or testis [43–45] (Fig. 18.1).

In patients with clinical orchitis, scrotal ultrasound should be considered as testicular malignancy has been reported to masquerade as orchitis [46], and at least 10% of men with a testicular malignancy will initially be incorrectly diagnosed with an acute inflammatory process or testicular torsion [47]. Additionally, a history of prior epididymoorchitis has been shown to be associated with an increased incidence of testicular cancer [48]. High-frequency transducer sonography (7.5–10 MHz) is considered the best imaging modality for evaluation of scrotal pathology [2]. Incidental testicular microlithiasis is a relatively common finding in up to 19% of scrotal ultrasounds performed for a variety of reasons [49], and has been hypothesized as an etiology of orchitis in some case reports [50, 51]. In the absence of risk factors for testicular malignancy, microlithiasis is not associated with an increased risk of testicular cancer [49].

Segmental testicular infarction appears as a wedge-shaped hypoechoic lesion in the testis and may be difficult to distinguish from a malignant process. Testicular tumor markers should be obtained in this setting to assist in the diagnosis. Arterial infarctions are more often visualized as wedge-shaped lesions in the upper poles of the testes, whereas venous infarctions (more commonly seen in epididymitis or germ cell tumors) appear in a more rounded pattern. Absence of vascularity on color Doppler ultrasound may also suggest infarction rather than a malignant lesion [17]. If the diagnosis remains unclear, T2-weighted and post-enhanced magnetic resonance imaging (MRI) has been shown to be useful [52].

Children with acute epididymitis and positive urine cultures should undergo renal ultrasound and VCUG. Ultrasound examination of the kidneys and urinary bladder without VCUG is adequate for children with acute epididymitis and a negative urine culture [37].

Treatment of Infectious Orchitis

The Center for Disease Control and Prevention (CDC) recommends a course of doxycycline 100 mg orally twice per day for 10 days, along with a single intramuscular injection of ceftriaxone 250 mg in young men in whom sexually transmitted infection is suspected, or a 10 day course of a fluoroquinolone in men in whom an enteric organism is suspected [19]. If sexually transmitted infection is suspected, treatment of sexual partners is recommended as well. Patients with severe bacterial orchitis should be admitted and treated with intravenous antibiotics including aminoglycosides, cephalosporins, or combinations of both, until culture results are available and sensitivity-specific adjustments can be made. Rarely, severe epididymoorchitis can result in testicular ischemia, abscess, or chronic pain, and orchiectomy may be required [53, 54].

Treatment of Acute Epididymitis

The management of epididymitis includes empiric antibiotics when infection is suspected and supportive therapies including bed rest, scrotal elevation, analgesics, and nonsteroidal anti-inflammatories. If there is concern for a sexually transmitted infection, the patient should be treated empirically for *N. gonorrhea* and *C. trachomatis* using the CDC guidelines as described above [19, 42]. Sexual partners should be treated as well to prevent pelvic inflammatory disease, infertility, and chronic pelvic pain in the female partner. Without treatment of the partner, the couple will be at risk for recurrent transmission and infections. Men older than 35 with signs of inflammation or infection on urinalysis should be treated empirically for a bacterial source [42] (Table 18.1).

If the patient appears toxic, has systemic symptoms (fevers or leukocytosis, necrotizing fasciitis, testicular infarction) or has significant comorbidities (immunosuppression, uncontrolled diabetes mellitus), then hospitalization is warranted where close observation, supportive care, parenteral antibiotics, and fluid resuscitation can be administered as needed [18, 42].

Table 18.1 Recommended workup and management of epididymitis

Age	Younger than 35	Older than 35
Lab tests	First voided urine: Microscopic exam ≥10 WBCs/hpf, positive leukocyte esterase Urethral secretions: Microscopic exam ≥2 WBCs/hpf, gram stain Urine NAAT	First voided urine: Microscopic exam ≥10 WBCs/hpf, positive leukocyte esterase
Treatment	Empiric antibiotics to cover *N. gonorrhea* and *C. trachomatis* [a]Ceftriaxone 250 mg IM ×1 and doxycycline 100 mg PO bid ×10 days	Empiric antibiotics to cover enteric bacteria Levofloxacin 500 mg qd ×10 days or ofloxacin 300 mg bid ×10 days

[a]Patients younger than 35 with allergies to penicillins or tetracyclines should be treated with levofloxacin or ofloxacin. If *N. gonorrhea* is suspected, patients need to be desensitized to penicillin on account of the high rate of fluoroquinolone resistance evolving in *N. gonorrhea* [42].

Treatment of Chronic Epididymitis

Although there is no level-one evidence for the optimal treatment of chronic epididymitis, local supportive therapy including heat, nerve blocks, analgesics, tricyclic antidepressants, anticonvulsants such as gabapentin, and anti-inflammatory drugs are common practice and may offer some relief [18]. Other treatment options implemented for chronic epididymitis include phytotherapy, anxiolytics, narcotics, acupuncture, and steroid injection therapy [25]. Despite evidence that up to 75% of patients do not have an identifiable bacterial urinary tract infection in the setting of clinical epididymitis, antibiotics are still routinely given. Antibiotic administration does not decrease the duration of symptoms or the return to full activity in men without an identifiable bacterial pathogen and are overprescribed for epididymitis [18].

Surgical Treatment of Chronic Epididymitis

Surgical treatment for chronic epididymitis is poorly studied in clinical trials, with no level-one evidence to support the use of a specific surgical procedure. We do not advocate orchiectomy for chronic epididymoorchitis, but if orchiectomy is recommended, the patient should previously have failed conservative therapy and must be apprised of the risks and benefits of orchiectomy, including the risk of incomplete pain resolution. If orchiectomy is performed for chronic pain, an inguinal approach may have the greatest chance of pain relief [55].

Epididymectomy has been performed for chronic epididymitis, with varying improvement in pain symptoms. In one study, ten patients with chronic epididymitis underwent epididymectomy for intractable symptoms. Only one of these patients had significant improvement in pain [55]. Other authors have reported higher success rates. Chronic or recurrent epididymitis and persistent unilateral epididymalgia with point tenderness to the epididymis may be reasonable indications for epididymectomy [56]. A retrospective review of 32 men who underwent epididymectomy for chronic epididymitis showed that outcomes were best when the patient had a palpable epididymal abnormality on physical examination. Men in this study without a palpable abnormality but with sonographic changes had slightly worse outcomes, and those without either a palpable abnormality or a demonstrable ultrasound abnormality did not improve with epididymectomy [36].

Subinguinal microsurgical denervation of the spermatic cord may be offered for symptomatic relief of chronic scrotal pain in select patients. This has been shown to be effective in management of post-vasectomy pain syndrome of at least 3 months duration, and appears to be most successful in patients who experience temporary relief following cord block [57]. Recently Calixte et al. performed a large retrospective review of 860 cases of targeted robotic microsurgical denervation of the spermatic cord from 2008 to 2016, with a wide variety of underlying etiologies of chronic pain including trauma, prior inguinal hernia repair or other genitourinary surgery, varicocele, post-vasectomy, or idiopathic. Post-operative pain completely resolved in 49% of cases, decreased by 50% in 34% of cases, and persisted in only 17% of cases. Pain improved both subjectively and objectively, and pain improvement increased over time, to 83% of patients reporting reduction in pain by 4 years post-operatively [58].

Treatment of Purulent and Atypical Epididymitis

The diagnosis of purulent epididymitis is made with the combination of physical examination, ultrasound evaluation, and occasionally needle aspiration of the epididymis. Epididymectomy is performed when possible and orchiectomy is performed when an abscess or necrosis of testicular tissue is present. Common causative organisms include *N. gonorrhea*, *C. trachomatis*, and *E. coli* [59].

Corticosteroids should be utilized as first-line treatment for pain and swelling in sarcoid epididymitis. In the rare case where surgical exploration is undertaken, a frozen section should be obtained to prevent an unnecessary epididymectomy or orchiectomy [40, 60]. Patients with oligospermia should consider sperm baking in the setting of sarcoid epididymitis [61]. Similarly, treatment of Behcet's disease is targeted at symptomatic relief, mainly with corticosteroids [62].

Treatment of epididymal tuberculosis should consist of a 6 month course of a standard antituberculosis therapy, with 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin. In areas of high isoniazid resistance, ethambutol may be added to the continuation phase [63]. Men with BCG induced epididymitis are treated with isoniazid and rifampin, with or without pyrazinamide [64].

Brucellosis caused by infection with *B. melitensis* may result in epididymoorchitis in ~9% of cases [65, 66]. These patients should be treated with doxycycline and rifampin for 60 days [66, 67].

Epididymitis in children is often secondary to viral infections and should be treated conservatively with ice packs and analgesics [68].

Amiodarone-induced epididymitis is managed by lowering the dose of Amiodarone.

Treatment of Noninfectious Epididymoorchitis

Conservative therapy for patients with noninfectious epididymoorchitis includes nerve blocks, analgesics, scrotal elevation, bed rest, and nonsteroidal anti-inflammatory medications [18].

Segmental testicular infarction may be managed conservatively. If tumor markers are negative and clinical suspicion for malignancy is low, it is reasonable to follow these patients with serial exams and imaging until the diagnosis becomes clear. In most cases, the infarcted lesion will gradually regress over 6–12 weeks [69]. However, in cases where it remains difficult to distinguish a segmental testicular infarction from a malignant lesion, radical orchiectomy should be pursued [17].

Testicular Torsion and Torsion of the Testicular and Epididymal Appendages

Differential Diagnosis of the Acute Scrotum

The differential diagnosis of the acute scrotum is broad and primarily includes acute epididymoorchitis, testicular torsion, and torsion of the testicular appendages. Alternative etiologies of acute scrotal pain may include testicular or paratesticular tumors, symptomatic distal ureterolithiasis, scrotal trauma, varicocele, incarcerated inguinal hernia, hyperactive cremaster muscle reflex with resultant testicular retraction, or other genital infections. A thorough history and physical examination is the key to making an accurate diagnosis. Leukocytosis or pyuria may or may not aid with differentiating the diagnosis. Additionally, while color Doppler ultrasound has traditionally been thought to have the highest sensitivity and specificity for differentiating testicular torsion from other etiologies of the acute scrotum, studies have shown that torsion is possible in the setting of preserved blood flow [70–72]. While Doppler ultrasound is not required if the clinical history and physical exam are consistent with a diagnosis of testicular torsion, any asymmetry or decrease in flow on Doppler ultrasound should prompt emergent surgical exploration.

The sensitivity of scrotal ultrasound to diagnose scrotal pathology is high, and as such, it is commonly used by primary care and emergency medicine physicians as well as urologists as an extension of the physical exam to confirm a diagnosis or rule out more serious pathology which may require surgical intervention. Kashanian et al. recently evaluated 7668 scrotal ultrasounds performed over a 12 year time period for scrotal or testicular pain and found that 80% of these ultrasounds revealed a normal or benign finding. A finding necessitating surgical intervention (including suspicious intratesticular lesion, testicular torsion, scrotal abscess, or infiltrative testicular process) was identified in only 2.2% of scrotal ultrasounds, with less than 1% of ultrasounds revealing an intratesticular lesion concerning for malignancy. The authors concluded that while scrotal ultrasound may identify benign scrotal pathology, the likelihood of finding serious or concerning medical pathology on ultrasound performed for pain alone remains low [73].

Clinical Signs, Symptoms, and Presentation of Torsion of the Testis and Appendages

Testicular torsion can be seen in patients of any age, but most commonly occurs in males between the ages of 12 and 18. Testicular torsion occurs in 3.8 per 100,000 men younger than 18 years annually, and accounts for 10–15% of cases of acute scrotum in children [74]. The incidence of bilateral testicular torsion (synchronous or metachronous) is 2% [75].

The most consistent presentation of testicular torsion is acute onset of severe testicular pain, which may be accompanied by nausea, vomiting, and even low grade fever. The hemiscrotum of

the affected side is typically swollen, tender, and inflamed on physical examination, with a high-riding testis and absence of the cremasteric reflex. Barbosa et al. developed a validated scoring system, the "TWIST" score, using testicular swelling, firm testicle, absent cremasteric reflex, nausea/vomiting, and high-riding testis to determine the likelihood of a diagnosis of testicular torsion based on physical exam. Cutoff scores of two for low-risk and five for high-risk of testicular torsion were found to have 100% negative and positive predictive values with specificity of 97% and sensitivity of 54% [76].

Torsion of the spermatic cord can occur within the tunica vaginalis (intravaginal), or along with the tunica vaginalis (extravaginal). 10% of cases are familial, and 80% of intravaginal torsions are associated with a "bell-clapper" deformity, in which the tunica vaginalis inserts high in the scrotum, preventing full descent of the testis and allowing the testis and spermatic cord to rotate freely within the tunica vaginalis [74]. In the case of extravaginal torsion, the tunica vaginalis is incompletely tethered to the scrotal wall, which allows the spermatic cord and tunica vaginalis to rotate together within the scrotum [77] (Fig. 18.2).

On physical examination, the torqued testicle is tender and high-riding with a horizontal lie. Irreversible ischemia begins at 6 h after the initiation of torsion, or from the onset of symptoms depending on the variability in testicular blood flow following torsion [78]. Torsion of the spermatic cord results in testicular ischemia by causing venous engorgement, edema, and hemorrhage which result in arterial compromise. Resolution of the torsion may subject the testis to ischemia-reperfusion injury [79].

Intermittent testicular torsion is episodic twisting of the spermatic cord with spontaneous resolution [80]. Patients in the appropriate age group with acute scrotal pain and rapid resolution should be suspected of having intermittent torsion, and should be treated with elective bilateral orchiopexy [81]. Clinicians must also be aware of the possibility of testicular torsion in patients who have had prior orchiopexy, as such cases have been reported [82]. The risk of testicular torsion is also increased in the presence of cryptorchidism, with 73% of cases occurring on the left side. These patients present with an empty ipsilateral hemiscrotum, a tender, firm mass in the groin, and inguinal swelling and erythema.

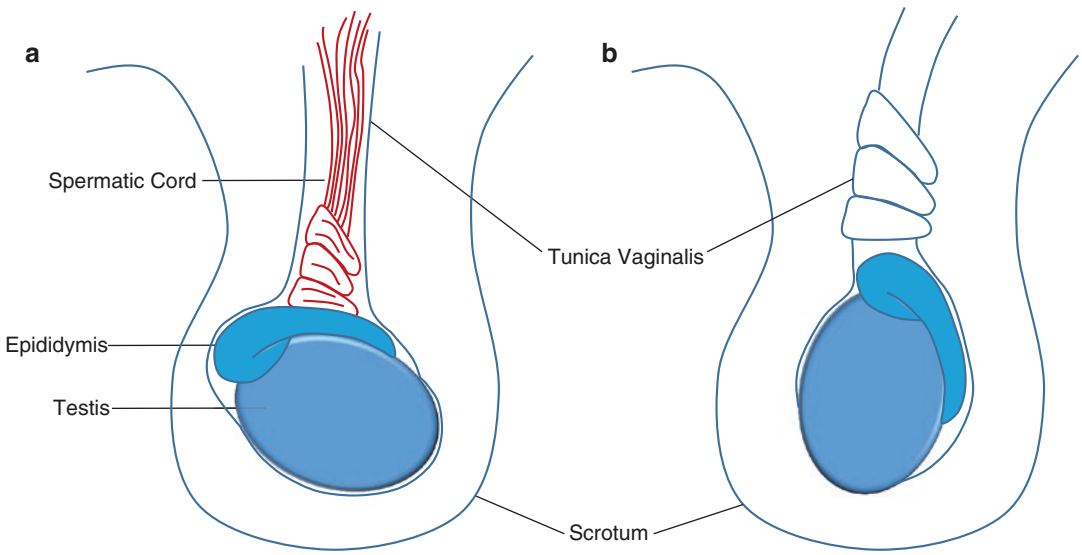

Fig. 18.2 Testicular torsion. (**a**) Intravaginal torsion, "Bell-clapper" deformity. (**b**) Extravaginal torsion. (Modified from Kavoussi PK, Costabile RA. Disorders of scrotal contents: orchitis, epididymitis, testicular torsion, torsion of the appendages, and Fournier's gangrene. In: Chapple CR, Steers WD, editors. Practical urology: essential principles and practice. London: Springer-Verlag; 2011.)

Doppler ultrasound is useful to confirm the diagnosis. The rates of surgical testicular salvage in this setting is poor due to delay in presentation, diagnosis, or referral to a urologist [83].

Extravaginal testicular torsion occurs in the perinatal period, is occasionally bilateral, and presents in neonates as scrotal swelling with discoloration and a firm, painless mass in the scrotum [84, 85]. Intrauterine testicular torsion is estimated to occur in 6 per 100,000 births and may result in "vanishing testes" as the infarcted testis is resorbed [86]. In neonates, the testis is usually necrotic from infarction at the time of birth. Risk of torsion is increased with complicated pregnancies and vaginal delivery [87]. The sonographic appearance demonstrates an enlarged heterogeneous testicle without color Doppler flow to the testis or spermatic cord, skin thickening, and an ipsilateral hydrocele [86, 88].

Torsion of the testicular or epididymal appendages should be high on the differential diagnosis for the patient presenting with an acute scrotum. Of all appendiceal torsions, 91–95% involve the appendix testis, and are most commonly seen in boys between seven and 14 years of age [89]. The clinical presentation of torsion of the appendages is similar to that of testicular torsion, but often with a more gradual onset of pain. On physical examination there is typically a palpable small, firm nodule on the superior portion of the testis, which may be associated with the classic "blue dot sign" with bluish discoloration of the appendix visible through the overlying skin [90]. The cremasteric reflex is typically intact. Ultrasound may be useful in cases without a clear diagnosis based on clinical findings, and torsion of the appendix testis can occasionally be identified on ultrasound [43]. Torqued testicular appendages should be managed conservatively with analgesics. The pain typically resolves in 2–3 days with atrophy and occasional calcification of the appendage.

Treatment of Spermatic Cord Torsion

The ability to salvage a torqued testicle depends on the duration and degree of torsion. A testis will only survive 30 minutes of complete ischemia. In the clinical setting, the testis usually maintains some degree of blood flow via the microvasculature, independent of the degree of torsion. If the diagnosis is made and intervention occurs within the first 6 h after the onset of symptoms, there is a nearly 100% testicular salvage rate. The salvage rate drops to 50% after 12 h, and decreases to <10% after 24 h [77]. The variable salvage rate, and variable rate of return of blood flow after repair, depends on the variation in the microvascular perfusion of the individual testis [90]. Older age is a significant predictable risk factor for orchiectomy in patients between the ages of one and 25 with testicular torsion, due primarily to the delay in seeking medical attention in older males [91].

On presentation with history and physical exam findings consistent with testicular torsion, manual detorsion may be attempted as a bridge to definitive surgical intervention. Manual detorsion is traditionally taught as external rotation of the torqued testis, likened to "opening a book," with confirmation of intraparenchymal blood flow following detorsion. However, one should bear in mind that the spermatic cord does not always twist in the expected direction, so attempts at manual detorsion with external rotation may be ineffective and may cause further pain or degree of torsion.

Successful manual detorsion is often accompanied by significant and instantaneous relief of symptoms [92]. In a series of 133 patients, manual detorsion was attempted in 57% and was successful in 95% of these patients. Testicular salvage at the time of surgical exploration was 97% in patients who underwent successful manual detorsion, as compared to 75% in patients in whom detorsion was not attempted or was unsuccessful [93]. Manual detorsion in place of surgical exploration has recently gained interest. Demirbas et al. retrospectively evaluated 57 patients who presented with testicular torsion. Twenty patients underwent successful manual detorsion, and 28 patients in whom manual detorsion was not attempted (n = 22) or was unsuccessful (n = 6) underwent emergent exploration. Elective orchiopexy was performed fol-

lowing manual detorsion after a median of 10 days. No episodes of retorsion occurred in patients awaiting elective orchiopexy following manual detorsion. Median follow up was 22 months, and none of the 20 patients who underwent successful manual detorsion developed testicular atrophy, nor did the six patients who underwent emergent orchiopexy following unsuccessful manual detorsion, suggesting that manual detorsion may be an acceptable alternative to emergent orchiopexy [94]. However, immediate surgical exploration and bilateral orchiopexy with orchiectomy of an infarcted testicle remains the standard of care [95].

The rate of testicular atrophy following orchiopexy at the time of exploration for testicular torsion has been found to range from 25 to 50% [96, 97] and depends primarily on the duration of symptoms, with favorable outcomes in men with less than 6–8 h, as well as degree of torsion less than 360° [96]. Several groups have suggested performing an incision of the tunica albuginea and placement of a tunica vaginalis flap at the time of orchiopexy to relieve elevated testicular compartment pressures resulting from free radical damage and edema following testicular reperfusion after detorsion. While this technique has shown promise, additional research should be done before implementing this technique into standard practice [77].

Patients with intermittent testicular torsion should undergo elective bilateral orchiopexy. If untreated, these patients are at risk for developing an episode of complete testicular torsion with subsequent infarction and testicular loss [80]. Ninety-seven percent of patients treated with prophylactic bilateral orchiopexy have complete resolution of their symptoms with a high likelihood of preventing future infarction [81].

The rates of testicular salvage in the setting of extravaginal torsion are extremely low [77]. In a survey of 121 pediatric urologists, timing and surgical approach in the management of prenatal torsion was variable, but postnatal torsion was treated as a surgical emergency [98]. The risk of testicular loss should be balanced with the risk of anesthesia in neonates with testicular torsion. Testicles found to have extravaginal torsion at the time of delivery are never salvageable, so it may be argued that emergency exploration is not indicated. However, there is occasionally a chance of testicular salvage in neonatal torsions first identified between birth and 1 month of age with emergent exploration [87], and some authors advocate emergent exploration and contralateral orchiopexy in all newborns with intrauterine torsion to decrease the risk of anorchia in the setting of contralateral torsion [99].

Fertility can be adversely affected in men who have had testicular torsion, but the mechanism of this remains unclear. In animal studies, torsion for 1 h at 720° induces ischemia sufficient to disrupt the seminiferous epithelium with permanent disruption in spermatogenesis due to induction of germ cell-specific apoptosis despite torsion reduction at 1 h. Torsion sufficient to cause aspermatogenesis in animal models has led to long-term reductions in testosterone production [90]. While it has been shown that sperm motility and morphology can be impaired following torsion in humans, the patient's age at the time of torsion, ischemia time, and treatment for torsion do not appear to correlate with antisperm antibody levels, semen parameters, or long-term endocrine profile [77, 100]. Additionally, a recent study of 63 couples in which the male had undergone orchiopexy ($n = 41$) or orchiectomy ($n = 22$) for testicular torsion showed equivalent rates of pregnancy and time to pregnancy as compared to the general population [101].

Fournier's Gangrene

Definition and Etiology

Fournier's gangrene is a polymicrobial necrotizing fasciitis involving the scrotum, genitalia, perineum and perirectal areas which may extend to the lower abdominal wall or thighs. Inflammation and edema can cause subcutaneous arterial obliterative endarteritis which leads to further perifascial dissection and spread of the bacteria with progression of soft tissue necrosis. This is a urologic emergency with a rapidly progressive and possibly fatal course if left untreated,

with studies reporting a rate of fascial necrosis as high as 2–3 cm per hour, and mortality rate of 20–40% and ranging as high as 88%.

While the disease was originally considered to be idiopathic, less than 25% of cases are now considered idiopathic in origin [102]. The majority of cases arise from local dermatologic, anorectal (perforated appendicitis, diverticulitis, colorectal cancers, perirectal abscess, anal fissures, hemorrhoidectomy) or genitourinary infections (renal abscess, urethral stone or stricture, recent instrumentation, epididymitis, neurogenic bladder, chronic urinary tract infections, genital trauma) [103, 104].

Risk Factors

The majority of patients are over 50 years old, with a male to female ratio of 10 to 1 [104]. The most common predisposing risk factor in men and women for development of Fournier's gangrene is diabetes mellitus. This is thought to be due to immunosuppression and small vessel disease, which is exacerbated by poor hygiene [102]. Alcoholism is also commonly associated with the disease. Additional risk factors include chronic liver or kidney disease, cardiac disorders, advanced age, malignancy, and chemotherapy, as well as HIV and other immunosuppressed states [103–105]. On multivariate analysis, increasing age, high hospital volume, Medicaid insurance status, and presence of renal failure or coagulopathy were associated with increased risk of mortality [106].

Anatomic Barriers to the Spread of Infection in the Genitalia and Perineum

Anatomic barriers to the spread of necrotizing fasciitis include the dartos fascia of the penis and scrotum, Colles' fascia of the perineum, and Scarpa's fascia of the anterior abdominal wall (Fig. 18.3). The testes tend to be spared by this disease process due to the separate blood supply from the testicular arteries which arise from the aorta, as opposed to the branches of the pudendal arteries which supply the scrotal skin or the inferior epigastric and deep circumflex iliac arteries which supply the lower abdominal wall skin. Orchiectomy is rarely required, but if the testicle is found to be necrotic this suggests infectious spread to the retroperitoneum [104, 107]. Similarly, the corpora cavernosum and spongiosum tend to be spared, though thrombosis of the corpora has been reported [108].

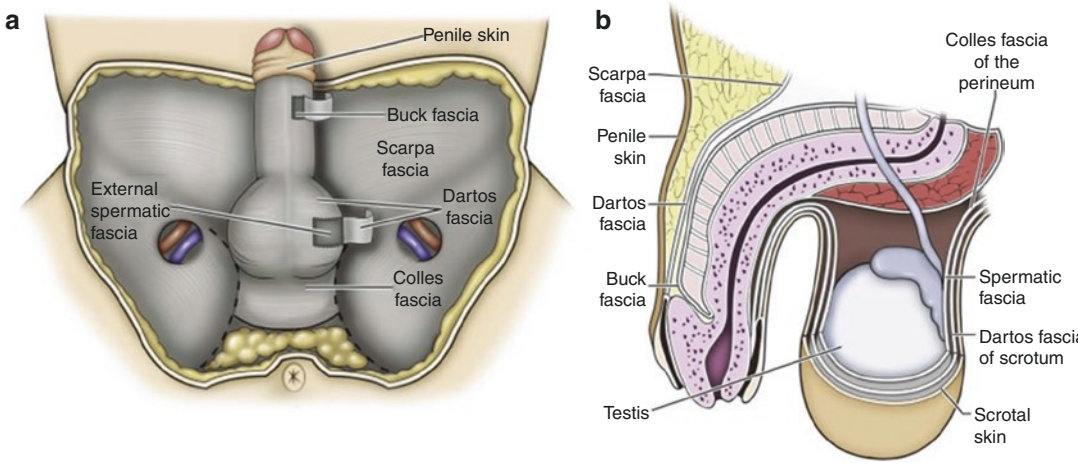

Fig. 18.3 Anatomic fascial layers. (**a**) Lithotomy view. (**b**) Sagittal view. (Reprinted from Celigoj FA, Costabile RA. Surgery of the Scrotum and Seminal Vesicles. In: Wein AJ et al, editors. Campbell-Walsh Urology. Philadelphia: Elsevier, Inc.; 2016)

Infectious Organisms Associated with Fournier's Gangrene

Fournier's gangrene is typically a polymicrobial disease, involving three or more anaerobic and aerobic bacteria which have a synergistic effect and induce rapid spread. The most common aerobic organisms include *E. coli*, *Klebsiella*, and *S. aureus*. Additional common microbes include *Proteus*, *Pseudomonas*, *Streptococcus*, *C. perfringens*, *Bacteroides* and *Enterococcus* [104]. Candidal infections have also been reported in immunocompromised patients [109].

Recent work has demonstrated the emergence of multi-drug resistant organisms as causative agents of Fournier's gangrene. A study of 59 cases over a 10 year period of time showed that multi-drug resistant organisms were the causative agent in 21% of patients, and most commonly included MRSA and ESBL *E. coli* [110]. Additionally, these multi-drug resistant organisms may be found in monomicrobial infections [109].

Clinical Signs and Symptoms

Typical symptoms of Fournier's gangrene include scrotal swelling, pain, and fever. The average duration of symptoms prior to seeking medical care is 3–5 days. Eighty-four percent of patients with Fournier's gangrene have bilateral scrotal involvement [111]. There is typically erythema and crepitus in the area of necrosis. There may be visible areas of gangrene or skin blistering as well. Nearly 10% of patients are unconscious on presentation. Sepsis can be seen in 43% of patients with Fournier's gangrene, and there is a 50% mortality rate among patients with sepsis. Necrotizing fasciitis typically has a rapid onset with a fulminant course, although less commonly it can have an insidious onset and slower progression [112]. Secondary complications of Fournier's that portend a higher risk for mortality are respiratory failure, renal failure, septic shock, hepatic failure, and disseminated intravascular coagulopathy [113].

Diagnostic Evaluation

Diagnostic evaluation should begin with a thorough history and physical examination. Diagnostic imaging can be helpful when the diagnosis is not clear from the clinical evaluation. Subcutaneous gas in the scrotum is the most useful radiological finding to aid in the diagnosis, and may be identified in 18–62% of cases by plain film, scrotal ultrasound, or computed tomography (CT) [114]. CT may also be helpful in identifying asymmetric fascial thickening, subcutaneous emphysema, and fluid or abscess formation, as well as defining the extent of disease [115, 116].

The Fournier's Gangrene Severity Index has been developed and validated to assist with identifying factors that may influence survival. If the overall severity score is less than 9, the patient has a 96% chance of survival; whereas if the score is 9 or greater, the mortality rate increases to 46%. Prognostic factors included in the Fournier's severity index include temperature, heart rate, serum sodium, serum potassium, serum creatinine, hematocrit, white blood cell count, and serum bicarbonate [117]. Identification of prognostic factors may be useful for counseling and allocation of resources [118].

A simplified index has been proposed using creatinine, hematocrit, and potassium, and was found to have a sensitivity of 87% and specificity of 77% in predicting mortality, with demonstration of non-inferiority compared to the Fournier's Gangrene Severity Index. [119] Additional studies have suggested that platelet count at presentation, and platelet count, mean platelet volume, and neutrophil-to-lymphocyte ratio following initial debridement and at discharge, blood urea nitrogen (BUN) levels, serum magnesium levels, and hemoglobin A1c > 7 may also affect mortality [120–123].

Treatment

Treatment of Fournier's gangrene should include emergent radical surgical debridement and intravenous broad spectrum antibiotics. When culture

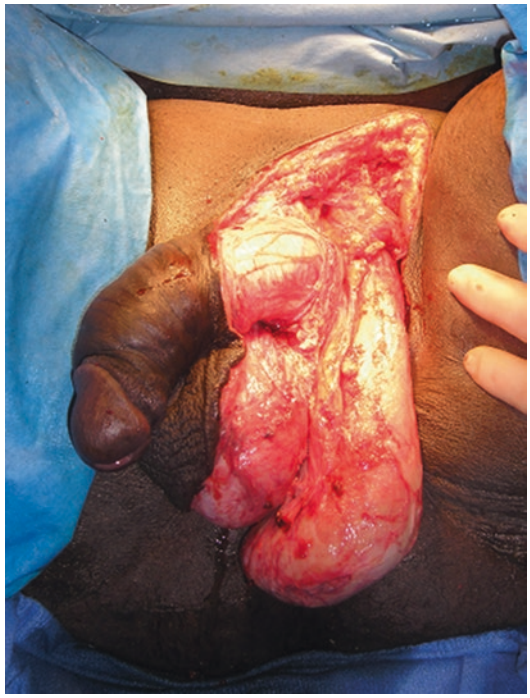

Fig. 18.4 Wide local debridement of Fournier's gangrene. (Reprinted from Kavoussi PK, Costabile RA. Disorders of scrotal contents: orchitis, epididymitis, testicular torsion, torsion of the appendages, and Fournier's gangrene. In: Chapple CR, Steers WD, editors. Practical urology: essential principles and practice. London: Springer-Verlag; 2011.)

results are available, the antibiotics can be tailored to the organisms based on sensitivities. Treatment should be performed expeditiously and aggressively, as Fournier's gangrene is a life-threatening process. All nonviable and necrotic tissue must be aggressively excised (Fig. 18.4).

Transfer of patients with necrotizing soft tissue infections to a tertiary care center may be considered as studies have shown that transfer from one hospital to another does not significantly affect morbidity or mortality [124]. However, this is not required and should not delay rapid surgical debridement. Empiric triple-therapy broad-spectrum intravenous antibiotics should be administered to cover possible bacterial organisms. This typically consists of penicillin or a third-generation cephalosporin, an aminoglycoside, and metronidazole or clindamycin. Vancomycin should be given in cases of suspected MRSA. Amphotericin B should be added if fungal infection is suspected [104]. Aggressive fluid resuscitation is required, and adequate nutrition with early enteral feeding when possible is important for wound healing.

Repeat surgical exploration should be performed in 24–48 h to ensure source control. The patient may require multiple debridements to obtain source control, with two to three operations being the average. During the period of acute debridement, the wound may be managed with local wound care. If the source of the infection is anorectal, or the wound is contaminated with stool, fecal diversion should be performed. However, fecal diversion in the form of surgical colostomy may not be mandatory and may be associated with high morbidity [125]. Similarly, patients may require urinary diversion with suprapubic cystotomy, especially in the setting of underlying urinary tract infection.

Once source control is obtained, the wound may be closed primarily if possible, or may heal by secondary intention. A flap or graft is rarely required for completion of the wound closure, even for large wounds [126]. However, fasciocutaneous rotational thigh flaps may be used for coverage with good cosmetic results [111, 127]. Wound closure is performed as soon as there is no evidence of infection of remaining necrotic tissue, and there is a viable tissue bed that will allow for reapproximation or grafting [112]. Patients with less than 50% scrotal skin loss can almost always have the wound closed primarily without major difficulty. A scrotal advancement flap may be utilized for small scrotal defects that cannot be closed without tension [128]. The testes may be placed in thigh pouches until the time of definitive reconstruction in cases with major scrotal skin loss [129]. Vacuum-assisted closure devices have been utilized to help these complex wounds heal after wide excision and debridement. This technique has been shown to be as effective as conventional wound care in healing wounds. These patients also require fewer dressing changes, have less pain, fewer skipped meals, and greater mobility [130]. Vacuum-assisted closure devices may have difficulty

maintaining a seal over the complex groin anatomy, and several techniques including partial wound closure and *in situ* foam fixation have been employed to facilitate formation of a seal to maximize the benefits obtained from these devices [131].

In addition to the traditional treatment regimen of radical debridement, fluid resuscitation, and broad-spectrum antibiotics, investigational therapies have been utilized in an attempt to minimize the morbidity and mortality of this devastating disease. Intravenous polyspecific immunoglobulin G (IVIG) has been used as an adjunct therapy to surgical debridement and broad spectrum antibiotics to treat necrotizing soft tissue infections in several centers. However, a recent prospective trial assessing the effects of IVIG on self-reported physical functioning in an ICU setting at 6 months showed no difference as compared to placebo [132]. Adjuvant hyperbaric oxygen therapy may reduce the number of surgical debridements required, accelerate wound healing, and may improve survival [133, 134]. Unfortunately, this technology is costly and only available in select centers. Aggressive surgical debridement, resuscitation, and antibiotic use remain the standard of care for management of Fournier's gangrene.

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19 Overview of the Evaluation of Lower Urinary Tract Dysfunction (LUTD)

Annabelle Auble and Jean-Nicolas Cornu

Introduction

The vesicourethral unit comprises the bladder and urethra, working in co-operation to store and void urine. To obtain this physiological balance, a fully functional bladder (detrusor, urothelium), a normal urinary sphincter and a healthy urethra are necessary. A perfect coordination driven by the central and peripheral nervous system is also required.

Lower urinary tract dysfunction (LUTD) is highly prevalent in the population, as underlying causes increase with age [1, 2]. Disorders of the storage phase include all symptoms related to failure of the bladder to keep urine stored quietly, until its maximum capacity: those include frequency, urgency, incontinence, abnormal sensations of filling [3]. Disorders of the voiding phase include all symptoms related to a failure of obtaining correct, complete, continuous, spontaneous, on-demand micturition (whatever the underlying pathophysiology) [3]. Storage and voiding symptoms may be associated in the same patient. Post-micturition symptoms are usually associated with voiding phases issues. A global classification of symptoms is presented hereunder (Table 19.1).

Symptoms related to LUTD, named Lower Urinary Tract Symptoms (LUTS), are spontaneously identified as related to the urinary tract by the patient and can dramatically impact quality of life. A complete clinical evaluation (especially when the patient is seen for the first time or referred for an expert advice) is necessary to (1) correctly identify and label the LUTS, (2) evaluate the symptom intensity, bother and quality of life, (3) suspect the potential aetiology (LUTD), (4) rule out complications, red flags and emergency and finally (5) guide further investigations and propose an approach for LUTD management [4].

The present chapter presents the basic, standard and advanced aspects of practical clinical evaluation of LUTS through patient interview, clinical examination and clinical tests during a urological visit. Underlying clinical concepts, pathophysiology, specialized investigations and therapeutic options are discussed elsewhere.

First, clinical characterisation of each symptom and directly related clinical tests are presented. Then, general items of clinical evaluation (questionnaires, patient history, general tests, biology, imaging and urodynamics) are detailed with their potential roles and indications in LUTS evaluation.

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Identification and Specific Evaluation of Storage and Voiding Symptoms

Storage Phase

The bladder is storing urine 99% of the time. During this phase, the bladder is filled with urine brought by the ureters. Urine transport is possible because of antegrade peristaltic waves, pushing the urine is the bladder. Decompensation may occur when bladder pressure exceeds 40 cm of water [5]. Thus, a correct compliance of the bladder wall is necessary for an adequate bladder filling without pressure increase. Compliance is calculated by dividing the volume variation (δV) by the change in detrusor pressure (δPdet). It is expressed in ml/cm H_2O.

During filling, sensations through bladder afferences have to be normal (first sensation of filling, first desire to void, strong desire to void), non-painful, progressive and happening for physiological volumes.

Urine is also stored during the night, normally avoiding the symptom of being awaken by the need to pass urine (defining nocturia).

Lastly, the urine has to be kept inside the bladder, without involuntary loss of urine outside micturition (defining urinary incontinence) [6], or during the night (defining nocturnal enuresis).

Evaluation of Storage Symptoms during Patient Interview

Storage symptoms, including nocturia, represent the majority of patient complaints [7]. Those symptoms are also the most bothersome and impacting very much quality of life. They are identified during patient interview.

Lower urinary tract symptoms have been defined by the International Continence Society (ICS) in 2002 with continuous updates [2].The use of this terminology is now consensual worldwide and is detailed in the following table (Table 19.2). Labelling the underlying dysfunction often requires further investigation (Table 19.2).

Table 19.1 Lower urinary tract systems

Storage symptoms	Voiding symptoms	Post void symptoms
Frequency	Slow/splitting/intermittent stream	Feeling of incomplete emptying
Urgency	Hesitancy	Post-micturition dribble
Incontinence	Straining	
Increased/reduced/ absent/painful bladder sensation	Terminal dribble	
Nocturia		

Table 19.2 Lower urinary tract symptom terminology

Storage symptoms	
Increased daytime frequency	The complaint by the patient who considers that he/she voids too often by day (term is equivalent to pollakiuria used in many countries).
Nocturia	The complaint that the patient has to wake at night one or more times to void.
Urgency	A sudden compelling desire to pass urine which is difficult to defer.
Urinary incontinence (UI)	Any involuntary leakage of urine
Stress urinary incontinence (SUI)	Involuntary leakage on effort or exertion, or coughing or sneezing
Urge(ncy) urinary incontinence (UUI)	Involuntary leakage accompanied by or immediately preceded by urgency
Mixed urinary incontinence (MUI)	Involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing
Enuresis	Any involuntary loss of urine

Table 19.2 (continued)

Storage symptoms	
Increased daytime frequency	The complaint by the patient who considers that he/she voids too often by day (term is equivalent to pollakiuria used in many countries).
Nocturnal enuresis	Loss of urine occurring during sleep (involuntary symptom as opposed to nocturia which is a voluntary symptom)
Continuous urinary incontinence	Continuous leakage of urine
Other types of urinary incontinence	May be situational, for example incontinence during sexual intercourse, or giggle incontinence
Bladder sensations during storage phase	
Normal bladder sensation	Aware of bladder filling and increased sensation up to a strong desire to void
Increased bladder sensation	Aware of an early and persistent desire to void
Reduced bladder sensation	Aware of bladder filling but does not feel a definite desire to void
Absent bladder sensation	No awareness of bladder filling or desire to void
Nonspecific bladder sensation	No specific bladder sensation but may perceive bladder filling as abdominal fullness, or spasticity (most frequently seen in neurological patients)
Voiding symptoms	
Slow stream	The perception of reduced urine flow, usually compared to previous performance or in comparison to others
Splitting or spraying	Description of the urine stream
Hesitancy	Difficulty in initiating micturition, resulting in a delay in the onset of voiding after the individual is ready to pass urine
Intermittent stream (intermittency)	Urine flow which stops and starts, on one or more occasions, during micturition
Straining	The muscular effort used to either initiate, maintain, or improve the urinary stream
Terminal dribbling	A prolonged final part of micturition, where the flow has slowed to a trickle/dribble
Post micturition symptoms	
Felling of incomplete emptying	A feeling experienced by the individual after passing urine
Post micturition dribble	The involuntary loss of urine immediately after an individual has finished passing urine, usually after leaving the toilet in men or after rising from the toilet in women
Other symptoms	
Symptoms associated with sexual intercourse	e.g. dyspareunia, vaginal dryness, and incontinence (should be described as fully as possible—It is helpful to define urine leakage as: During penetration, during intercourse, or at orgasm)
Symptoms associated with pelvic organ prolapse	e.g. “something coming down,” low backache, vaginal bulging sensation, and dragging sensation (may need to digitally replace the prolapse in order to defecate or micturate)
Genital and lower urinary tract pain	Pain, discomfort and pressure may be related to bladder filling or voiding or may be felt after micturition, or even be continuous. The terms “strangury,” “bladder spasm,” and “dysuria” are difficult to define and of uncertain meeting and should not be used, unless a precise meaning is stated. Dysuria literally means “abnormal urination.” however, it is often incorrectly used to describe the stinging/ burning sensation characteristic of an urinary infection
Painful bladder syndrome symptoms	
Bladder pain syndrome/ painful bladder syndrome/ interstitial cystitis (BPS/ PBS/IC)	Suprapubic pain related to bladder filling and associated with other lower urinary tract symptoms, usually increased frequency (but no urgency) (diagnosed only in the absence of UTI or other obvious pathology). This is a specific diagnosis usually confirmed by typical cystoscopic and histological features

This terminology refers specifically to symptoms elicited in a history; subtly different definitions are in use in other specific scenarios, for example when using frequency/volume charts. More information on all of the terminology is available in "The Standardisation of Terminology in Lower Urinary Tract Function Report."

Once symptoms have been identified, further clinical assessment is necessary to characterize the clinical picture.

Urgency, as the cornerstone of overactive bladder syndrome, is characterized by a sudden compel to pass urine that is difficult to defer. It has to be differentiated from pain, or normal filling sensation (strong desire to void) when the bladder is full. Many ways have been described to ask the right question to the patient and not be too suggestive to avoid overdiagnosis, and try to quantify the intensity of the symptom [8], including standardized questionnaires (see hereunder). Circumstances of urgency—if any—must be specified by the patient, especially precipitating factors (shower, hands in cold water, approaching home door, cold weather, stand up position, etc.).

Frequency and nocturia can be overestimated by the patient and are at best recorded on a bladder diary.

Incontinence is sorted among different subtypes and further characterized by pad test and clinical examination (as described thereafter). Types of incontinence diagnosed at the time of patient interview include (following ICS general definitions [6]):

Urinary stress incontinence: Urinary stress incontinence is the involuntary leakage of urine on effort or exertion or on sneezing or coughing. It occurs with a rise in intraabdominal pressure in the absence of detrusor overactivity. It is usually due to intrinsic urethral sphincter deficiency and/or hypermobility of the urethra.

Urgency urinary incontinence: Urgency incontinence occurs in the same time or just after an urgency. Warning time (evaluation the interval between the onset of urgency and the time of micturition or incontinence) will be assessed.

Postural urinary incontinence: Postural urinary incontinence is the involuntary leakage of urine caused by change of position like getting up or standing up.

Mixed urinary incontinence: There is an association of urge and stress urinary incontinence.

Circumstances of urinary incontinence may be difficult to specify for patients.

When several types of urinary incontinence coexist, the main complaint is alleged.

Nocturnal enuresis: Nocturnal enuresis means any leakage of urine during sleep.

Continuous incontinence Continuous urinary incontinence is the complaint of continuous leakage of urine. A severe intrinsic sphincter deficiency may occur continuous incontinence.

Insensible urinary incontinence Urinary incontinence is the complaint of involuntary leakage of urine without patient being aware of predisposing factors. In this case the patient is conscious about incontinence by being wet rather than feeling a leakage.

Coital incontinence: Patient complaint of involuntary leakage of urine during sexual intercourse. It can occur during sex or especially during orgasm (climaturia).

In case of extra-urethral incontinence, involuntary loss of urine is observed by an another external orifice. Congenital abnormality or fistula between bladder and vagina would be checked at physical examination (see under). A "color test" may be performed by the clinician: the bladder is filled with a coloured solution (methylene blue), and the catheter is left in place to block the urine flow. Any issue of blue fluid, notably through the vagina, can be ascertained.

Overflow incontinence is the involuntary loss of urine associated with overdistension of the bladder secondary to inefficient bladder emptying. The bladder is overfilled and empties only when the volume exceeds the anatomical capacity. Chronic retention is an important condition to consider in any patient with incontinence. A palpable bladder is an important item during the physical examination.

Many different underlying mechanisms can explain storage symptoms and are to be suspected at every stage of the initial work-up:

- bladder disease (bladder tumour, stone, foreign body, fibrosis, radiation cystisis)
- bladder outlet obstruction
- abnormal bladder sensitivity (afferent pathway)
- detrusor overactivity
- neurological dysfunction (spinal cord injury, supra thamalamic dysfunction, peripheric nerve injury)
- sphincter deficiency, urethral instability, urethral hypermobility

Nocturia can be due to reduced functional bladder capacity, 24 hr. polyuria, nocturnal polyuria, or sleep disturbances, as assessed by a bladder diary. Further causes are diagnosed by specific investigations (Table 19.2).

Frequency-Volume Chart (Bladder Diary)

To better assess storage symptoms, especially frequency and nocturia, a frequency– volume chart (FVC) is required. If possible, it is ideally obtained at the time of the consultation. Standard evaluation includes hours of voiding, symptoms at the time of voiding, episodes of incontinence (if any), and most importantly, the volume of each micturition. At the moment no standard method exist for ambulatory measurement of micturition volume, but some tools are under development (ultraprecise body mass measurement after and before voiding, connected penile cuffs, etc.). When adding pads weight evaluation, fluid intake, and recording of activities to a FVC, a complete "voiding diary" is obtained.

The FVC is usually recommended for a minimum of 3 days [9]. Seven days FVCs have been proposed through clinical research protocol but are barely used in clinical practice. The duration of the FVC/bladder diary needs to be long enough to avoid sampling errors, but short enough to avoid non-compliance. There is no strict rule for the timing of FVC completion, but it should at best reflect the usual conditions of the patient (working hours, holidays, week-end, etc.).

The primary goal of FVC is to collect objective data about frequency, micturitions during hours of sleep, as well as the amount of urine per micturition (real life functional bladder capacity), and total volume of urine per 24 hours. FVC is the cornerstone of storage symptoms evaluation, and may be also useful during follow-up. Here are reviewed the main abnormalities that can be found on a FVC.

24 Hours Urine Production

A correctly filled FVC results in the opportunity to assess the total urine production during 24 h. Polyuria, defined by more than 40 mL/kg urine output over a 24-hour period [10], might explain a number of storage symptoms because the functional bladder capacity is often reached during night and day. Ruling out a polyuria and adapting fluid intake may thus decrease, at no cost, the intensity of storage symptoms. In case of polyuria, polydipsia may be suspected, potentially related to extra-urological diseases.

In some other cases, reduced urine production may be seen (e.g. less than 1 L per day). This reduced voiding volume per day may be due to a voluntary reduction of fluid intake by the patient to minimize frequency, nocturia or urgency episodes.

Daytime Urinary Frequency and Functional Bladder Capacity

Increase daytime urinary frequency (out of a context of polyuria) occurs when functional bladder capacity is weak. The average voiding volume reflects the functional bladder capacity. The threshold usually admitted for frequency is 8 voids per day, with intervals of more than 2 h between micturitions, but the symptom bother is at least as important.

A reduced functional bladder capacity may be interpreted in line with the symptoms leading to voids (normal sensation or urgency). Increased frequency may be associated or not with nocturia.

Nocturia

Nocturia is defined by the fact of waking up at night to pass urine. Especially if nocturia is an isolated symptom, FVC is mandatory to assess it and interpret the number of voids, and the hours

of undisturbed sleep. As one episode of nocturia is very common after 50 years old [11], some authors have proposed to introduce the concept of "significant" nocturia in case of 2 episodes or more. Most importantly, a basic evaluation has to be done on every FVC to assess the following [10]:

- **24 h polyuria (see above),** defined by adding all voided volumes during 24 h.
- **Nocturnal polyuria,** defined by an excess of urine production during night time. The so-called nocturnal polyuria index is the percentage of urine produced during the night, obtained by dividing the amount of urine produced at night (adding all nocturia episodes + first morning void) by the 24 h urine volume. Above a limit of 33%, nocturnal polyuria can be ascertained. This threshold has been largely debated without clear consensus in the literature, because this threshold may vary with age [11]. Identification of nocturnal polyuria is very important because underlying causes (heart failure, renal impairment, obstructive sleep apnea) are often extra urologic and need specific investigations not to be missed [4, 11].

Pad Testing

Pad testing is a simple, non-invasive objective method for detecting and quantifying urine leakage. It is considered as a basic item for evaluation of incontinence. The principle of the test is to wear a pad and have normal activities, approaching the usual daily activities of the patient.

To obtain a reliable pad –test result (especially in subjects with variable or intermittent urinary incontinence), the test should be done over a long period of time. For instance, home pad tests lasting 24–48 h are superior to 1 h test in detecting urinary incontinence. Standard test are thus usually done for 3 days. One hour past test, as formalized by the ICS, can be used in clinical protocols [6]. In this ICS-Pad test, the upper limit of weight increase for the 1-hr test in continent women is 1.4 g.

The normal upper limit in a 24 h test is 2–4 g, accounting for sweating or vaginal discharge especially in women.

Voiding Phase

Voiding phase represent less than 1% of time. Normal voiding occurs on demand, promptly, with normally strong continuous flow and complete emptying without pain.

Voiding symptoms are reflecting abnormal bladder emptying, and can result of:

- Impaired bladder contractility
- Failure of urethral sphincter relaxation
- Bladder outlet obstruction, whatever the cause.

Some recent papers have identified potential clinical signs in favour of underactive detrusor rather than (or associated to) obstruction, with urodynamics being the gold standard. Basic evaluation, described hereunder, is the cornerstone of initial patient work-up before more invasive tests.

Identification of Voiding Symptoms during Patient Interview

Voiding symptoms are various in term of types and intensity. As every single individual would use his own words to qualify his symptoms, standardized symptoms have been defined by the ICS (ICS terminology for voiding symptoms [3, 6]):

- ***Hesitancy*** is the term used when an individual describes difficulty in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine.
- ***Straining to void*** describes the muscular effort (abdominal or suprapubic pressure, Valsalva manoeuvers) used to either initiate, maintain or improve the urinary stream.
  - ***Position dependant micturition*** is the term used when the individual has to void in abnormal position (bent forward, tilted behind, half sat) to initiate, maintain or improve the micturition.
  - ***Dysuria*** is the term used when the individual describes pain when is voiding.
  - ***Slow stream*** is reported by the individual as his or her perception of reduced urine flow, usually compared to previous performance or in comparison to others.

- ***Splitting or spraying*** of the urine stream may be reported.
- ***Intermittent stream (Intermittency)*** is the term used when the individual describes urine flow which stops and starts, on one or more occasions, during micturition.
- ***Terminal dribble*** is the term used when an individual describes a prolonged final part of micturition, when the flow has slowed to a trickle/ dribble.
- ***Urinary retention*** is the term used when an individual complaints any voluntary micturition.

Post-micturition symptoms. Post micturition symptoms are experienced immediately after micturition. They are usually associated with voiding symptoms, but can be isolated. An exploration of the voiding phase is required in those specific cases.

- Feeling of ***incomplete emptying*** is a self-explanatory term for a feeling experienced by the individual after passing urine.
- ***Post micturition dribble*** is the term used when an individual describes the involuntary loss of urine immediately after he or she has finished passing urine, usually after leaving the toilet in men, or after rising from the toilet in women.
- ***Need to immediately re-void****:* the individual complaints a new desire to void just after voiding

The goal of patient interview is to identify and characterize at best what is the patient complain. However, this will always remain subjective and the systematic next step is the uroflowmetry, which is the reference tool for obtaining an objective evaluation of bladder emptying.

Uroflowmetry

Uroflowmetry measures the urinary flow rate (i.e. the volume of urine voided per unit of time, expressed as milliliters per second (mL/s)). Patients void in to a uroflowmeter, which records the urine flow directly. The result is presented as a curve, plotting the flow rate (vertical axis) according to the moment of micturition (time, horizontal axis). A normal pattern of uroflowmetry is represented hereunder (Fig. 19.1).

Uroflowmetry is usually associated with measurement of post-void residual volume (PVR), either by suprapubic ultrasound or urethral catheterization.

It must be understood that uroflowmetry is the result from the combination of detrusor function AND urethral pressure, and thus reflects bladder emptying. As both obstruction and impaired bladder function can impact uroflowmetry parameters and flow patterns, only indirect clues can be found towards a potential underlying cause. The pathophysiology of impaired bladder emptying is at best evaluated by pressure –flow study, linking the urinary flow rate to the detrusor pressure (see appropriate section).

Conditions of uroflowmetry are important to know for a correct interpretation: spontaneous or after filling (e.g. cystoscopy, stress test, or cystometry), position (sitting, standing, etc. compared to usual habits), and environment (should be quiet, patient alone, without external stress), sensation of bladder filling just before the uroflowmetry (no desire to void, mild desire to void, strong desire to void).

A number of parameters are derived from the analysis of the uroflow graph. It can state whether the micturition is normal or not, but the origin of impaired voiding (bladder/ detrusor, obstruction, dyssynergia…) can only be suspected at this stage, pressure-flow study remain-

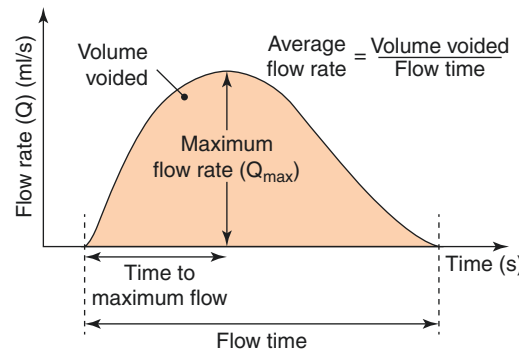

Fig. 19.1 A typical flow meter readout demonstrating the International Continence Society Nomenclature

ing the reference for defining obstruction or underactive detrusor.

Voided volume. Voided volume is the total voided volume during uroflowmetry. It is represented by the area under the curve. For a correct interpretation, a voided volume of more than 150 mL is required, since the normal urinary flow depends on bladder volume. A normal value (for a patient with desire to void) is within the range of normal bladder capacity, i.e. around 400-500 mL. Post-void residual is confronted to voided volume (see hereunder). When voided volume is unusually high (over 600 mL), especially without strong desire to void before uroflowmetry, an abnormal bladder capacity is suspected (in favour of chronic urinary retention, bladder distension, impaired bladder sensitivity, etc.).

Most importantly, the voided volume can be put in perspective with functional capacity of the bladder (usual volumes seen in the bladder diary).

Maximum flow rate. Maximum flow rate (Qmax) from the entire void is the highest point of the curve. It is the most popular parameter as it is the key for diagnosing bladder emptying.

Usually, male produce a maximum flow rate of 30–40 mL/s and females a maximum flow rate of 40–50 mL/s. This difference is due to the passive urethral resistance that is higher in men due to the length of the urethra. However, these values decline with age, notably in men.

The cut-off of 15 mL/s is usually taken to set the definition of impaired voiding [4]; 10 mL/s is cited by some international guidelines to indicate surgery for male LUTS management [12]. Moreover, under 10 mL/s, a vast majority of men show bladder outlet obstruction on urodynamics [13]. Furthermore, Qmax is taken as the main outcome of all studies focused on voiding LUTS and benign prostatic obstruction in men.

Most importantly, Qmax has to be interpreted in line with the pattern of the curve, because it can be related to a voluntary increase of abdominal pressure (Valsalva manoeuver).

Average flow rate is reflecting micturition more globally, but it ignores variations of flow and duration of voiding.

Flow time is time over which actual flow occurred. It is inferior to voiding time in case of intermittent flow.

Voiding time is the total duration of micturition, regardless of whether flow was present. It is usually prolonged in case of impaired voiding, regardless of aetiology.

Time to maximum flow is the time taken to achieve maximum flow from the onset of flow.

Post-void residual. It can be assessed by transabdominal ultrasound, bladder scan or catheterisation. The residual urine after bladder emptying is normally very low. It should be 0 mL but a mild residual of <50 mL can be seen in aged patients, or when a degree of cystocele is present. A residual volume of more than 100 mL is usually considered as abnormal. High PVR volumes can be a consequence of obstruction and/or poor detrusor function (detrusor underactivity); very high PVR volumes are considered as an indirect sign of detrusor underactivity or chronic retention [14].

Lastly PVR may be controlled as it depends on bladder filling before uroflowmetry (an excessive bladder volume may lead to an increase of post void residual).

In addition to parameters, **flow pattern** is the other important information given by uroflowmetry.

Normal flow pattern is homogeneous, with a rather fast increase and a progressive decrease of flow (see here under).

Abnormalities of flow as demonstrated by uroflowmetry involve certain characteristic flow patterns;

- Fast bladder—This is an exaggeration of the normal curve and may be due to a raised end fill bladder pressure associated with detrusor overactivity or due to a significantly low outflow resistance (see here under)
- Prolonged flow—This is a slow flow rate over a prolonged period of time requiring a long

time to reach a maximum flow. This is frequently seen with Bladder outlet obstruction (BOO), although a poorly contractile detrusor may give this picture (see here under)
- Intermittent flow—This irregular spiking pattern is frequently due to abdominal straining to augment the pressure required to overcome a bladder outlet obstruction or to add intra-abdominal pressure to a poorly contractile detrusor. Rarely sporadic sphincter contractions may cause this pattern (see here under)
- Flat Plateau—A low maximum flow rate which plateaus throughout the majority of the void, like a "box," is characteristic of a urethral stricture (see here under)

Alternative, Non-invasive Assessment of Voiding Phase

Voiding symptoms are either the result of bladder outlet obstruction (BOO) or decreased bladder contractility. Pressure-flow study is the current standard diagnostic test for BOO, but is part of a urodynamic evaluation [15].

Number of less invasive techniques have been developed, providing alternatives to PFS for BOO diagnosis, but for the moment none of them is recommended by the EAU guidelines for initial LUTS baseline assessment. Those include penile cuff test, or ultrasound imaging (measurement of bladder wall thickness or prostatic protrusion) (see under).

Penile cuff test. The basic theory of penile cuff test is to provide a measure of detrusor contractility in men by recording the isovolumetric bladder pressure [16].

An inflatable cuff is placed around the penile shaft and is inflated automatically during micturition until the urinary flow is interrupted. The cuff is then rapidly deflated to allow the flow to resume. During the cycle, the pressure that interrupts flow is equal to the isovolumetric bladder pressure. Based on the PFS results, the sensitivity of PCT was 89.7%, the PPV 54.2%, the specificity 71.8%, and the NPV 94.9% [17].

The role of PCT in clinical practice has not been yet established.

Systematic Items of Clinical Evaluation in Patients Presenting with Lower Urinary Tract Symptoms

Medical History

The importance of assessing the patient's history is well recognised [18].

A medical history aims at identifying the potential causes of LUTS (e.g. a history of bladder surgery), relevant comorbidities that can influence micturition, including systemic, medical and/or neurological diseases (e.g. diabetes). In women, an obstetric and gynaecological history is mandatory to get information about previous deliveries, parity, etc.

In addition, current medications must be reviewed, since some of them influence urine production (e.g. diuretics). Lifestyle habits (e.g. sleep, smoking) are also of critical importance and emotional and psychological factors must be reviewed (e.g. stress, anxiety, psychiatric issues, history of psychological trauma, drug use, sexual abuse, etc.). Familial environment is important to assess as well and professional activities, since symptoms may have a different impact on quality of life. Of course, diet and drinking habits are also essential, the latter being precisely evaluated though a bladder diary.

Finally, previous treatment of LUTS and their efficacy and tolerance must be assessed. Indeed, most treatment evaluations have been conducted in patients without previous urological surgery or specific medications (which are often considered as exclusion criteria when evaluating a new treatment). But previous surgery (e.g. sling in women or prostate surgery in men) dramatically change the situation, and guide further assessment [4].

Other Urological Symptoms

Beside storage, voiding and post-micturition symptoms described here above, a number of urological symptoms must be assessed.

Those include hematuria and pain.

Macroscopic hematuria may reveal a urinary tract infection, a tumour or inflammation of the urinary tract, or may be due to urolithiasis. Thus if present, imaging, urine culture, cytology and endoscopy may be prescribed as first line investigations.

Genital and Lower Urinary Tract Pain

Pain, discomfort and pressure are part of a spectrum of abnormal sensations felt by the individual. Pain may be related to bladder filling or voiding, may be felt after micturition, or be continuous.

According to the International continence society [3, 6] pain should also be characterised by type, frequency, duration, precipitating and relieving factors and by location as defined below:

- ***Bladder pain*** is felt suprapubically or retropubically, and usually increases with bladder filling, it may persist after voiding.
- ***Urethral pain*** is felt in the urethra and the individual indicates the urethra as the site.
- ***Vulval pain*** is felt in and around the external genitalia.
- ***Vaginal pain*** is felt internally, above the introitus.
- ***Scrotal pain*** may or may not be localised, for example to the testis, epididymis, cord structures or scrotal skin.
- ***Perineal pain*** is felt: in the female, between the posterior fourchette (posterior lip of the introitus) and the anus, and in the male, between the scrotum and the anus.
- ***Pelvic pain*** is less well defined than, for example, bladder, urethral or perineal pain and is less clearly related to the micturition cycle or to bowel function and is not localised to any single pelvic organ.

Sexual Symptoms

Sexual function should be assessed when evaluation LUTS in men or women.

Evaluation of sexuality include activity, general satisfaction, specific symptoms (dyspareunia in women, erectile and ejaculatory function in men), desire, arousal, orgasm, etc. When a specific evaluation is required because of a specific symptom or before a treatment that could influence sexual activity), a validated symptom questionnaire is preferred (such as the International Index for Erectile Function (IIEF) in men).

In women, specific questionnaires may explore solely the sexual function or include more generally evaluation of pelvic floor dysfunction, including pelvic organ prolapse-related symptoms (e.g. PISQ (Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire) and PFDI (Pelvic Floor Distress Inventory) [19]).

Bowel Dysfunction

A complete evaluation of the pelvic floor is mandatory including bowel symptoms. This is because:

1. a number of physiological reflexes involve both the urinary and digestive tract
2. some bowel problems can directly cause LUTS
3. a number of pathophysiological pathways involve both organs because of common causes or because of pelvic organ interaction
4. treatments proposed for LUTS management (either medical or surgical) may have an important impact on bowel function
5. Diagnosing both LUTS and bowel issue may lead to a more precise diagnosis

Those symptoms include:

- Anal incontinence (fecal or flatal)
- Passive fecal incontinence or soiling
- Fecal urgency with or without incontinence
- Diarrhea
- Constipation
- Straining to defecate
- Digitations
- Feeling of incomplete evacuation
- Diminished rectal sensation
- Rectal bleeding or mucus
- Anorectal prolapse

A number of specific investigations can be conducted and a specific consultation may be solicited (see [6]).

Physical Examination

As recommended by the ICS and all clinical guidelines, physical examination is an essential part of the assessment of all patients with LUTD. In addition of a general assessment (body mass index, etc.) it includes focused abdominal, pelvic, perineal and neurological examination of the pelvic floor.

Abdominal evaluation. A palpable, full bladder may diagnosed by abdominal palpation or by suprapubic percussion. Suprapubic pressure may induce a desire to pass urine or lead to overflow incontinence in case of chronic retention. Scars of previous interventions can be located. Palpation and percussion of the lumbar area look for a kidney mass or provoked pain.

Perineal/genital inspection. Inspection focuses on the aspect of the skin and potential anatomical abnormalities. In men, one would look for urethral discharge, meatal stenosis, phimosis, skin/ penile lesion, increased volume of the scrotum. In women, the aspect and location of the urethral orifice is described, as well as the introitus aspect.

Vaginal examination in women. Examination of the vagina includes description of the vaginal walls, pelvic organ prolapse related abnormalities as described in [6], and any palpable abnormality.

The cough test is a crucial item, looking for stress urinary incontinence during a brutal increase in abdominal pressure. A leak of urine may be observed, depending on the bladder filling (normally around 300 mL). Presence of a positive cough test is an objective evidence of stress urinary incontinence.

Urethral hypermobility is also assessed, usually digitally. In case of mobile/hypermobile urethra and a positive stress test, the effect of the Bonney manoeuver (mimicking a Burch colposuspension) and/or the Ulmsten manoeuver (supporting the urethra bilaterally with no pressure, mimicking a synthetic sling placement) can be evaluated. A test is considered positive if it corrects the incontinence symptom. In case of a fixed urethra, no movement of the anterior vaginal wall is seen during cough, and usually no supporting manoeuver of the urethra corrects urinary leakage.

Pelvic floor muscle function is assessed manually during vaginal palpation and is determined on a scale from 1 to 5. Pelvic floor muscle function can be assessed much more precisely with additional investigations as described in the ICS report [6]; factors to be assessed include strength, duration, displacement and repeatability.

Male genitalia examination. In men, the aspect of the penis is described, with palpation of corpus cavernosa (e.g. plaque), skin lesion, lymph nodes, testis volume and consistency, scrotal volume and transillumination if necessary. Inguinal hernia is ruled out.

Rectal examination. Digital rectal examination may be required to look for a reduced pelvic floor muscle and/or contractility of the sphincter. It may be associated with vaginal palpation in women to diagnose elythrocele or rectocele.

In men, digital rectal examination is required to evaluate prostate size, look for a prostatic nodule or a rectal mass [20].

Neurological examination. A neurogenic origin of LUTS must be ruled out if present because

if modifies the initial work-up, and most of time treatment strategy. A first round is possible through patient history, including back problems. A gait disorder can be ruled out at the consultation because a very frequent association exists between gait disorders and LUTS of neurological origin. A focal motor or sensory sign can be suspected by patient interview.

For patients with possible neurogenic lower urinary tract dysfunction, a more extensive neurological examination is needed. Neuro-urological status should be described as completely as possible (Fig. 19.2) [6].

Use of Questionnaires for LUTS Evaluation

Several questionnaires have been developed which are sensitive to symptom changes and can be used to monitor treatment [21, 22]. Symptom scores are helpful in quantifying LUTS and in identifying which type of symptoms are predominant, yet they are not disease-, or age-specific. Some questionnaires are gender-specific, while others are validated in both men and women.

Furthermore, some questionnaires are dedicated to symptoms, while others target bother,

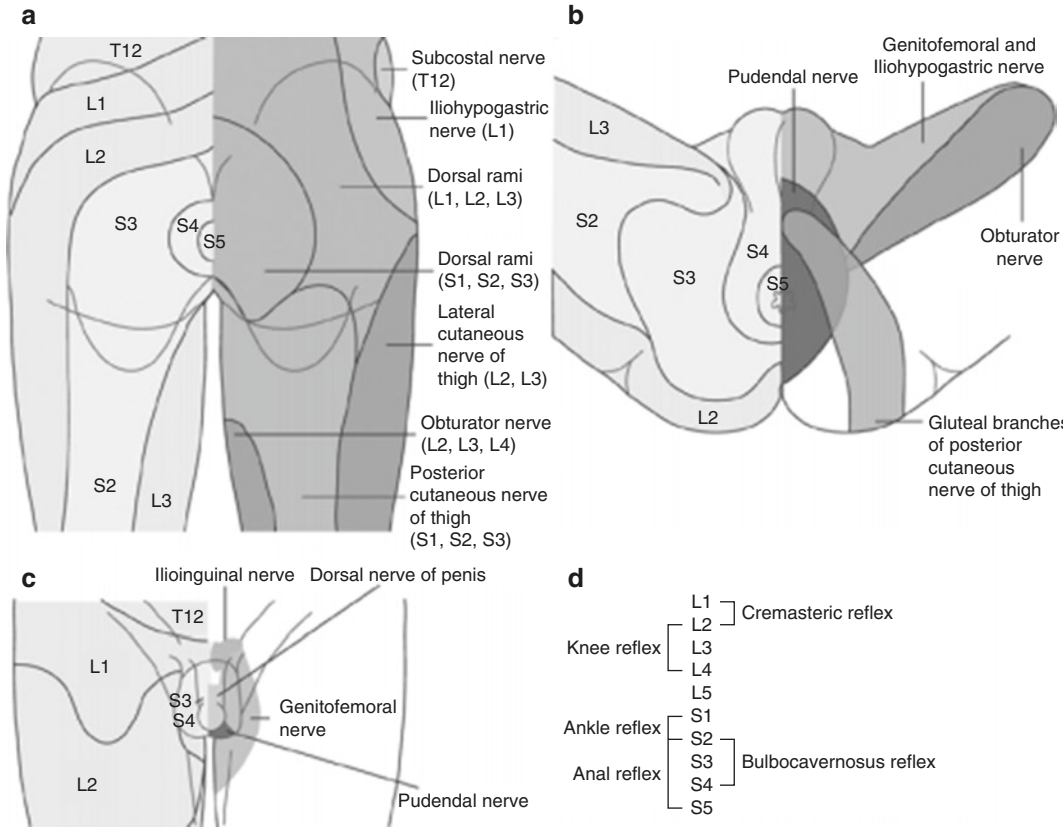

Fig. 19.2 Lumbosacral dermatomes, cutaneous nerves, and reflexes. The physical examination includes testing sensations and reflexes mediated through the lower spinal cord. Abnormal findings would suggest a lesion affecting the lumbosacral segments; mapping out distinct areas of sensory impairment helps to further localise the site of the lesion. Distribution of dermatomes (areas of skin mainly supplied by a single spinal nerve) and cutaneous nerves over the perianal region and back of the upper thigh (**a**), the perineum (**b**), male external genitalia (**c**) and root values of lower spinal cord reflexes (**d**)

quality of life, or satisfaction. All these aspects are gathered under the umbrella of patient-reported outcomes (PROs). Those modern tools aim at evaluating the results of medical or surgical treatment with a multi-dimensional assessment.

The main questionnaires used in clinical practice are presented below.

The International Prostate Symptom Score (IPSS)

The IPSS is an 8-item questionnaire, consisting of seven symptom questions and one quality-of-life question [23]. It is the gold standard of male LUTS baseline evaluations. I-PSS is sometimes split in "voiding" and "storage" subscores, whilst this has not been formally validated. Despite being known as a "prostate symptom score", it is absolutely non-specific for prediction of BOO or any other underlying pathophysiology.

The IPSS score (ranging from 5 to 35) is categorised as 'asymptomatic' (0 points), 'mildly symptomatic' (1–7 points), 'moderately symptomatic' (8–19 points), and 'severely symptomatic' (20–35 points). Limitations include lack of assessment of incontinence, post-micturition symptoms, and bother caused by each separate symptom.

The International Consultation on Incontinence Questionnaires

Sixteen ICIQ modules/questionnaires are currently available for use according to symptoms:

- Lower urinary tract symptoms:
  - Males: ICIQ-MLUTS
  - Females: ICIQ-FLUTS
  - ICIQ-Bladder diary
- Urinary incontinence
  - ICIQ-UI Short Form
- Vaginal symptoms
  - ICIQ-VS
- Bowel symptoms
  - ICIQ-B

ICIQ modules/questionnaires are currently available for use according to symptoms to specific patient groups:

- Nocturia: ICIQ-N and ICIQ-Nqol
- OverActive Bladder: ICIQ-OAB and ICIQ-OABqol
- Long term catheter: ICIQ-LTCqol

Following ICIQ modules are in development:

- Children: ICIQ-CLUTS
- Absorbent pads: ICIQPadprom
- Underactive Bladder: ICIQ-UAB/UAB PRO
- Neurogenic: ICIQ-Neurogenic
- ICIQ-VSqol
- ICIQSatisfaction

The quality of life questionnaires (e.g. King's Health Questionnaire) cover specific issues that are a consequence of symptoms, such as life limitations and emotional impact.

Sexual matters modules specifically evaluate the impact of lower urinary tract symptoms on this aspect from the male and female perspective (ICIQ-MLUTSsex, ICIQ-FLUTSsex) (Table 19.3).

The Urinary Symptom Profile Questionnaire [24] has been developed to cover in one questionnaire voiding symptoms, incontinence and overactive bladder [24].

The Neurogenic Bladder Symptom Score (NBSS) has been validated in neurological patients to measure urinary symptoms and their consequences [25]. Others quality of life scales with bladder related questions exist according to specific neurologic disease (see here under) (Table 19.4).

A systematic review (SR) evaluating the diagnostic accuracy of individual symptoms and questionnaires, compared with urodynamic studies (the reference standard) for the diagnosis of BOO in males with LUTS found that individual symptoms and questionnaires for diagnosing BOO were not significantly associated with one another [26].

Table 19.3 ICIQ module description

Name	Scope of assessment	Domains	Items	Grade
ICIQ-MLUTS (ICS*male*SF)	Male lower urinary tract symptoms and associated batter.	Voiding Incontinence Individual items evaluating frequency arid nocturia	13	A
ICIQ-FLUTS (BFLUTSSF)	Female lower urinary tract symptoms and associated bother.	Filling Voiding Incontinence	12	A
ICIO-Bladder Diary	Prospective bladder events	Voided volumes Leaks Bladder sensations Fluid input Pad use	24 h monitoring	A+
ICIQ-VS	Vaginal symptoms including prolapsed and associated bother.	Vaginal symptoms Sexual matters Quality of life	14	A
ICIQ-B	Bowel symptoms including anal incontinence and associated bottler	Bowel pattern Bowel control Quality of life	21	A+
ICIQ-UI Short Form	Urinary incontinence.	Urinary incontinence frequency, overall interference Perceived cause of incontinence	4	A
ICIQ-LUTSqol (King's Health Questionnaire)	HRQL issues associated with urinary symptoms and associated bather.	Life restrictions Emotional aspects Preventive measures	22	A+
ICIQ-MLUTSsex (ICS*male*)	Male sexual matters associated with urinary symptoms and associated bottler.	Erection and ejaculation issues Overall interference	4	A
ICIQ-FLUTSsex (BFLUTS)	Female sexual matters associated with urinary symptoms and related bother.	Pain and leakage with sexual intercourse Overall interference	4	A
ICIQ-FLUTS Long Form (BFLUTS)	Detailed assessment of female lower urinary tract symptoms and associated bother.	Varied lower urinary tract symptoms	18	A
ICIQ-MLUTS Long Form (ICS*male*)	Detailed assessment of male lower urinary Had symptoms arid associated bother.	Varied lower urinary tract symptoms	23	A
ICIQ-N	Comprehensive assessment of symptoms of nocturia and associated bother.	Frequency Nocturia.	2	A
ICIQ-OAB	Comprehensive assessment of symptoms of overactive bladder and associated bother.	Frequency Nocturia Urgency Urgency incontinence	4	A
ICIQ-OABqol(QAB-q)	Detailed -assessment of health-related quality of life issues associated with overactive bladder.	Coping Concern/Worry Sleep Social Interaction	25	A
ICIQ-Nqal (NQOL)	Detailed assessment of HRQL issues associated with nocturia.	Issues associated with sleep disturbance Life restrictions Preventive measures	13	A+
ICIQ-LTCqol	Detailed assessment of HRQL associated with long term catheter use	Catheter function and concern Lifestyle impact	19	B

Table 19.4 Disease-specific quality of the life instruments with items related to neurogenic bladder dysfunction

Population	Instrument	Bladder related questions
SCI	Qualiveen	30 questions about limitations, conscrainc, fears, and feelings related DO bladder function
	The Spinal Cord Injury Secondary Conditions Scale	Bladder dysfunction: incontinence, bladder or kidney stones, kidney problems, urine leakage, and urine back up Urinary tract infections
	Spinal Cord Injury-Functional Index	Eleven items related to ability to carry our bladder related tasks (catheter care, genital hygiene)
MS	MSQOL-54	Social impact of bladder function
	MSB-M	Bother associated with urinary urgency
	Functional assessment of MS	Urinary urgency and frequency
	Hamburg Quality of Life	Bladder control
	Questionnaire in MS	
	MS QOL Inventory	Frequency of incontinence, urgency Impact of bladder of physical activities
SB	QOL in SB Questionnaire	Ability to self-catheterize

Additional Explorations of LUTS Evaluation

Urine Analysis

Urinalysis (dipstick or sediment) must be included in the primary evaluation of any patient presenting with LUTS to identify conditions, such as urinary tract infection (UTI), microhaematuria and diabetes mellitus.

Urine analysis must always be performed to rule out a urinary tract infection if symptoms are present, and hematuria (bladder cancer, prostate cancer), especially in current or former smoking patients.

Blood Tests

Renal function may be assessed by serum creatinine or estimated glomerular filtration rate (eGFR).

Serum PSA levels are required when a risk of prostate cancer is high [4]. It has also a role in the context of LUTS due to benign prostatic obstruction. Serum PSA is a stronger predictor of prostate growth than prostate volume [27]. In addition, the PLESS study showed that PSA also predicted the changes in symptoms, QoL/bother, and maximum flow-rate (Qmax) [28].

In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression [29].

Endoscopy

Patients with a history of microscopic or gross haematuria, stone disease, urethral stricture, or bladder cancer, who present with LUTS, should undergo urethrocystoscopy during diagnostic evaluation. Endoscopy may also be performed before surgical management of male LUTS/BPO [4]. There is a poor correlation between urethrocystoscopy results and urodynamic findings.

Imaging

Cystography—Voiding Cysto-Urethrography

It must be remembered that simple cystourethrography can be carried out in all X-ray departments and can provide true, high quality, lateral views of the urethra during voiding.

Cystourethrography allows radiographic data relating to bladder morphology e.g. diverticula, vesicoureteric reflux and the appearances of the bladder outlet and urethra. It may remove to fis-

tula. Retrograde urethrography may additionally be useful for the evaluation of urethral strictures when suspected.

Ultrasound

The patient should be scanned at the time that they feel "full" thereby providing an idea of the functional bladder capacity. Similarly the patient should be scanned as soon after voiding as possible in order to provide accurate assessment of the true bladder residual.

Assessment of prostate size is important in men, especially before treatment of LUTS/BPO.

Transrectal ultrasound (TRUS) is more accurate in determining prostate volume than digital rectal examination [30].

MRI

Cerebral or medullar MRI could be an additional diagnostic investigation if a neurological disease is suspected, such as multiple sclerosis, Parkinsonian syndrome.

There is a general consensus that MRI provides good global pelvic floor assessment, including pelvic organ prolapse (POP), distal bowel function and integrity of the pelvic floor support. However, it is not recommended as a routine test for baseline evaluation of LUTS [31].

CT Scan

CT scan cis optional in patient where a spine disorder is suspected (degenerative disease, disk prolapse, lumbar canal stenosis).

Neurophysiological Evaluation

Accurate electromyographic evaluation of the urethral sphincter is possible with a concentric needle electrode but it is a painful investigation and cannot be carried out during voiding.

Four different neurophysiological methods have been described:

- Electromyography—Needle electrodes are placed in to a muscle mass or surface electrodes are used to record electrical action potentials generated by depolarization of muscle. Potential sampling sites include; the intrinsic striated muscle of the urethra, the periurethral striated muscle, bulbocavernosus muscle, external anal sphincter, and pubococcygeus muscle. These have a characteristic waveform and in disease this may be altered or the impulse may be recorded at an inappropriate time, such as in detrusor sphincter dyssynergia, where the urethral striated muscle contracts during voiding.
- Nerve conduction latency studies—determine time taken (latency) for a response to occur in a muscle following peripheral nerve stimulation
- Reflex latency studies—assess the latency of a reflex arc, assessing the nerve conduction velocity in both the afferent and efferent limbs of the reflex.
- Sensory testing—a standard electrical stimulus is applied to the bladder/urethra to give the least current required for the patient to perceive a stimulus. This is known as the vesical/urethral sensory threshold.

Urodynamics

UDS has long been considered a useful tool for the diagnosis and treatment of lower urinary tract symptoms (LUTS), incontinence, voiding dysfunction, and neurogenic bladder.

UDS may change the clinician's diagnosis before treatment.

UDS is potentially useful for several reasons:

1. to identify factors contributing to lower urinary tract dysfunction
2. to predict the consequences of lower urinary tract dysfunction on the upper tracts
3. to predict the consequences and outcomes of therapeutic intervention
4. to confirm and/or understand the effects of interventional techniques
5. to investigate the reasons for treatment failure

Patients should be informed of the following:

- Steps of urodynamic exploration
- UDS is an interactive examination, which assesses lower urinary tract dysfunction and serves as an adjunct to the comprehensive evaluation of patients with LUTS.
- Outcome(s) of UDS for his/her LUTD
- Necessary of urethral and rectal catheterization
- Necessary to perform urine analysis before
- Risks: bleeding, infection, urethral trauma, and pain
- UDS may be unpleasant sensation but usually not painful

In routine, urodynamic investigations study includes:

- free uroflowmetry
- post voided residual assessed by ultrasounds or catheterization
- filling cystometry: assessment of
  - bladder compliance
    describes the intrinsic ability of the bladder to change in volume without significantly altering detrusor pressure.
  - bladder sensation:
    First desire to void
    Normal desire to void
    Strong desire to void
    Desire at which the patient cannot delay micturition (Maximum cystometric capacity)
    Urgency—sudden compelling desire to void
    Bladder pain—should not occur during filling
  - bladder stability
    Detrusor activity—during the storage phase the detrusor muscle should be inactive.
    Any activity should be correlated with episodes of urgency and/or incontinence. The volume at which this occurred should be noted. Provocation maneuvers may be employed to stimulate detrusor overactivity.
  - bladder capacity
    Maximum cystometric capacity is the volume at the end of the storage phase.
    It may be reduced in patients with a small contracted bladder and increased due to repeated stretching in patients with chronic outflow obstruction.
- voiding cystometry (Pressure Flow Study = PFS)
  - bladder contractility
    detrusor function
    - Detrusor underactivity—A detrusor contraction insufficient to achieve complete bladder emptying
    - Acontractile detrusor—No detrusor activity
    - Premicturition pressure—pressure recorded prior to the initial isovulometric contraction in the bladder
    - Opening pressure—pressure recorded at the onset of urine flow
    - Opening time–time from initial rise in detrusor pressure to actual flow
    - Maximum pressure—peak amplitude of voiding pressure
    - Pressure at maximum flow—lowest pressure recorded at maximum flow rate
    - Closing pressure—the pressure as measured at the end of flow
    - Minimum voiding pressure—minimum pressure sufficient to produce flow

    Bladder Contractility index (BCI) describe by Abrams is based on the projected isovolumetric pressure formula (PIP = Pdet. Qmax +5Qmax) that divides contractility into three groups (strong >150, normal 100–150, and weak <100) [32].
  - Bladder outflow obstruction—characterized by increased detrusor pressures and reduced flow rates
  - Bladder Outflow Obstruction Index (PdetQmax–2Qmax, with obstructed 40, equivocal 20–40, and unobstructed <20) have been developed to diagnose and quantify the severity of outlet obstruction on PFSs [33].

Urethral Pressure Profilometry

Measurements may be made at one point in the urethra over a period of time, or at several points along the urethra consecutively forming a urethral pressure profile (UPP).

At rest the urethral pressure profile denotes the intra-luminal pressure along the length of the urethra. All systems are zeroed at atmospheric pressure. For external transducers the reference point is the superior edge of the symphysis pubis. For catheter mounted transducers the reference point is the transducer itself. Intravesical pressure should be measured to exclude a simultaneous detrusor contraction. The subtraction of intravesical pressure from urethral pressure produces the urethral closure pressure profile.

Intra-luminal urethral pressure may be measured:

At rest (the storage phase), with the bladder at any given volume to assess the resting urethral pressure profile (UPP).

During coughing or straining to assess the tress urethral pressure profile.

Although UPP has the potential to be highly informative, the test has multiple problems, the most significant being the large overlap in values obtained from normal and symptomatic patients. UPP does not discriminate SUI from other urinary disorders, provide a measurement of the severity of the condition or predict a return to normal following successful intervention.

Technique

Cystometry involves the measurement of both the intra-vesical and the intra-abdominal pressure simultaneously. Electronic subtraction of the latter from the former enables the detrusor pressure to be determined.

The intra-abdominal pressure is measured via a pressure recording rectal catheter, inserted 10–15 cm above the anal duct, but may also be inserted into the vagina or a stoma.

The patient is asked to cough to check for dampening of the signal, this is repeated throughout the procedure as a quality control method (a cough should increase both intra-abdominal pressure and intra-vesical pressure but only show as a blip on the detrusor trace).

All systems are zeroed at atmospheric pressure.

For catheter mounted transducer, the reference point is the transducer itself.

For external transducers, the reference point is the level of the superior edge of the symphysis pubis.

The two pressure measurement lines are then connected to the transducers incorporated in the urodynamic apparatus.

The lines are flushed through, great care being taken to exclude all air bubbles from both the tubing and transducer chambers.

Saline serum at room temperature is then instilled into the bladder at a predetermined rate under the control of a peristaltic pump.

Medium (50 mL/min) is used routinely, although slower filling rates (20 mL/min) approaching the physiological range are mandatory in the assessment of the neuropathic bladder.

Electromyographic study may be associated in UDS.

EMG reflects the activity of the external urethral sphincter, the peri-urethral striated musculature, the anal sphincter and the striated pelvic floor muscles. Correct interpretation may be difficult due to artefacts introduced by other equipment. In the urodynamic setting, an EMG is useful as a gross indication of the patient's ability to control the pelvic floor. Possible pathological findings include inadequate recruitment upon specific stimuli (e.g. bladder filling, involuntary detrusor contractions, onset of voiding, coughing, Valsalva manoeuvre) suggesting a diagnosis of DSD [34].

It is essential that urodynamic studies are carried out or supervised by experienced investigators:

1. Always take a clinical history of the patient before carrying out the study and counsel the patient before they attend on the day and at the start of the study as to the nature of the test.
2. Make sure the urodynamic equipment is regularly serviced and calibrate the transducers on a regular basis.
3. Make sure that the lines are zeroed at the start of the study, check subtraction is perfect

before starting the study with a detrusor pressure between 0 and 5 cm H2 O, and ask the patient to cough and verify that the rectal and vesical pressure lines track together in their response. If in doubt about artefact, repeat the study.

4. Choose the correct filling rate for the study, e.g. normal filling at 50 mL/min and slower filling at a rate of 10–20 mL/min for neuropaths and patients with a reduced functional capacity.
5. Leak point pressure: The abdominal pressure or vesical pressure at which leakage occurs is a major problem because there is no standard technique with regard to:
   (a) Catheter caliber
   (b) Presence of prolapse
   (c) Bladder volume at which the leakage is measured
   (d) Valsalva versus cough
   (e) Straining (contraction/relaxation of pelvic floor)
   (f) Absolute measurement or relative measurement compared to baseline
   (g) No defined threshold values for treatment decision

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Benign Prostatic Hyperplasia (BPH)

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BPH: Epidemiology, Natural History and Pathophysiology

Epidemiology research strictly depends upon the definition of the disease/condition, considering that there is no consensus on a unique definition on BPH, exact measures of prevalence and incidence are not without problem [1]. Abrams et al. in 2002, standardized the different definitions dividing the objective finding of Benign Prostatic Enlargement (BPE), the histological diagnosis (Benign Prostatic Hyperplasia: BPH) and the obstruction which can derive from BPH (Benign Prostatic Obstruction: BPO) [2]. Data from population based studies [3–5], suggest an overall prevalence between 2 and 25%, however prevalence of the disease strictly depends on age reaching 43% in older patients. As well standing to the available evidence incidence of BPH/LUTS ranges from 9 to 41 per 1000 persons per year. As stated earlier the clinical condition of BPE is due to BPH which usually develops after the fourth decade of life. The natural history of BPH is best analyzed from longitudinal studies of community-dwelling men. In the Olmsted county study, which followed for 12 years a randomly selected cohort of 2115 men aged 40–79 years, there was an average increase in the IPSS of 0.18 points per year, ranging from 0.05 for men in their fifties to 0.44 for those in their seventies [3]. There was also a decrease in peak flow rate of 2% per year and a median prostate growth of 1.9% per year. As well data from the Medical Treatment of Prostatic Symptoms Study (MTOPS) suggest that disease progression is characterized by worsening of symptoms (79%), acute urinary retention (14%) and the need of surgery (2%) [6, 7]. Historically first studies on BPH pathophysiology have been performed by McNeal and colleagues. Histologically BPH is a true hyperplastic process with an increase in cell number [8]. The development of BPH is mainly driven by age and sexual hormones. Most of the evidence suggest an initial phase of increase cell proliferation followed by a decrease in cell turnover which leads to an increase in the total number of cells. The prostate grows mainly under the interaction between androgens and the androgen receptor. Dihydrotestosterone plays a central role together with high levels of AR, especially in the aging prostate, in the development of BPH. Several studies have as well demonstrated an important role of oestrogens in the development of BPH by influencing the expression for the androgen receptor in the prostate. Nonetheless, several grow factors (i.e. FGF, TGF-beta, EGF) influence the proliferation of the prostatic cells acting together with the abovementioned hormones in the development of BPH [9]. In the past years,

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several authors have focused in the interaction between prostatic inflammation and BPH. The evidence suggest BPH may be considered an immune mediated inflammatory disease. Several stimuli, including infectious agents, urinary reflux, metabolic syndrome, the ageing process, and autoimmune response, have been described as triggers for the dysregulation of the prostatic immune system via different molecular pathways involving the development of inflammatory infiltrates. From a pathophysiological standpoint, subsequent tissue damage and chronic tissue healing could result in the development of BPH nodules [10]. Once the process of enlargement of the prostate is initiated the patient may remain asymptomatic for a certain number of years. Thereafter, as a consequence of BPO, the patients may present some LUTS including voiding, storage or post-micturition symptoms. As a response to the progressive increase in urethral resistance, the bladder compensates with hypertrophy or smooth muscle cells, widening of intracellular spaces and interstitial collagen deposition (fibrosis) with a consequent increased bladder mass. The increased bladder mass, can initially be sufficient to maintain an adequate detrusor contractility and bladder emptying. However, if the obstruction is not resolved, the bladder decompensates with subsequent risk of complications. As a consequence of the impaired contractility, the decompensated bladder can no longer completely empty with increased residual urine leading to urinary tract infections, bladder stones, acute and chronic urinary retention, renal insufficiency and failure [11].

Diagnosis

According to the European Association of Urology guidelines recommended tests, to be performed in all patients with bothersome LUTS and BPE included: medical history, quantification of symptoms and bother, physical examination, urinalysis, serum prostate antigen (PSA), frequency volume chart, uroflowmetry with post-voiding residual volume and ultrasound imaging of the prostate. Optional tests were considered: upper urinary tract imaging, pressure-flow studies and endoscopy of the lower urinary tract [12].

Standard Assessment of Patients with LUTS Due to BPH

The importance of medical history in identifying potential causes of LUTS has been well recognized by all the available international guidelines [13]. History and physical examination aim at diagnosing concomitant conditions of the bladder, the central nervous system, or other organs that may be responsible for LUTS beyond benign and malignant disorders of the prostate. Clinicians should always investigate comorbidities, current medications, lifestyle habits, emotional and psychological factors which may explain symptoms. LUTS related to BPH, including storage (urgency, urge incontinence, frequency, nicturia), voiding (hesitancy, weak stream, intermittency) and post micturition symptoms (incomplete voiding sensation) should be also assessed.

Frequency Volume charts require patients to record the time, volume and type of every drink they take, and the time and amount of urine at each voiding episode. From these data, several variables are derived, e.g. the 24-h voiding frequency, nocturnal frequency and mean voided volume.

The International Continence Society has agreed definitions for these variables to ensure that practice is consistent and research is comparable [2]. The duration of FVCs is still a matter of debate, the latest evidence shows a range of durations between 1 and 7 days [14]. The available guidelines suggest using at least a 3-days diary to balance consistency and compliance.

Several validated questionnaires can be used to assess male LUTS (i.e. International Prostate Symptom Score: IPSS; International Consultation on Incontinence Questionnaire ICIQ-MLUTS; Danish Prostate Symptom Score DAN-PSS; AUA symptom score) and they may help clinicians in identifying/quantifying the predominant type of LUTS as well as in monitoring disease progression [15, 16]. More specifically, American Urological Association symptom index was

found to be internally consistent (Cronbach's $\alpha = 0.86$) and the score generated had excellent test–retest reliability ($r = 0.92$). Scores were highly correlated with participants' global ratings of the magnitude of their urinary problems ($r = 0.65$–0.72) and discriminated well between BPH and control individuals (receiver operating characteristic area 0.85). Finally, the index was sensitive to change with preoperative (surgical) scores decreasing from a mean of 17.6 to 7.1 by 4 weeks after prostatectomy ($P < 0.001$) [17]. All the available guidelines recommend using questionnaires in the evaluation of patients with BPH. A general physical examination with specific attention to the presence of absence of a distended bladder, excoriation of the genitals secondary to urinary incontinence, evidence of urethral discharge and a focused neurologic examination is also highly recommended. Physical examination is essential to investigate possible alternative diagnosis of LUTS as: urethral discharge, meatal stenosis, phimosis and penile cancer. Digital rectal examination (DRE) should always be performed in patients with LUTS in order to exclude cancer. In patients with BPH, DRE may be helpful in assessing prostate volume. According to the available evidence, there is a distinct underestimation of prostate size by digital rectal examination (DRE) when compared with ultrasound [18]. Data from the Krimpen study, suggest DRE is enough accurate to differentiate prostate volume higher or lower than 50 g (AUC = 0.92) [19].

Urinalysis is considered an inexpensive test which do not require sophisticated technologies and is generally recommended by almost all BPH guidelines [12]. In the past years the use of PSA as a screening tool has been an important matter of debate. According to the latest EAU guidelines, based on data from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial men who have less than a 15-year life expectancy are unlikely to benefit from PSA screening [20]. More specifically, guidelines suggest to offer an individualized risk-adapted strategy for early detection to a well-informed man with a good performance status and a life-expectancy of at least 10 to 15 years. In patients with BPH, PSA levels are well correlated with prostate volume [21]. Serum creatinine evaluation is recommended by several BPH guidelines. However, there is no evidence on its utility in the first-line evaluation of men with LUTS related to BPH. Renal insufficiency appears to be no more common in men with BPH than in men of the same age group in the general population. In several large clinical BPH trials, renal failure has been reported in less than 1% of the population evaluated [1].

Uroflometry is a recommended diagnostic test in the initial workup of patients with LUTS; it is a simple, non-invasive test that can identify patients with abnormal voiding pattern and monitor changes in voiding dynamics over time in watchful waiting programs and follow-up of medical therapy, physical treatment or surgical therapies. The prognostic ability of maximum free flow rate (PFR) in bladder outlet obstruction diagnosis is known to be in the range of 90, 67 and 30% for PFR values of less than 10 ml/s, 10–14 ml/s and greater than 15 ml/s respectively. Uroflow studies presented some limitations which include: variability over repeated test related to patient's learning effect, circadian effect, uro-flowmeter artefacts and intra-observer, inter-observer variation from manual correction of uroflow traces [22].

Measurement of post-void residual has been recommended as part of the initial evaluation although there is a weak evidence for it. The relation between elevated PVR and UTI is in fact evident in the pediatric and neurogenic populations but scanty in the BPH patient. PVR values below 50–100 mL are considered to be normal and value >300 mL is used to identify patients at risk of unfavorable outcome. Data from Oelke study on diagnostic accuracy of noninvasive tests to evaluate bladder outlet obstruction in men suggest using a PVR threshold of 50 mL, the diagnostic accuracy of PVR measurement has a PPV of 63% and a negative predictive value (NPV) of 52% for the prediction of BOO [22]. In the evaluation of patients with LUTS due to BPH ultrasound may play an important role in the

differential diagnosis particularly in the evaluation of patients with haematuria, large PVR and history of urolithiasis. Prostate ultrasound gives us information on total prostate volume, transitional zone volume and prostate shape and is indicated when prostate size can influence medical or surgical treatment [12]. US may be performed either transrectally or supra-pubically considering that a very strong correlation exists between supra-pubically and transrectally performed measurements for both the total prostate gland ($r = 0.948$, $p < 0.001$) and the TZP volume ($r = 0.953$, $p < 0.001$) [23].

Optional or Investigational Tests

Pressure flow studies are considered an optional test by several international guidelines. The gold standard for the diagnosis of BOO is represented by invasive urodynamics, however discomfort and complications may limit its use. Pressure-flow study has the unique capacity to diagnose BPO, detrusor overactivity and detrusor underactivity. According to EAU guidelines, in patients younger than 50 or older than 80, patients who have had previous un-successful invasive treatments, who cannot void more than 150 cc, who have Qmax>10 ml/s or in men who have post void urine volume (PVR) > 300 cc should undergo PFs.

Endoscopy is an optional test in all guidelines in patients with BPH, considering that it cannot diagnose BOO. The test could be useful in the evaluation of patients with LUTS but is appropriate in men with a history of microscopic or gross haematuria, urethral stricture, bladder cancer, or prior lower urinary tract surgery. It should not be performed whenever watchful waiting or medical therapy has been proposed as the treatment of choice and it remains optional in patients scheduled for surgery.

Some other non-invasive tests have been proposed however none of them can substitute invasive urodynamics. The penile-cuff test (PCT) and the external condom test have been introduced as a non-invasive alternative to PFS to determine the isovolumetric bladder pressure and also flow rate. This method, in which flow is interrupted to estimate isovolumetric bladder pressure, shows promising data, with good test repeatability and interobserver agreement. Bladder, detrusor wall thickness and bladder weight can be measured simply with suprapubic ultrasound. Overall some evidence suggests good accuracy of this measurements in diagnosing BOO due to BPH however the lack of standardization, and lack of evidence to indicate which measurement (BWT/DWT) is preferable render the test still investigational. Ultrasound measurement of IPP assesses the distance between the tip of the prostate median lobe and bladder neck in the midsagittal plane, using a supra-pubically positioned US scanner, with a bladder volume of 150–250 mL; grade I protrusion is 0–4.9 mm, grade II is 5–10 mm and grade III is >10 mm. Although the available evidence suggests a good performance in diagnosing BOO, the lack of standardization, and of data on inter-intra observer variability and learning curve still render the test investigational. According to the latest systematic review performed by the EAU non neurogenic LUTS guidelines panel and although all these tests have shown promising results for the noninvasive assessment of BOO, invasive urodynamics remain the gold standard [24].

BPH: Pharmacological Treatment

In the past years several pharmacological treatments have been approved to manage LUTS related to BPH. Moreover, the possibility to combine different pharmacological treatments enables a tailored treatment for each patient. Table 20.1 summarized the recommended and optional diagnostic tests according to different International guidelines.

Watchful Waiting

The simple diagnosis of LUTS due to BPH does necessarily trigger treatment. Most national and international guidelines suggest that patients with mild symptoms and no bother can be safely managed in a watchful waiting program. A good

Table 20.1 A summary of the recommendations for diagnostic testing in the basic management of men with BPH/LUTS

	EAU Guidelines 2018	AUA Guidelines 2018	NICE Recommendations 2015
History and physical examination	R. Baseline	R. Baseline	R. Baseline
Use of symptom score	R. Baseline	R. Baseline	R. Baseline
Urine analysis	R. Baseline	R. Baseline	R. Baseline
Serum creatinine	R∗	Not. R	R∗
Serum PSA	R. Baseline	Not. R	R∗
Use of a voiding diary	R+	R	R. Baseline
Uroflowmetry	R+	R before surgery	R+
PVR measurement	R. Baseline	R before surgery	R+
Prostate volume/shape	R+	R before surgery	NR
Imaging urinary tract	R if significant PVR	R	R∗[3]
Pressure-flow study	R∗[1]	R∗	R before surgery
Endoscopy	R∗[2]	R∗before surgery	R∗[2]

R∗ Recommended in selected cases, *R+* Recommended if bothersome symptoms; 1 patients younger than 50 or older than 80, patients who have had previous un-successful invasive treatments, who cannot void more than 150 cc, who have Qmax>10 ml/s or in men who have post void urine volume (PVR) > 300 cc. 2 History of: recurrent infection, sterile pyuria, haematuria, profound symptoms and pain. 3 History of chronic retention, haematuria, recurrent infection, sterile pyuria, profound symptoms, pain

number of patients will never progress to pharmacological or surgical treatment [12]. Watchful waiting is a viable option for many men with non-bothersome LUTS as few will progress to AUR and complications (e.g. renal insufficiency or stones) [12], whilst others can remain stable for years. Some studies report as much as 85% of the patients may remain stable at 1 year. The available guidelines recommend watchful waiting in men with mild/moderate symptoms, minimally bothered by their symptoms.

Alpha Blockers

α1-blockers are the first-line treatment in the management of BPH because of their speed of action, safety, tolerability and efficacy. α1-blockers aim to inhibit the effect of noradrenaline on smooth muscle cells in the prostate, resulting in a reduce prostate tone and BOO. Alfuzosin, doxazosin, and terazosin are usually considered nonselective drugs, inhibiting all the different α1-receptor subtypes conversely, tamsulosin and, above all, silodosin has higher selectivity for α-1A- receptors. Multiple, placebo-controlled, randomized, double- blind study of adequate size and duration confirmed the positive effect of α1AR antagonists on LUTS. Although head-to-head comparative studies are rare, they are currently regarded as equally clinically effective drugs in improving patient symptoms (IPSS improvement of about 35–40%), patient quality of life, and maximum flow rate (Q max; Q max improvements of 20–25%) [25]. Adverse events most frequently involve orthostatic hypotension, dizziness, and asthenia suggesting that AR receptors expressed in blood vessels and CNS are of importance. Major differences do exist in the adverse events (AEs) of the different drugs. Postural hypotension is more prevalent with non-selective α -blockers (prevalence rates close to 10%). Conversely, ejaculatory dysfunction is more frequent with tamsulosin and silodosin (prevalence more than 10%) [25]. Alpha 1 blockers are considered first line treatment because of rapid onset of action, good efficacy and low rate of AEs. Ophthalmologist should be informed before cataract surgery. Elderly patients should be aware of the risk of orthostatic hypotension as well as sexually active patients about the risk of EjD.

5α-Reductase Inhibitors

5-ARIs decrease the conversion of testosterone to dihydrotestosterone, which is the more powerful

metabolite. Finasteride inhibits subtype 2 of 5α-reductase, mainly present within the prostate, whereas dutasteride blocks both subtypes 1 and 2 of 5α-reductase. 5α-reductase inhibitors act by inducing apoptosis of prostate epithelial cells leading to prostate size reduction of about 18–28% and a decrease in circulating PSA levels of about 50% after 6–12 months of treatment [26, 27]. Several RCTs showed that 5ARI was significantly more efficacious than placebo both in treating LUTS and reducing prostate volume if prostate volume was larger than 30 cc and therapy was continued for at least 6–12 months. After 2–4 years of treatment, 5-ARIs improve IPSS by approximately 15–30%, decrease prostate volume by 18–28%, and increase Qmax by 1.5–2.0 mL/s in patients with LUTS due to prostate enlargement. Both finasteride and dutasteride are usually well tolerated. However, AEs are not uncommon, especially regarding sexual function. Loss of libido, ED, and ejaculatory dysfunction are present in about 5, 6, and 3%, respectively, in patients taking finasteride according to a recent Cochrane meta-analysis [19]. Similarly, Dutasteride is associated with risks of loss of libido, ED, and ejaculatory dysfunction in 4, 7, and 2%, respectively. Treatment with 5-ARIs should be considered in men with moderate-to-severe LUTS and an enlarged prostate (>40 mL) and/or elevated PSA concentration (>1.4–1.6 ng/mL). Due to the slow onset of action, they are suitable only for long-term treatment (years). Their effect on the serum PSA concentration needs to be considered in relation to PCa screening.

Combination Treatment with Alpha Blockers and 5ARI

Due to the opportunity to prevent disease progression with long-term use of 5-ARIs as well as to obtain short-term improvement with α-blockers, combination therapies with the two categories of drugs have been widely tested. CombAT (Combination of Avodart and Tamsulosin) study and MTOPS (Medical Therapy of Prostatic Symptoms) trials have confirmed efficacy and safety of combination treatment [26]. Long term data showed that combination treatment is superior to monotherapy for symptoms and Qmax, and superior to α-blocker alone in reducing the risk of AUR or need for surgery, and BPH progression defined by an IPSS increase of at least four points, UTI, incontinence, or an increase in creatinine >50%. Moreover, data from CONDUCT study compared efficacy and safety of a fixed-dose combination (FDC) of dutasteride and Tamsulosin to a WW approach with the potential initiation of tamsulosin (step-up approach) in a two-year RCT. The change in IPSS at 24 months was significantly greater for FDC than WW-All (−5.4 vs. −3.6 points, $P < 0.001$). With FDC, the risk of BPH progression was reduced by 43.1% ($P < 0.001$); 29% and 18% of men in the WW-All and FDC groups had clinical progression, respectively, comprising symptomatic progression in most patients [28]. Side effects were more common in the combination arm [26]. According to the available guidelines combination therapy should be offered to symptomatic patients, at increased risk of progression and with prostate volume >40 cc when long term treatment is planned.

Antimuscarinics (AM)

Antimuscarinics are mainly indicated in those patients with predominant storage LUTS. Antimuscarinics act predominantly on M2 and M3 receptors which are located in the detrusor muscle. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by the central nervous system. Several randomized clinical trials have assessed the efficacy of antimuscarinics in patients with storage LUTS when compared to placebo. In 2008 a large systematic review and metanalysis by Chapple et al. summarized data from 73 randomized clinical trials. Active treatments were more effective than placebo in terms of reduction in incontinence episodes, mean change in the number of micturitions per day, mean change in the number of urgency episodes per day and the mean change in the volume voided per micturition. In terms of tolerability most of the active treatments presented high rates of withdrawals (RR range: 1.33-2.44) when compared to placebo. In terms of side effects dry mouth was

the most frequently reported adverse event, reported by 29.6% and 7.9% of active treatment and placebo-arm patients, respectively. The next most common adverse event was pruritus (15.4% on treatment vs. 5.2% on placebo) [29]. Not all antimuscarinics have been tested in elderly men, and long-term studies on the efficacy of muscarinic receptor antagonists in men of any age with LUTS are not yet available. In addition, only patients with low PVR volumes at baseline were included in the studies. These drugs should therefore be prescribed with caution, and regular re-evaluation of IPSS and PVR urine is advised.

Combination Between Alpha Blockers and AM

In patients with both storage and voiding symptoms combining alpha blockers and antimuscarinics is indicated according to the latest EAU guidelines [12]. Kim et al. evaluated efficacy and safety of initial combination treatment of an alpha blocker with an anticholinergic in benign prostatic hyperplasia patients in a metanalysis including 16 studies with a total sample size of 3548 subjects. The pooled overall SMD change of storage IPSS improvement from baseline was −0.28 (95% CI: −0.40–0.17). The pooled overall SMD changes of QoL, Qmax, and PVR were − 0.29 (95% CI: −0.50–0.07), 0.00 (95% CI: −0.08–0.08), and 0.56 (95% CI: 0.23–0.89), respectively. There was no significant difference in the number of acute urinary retention (AUR) events or PVR. Study discontinuation occurred more frequently in patients with add-on combination therapy than in patients with placebo add-on (4.7–7% and 1.5–4%, respectively) [30].

Phosphodiesterase 5 Inhibitors

Phosphodiesterase 5 inhibitors (PDE5Is) increase intracellular cyclic guanosine monophosphate, thus reducing smooth muscle tone of the detrusor, prostate and urethra. Moreover, reflex pathways and neurotransmission of the urethra, prostate, or bladder may be altered. Only recently PDE5i have been introduced in the guidelines for the treatment of storage LUTS with/or without concomitant ED. According to the latest metanalysis on 13 randomized clinical trials including a total of 3973 treated patients, tadalafil 5 mg improves total IPSS (SMD = − 2.02, 95% CI = − 2.52 to −1.53, $P < 0.00001$), BPH index (SMD = −0.58, 95% CI = −0.84 to −0.33, $P < 0.00001$) and erectile function when compared to placebo. Improvement may be seen within a week of initiation of treatment. A Meta-regression of available clinical trials showed that baseline IPSS, dosage of PDE 5I, and country affect clinical improvement compared with placebo. No effect on urinary flow has been recorded in clinical trials. Adverse events mainly include: flushing, gastroesophageal reflux, headache, dyspepsia, back pain and nasal congestion [31, 32]. The latest EAU guidelines recommend the use phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction. It is important to consider the limited information on long term effects reduction of prostate size and disease progression. Only small, clinical, pilot studies were conducted to assess α1-blocker/PDE5-I for the treatment of LUTS/BPH. These data were pooled in a meta-analysis by Gacci and colleagues. The metanalysis evaluated a total of 278 patients with PDE5-I/α1-blocker combination therapy and demonstrated increases of IPSS (1.8 points), International Index of Erectile Function (3.6 points), and Qmax (1.5 ml/s) when compared to α1-blockers alone. AEs with combination therapy occurred in 6.8% of patients and in 5.1% of patients receiving α1-blockers. Overall, there were no serious AEs, and combination treatment was well tolerated [31]. The present combination may be use-full particularly in sexually active patients with both storage and voiding LUTS, however no specific recommendations are yet available on the guidelines.

Plant Extracts

Phytotherapy is a popular prescribed treatment for LUTS/BPH that falls within the framework of complementary medicine in most countries although some products are registered as drugs

particularly in Europe. Plant extracts suffer differences in the pharmaceutical preparation as the extraction procedures may differ among different commercial products, so the activity (efficacy, bioavailability, and pharmacodynamics) of individual components is not comparable; furthermore, some preparations contain mixture of different extracts. The origin of phytotherapeutic agents include: American dwarf palm, Saw palmetto, African plum tree, South African star grass, Pine Spruce, Stinging nettle, Rye, Pumpkin and Cactus flower extracts. Active components comprise: phytosterols (alpha-sitosterol), phytoestrogens fatty acids (lauric and myristicacid), lectins, flavonoids, plant oils, and polysaccharides. Serenoa repens, extracted from the American dwarf palm is one of the most frequently used products commercialized worldwide. The drug is considered to have antiandrogen, antiproliferative, and anti-inflammatory activities. Two meta analyses of Permixon studies performed by P. Boyle suggested a significant improvement of IPSS (−4.7), nocturia (1.0 over placebo), and maximum flow rate (2.3 mL/s over placebo). A Cochrane meta-analysis suggesting that men treated with Pygeum africanum were twice as likely to report symptom improvement whilst men treated with Secale cereale were twice as likely to benefit from therapy compared to placebo and that Serenoa repens was not superior to placebo, finasteride, or Tamsulosin for IPSS but confirmed that several different extract technique can influenced the observed results. Side-effects during phytotherapy are generally mild and comparable to placebo. Serious adverse events were not related to the study medication [33]. Due to the large heterogeneity in composition and formulation, guidelines do not give specific recommendation on the use of plant extract for the treatment of patients with BPH.

Beta-3 Agonist

Beta-3 adrenoceptors are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation. Mirabegron 50 mg is the first clinically available beta-3 agonist with approval for use in adults with OAB. A metanalysis identified five RCTs which compared solifenacin with mirabegron. Mirabegron achieved the same effect as solifenacin in treating OAB. The mean number of incontinence episodes per 24 h ($p = 0.20$), mean number of micturitions per 24 h ($p = 0.11$), mean number of urgency episodes per 24 h ($p = 0.23$), and mean volume voided per micturition ($P = 0.05$) suggested that mirabegron and solifenacin had no significant differences in terms of OAB treatment. With regard to drug-related AEs and dry mouth, mirabegron showed better tolerance than solifenacin. Post-voiding residual volume showed a distinct difference in the two groups. Hypertension and tachycardia did not show a significant difference between the two groups, but the pulse rate did [34]. The most common treatment-related adverse events in the mirabegron groups were hypertension, urinary tract infections, headache and nasopharyngitis. The current EAU guidelines recommend to use beta-3 agonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms. It is important to consider the lack of data on long term efficacy and safety. Overall four randomized clinical trials have evaluated the use of combination/add-on therapy in the management of patients with OAB symptoms [35–38]. These trials have evaluated different combination doses of Solifenacin (2.5 mg, 5 mg and 10 mg) and Mirabegron doses (25 mg and 50 mg). In terms of improvement in symptoms and incontinence episodes all combinations were superior Solifenacin monotherapy. In terms of tolerability combination treatment was well tolerated across all trials. AEs were slightly more frequent in the combination arms when compared to the monotherapy arms. The abovementioned trials have been published between 2015 and 2018 therefore no recommendations are yet available on the guidelines.

BPH Surgical Treatment

The current European Urology Association (EAU) Guidelines recommends surgical treatment in presence of recurrent or refractory uri-

nary retention, overflow incontinence, recurrent UTIs, bladder stones or diverticula, treatment-resistant macroscopic haematuria due to BPH/BPE, or dilatation of the upper urinary tract due to BPO, with or without renal insufficiency (absolute operation indications, need for surgery). Additionally, surgery is usually needed when patients have not obtained adequate relief from LUTS or amelioration of PVR using conservative or medical treatments (relative operation indications) [12].

Likewise, American Urology Association (AUA) Guidelines considers surgical intervention is an appropriate treatment option for patients with moderate-to-severe LUTS despite medical therapy and for patients who have developed acute urinary retention or other BPH-related complications [39]. In some cases, patients will have tried medical therapy before proceeding with surgery otherwise some patients may wish to have the most effective therapy initially if their symptoms are particularly bothersome. In such circumstance, the decision to elect surgery as the primary treatment option should be based upon the patient's own views of treatment risks versus benefits. Technological advances have continuously lead new surgical techniques aimed to be less invasive with high efficacy as well as previous techniques have been ameliorated and largely validated in several clinical trials. Thus, several approaches are now available (Table 20.2) making the choose multi-factorials. This decision mainly depends, on prostate size, comorbidities of the patient, ability to have anesthesia, patients' preferences, willingness to accept surgery-associated specific side-effects, availability of the surgical armamentarium, and, last but not least, experience of the surgeon with a particular surgical technique.

Minimally Invasive Surgery

Many patients seek a higher symptoms improvement than medical therapy but are not willing to surgical treatment. Likewise, some patients are poor candidates for surgical therapy and are irresponsive to medical therapy. Thus, some minimally invasive surgical procedures have been developed and usually performed in an outpatient setting.

Prostatic Urethral Lift (PUL)

PUL involves the transurethral placement of small permanent intraprostatic implants (comprising of nitinol, polypropylene, and stainless steel) to retract the obstructive lateral prostatic lobes away from the prostatic urethral lumen, creating an anterior channel, hence treating benign prostatic obstruction without tissue demolition. In 2014 a systematic review and meta-analysis was performed to assess PUL outcomes. The study reported an improvement of symptoms (mean gain range of 1.3–1.6, IPSS difference of 7.2 to 8.7 points), Q_{max} (3.4–4.0 mL/s), and QoL (2.2–2.4 points). Likewise, sexual function was preserved with a small improvement. However, most of the studies have only 12-months long follow-up, making controversial the true advantage of the devices [40]. Thus, PUL should be offered as surgical option to patients with LUTS interested to preserve ejaculatory function and with prostate volume < 70 ml in absence of middle lobe. However, patients should be informed about absence of long-term data [12].

Temporary Implantable Nitinol Device (TIND)

The TIND is nithinol temporary device which is implanted to increase prostatic urethral patency. The TIND is crimped and delivered thought cystoscope sheath, released and active into prostatic urethra. It is hypothesized that the radial force exerted by active TIND into prostatic urethra causes a bladder neck incision and reduces bladder outflow obstruction. Porpiglia et al. performed the first clinical trial in human setting, with a 3-year follow-up. The 32 enrolled patients were > 50 years old, had an IPSS ≥10, peak urinary flow (Qmax) < 12 mL/s and a prostate volume < 60 mL. At 12-mo follow-up, a significant improvement in IPSS of 45% ($p < 0.001$) and in Qmax of 67% (+4.4 ml/s; $p < 0.001$) compared to mean baseline parameters were observed. Furthermore, no patients needed further medical or surgical therapy at 12 months. After 36 months,

Table 20.2 Overview of main features of the most popular surgeries for BPH treatment

		Simple prostatectomy			Trans-urethral surgery				
		Open	Laparoscopy[a]	Robot-assisted[a]	mTurp	bTurp	Holmium Enucleation	180 W PVP	Thullium Enucleation
Prostate volume		≥80 ml			30–80 ml	30–80 ml	No upper limit	No upper limit	
Efficacy	Range of increase Qmax, ml/s	16.5–20.2	15.1–21.2	15–22	9.7–13	Comparable t to mTurp	25.1–27.1	19.4–22.6	18.2–20.3
	Mean IPSS reduction, %	63–86	66–88	67–78	62		72–82	53–82	70
	QoL score improvement, %	60–87	n.a.	n.a.	69		70	34–65	60–70
	PVR reduction, %	86–98	n.a.	n.a	77		84	82	90
	Retreatment risk, %	5	n.a.	n.a	6.6		6.7	11	3.4
Tollerability	Transfusion rate, %	7–14	<1	<1	3–5		8	1–3	5
	Transient incontinence, %	<10	<1	<1	0.5–2.2		1.5	6.5	2.1
	Urethra stricture risk, %	2–6	1	1	2–3.8		4.4	2	1.9
	TUR syndrome risk, %				0.8–1.1				
	Retrograde ejaculation, %	80–90	Comparable to open	Comparable to open	53–65.4	Comparable mTurp	Like mTurp	Like mTurP	Like mTurp
	Advantage and drawbacks	Standard reference	Efficacy comparable to open although higher operative time and lower blood loss Laparoscopic skill is required Long term outcomes need to be evaluated		Standard reference	To avoid Tur-syndrome	Large adenoma Working under anticoagulation medication Longer learning curve	Large adenoma Working under anticoagulation medication	Confirmatory studies are required

Formed from reported data on EAU 2017 Guidelines

[a]Adapted from: Autorino R et al., Perioperative Outcomes of Robotic and Laparoscopic Simple Prostatectomy: A European–American Multi-institutional Analysis, Eur Urol 68 (2015); 86–94

IPSS and Qmax worsened, although they were still better than baseline [41]. This treatment looks to be a valid option for sexually active patients who wish to preserve ejaculatory function however a large multi-institutional study is ongoing whereby the procedure is not yet recommended by AUA and EAU.

Intraprostatic Drugs Injection

Some agents are injected into prostatic gland to determine cellular apoptosis and thus glandular volume reduction with symptom ameliorant. Among those agents, ethanol has been evaluated by several studies reporting transient symptomatic improvement with 40% risk of retreatment [42]. Furthermore, Onabotulinum toxin A have been investigated in a randomized trial enrolling 380 patients. Patients were randomized to receive 100 U, 200 U, 300 U of Onabotulinum toxin A vs. placebo. Overall, an improvement of BPH parameters was found (i.e. IPSS -5.5 to 6.6 points according to the dose, Q_{max} + 2.0 to 2.4 mL/s, according to the dose) however a similar amelioration was also observed in control arm. Thus, the authors concluded that there is no evidence of clinical benefits in medical practice [43]. According to EAU Guidelines, Botulinum toxin injection as treatment for male LUTS is not more recommended [12].

Prostate Artery Embolization

Prostate artery embolization (PAE) is an interventional radiological technique involving the injection of small particles directly into the prostatic arteries bilaterally, leading to devascularization of hypervascular nodules. The reduction of prostate's blood supply causes necrosis and glandular shrink. The procedure is usually performed under local anaesthesia and X-ray guidance while the gland is approached through the right or left femoral artery. Since its introduction in 2001, this treatment looks to be a challenge due to variation in prostatic artery anatomy that can make identification and embolization of the artery difficult. However, the enhancement of computed tomography has ameliorated pre-operative vessels identification leading more popular the technique.

A recent systemic meta-analysis including five studies and 708 patients, showed that prostatic embolization improves IPSS, prostate volume and maximum urinary flow rate, with no deterioration in International Index of Erectile Function (IIEF whereas less efficiently than standard surgery (Zumstein V). However, comparative studies with longer follow-up are still required to establish the true role of prostatic embolization in the treatment pathway for LUTS/BPH.

Trans Urethral Resection of Prostate (TURP)

TURP is the most popular surgical treatment for BPH with numerous technical improvements within the last years. Furthermore, its principle to remove tissue from the transition zone of the prostate to reduce bladder outflow obstruction and consequently urinary symptoms, has been unchanged over the years. The choice of this technique it is generally suggested when prostate volume is not more than 80 mL. Several trials over the last years have showed TURP efficacy so that it is considered the reference standard treatment. Recent meta-analysis including 20 randomized clinical trials and a maximum follow-up of 5 years, showed a mean improvement of Q_{max} (+162), reduction of IPSS (−70%), QoL score (−69%) and PVR (−77%) [44]. Regarding the surgical complications, a 1% risk of urinary incontinence was reported while the risks of bladder neck contracture, bleeding requiring transfusions, urethral stricture were not more than 5%. Furthermore, the development of bipolar resectoscope has made possible to perform the procedure in saline solution avoiding the risk of transurethral syndrome with efficacy comparable to monopolar resectoscope [45].

Laser Surgery

Development of laser technology has instituted new techniques for the treatment of benign prostate enlargement. At present, the most frequently

used lasers are holmium (Ho):YAG, potassium titanyl phosphate or lithium triborate (GreenLight), thulium, and diode laser.

Holmium Laser Enucleation of the Prostate (HoLEP)

The surgical technique has been initially descripted by Gilling et al. Briefly, the surgical technique involves the development of the plane between prostatic adenoma and capsule through laser incisions to remove the adenoma and push it in the lumen of the bladder. Then, an endoscopic morcellator is used to evacuate the adenoma [46].

Up to now, several meta-analysis have compared HoLEP with TURP. No significative differences have been detected about symptoms improvement although in three meta-analysis was found that HoLEP is comparable or superior to TURP due to more pronounced reduction of voiding-related symptoms and increase of urinary flow rate [47]. It has been postulated that enucleation of the obstructing prostatic adenoma resulting in a wide prostatic cavity, similar to open prostatectomy, provides superior voiding function. Likewise, late complications after HoLEP are similar to other transurethral procedures and include bladder neck stenosis (0–3%), urethral strictures (2–8%), and urinary stress incontinence (0–3%). Compared to open prostatectomy for prostates with a volume of more 80-100 ml, randomized clinical trials indicate that HoLEP is comparable in term of urinary symptoms improvement and durability with lower morbidity (less blood loss and shorter catheterization). However, longer surgical time is required (mean + 40 minutes) as well as at least 20 procedures are necessary to became familiar with the procedure.

Photoselective Vaporization of the Prostate (PVP)

The introduction of potassium titanyl phosphate (KTP) laser has aroused new interest in the laser technique. Indeed, the KTP-PVP has significantly evolved from the original 80 Watt, to the current 180 Watt laser equipped with a liquid cooled fiber able to emit a higher amount of energy resulting in faster vaporization. The main principle of surgical technique is to achieve a nonobstructive prostatic urethra with a smooth tissue surface. Such objective is obtained through tissue ablation gained by side sweeping of the laser fiber bean that is moved in anterior and posterior fashion. Compared to standard TURP, 80-W and 120-W PVP improvement of IPSS, maximum flow rate, and postvoid residual volume was comparable between techniques, whereas operating time was by around 20 min longer with PVP [48]. With the 180-W laser efficacy is comparable to TURP in terms of IPSS, Qmax, PVR volume, prostate volume reduction, PSA decrease and QoL questionnaires. The 180-W PVP is superior to TURP in terms of catheterization time, length of hospital stay and time to stable health status [49]. Again, 180-W PVP is non-inferior to TURP in terms of peri-operative complications, being considered safe in high-risk patients under anticoagulation treatment [12].

LASER Ongoing Validation

At present, limited number of studies are available for thulium laser prostatectomy and diode laser vaporization of prostate although the two lasers have gained enough interest to be included in EAU Guidelines [12]. Thulium laser allows rapid vaporization as well as smooth incision of the prostatic tissue, thus it is currently applied in different approaches, using either enucleation technique, vaporization techniques or techniques combining both principles such as vaporesection or vapoenucleation. Early studies showed efficacy and safety comparable to TURP in terms of symptoms improvement, voiding parameters complications rate however quantity of studies on thulium is currently inferior when compared to TURP, HoLEP and PVP [50]. The light of diode lasers is generated by semiconductors so with a wavelength depending on the semiconductor used. The diode is currently applied for both vaporization and enucleation of the prostate. Preliminary data on 980 nm laser vaporization show high rate of post-operatively dysuria, high rate of re-operation rates although significant and rapid improvement of symptoms, voiding parameters are achieved. Furthermore, absence of longer follow-up as well as comparative studies make the use of diode laser still experimental.

Simple Prostatectomy

Open prostatectomy typically is performed on patients with prostate volumes greater than 80 to 100 mL especially when there is a concomitant pathology, i.e. large bladder calculi or diverticula. Another indication is the inability to place patient in dorsal lithotomy position required for endoscopic BPH surgery. Main contraindications include the presence of prostate cancer or previous pelvic surgery that may be inaccessible the prostate gland. Although laparoscopic and robot-assisted simple prostatectomy is nowadays feasible three different techniques have been descripted for open simple prostatectomy. Historically, Fuller in USA and McGill in UK described the retropubic (trans-vesical) approach. Otherwise, the prostatic adenoma is removed by a transverse incision in the anterior prostatic capsule in the transcapsular approach described by Terence Millin in 1945. Finally, the third approach was via perineum which was introduced by Hugh Young in 1903 at it is rarely performed.

Due to developing of new endoscopic techniques, open partial prostatectomy is nowadays less performed with national surveys showing that less than 20% of BPH procedures are open partial prostatectomies [51] Perioperative hemorrhage is the major concern for which authors have proposed some tips as ligation of dorsal vein complex or prostatic arterial pedicle. Then, urinary extravasation in the immediate postoperative period may be the result of incomplete closure of prostatic capsule or vesical incision. Damage of urinary sphincter as well as late complications – i.e. epididymitis, bladder neck contracture – are not common [52]. Finally, a nation-wide analysis including over 20.000 cases with a long follow-up showed a lower reoperation rate after open prostatectomy compared to TURP (respectively, 3.4% vs. 7.4% at 8-years after primary surgery) [52].

Laparoscopic approach for simple prostatectomy initially descripted by Mariano et al. in 2002 while.

Sotelo et al. reported the feasibility of robot-assisted approach in 2008. Afterwards, both the procedures were embraced by others to overcome the drawbacks of open technique.

At present, a meta-analysis including 764 patients from 27 studies has underlined the reproducibility of both laparoscopic approaches confirming that either techniques provides functional improvements similar to those of open with a longer operative time but less blood loss and shorter hospital stay [53]. Furthermore, no significative differences were detected between the two approaches in terms of improvements in Qmax, IPSS and peri-operative complications. Authors have also suggested personal tricks and nuances to optimize the procedure anyway respecting the principles of transcapsular and transvesical open approaches [54]. However, laparoscopic approach is considered as alternative to open simple prostatectomy for large prostate although studies of long-term efficacy are still required [12].

Conclusions

The management of patients with LUTS due to BPH has completely changed in the last decade with the development of new drug therapies and the introduction of the multimodality and combination treatment. Patients generally prefer pharmacological or non-invasive treatments and delay surgical treatment. Patients now usually receive surgery when they are older, with more comorbidities and larger prostate which determine a more challenging surgical procedure. The implementation of laser technology and techniques including enucleation or vaporization have challenge the TURP as the new standards although a proper knowledge of the pathophysiology of patients with LUTS related to BPH/BPO and a correct diagnosis still remain the pillars of a successful LUTS/BPH management.

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21 Practical Guidelines for the Treatment of Erectile Dysfunction and Peyronie's Disease

Julian Marcon and Christian G. Stief

Management of Erectile Dysfunction

Male Erection and Erectile Dysfunction

An elaborate interaction of neurological, vascular and psychological factors is necessary for the mechanism of male erection. Sexual arousal, for instance in the form of visual or haptic stimuli, is processed in several parasympathetic loci of the brain, such as the limbic system. Via the mediation of multiple neurotransmitters (e.g. dopamine, oxytocin and serotonin) neural impulses are sent to the parasympathetic erection center (S_2–S_4). Vegetative nerve fibers run from the spinal erection center through the pelvis and enter, in the form of the cavernous nerves, the penile cavernous bodies. Non-adrenergic non-cholinergic (NANC) synapses release nitric oxide (NO). Additionally, cholinergic signals from nerve fibers stimulate the epithelioid nitric oxide synthase (eNOS) in the corpora, leading to the transformation of l-arginine and oxygen to NO. Consecutively, activation of the guanylyl cyclase by NO causes the enzymatically triggered transformation of 5-guanosine triphosphate (5-GTP) to 3′5′-cyclic guanosine monophosphate (3′5′-cGMP). At the same time, 3′5′-cGMP is cleaved by enzymatic activity of phosphodiesterase-5 (PDE-5). By prostaglandin-mediated activation of the adenylyl cyclase, ATP is converted to cAMP as the other second messenger. Both messengers activate cAMP- and cGMP-dependent protein kinases, which via phosphorylation of target proteins causes cell hyperpolarization, sequestration of intracellular calcium and blockage of calcium influx, leading to a decrease of intracellular calcium. This decrease results in smooth muscle relaxation in the cavernous trabeculae. Arterial blood streams into the cavernous bodies of the penis, causing penile tumescence and an erect state. The increasing corporeal blood volume leads to an occlusion of efferent veins along the tunica albuginea, inducing penile rigidity. In the rigid phase, an intracorporeal pressure of several hundred millimeters of mercury is reached, the ischiocavernosus muscles are synchronously contracted. A continuous transgression of 3′5′-cGMP threshold levels, with simultaneous degradation by PDE-5, supports maintenance of rigidity. Following sexual activity, nerve signaling induces calcium influx into the cell, causing a contraction of smooth muscle tissue, leading to detumescence [1, 2].

Erectile dysfunction (ED) is a functional disorder and is defined as the continuing inability to gain and maintain an erection sufficient for satisfactory sexual activity. Degrees of severity can vary in patients, not least because expectations

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towards sexuality are individually different. Temporary episodes of ED, often linked to external stress factors and a resulting negative impact of catecholamine secretion appear at least once in a majority of men. While appropriate episodes are commonly self-limited, persevering disorders require medical attention. A primary ED is defined by an occurrence with the beginning of sexual activity, which is usually in early adolescence. Affected men never had normal erections before. A secondary ED is considered a new event at a later time, with normal prior erectile function [3].

Epidemiology and Etiology of ED

In the German Cologne study, ED was prevalent in 19.2% of men between 30 and 80 years. It showed a higher occurrence with increasing age. Affected men often suffered from a greatly decreased quality of life [4]. A multinational study on self-reported ED in 2912 men between 20 and 75 years described an overall prevalence of 16%. ED was associated with other comorbidities such as cardiovascular disease, diabetes, dyslipidemia and depression [5]. Loss of erectile function has both been recognized as an independent risk factor for and an indicator of coronary heart disease [6]. ED can occur in consequence to hormonal disorders (e.g. hypothyroidism or hypogonadism), genital diseases (e.g. Peyronie's disease), pelvic or penile trauma and psychological reasons. Neurological disorders associated with ED can affect central (e.g. multiple sclerosis) or peripheral nerve structures (e.g. autonomous polyneuropathy). External factors, such as the abuse of drugs, alcohol or tobacco can cause ED. Other etiologies include renal or hepatic impairment and an association with benign prostatic hyperplasia. Iatrogenic causes of ED include a drug-induced etiology and previous pelvic surgery or radiation therapy for malignant tumors. Irritation or damage of the neurovascular bundles along the dorsal capsule of the prostate can subsequently lead to partial or complete ED [1]. More recent data could link ED to chronic prostatitis/chronic pelvic pain syndrome and other comorbidities, such as psoriasis, inflammatory bowel disease and gouty arthritis [3].

Diagnostic Work-Up of ED

Patient history is a crucial aspect in the diagnostic process and should include a detailed description of the individual sexual history. The beginning of sexual development and appropriate experiences should be part of the conversation. The start and duration of ED symptoms should be discussed. Further points should address the patient's sexual orientation, prior and present relationship status and, if applicable, previous treatments of sexual dysfunction. Information on the current status of libido as well as the presence of normal orgasm and ejaculation are ideally provided by the patient. A history of pelvic or genital trauma should be explored, as well. To objectivize symptoms and to determine the grade of ED severity, especially under ongoing therapy, usage of a standardized questionnaire is recommendable. Initially created for the assessment of medical therapy success, the International Index of Erectile Function (IIEF—currently in the fifth edition) is generally used. The IIEF score addresses frequency, maintenance and quality of erections as well as the patient's libido and general sexual satisfaction. A shorter six-item version (IIEF-EF) covers erectile function only. It distinguishes between normal erectile function (26–30 points) as well as mild (22–25 points), mild-moderate (17–21 points), moderate (11–16 points) and severe ED (6–10 points). A study analyzing 17 randomized-controlled studies calculated minimal clinically important differences (MCID) for the erectile function domain of the IIEF score as $\geq$4 points [7, 8]. Another abridged five-item version of the IIEF score (IIEF-5), ranging in severity from no ED (22–25 points) to severe ED (5–7 points), has been validated for the evaluation of ED and is widely used [9].

Other commonly used scoring systems include the Erection Quality Score (EQS), the Erection Hardness Score (EHS) and the Sexual Encounter Profile (SEP), the latter being based on patient diary notes. The occurrence and dynamics of nocturnal penile erections should also be addressed, a

lack of which is an indicator of advanced vascular dysfunction. Four to five episodes of penile tumescence, each between 10 and 40 minutes, is considered physiological. The patient's past medical and surgical history should be addressed, including a history of cardiovascular, neurological and metabolic disorders. In terms of past surgery, prior genital and abdominopelvic operations need to be discussed in particular.

Previous or current medications should be covered in the discussion, as well, as there are several substances with a potentially negative impact on sexuality. This is mostly due to a hormonal disequilibrium in testosterone, gonadotropin and prolactin balances. Among the drugs that are known to be associated with ED are:

- *Antihypertensive drugs* (ß-blockers and thiazide diuretics) - > influence on testosterone biosynthesis and enhanced zinc excretion (total and free testosterone levels reduced) [10]
- *Statins* (atorvastatin, simvastatin) - > inhibition of testosterone biosynthesis (total and free testosterone levels reduced) [11]
- *Psychopharmaceuticals* [12]
  - Tricyclic antidepressants (TCA) (imipramine, desimipramine) -> increase of prolactin levels
  - Selective serotonin reuptake inhibitors (SSRI) (fluoxetine, paroxetine) -> increase of prolactin levels
- *Opioids/sedatives* (benzodiazepines) -> central inhibition of gonadotropin release (total testosterone, FSH and LH levels reduced)
- *Antimycotics* (clotrimazole, ketoconazole) -> inhibition of testosterone biosynthesis
- *5α-reductase inhibitors* (5-ARI) (finasteride, dutasteride) -> decrease of dihydrotestosterone, increase of estradiol [13]

With respect to *external noxae*, the role of nicotine abuse is unclear. A small study in a small non-smoking cohort found a positive association between acute nicotine application and decreased sexual function [14]. However, a more recent large meta-analysis, including more than 50,000 cases, could not find an appropriate association between tobacco smoking and ED [15]. Yet, cessation of smoking is regarded as beneficial for erectile function [16]. A recent meta-analysis investigated the effect of alcohol consumption on the risk of ED. Light to moderate consumption (less than 21 drinks per week) was hereby inversely associated with ED, high consumption had no impact on prevalence [17]. Studies on the association of ED and recreational drugs are scarce, one trial suggested a negative effect of illicit drugs (heroin, amphetamine and MDMA) on sexual function [18].

Physical examination should contain an assessment of all organ systems involved in erectile function, including a vascular, hormonal, neurological and urological status. If measurement of heart rate and blood pressure was not performed within the past three to six months, it should be done at first presentation. Abnormalities in these parameters or a suspected vasculogenic ED should be followed up with a cardiologist to estimate the patient's cardiovascular risk. Indicators of hormonal dysfunction, e.g. a gynecomastia, should also be evaluated [19].

A *genital examination* should include a palpation of the testes for indurations or suspicious masses (e.g. testicular cancer), measurement of testicular volume and assessment of the penis for abnormalities or deformation (e.g. Peyronie's disease).

Digital-rectal examination can provide information on the presence of prostatic enlargement or suspicious indurations. An association between lower urinary tract symptoms and sexual dysfunction has been described [20].

Sonography should be incorporated in the diagnostic process. Sonography of the testes may reveal suspicious lesions, a varicocele or hydrocele and can support determination of testicular volume.

With regard to *laboratory testing*, determination of early morning serum total testosterone, prolactin and luteinizing hormone (LH) can reveal hormonal imbalances. A blood lipid profile and, serum glucose and glycosylated hemoglobin, to exclude metabolic disorders or diabetes should also be part of blood testing. Determination of prostate-specific antigen (PSA) is useful in distinct patient groups [21].

There is a variety of *specific examinations*, which are not part of the standard work-up of ED.

Intracavernous injection of vasoactive agents to induce erection, with or without performance of color-coded duplex sonography, can be performed to assess concomitant localized disease (e.g. Peyronie's disease). It is also used to discern psychogenic from organic ED, although results can be inaccurate. Regarding the interpretation of results, a response to low doses can indicate a psychologically or hormonally caused ED, while a response to only high dosages suggests a vascular etiology. A lack of response to high doses can be interpreted as veno-occlusive dysfunction [22]. Neurophysiological assessment of the bulbocavernosus reflex latency (BCR) or pudendal somatosensory evoked potentials (SSEP) can be used when a neurological etiology is suspected. Performance of invasive cavernosography or cavernosometry can be used to evaluate intracavernous pressure and to visualize vascular anomalies. Nowadays, these invasive examinations only play a role in rare, posttraumatic cases, eligible for vascular surgery [23]. Measurement of nocturnal erections using a special electronic device is positive, if a rigidity of 60% on the tip of the penis is recorded on two separate nights. However, it has poor reliability in terms of a distinction between organic and psychogenic ED and is mostly used for forensic purposes, e.g. in men charged with rape [24].

ED and Cardiovascular Disease

As described above, presence of vasculogenic ED should be followed up with an assessment of the cardiovascular system. In this context, ED can play a role in the early detection of cardiovascular disease, even in the absence of cardiac symptoms at that time. A multidisciplinary consensus panel defined three cardiovascular risk groups for patients with ED. This algorithm can also help to determine whether patients with known cardiovascular disease are safe to perform sexually. A main criterion is the patient's exercise ability. Benchmarks are the ability to walk one mile in 20 minutes or to climb two flights of stairs in ten seconds [25]. Patients in the *low-risk group* do not bear a significant cardiac risk for sexual activity, e.g. under the following conditions:

- Mild valvular disease
- Left ventricular dysfunction/congestive heart failure (NYHA classes I/II)
- History of successful cardiovascular revascularization (e.g. by stenting, bypass grafting)
- Asymptomatic controlled hypertension

Patients in the *high-risk group* are threatened by significantly increased cardiac risk during sexual performance, e.g. under following conditions:

- Uncontrolled hypertension
- Severe congestive heart failure (NYHA class IV)
- Myocardial infarction within the past two weeks without intervention
- High-risk arrhythmia (e.g. uncontrolled atrial fibrillation, exercise-induced ventricular tachycardia)
- Unstable or refractory angina pectoris
- Severe valvular disease

Patients who do not match low- or high-risk categories, are considered to be of indeterminate risk. An additional stress test, in the form of a four-minute Bruce treadmill protocol, without signs of arrhythmia or symptoms is performed to determine the final risk category (low- or high-risk). Patients in the *indeterminate-risk group* include those with:

- Myocardial infarction within the past two to eight weeks without intervention
- Mild to moderate stable angina pectoris
- Congestive heart failure (NYHA class III)

Patients in the low-risk group can safely continue with sexual activity and initiate ED therapy.

In high-risk patients, treatment should be postponed until a stable cardiac status has been attained. These patients should be referred to a cardiologist to direct further diagnostic assessment and therapy [3, 25, 26].

Conservative Treatment of ED

General Considerations

A variety of conservative treatment options for ED are available, which can be used separately or as part of combination regimens. A first and essential step should address the adjustment of lifestyle and cardiovascular risk factors, such as weight optimization and regulation of an existing arterial hypertension. Patients with poorly controlled diabetes are more at risk to develop ED, an optimization of glycosylated hemoglobin can improve erectile function [27]. Patients with obstructive sleep apnea can preserve or enhance their sexual function by undergoing long-term continuous positive airway pressure (CPAP) treatment [28]. A healthy diet, e.g. the Mediterranean diet with an emphasis on fruits and vegetables, fish, cheese and yogurt, in combination with regular physical exercise is beneficial for erectile function. Moreover, a termination of exposure to external noxae, such as the cessation of smoking should be aimed for. By an adjustment of these factors an improvement of ED symptoms can be achieved. Further, these measures can lead to an improved response to medical therapy [29]. However, patients should be informed that although a modification of lifestyle factors and therapy regimens can yield partial reversibility and have a positive impact on symptoms, in most cases ED cannot be cured. If curable causes of ED are present, they should be addressed prior to further therapy steps. An algorithm regarding conservative and surgical treatment options is provided in a flow diagram in Fig. 21.1.

Potentially Curable Conditions in ED

Hormonal Disorders: Hypogonadism and Hyperprolactinemia

Testosterone is an essential hormone regarding male sexual and reproductive function. Biosynthesis in testicular Leydig cells (95%) and the adrenal cortex (5%) is centrally regulated by a secretion of luteinizing hormone (LH) in the pituitary gland. A negative feedback mechanism prevents overstimulation. As an anabolic steroid testosterone plays an important role in muscle

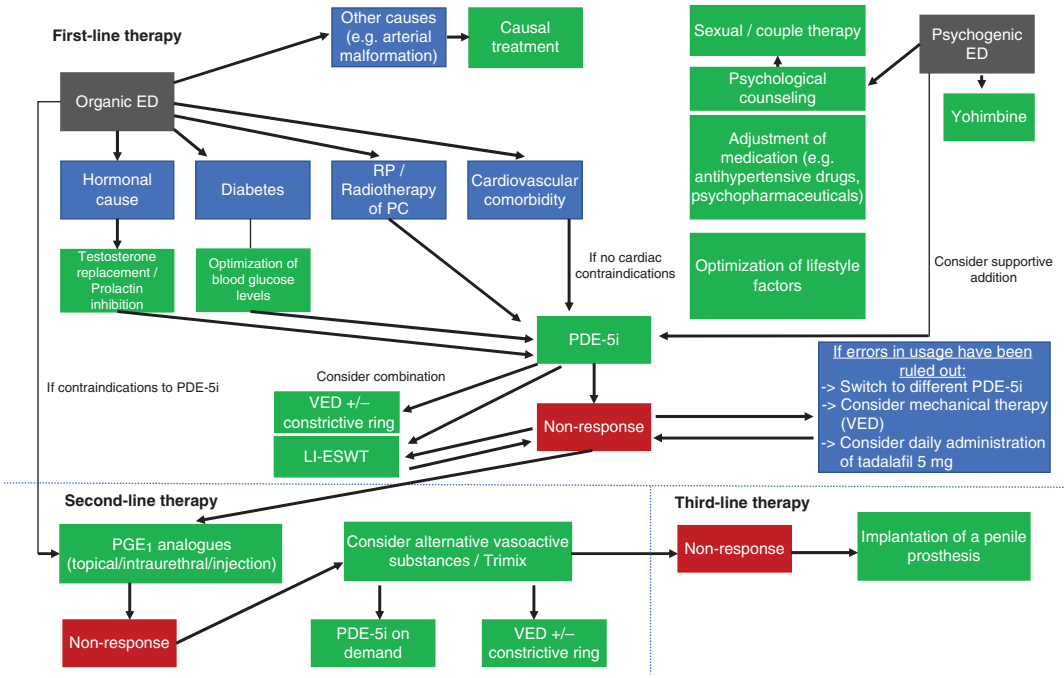

Fig. 21.1 Treatment algorithm for ED (modified after [Trottmann et al. 2018])

and bone metabolism. It promotes body hair growth and the development of secondary sexual organs. Several steps in erectile physiology are testosterone-dependent: Neural processes on the spinal level, parasympathetic signal transfer in the cavernous bodies and smooth muscle relaxation require sufficient testosterone levels. Insufficiency, present in up to 40% of men above 40 years, can therefore lead to ED and to an apoptosis of smooth muscle cells [30]. Relevant threshold levels of testosterone are reported to range between 2.3 and 3 ng/mL (8–10.4 nmol/l). Testosterone substitution (TS) has been shown to significantly improve PDE-5 inhibitor response in men with ED and testosterone levels lower than 3 ng/mL [31]. Several application forms are available, such as topically applicable gels and intramuscular injections of depot preparations (e.g. testosterone undecanoate every 10–14 weeks). Before treatment is started, patients should undergo a blood test, including determination of PSA, hematocrit, liver function and a lipid profile. Patients should be informed about an elevated cardiovascular risk under TS, high risk patients should be referred to a cardiologist before therapy start. In adult men with late-onset hypogonadism, TS is only to be carried out after failure of conservative lifestyle adjustments. Testosterone-related, inhibitory effects on spermatogenesis should be addressed and therapy held in couples trying to conceive. A digital-rectal examination of the prostate should be performed to rule out irregularities. TS is contraindicated in patients with untreated prostate cancer. Men with a history of the disease, and low risk of tumor recurrence (Gleason score < 8, PSA < 10 ng/mL, pathological stage pT1–2), may be substituted under close-meshed surveillance. TS in prostate cancer patients is regarded as controversial, due to the unclear role of externally applied testosterone as a promoter in prostate cancer. Generally, a follow-up of patients receiving TS at 3, 6 and 12 months should include determination of hematocrit, PSA and testosterone levels, further controls thereafter should be performed annually. If the hematocrit exceeds 50%, substitution should be held until further clarification of etiology. Discontinuation or a dose-reduction should be performed if the hematocrit under therapy reaches levels of 54% or more. Due to the variety of underlying causes of hypogonadism, consultation of an endocrinologist in complex cases can be helpful prior to initiation of TS [32, 33]. In men, prolactin is being excessively secreted before sexual climax, although its exact function remains unknown. Hyperprolactinemia has a negative effect on male sexuality and can either be drug-induced or the result of a prolactinoma. A prolactinoma, either occurring as a micro- (size: <1 cm) or macroprolactinoma (size: >1 cm) is a tumor of the pituitary gland, which produces large amounts of prolactin. Diagnosis is established by measurement of prolactin levels and consecutive magnetic resonance imaging (MRI) of the brain. Treatment consists mostly of medication with dopamine agonists (e.g. 20–40 mg bromocriptine per day). Microsurgery is necessary only in large tumors and has to be followed with life-long medication, as drug discontinuation results in recurrence in a majority of patients [34].

- In men with testosterone levels lower than 3 ng/mL substitution of testosterone can benefit sexual function and PDE-5i response
- Careful evaluation of etiology and necessary laboratory testing should be performed prior to substitution
- In prolactinoma, usually life-long therapy with dopamine agonists is indicated

Psychogenic ED

Numerous psychological factors have to be considered when counseling patients with ED. For one, perception of sexuality is influenced by individual preferences, cultural background and upbringing. Previous negative or unfulfilling sexual experiences, abusive or dysfunctional sexual relationships, can contribute to a negative self-image and result in low sexual confidence. A resulting anxiety with regard to sexual performance is commonly found in men with long-term erectile disorder. Sexual therapy, such as psychodynamic approaches, couple counselling or behavioral therapy, can benefit the treatment of both patients with psychogenic ED and, as an additional supportive component, those with ED of mixed etiology. Regular follow-up with the

sexual therapist is important for treatment success. Early involvement of the partner has also been shown to be advantageous. Medical therapy with phosphodiesterase-5-inhibitors (described in detail below) can support psychological counseling. The combination of both approaches has been demonstrated to be superior to medical therapy only in terms of treatment discontinuation [35, 36]. A recent large study found a strong association between major depressive disorder and ED, with the highest risk for untreated patients [37]. However, medical therapy for depression can cause sexual dysfunction, as well [38].

- Psychological counseling is indicated in patients with psychogenic ED with associated anxiety, depression or self-esteem issues
- PDE-5i treatment can accompany and support psychological therapy
- Psychopharmaceuticals can be the cause of sexual dysfunction

Pharmacological Therapy of ED

Phosphodiesterase-5 Inhibitors (PDE-5i)

The gold standard and first-line option in medical treatment of ED is the oral therapy with inhibitors of phosphodiesterase-5 (PDE-5i), an enzyme found in the cavernous smooth muscle tissue [3, 26]. PDE-5 catalyzes the degradation of the neurotransmitter 3′5′-cyclic guanosine monophosphate (3′5′-cGMP). Sexual stimulation results in cavernous NO production and the formation of 3′5′-cGMP, an essential neurotransmitter in erectile physiology. Persistently high levels of 3′5′-cGMP allow for continuous penile rigidity during sexual activity. Reduced 3′5′-cGMP levels can be found both in organic and psychogenic ED. A complete absence of the neurotransmitter can occur after pelvic surgery with bilateral nerve injury or in other cases of neurogenic ED, e.g. autonomous neuropathy in patients with diabetes. When sexual arousal occurs in these men, production of NO is not triggered by cholinergic stimulation and in consequence activation of the guanylate cyclase is missing. As a result, 3′5′-cGMP is not formed, leaving no actionable target for PDE-5i [2]. The introduction of oral PDE-5i substances in the late 1990s has revolutionized ED treatment. Up to that point, ED was mainly treated with intracavernous injections [13]. Sildenafil was the first PDE-5i to be approved in 1998, followed by tadalafil, vardenafil and most recently avanafil. These four main substances have been investigated in large randomized, placebo-controlled trials and were all associated with highly significant increase of erectile function and rates of successful intercourse, measured by commonly used scoring systems (SEP, IIEF). All four substances were shown to have a good long-term efficacy and high patient satisfaction rates [39–42]. All agents have also shown favorable results in distinct populations with ED, e.g. patients with diabetes or with a history of prostatectomy. Other PDE-5i agents were approved in Brazil/Argentina (Lodenafil), South Korea/Russia (Udenafil) and South Korea (Mirodenafil). They all showed significant improvement of erectile function in placebo-controlled trials, however, due to their limitation to these countries, they are not further explored in this chapter [43–45]. PDE-5i have been demonstrated to have similar safety profiles [46]. However, there are some differences regarding bioavailability, enzymatic affinity to PDE-5 and adverse treatment effects. Table 21.1 provides an overview of substances and their pharmacological characteristics. Table 21.2 lists frequent side effects of all

Table 21.1 Pharmacological properties of the four main PDE-5i (modified after [55])

	Sildenafil	Tadalafil	Vardenafil	Avanafil
Dosage	25/50/100 mg	5/10/20 mg	5/10/20 mg	50/100/200 mg
T_{max}	30–120 min	120 min	30–120 min	15–30 min
Half-life time	3–5 h	17.5 h	4–6 h	6–17 h
Recommended administration before sexual activity	60 min	>30 min	25–60 min	15–30 min
Nutritional impact	Yes	No	Yes (fatty meals)	Yes (fatty meals)

Table 21.2 Adverse event profile of PDE-5i (modified after [55])

	Sildenafil	Tadalafil	Vardenafil	Avanafil
Flushing	10–19%	1–3%	8–11%	3–10%
Headache	16–28%	3–15%	16%	9.3%
Dyspepsia	3–17%	1–10%	3–4%	≥1%
Rhinitis	–	–	9%	–
Myalgia	<2–4%	1–4%	<2%	<1%
Impaired color vision	1–11%	<0.1%	<2%	–
Back pain	2–4%	1%	2%	1–3%
Dizziness	2–4%	1%	2%	≥1–2%

PDE-5i. With respect to pharmacokinetics, there are differences in the time to achieve maximum plasma concentrations as well as in their half-life time. Maximum concentrations of PDE-5i are achieved after 30–120 min, with wider ranges for tadalafil [47, 48]. The onset of effect varies between different PDE-5i. The time interval, after which more than half of the patients report an effect, ranges between 10 and 30 min. The earliest response was hereby reported for avanafil. There is also variation in the duration of effect, with sildenafil and vardenafil lasting shorter (both about 8 h) than avanafil (up to 17 h). Tadalafil outlasts all other PDE-5i regarding effect duration with up to 36 h of response. Due to an alimentary influence in terms of reabsorption and a potential delay in the onset of effect, sildenafil should not be taken with meals. While there is no comparable influence on the metabolization of tadalafil, the effect of vardenafil and avanafil may be delayed or decreased, through reduced intestinal absorption, by fat-rich food [49, 50]. With regard to pharmacodynamics, the diverse affinity to the target enzyme is responsible for the different dosages and the varying onset and duration of effect. Inhibition of other PDE enzymes can lead to, usually self-limited, side effects, such as the impairment of color vision by PDE-6 inhibition caused by sildenafil. Hypotension can occur by inhibition of PDE-1 after vardenafil administration. Besides cardiovascular illness (described below), contraindications to PDE-5i comprise existing ophthalmological conditions like a retinitis pigmentosa or a non-arteritic anterior ischemic optic neuropathy (NAION). With respect to drug interactions, combination with α-blockers, e.g. in patients with male lower urinary tract symptoms (LUTS) should be carefully pondered, as hypotensive episodes may occur. As described below, due to the risk of hypotensive crisis, simultaneous use of nitroglycerines is contraindicated. Caution must be taken in patients with hematologic diseases, such as sickle cell anemia or leukemia, as there is an elevated risk of priapism. There is currently no evidence of a tolerance effect to PDE-5i. A gradual loss of effect during treatment may be due to progression or emergence of causal conditions, like vascular disease or diabetes. Regardless of the high long-term efficacy of PDE-5i, more than half of responding patients eventually drop out of therapy [51]. Reasons for PDE-5i discontinuation include "drug-dependent sexuality" (31%) or financial aspects (approximately 30%). In about 27% of cases, unassisted intercourse was possible with time [52]. PDE-5i are mostly used in an on-demand setting, with an intake before planned sexual activity. Tadalafil is the only substance approved for administration in a low daily dosage (2.5–5 mg per day). It has been associated with higher IIEF scores compared to an on-demand regimen [53]. Daily dosing benefits patients in terms of sexual spontaneity, while a permanent improvement of the cavernous bodies could not be shown [54].

- PDE-5i are established as a first-line therapy in patients with ED of different etiologies
- Long-term results and patient satisfaction rates are high
- A high percentage of patients discontinues PDE-5i due to an unwillingness towards medication, spontaneous cure or financial reasons

- Oral PDE-5i therapy requires functioning parasympathetic nerve fiber signaling in the cavernous tissue and intracavernosal presence of 3′5′-cGMP
- Differences in pharmacokinetics/pharmacodynamics and the side effect profile of substances should be minded before treatment start

Non-Responders to PDE-5i

Approximately 30–40% of all patients fail to show adequate response to PDE-5i treatment. Real non-response is hereby characterized by severe impairment of cavernous smooth muscle tissue, either caused by damage of neural structures or veno-occlusive dysfunction. Non-response to PDE-5i can also be the result of insufficient patient education. Patients should be informed on the necessity of sexual arousal in order for the substances to take effect. The release of pro-erectile NO from parasympathetic nerve fibers in the cavernous bodies requires an according stimulus. Among all PDE-5i agents, sildenafil is the most sensitive substance to simultaneous food intake, while metabolization of vardenafil and avanafil are mostly influenced by grassy foods. Tadalafil is the most resistant PDE-5i regarding effect delay by food. The nutritional effect on gastrointestinal reabsorption should be communicated with the patient in order to choose the right drug. Appropriate scheduling of food intake is key [49, 50]. Selection of an adequate dose is also important for therapy success. Frustration with treatment can be a consequence of a time interval either too short or too long between oral intake and attempts of sexual activity. Most substances require an onset of effect of 15–30 min and, due to the different half-life kinetics of PDE-5i, not all substances are effective for the same periods of time. Patients may benefit from a "trial session", taking the drug once or multiple times before masturbation attempts thus allowing evaluation of the effect and potential adverse events. This is often regarded as less stressful, compared to sexual activity with a partner. Furthermore, an optimization of comorbidities, such as treatment of a relevant hypogonadism, diabetes or hypertension, should always be performed. Administration of statins in PDE-5i non-responders showed favorable results regarding sexual function [56]. If multiple drug intakes under optimized conditions failed to show adequate results, switching to a different substance may be helpful [57]. Doubling the maximum dose of sildenafil (200 mg) in a salvage setting was successful in approximately every fourth patient with ED in a non-responder cohort [58]. Switching to a daily dosing regimen, as opposed to an on-demand strategy, was demonstrated to be beneficial in non-responders to several PDE-5i substances. In a group of hypertensive patients with ED, more than a third could be rescued with daily dosing of vardenafil [59, 60].

- Real non-response to PDE-5i can indicate severe vascular and/or nerve damage
- Thorough patient counseling before PDE-5i treatment is important and can prevent frustrating experiences
- Statins have shown beneficial effect in PDE-5i non-responders
- Comorbidities should be sufficiently treated
- Daily dosing, doubling the maximum dose and substance switching are possible salvage strategies in non-responders

PDE5-i in Patients with Male LUTS

In the recent years, PDE-5i gained significance in the treatment of BPH/male LUTS. The usage of daily tadalafil was demonstrated to have a favorable effect on sexuality, storage and voiding LUTS. In this context, the effect of tadalafil is comparable to α-blockers. A combination of α-blockers with PDE-5i seems to be even more beneficial, without elevated risk of side effects [61]. A pooled data analysis investigated multiple placebo-controlled, randomized studies including over 1000 patients with simultaneous ED and LUTS. Significant improvement of both International Prostate Symptom Score (IPSS), objectivizing irritative and obstructive voiding symptoms, and IIEF-EF was shown. Daily dosage of tadalafil for LUTS is 5 mg [62].

- Daily application of tadalafil 5 mg is beneficial for both ED and LUTS

PDE-5i in Cardiovascular Risk Patients

Use of PDE-5i is not associated with an elevated risk of myocardial infarction. However, PDE-5i must not be administered in patients with a history of myocardial infarction, apoplexy or severe arrhythmia within the past 6 months. Other contraindications include unstable angina pectoris, a severe congestive heart failure (NYHA class IV), as well as significant hypo- (<90/50 mmHg) or hypertension (>170/100 mmHg). Due to the risk of life-threatening hypotension, the use of organic nitrates (e.g. nitroglycerine, isosorbide mononitrate) is strictly contraindicated. If chest pain occurs in patients after oral ingestion of PDE-5i, nitroglycerine has to be deferred for at least 12 (Avanafil), 24 (Sildenafil) or 48 h (Tadalafil). The concomitant use of antihypertensive drugs is regarded as safe [3].

- Absolute contraindications to PDE-5i (Nitroglycerines!) must be excluded before application

ED Following Pelvic Surgery

Pelvic surgeries make up an essential part of the management of patients with genitourinary or colorectal neoplasms. This includes procedures such as radical prostatectomy (RP) for prostate cancer, radical cystoprostatectomy for urothelial carcinoma of the bladder and anterior rectal resection for colorectal carcinoma. A common adverse effect of pelvic surgery is the irritation or injury of the cavernous nerves, resulting in neurapraxia and the loss of nocturnal and sexually caused erections. This leads to a hypoxic environment within the cavernous bodies, causing an accumulation of transforming growth factor ß1 (TGF-ß1) and endothelin 1 as well as a reduction of intracavernous PGE_1. These changes eventually cause a fibrotic transformation of the cavernous bodies, resulting in an apoptosis of smooth muscle tissue. In urologic oncology, RP is the most commonly performed pelvic surgery. Postoperative potency rates after radical prostatectomy for prostate cancer are approximately 20–30% [63]. For one thing, the grade of deterioration in terms of erectile function after RP is determined by the extent of intraoperative nerve sparing, with the best outcomes observed in bilateral nerve-sparing approaches. Furthermore, patient age and comorbidities (e.g. arterial hypertension, diabetes) have an effect on the postoperative functional outcome, whereas the best results could be demonstrated for healthy patients under the age of 65. Penile rehabilitation is reported to be most common in the first 18 months after surgery, but can be observed up to four years postoperatively. There are several medical regimens for penile rehabilitation after pelvic surgery: Oral PDE-5i medication, local PGE_1 therapy and combination treatments of both approaches are used, a decisive factor for therapy success is an early start of rehabilitation after, or even before, surgery. A study comparing early (two months) versus delayed (seven months) penile rehabilitation after RP could show significantly better erectile function in terms of IIEF score (22 vs. 16) and attained erections in the early rehabilitation group, both with (86% vs. 45%) and without (58% vs. 30%) medical PDE-5i support [64]. A recent meta-analysis including seven randomized-controlled trials could confirm an improvement of drug-assisted sexual performance for PDE-5i treatment (daily and on-demand). It could not find a benefit for unassisted erectile function following PDE-5i therapy and a wash-out period. A delay of treatment by six months does not seem to have a negative effect on assisted erectile function [65]. An improved preservation of cavernous tissue, i.e. penile length, was reported after nine months of daily therapy with tadalafil [66].

- A possible advantage of on-demand versus daily treatment regimens is indicated for different PDE-5i in the post-RP setting
- There is no conclusive evidence that a delay of postoperative PDE-5i medication negatively impacts the rate of drug-assisted erectile function
- Results on the recovery of unassisted erectile function remain controversial
- Daily tadalafil intake after prostatectomy may benefit penile tissue preservation

Alternative Oral Substances

Yohimbine

The alkaloid yohimbine has long been used in patients with psychogenic ED. It is derived from the bark of *Pausinystalia yohimbe*, a tree found in Central Africa. It is available as tablets, containing the active compound yohimbine hydrochloride. Yohimbine is declared to be an α_2-antagonist and is further reported to interact with vasointestinal polypeptide, dopamine and choline receptors, yet, the exact mechanism of action remains unknown. Given functional erectile mechanics, a positive effect on erectile function, through an influence on central mechanisms, has been described [67, 68]. A placebo-controlled study on 48 patients with ED showed a satisfactory improvement in 31% of cases after ten weeks of treatment with yohimbine [69]. Adverse events comprise fluctuations in blood pressure, increased sweating, episodes of anxiety and mania as well as headaches. In patients undergoing treatment with psychopharmaceutic agents or stimulants of the central nervous system, it is contraindicated. Most regimens use oral doses of 5–10 mg, taken three times per day. Due to the various side effects and unclear mode of action, treatment with yohimbine is reserved for selected patients, especially younger patients with psychogenic ED.

Red Korean Ginseng

Panax ginseng is a plant associated with positive effects on male sexuality in traditional Asian medicine [70]. A high concentration of the postulated active ingredients, called saponins, is especially found in red Korean ginseng (KRG). The mode of action is presumably associated with an antioxidant effect as well as an increase of endothelial NO synthesis. A study treated 90 patients with psychogenic ED with 1800 mg of KRG per day versus placebo. Results, based on interviews of patients and their partners, showed an increase of patient satisfaction and rigidity with comparison to the placebo group [71]. Another double-blind study examined the therapeutic effect of daily 2700 mg KRG in a cohort of 45 patients with ED of different etiologies over a period of eight weeks. Results showed significantly higher IIEF scores and higher rates of patient satisfaction in the treatment group [72]. Reported adverse events included dyspepsia, headaches and insomnia. Caution is advised regarding usage of KRG in diabetic patients, due to possible events of hypoglycemia. Regardless of a missing guideline recommendation, usage of KRG seems to be a safe additional treatment option in mild to moderate ED.

L-Arginine and L-Citrulline

L-arginine is an essential amino acid and a donor of NO. Several studies have investigated its beneficial role in ED treatment. In a prospective, randomized and double-blind study 50 patients with organic and complete ED were treated with 5 g of daily l-arginine for a total period of six weeks. The intervention group hereby showed a significantly higher percentage of patients able to perform sexual intercourse (31% vs. 12% in the placebo group) [73]. A newer study examined the use of a substance compound of l-arginine and pine bark extract in 124 patients with moderate ED over a surveillance period of six months. The authors reported a highly significant improvement in erectile function, with an increase of IIEF-EF of nearly 12 points (versus 4 points in the placebo group) after six months. The believability of these findings, however, remains questionable, as this increase would exceed high-dose PDE-5i treatment [74]. L-citrulline is a precursor amino acid of l-arginine in the urea cycle. In the cavernous bodies, it is a by-product in the reaction of l-arginine and oxygen to nitric oxide. It has been evaluated for its potential pro-erectile effect. A single-blind study including men with mild ED receiving 1.5 g of l-citrulline per day, over a period of one month, showed significantly improved erectile function in 50% of the men (versus roughly 8% in the placebo group) and a significantly superior percentage of men able to perform sexually [75].

Apart from mild, asymptomatic hypotensive changes of blood pressure, there were no reported side effects.

- Yohimbine can be considered in selected cases of psychogenic ED, however, the side effect profile has to be kept in mind (e.g. anxiety, blood pressure fluctuations)

- Red Korean ginseng has been reported to show favorable effects on rigidity and can be used as a supplementary medication in ED, however, with caution in diabetic patients
- Doses of 3–5 g per day for l-arginine and 1.5 g per day for l-citrulline remain possible supplementary therapy options in men with mild to moderate ED.

Mechanical Treatments

Vacuum Erection Devices (VED) and Constriction Rings

VEDs are plastic cylinders, which are placed over the penis and pressed onto the pubic bone, with the application of lubricant on the cylinder rim causing an airtight seal. The creation of a vacuum by an internal or connected pump leads to a passive blood influx into the cavernous bodies of the penis. Simultaneous use of a constriction ring at the penile basis prevents an immediate venous drain of the corpora. VEDs can both be used in patients with contraindications to medical or operative therapy of ED and as part of combination regimens, e.g. with PDE-5i. The latter have shown superiority compared to VED usage only in terms of higher rates of successful intercourse (70 vs. 46.6%). Application of a VED can help to achieve satisfactory intercourse in up to 90% of all ED cases, with patient satisfaction ranging between 27 and 94%. The majority of patients discontinues VED treatment at some point, mostly due to the feeling of a passively induced erection. Because of the corpora filling with venous, deoxygenated blood, erections may feel cooler, the penis can even appear cyanotic. Also, the penile base often lacks rigidity and therefore stability. Other adverse events of VEDs may include dysesthesia, pain, petechiae and hematoma as well as ejaculation disorders due to the constriction ring. The latter makes VEDs an improper option for couples trying to conceive. By removing the penis ring shortly after sexual activity, serious side effects such as skin necrosis can be prevented. Altogether, use of VEDs should not exceed half an hour. Patients with bleeding disorders or those receiving anticoagulation should refrain from usage of VEDs [76, 77].

- VEDs and constriction rings are a helpful mechanical addition to pharmacological treatment regimens
- High discontinuation rates are mostly due to uncomfortable, not fully rigid, erections

Low-Intensity Extracorporeal Shock Wave Therapy

The application of low-intensity extracorporeal shock wave therapy (LI-ESWT) is proposed to have a positive impact on neoangiogenesis, Schwann cell activation and stem cell recruitment. The mechanism of action is an induction of shear stress and damage to the endothelium by incoming shock waves. A neoangiogenic effect of shock wave therapy could be demonstrated in preclinical studies [78, 79]. LI-ESWT has previously been used in the treatment of bone fractures and cardiovascular disease [80]. The underlying technology differs between available devices. Its application on the cavernous bodies has been shown to yield short-term effect in PDE-5i responders in first studies [81, 82]. Moreover, evidence suggests that LI-ESWT may trigger therapy response in prior PDE-5i non-responders [80, 83]. Two recently published meta-analyses described increases of IIEF scores (one of them a significant increase) overall for treatment groups in included studies [84, 85]. However, due to limitations in the methodology of both analyses, these results have to be viewed with caution. Possible adverse effects have yet to be evaluated in further studies. Reported shock wave intensities range between 0.09 and 0.25 mJ/mm^2, the number of applied pulses per treatment ranges from 1500 to 5000. Application to multiple sites may be favorable, but results remain inconclusive [85].

- The hypothesized triggering of nerve regeneration deems LI-ESWT an innovative and potentially curable treatment option
- Heterogeneity in technology and study design make it difficult to determine the role of LI-ESWT in ED treatment
- Further long-term results from randomized, sham-controlled trials, using consistent study protocols, are warranted

Secondary Treatment Options

Prostaglandin E_1 Analogues

In PDE-5i non-responders or in patients undergoing treatment with NO donors for cardiovascular conditions application of locally vasoactive agents remains an established second-line therapy option [3, 26]. Alprostadil is an analogue of prostaglandin E_1 (PGE_1). It can cause cavernous smooth muscle relaxation independently from PDE-5 inhibition and presence of NO, by activating the adenylyl cyclase, leading to an increase of cAMP and to an outward transfer of intracellular calcium. The fact, that sexual arousal is not necessary for a PGE_1-induced erection, allows the application in a diagnostic setting to objectively evaluate erectile function, in order to discriminate between neurogenic and vascular ED.

Intraurethral and Topical Application of PGE_1 Analogues

Alprostadil can be introduced in the form of a pellet into the urethra using a special applicator (Medicated Urethral System for Erection, MUSE™). Urethral suppository doses range from 125 to 1000 µg. Onset of effect can be expected after 5–10 min, while the effect usually lasts for up to an hour. Therapy efficacy, in terms of at least one reported successful intercourse, could be registered in about 65% of patients vs. 19% receiving placebo in an initial study [86]. Transurethral alprostadil application has been shown to be significantly less efficacious compared to intracavernous injection. Local pain and hypotensive symptoms, such as headache and dizziness, are possible adverse events of PGE_1 analogues and may occur in about 29–42% and 2–14%, respectively. Local application can furthermore cause urethral bleeding or urinary tract infections in 5% and under 1%, respectively [87]. Application can be supported by using a constriction ring around the penile basis. A cream containing alprostadil (brand name Vitaros®) can be used for topical application on the glans penis at doses of 200–300 µg. A double-blind study could demonstrate significant superiority of topical alprostadil compared to placebo in men with ED of all severity grades. With only rare systemic events, the most common side effects are local erythema and pain [88]. Both topical and transurethral application forms are an alternative to patients refusing more invasive intracavernous injections. Patient counseling should, however, mention the inferior efficacy of these less invasive options compared to injection therapy. Also, the option to combine these treatments with oral PDE-5i therapy or mechanical devices, should be discussed.

- Topical and intraurethral alprostadil are suitable options for patients unwilling to perform injection therapy
- Compared to PGE_1 injection, topical and intraurethral application forms are less effective
- Combination with mechanical or oral treatment strategies should be discussed

Intracavernous Injection Therapy with PGE_1 Analogues

Prefabricated compounds for intracavernous injection contain lower doses of alprostadil, with comparison to the transurethral application form, due to the nonrequired urethral reabsorption. After local sterilization the penile shaft is unilaterally punctured, using a fine needle (usually 27–30 gauge), in the middle portion and the substance is administered into the cavernous bodies. Prior to therapy start, training of the technique with the patient and/or his partner in the office is crucial. Incorrect injections, applied subcutaneously, to the cavernous septum or puncturing the urethra, can cause damage, pain and patient frustration due to reduced or missing results.

Onset of effect is to be expected about 10–15 min after the injection. The duration of effect differs with regard to the applied dose, but generally ranges from 30–60 min. Different doses (10, 20 and 40 µg) are available in prefilled syringes, the starting dose is usually 5 µg, with further titration by 5–10 µg steps. At any dosage a combination with PDE-5i and mechanical devices is possible and can support therapy efficacy. Long-term response rates to PGE_1 injections were high at 93% of patients in a large prospective study with nearly 17.000 injections [89]. Patient satisfaction rates are

high, but vary between studies (67.3–78.3%) [89, 90]. Local side effects of intracavernous injections with PGE_1 analogues comprise penile pain (up to 70%), hematoma (8%), prolonged erections (4–5%) and the development of penile fibrosis as a consequence of numerous injections (2%). Local pain, if not self-limited, can be managed using topical application of local anesthetics. Penile hematoma is the most common side effect, occurring in 33–47% of patients. The occurrence of priapism is related to the used dose and substance, appearing more commonly after usage of papaverine, phentolamine or combination regimens. Patients with prolonged erections lasting for more than 4–6 h should seek medical attention. If conservative measures, such as ambulating or local cooling, remain unsuccessful, further steps should include the irrigation of the cavernous bodies with saline solution and/or the injection of vasoactive agents (e.g. etilefrine, norepinephrine) to achieve detumescence [91]. In about a third to half of the patients who develop fibrotic changes of the tunica albuginea under self-injection therapy, spontaneous healing of these plaques can be observed under temporary discontinuation of injections. The remaining 50% of patients with fibrosis develop penile deviation in the long run, often requiring corrective surgery. Although a return of spontaneous erections under self-injection therapy is reported, it is rare (<3%) [92]. Discontinuation of treatment can be observed in more than half of patients after 2 years and 67% after 4 years, and is lower compared to intraurethral PGE_1 application (57% after 3 months). Dropout is mostly due to motivational issues and a feeling of dependency on pharmacological support [93].

- Intracavernous injection of PGE1 analogues is a safe and established therapy option if PDE-5i are contraindicated or not effective
- Although long-term response remains high, therapy discontinuation occurs in a majority of patients

Alternative Vasoactive Agents for Injection

After treatment failure with the highest dose of PGE_1 analogues (40 μg alprostadil), there is little hope for medical treatment success. Yet, for PGE_1 non-responders and patients not tolerating alprostadil, alternative vasoactive options include phentolamine and papaverine. Phentolamine is an α-antagonist and causes vasodilatation. Papaverine inhibits phosphodiesterases-2, −3 and −4, causing an increase of cAMP and a decrease of intracellular calcium, which results in smooth muscle relaxation. Both agents are applied via intracavernous injection. Due to an observed superiority of a combined regimen, these substances are usually administered together or combined with a PGE_1 analogue. The substance combination is available in multiple countries in ampoules of 2 mL under the name ‘Androskat’. Each ampoule contains 30 mL of papaverine and 1 mL of phentolamine, the effect being roughly comparable to 10 μg of alprostadil. The combination of phentolamine, papaverine and a PGE_1 analogue, also known as ‘trimix’, has been associated with greater acceptance among ED patients, compared to PGE_1 monotherapy. A study comparing alprostadil monotherapy with trimix solutions found the latter to cause greater improvement of erectile function in nearly half of the cohort [94]. Major disadvantages include a higher risk of priapism, especially when using higher doses of the trimix, making a gradual titration necessary. Another drawback is the non-availability of prefabricated compounds, which requires the patient and/or their pharmacist to prepare the substance combination by themselves. Further, measurement of blood pressure is recommended after usage of higher doses, due to possible hypotensive drops after injection. Trimix therapy should therefore be initiated very cautiously, starting with lower doses (e.g. 10–20 μg alprostadil, 20 mg papaverine, 1 mg phentolamine) [95, 96]. The injection of a combination of phentolamine and vasoactive intestinal polypeptide (VIP) is another option in case of treatment failure with other substances. It was investigated in the early 1990s, when a superiority in

terms of patient preference to PGE_1 analogues could be demonstrated, due to a user-friendly auto-injection device. Response rates were between 80.6 and 85.5%, depending on the underlying cause of ED [97]. The substance combination remains available to this day to European physicians but has to be ordered from Denmark. Also, it does no longer feature the former auto-injection technique [13].

- Phentolamine/papaverine and 'trimix' combinations are efficient and possible alternatives to PGE_1 mono injection therapy
- The risk of priapism, the increased financial aspect of a combined injection regimen and the necessary self-preparation are drawbacks to this solution

Surgical Therapy of ED

Venous Ligation and Arterial Revascularization Surgery

Venous ligation surgery in ED was explored until the end of the twentieth century, with the intent to counter venous leakage. Results demonstrated no long-term benefit for patients and the procedure was ultimately abandoned [98]. Patients who suffered trauma to the perineum or the pelvis or such with congenital malformations may, after radiographic proof of an arterial stenosis, be offered revascularization surgery, with a postoperative success rate of up to 70%. Penile revascularization should include patients under 55 years of age who do not suffer from diabetes or generalized vascular disease. Absence of veno-occlusive dysfunction is an additional requirement for surgery and has to be excluded via cavernosometry and/or cavernosography. Nonetheless, due to only limited evidence regarding this approach, it remains investigational [99].

- Venous ligation surgery is obsolete nowadays owing to discouraging long-term results
- Arterial revascularization techniques are reserved for special cases of congenital or posttraumatic arterial malformations

Implantation of a Penile Prosthesis in ED

An invasive option and "last resort" for non-responders to pharmacological therapy (about 5–10% of all ED cases) or as an alternative for patients with a desire for non-medical permanent treatment, either due to poor tolerance or the relevant costs of appropriate therapies, is the operative placement of a penile prosthesis (PP). In the early 2000s, there were over 30.000 PP implantations performed in Europe and the United States [100]. There are generally two types of PPs available: Inflatable hydraulic PPs (IPP), either as two- or three-piece variants, and malleable PPs. Hydraulic prostheses generally enjoy a higher popularity (with satisfaction rates between 75 and 100%) among patients, given the more naturally mimicked erection mechanics and the better concealability. The mode of operation of hydraulic devices is elaborate: A scrotal pump connects the fluid reservoir, usually placed next to the bladder in the retroperitoneal space, with the cylinders in the penile corpora. Operation of the pump causes a fluid transfer between the different components, either leading to penile erection or detumescence. In the two-piece IPP variants, the reservoir is not a separate component, but part of the pump. While this model does not require additional placement of a reservoir, the limited filling volume of the smaller reservoir can lead to a reduced rigidity of the prosthesis. An example of a three-piece IPP model is provided in Fig. 21.2. Malleable, semirigid PPs are manually bendable to an upright position before sexual activity. With comparison to the hydraulic models, they are cheaper and not as demanding in terms of surgical technique. Disadvantages include a more artificial feeling and the missing concealability of the prosthesis. Approaches for implantation of penile implants either use infrapubic or penoscrotal access [101]. An essential complication following PP implantation are postoperative infections, occurring in 1–3% of cases. In 2000, inflatable prostheses were available with antibiotic impregnation, reducing the

Fig. 21.2 Three-piece penile prosthesis, Coloplast Titan® Touch model (image is courtesy of the Coloplast Corp)

risk of infection by nearly 58% after 6 months [102]. Infections require revision surgery, with a necessity for prosthesis explantation in a majority of cases (over 80%) and a possibility of IPP salvage surgery in less than 20% of affected patients. Regarding infectiological risk factors, a large analysis of more than 6000 cases of antibiotic-coated versus non-coated prostheses described a significantly higher revision rate for diabetic patients [103]. With respect to HbA1c levels, a recent study including 300 diabetic patients undergoing PP surgery could not find an association between high glycosylated hemoglobin (HbA1c > 9%) and prosthesis infection [104]. The mechanical durability of IPPs is estimated between 57 and 76% at 15 years after surgery [105]. Lower operation times, i.e. less exposure of the IPP to potential airborne bacteria, and the use of modern antibiotic-coated prostheses have more favorable outcomes. Covert infections are often the reason for prosthesis perforations. Distal perforations, e.g. through the glans or into the urethra, are hereby distinguished from proximal (e.g. scrotal) perforations. PP perforation requires revision surgery in all cases. Patient education is essential for a good outcome after PP implantation. Discontent after surgery can be based on unrealistic expectations, mostly in terms of penile length issues. Due to intra- and postoperative development of scar tissue, a reduction of penile length can occur. After wound-healing, patients should be instructed on the activation and deactivation of the scrotal pump in the office to prevent operating errors.

- Penile prostheses are a last resort for patients with therapy-refractory ED
- Experience gathered in the last decades regarding antibiotic coating and infection prevention deems penile prosthetis implantation a safe procedure
- Patient education pre- and postoperatively helps to improve outcomes and prevents handling errors

Management of Peyronie's Disease

Peyronie's disease (PD) is a connective tissue disorder, characteristically appearing as a fibrotic transformation of the penile tunica albuginea or the inter-corporeal septum. It is named after its first descriptor, Francois de LaPeyronie, in the eighteenth century [106]. PD typically presents with a sudden onset and can be divided into several phases of disease. It usually starts with an inflammatory or active stage, with a duration of 6–18 months, marked by painful erections. This is followed by intermediate and chronic states, during which penile pain commonly subsides. Development of fibrotic plaques can cause penile malformation, including penile curvature of different angles, penile shortening, as well as severe notching disfigurements such as hour-glass like distortions of the penis. In the chronic state, a consolidation of fibrotic plaques takes place, leading to a stabilization of penile malformation, usually within three years after disease onset.

Epidemiology, Etiology and Pathogenesis of PD

Prevalence of PD is subjected to a certain variability, due to different inclusion criteria of reporting studies. It is estimated to be present in about 3–9% of men of all ages, showing a peak prevalence in males between the ages of 40 and 60 and rare occurrence in young men under 20 years [107]. Incidence rates are higher in patients with certain comorbidities. Patients with

a history of radical prostatectomy for prostate cancer have a risk of nearly 16% of developing PD. Diabetic patients are also at a higher risk, making up roughly 30% of all patients with PD. In patients undergoing hemodialysis, prevalence rates even reach approximately 92%. Associations with other collagen storage disorders is indicative of a genetic component of PD. According studies have shown an upregulation in genes coding for metalloproteinases [108]. Related disorders include fibrotic alteration of the plantar (Morbus Ledderhose) and palmar (Dupuytren's disease) fasciae, the latter showing concomitant PD in 4% of cases. Most common medical conditions associated with PD include erectile dysfunction, dyslipidemia and arterial hypertension. Low androgen levels of testosterone and dehydroepiandrosterone (DHEA) are postulated to have an influence on matrix metalloproteinases and consecutively on disease development. While the etiology is unknown, it is generally accepted that PD is initiated by consequence of repetitive microtrauma to the tunica albuginea. This causes remodeling processes, analogous to scar formation in tissue repair. The inflammatory pathogenesis is to be differentiated from penile deformity in consequence of penile fracture, a traumatic rupture of the tunica albuginea, mostly occurring during sexual activity. Pathophysiological correlates of PD on the molecular level encompass an increased aggregation of inflammatory mediators and an imbalanced collagen/elastin ratio. In this context, involvement of the beta subunit of transformation growth factor (TGF-ß), a cytokine protein promoting inflammation and wound healing, has been examined [109]. In physiological tissue repair, fibroblasts are transformed to myofibroblasts, caused by an inflammatory response set in motion by a trauma-related extravasation of fibrin. Myofibroblasts are responsible for collagen synthesis in the wound, normally undergoing apoptosis thereafter. In pathologic tissue repair, however, the myofibroblasts persist, causing continuous collagen production. This is further supported by promoters of collagen synthesis, such as TGF-ß [110, 111]. Since most men are exposed to a certain amount of microtrauma from sexual activity during their lifetime, a multifactorial etiology, including microinjury of the tunica and genetic factors, seems probable.

Diagnostic Work-Up of PD

A complete and detailed *patient history* is key in diagnostic investigation. Character of clinical symptoms, their onset and duration should be reported. It can be helpful to involve the patient's partner in the discussion, as they can often provide helpful additions. Reported symptoms most often comprise erectile dysfunction, painful erections, penile curvature or other deformities, reduction of penile length and pain in the partner during intercourse. Several, non-validated and non-standardized, questionnaires covering PD-related symptoms exist. Most recently, the commonly used 'Peyronie's Disease Questionnaire (PDQ)' was included in a post-therapeutic quality of life study after collagenase injection therapy [112]. Questionnaires on PD should cover areas of malformation, penis size, sexual function and psychological distress from the disease. To cover questions on sexual and erectile function, usage of the IIEF scoring system is recommended. Sexual satisfaction, erectile dysfunction as well as an impairment of sexual intercourse by PD, either by pain or impossibility to penetrate, should be considered. Moreover, comorbidities are to be addressed, with special regard to known medical conditions associated with PD. These comprise hypertension, diabetes, dyslipidemia or hypogonadism. Psychological stress is most often caused by feelings of disfigurement and dwindling sexual confidence. Distress for the patient and their partner was recently reported to occur in up to 80% of cases. Evaluation for signs of depression, described in approximately 50% of PD patients, or relationship problems (more than 50%) should be part of the discussion and, if present, a referral to psychological care should be offered. Special emphasis should be put on reassuring the patient of the benign nature of PD. [113]. Family history of PD is usually difficult to assess, owing to the

issue of a generally problematic intra-familial communication of sensitive or sexual matters. However, reports on positive family history of Dupuytren's contracture may be helpful in order to estimate the risk of associated PD. Regarding direction and angle of penile curvature, the subjective patient statement is not sufficient for precise evaluation, as the degree of deformity is often overestimated [114]. Photography of the erect penis, performed at home or in the provider's office from multiple planes, are a more objective, yet still inaccurate, method. The most accurate technique is the intracavernous injection of vasoactive agents (e.g. PGE_1 analogues) with the aim to directly assess penile curvature in the erect penis with a goniometer and to simultaneously perform color-coded duplex ultrasound of penile vasculature [115]. Registration of a penile plaque, by the patient or the partner, should be included. Reported changes in penile form or curvature are helpful to estimate whether a stable phase has been reached. As the reduction of penis size can be essential in PD, it is important to address penile shortening. Moreover, the patient and their partner are questioned regarding events of traumatic intercourse, the reminiscence of a rupturing sound, pain or a penile hematoma during or after sexual activity can thereby be used as indicators of penile fracture.

Physical examination usually comprises the inspection and palpation of the penile shaft. If plaques are noted, their position and number should be recorded. Measurement of plaque size is mostly redundant, due to inaccuracy. Penile length should be documented as well. It is most accurately determined by stretching out the flaccid penis at an angle of 90° to the body and measuring from the dorsal penile basis, with skin and superficial fat over the pubic area impressed [116]. Length is then measured from the pubic bone to the urethral meatus. As described above, a reliable assessment of penile curvature can only be achieved after injection of vasoactive agents into the cavernous bodies.

Sonography of the penis can reveal calcified plaques, found in 30% of all patients regardless of the phase of disease, in the tunica albuginea and allows a rough measurement of their size. The measurement of non-calcified plaques, e.g. by a thickened tunica albuginea, is inaccurate. Due to a common association with ED, evaluation of penile vessels via color-coded duplex sonography can be performed at the same time, ideally after intracavernous injection of vasoactive substances. Magnetic resonance imaging (MRI) of the penis most accurately displays the position and size of tunical plaques. Due to its cost- and time-intensity it does, however, not play a role in routine work-up of PD. Modern imaging approaches, such as the use of three-dimensional photography, elastosonography as well as associated smartphone and tablet integration are emerging, their value has to be further evaluated [117].

Laboratory testing should, with regard to associated illnesses, include serum glucose, glycosylated hemoglobin and determination of testosterone levels.

Conservative Treatment of PD

General Considerations

Prior to discussion of therapy options, patients should be made aware of the reported studies regarding spontaneous regression of PD, occurring in 3–13% of patients, with the majority of cases showing disease stabilization or progression [118]. Spontaneous improvement is more likely to occur in younger patients and in those looking for medical attention within six months of symptom onset [119]. While the initial active phase is often associated with penile pain (35–45%), resolution of symptoms can be expected in 90% of men within a year [120]. Treatment in general, conservative or surgical, should always address the patient's individual symptoms, as PD is a disease with many faces. A variety of conservative treatment strategies have been examined throughout the years, all of which are mainly used for initial disease stage or in patients unfit or unwilling to undergo surgery. A treatment algorithm for the management of PD is provided below in a flow diagram in Fig. 21.3. Available options can be categorized into oral pharmaco-

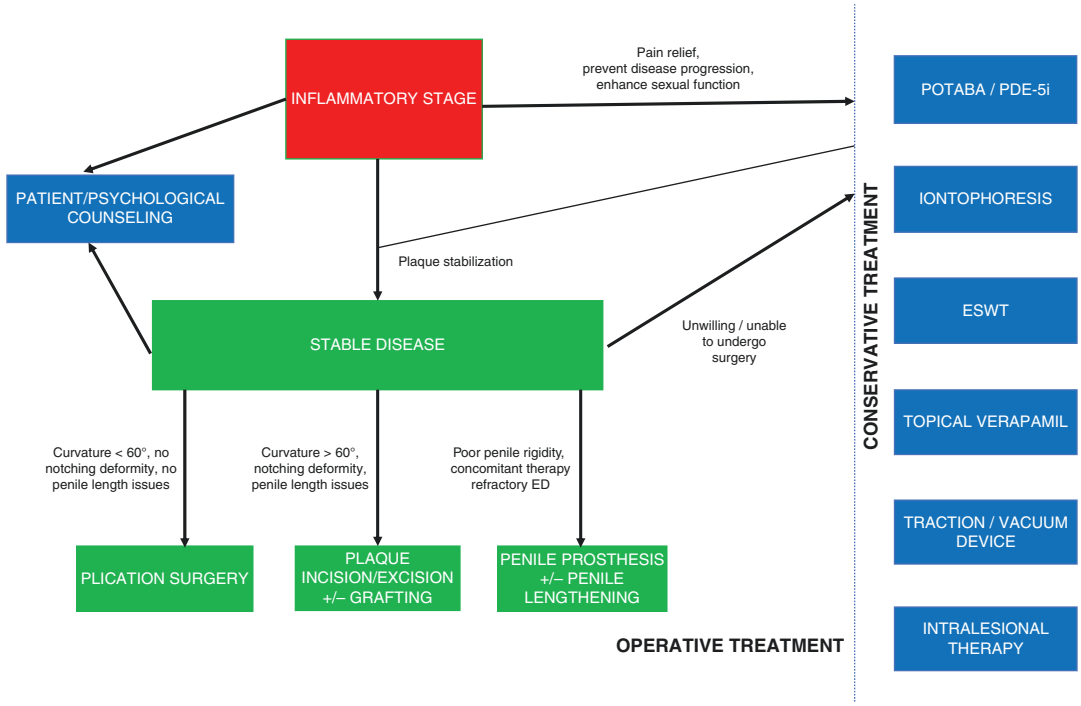

Fig. 21.3 Treatment algorithm for the management of PD

therapy, intralesional injections, radiotherapy and mechanical treatment, described in detail below in this order.

Oral Pharmacotherapy in PD

While there are several oral substances available for the treatment of PD, there is only very limited evidence supporting their role in a curative approach. Administration of oral drugs seems to be justified only in early phases and in less severe cases of penile deformity, with the aim of a quicker transition from the inflammatory to the chronic stage. Pharmacotherapeutic targeting is mostly based on preclinical studies on human and animal tissue. By increasing local NO levels and by inhibiting cAMP and/or cGMP, substances such as PDE-5i, l-arginine and pentoxifylline are postulated to counteract free radicals and a consecutive collagen deposition [121]. The following paragraph is to give a short overview on the most commonly used oral drugs, their mechanism of action, the main supporting studies, dosages and side effects.

Vitamin E

Vitamin E, also known as tocopherol, is a fat-soluble vitamin, with a proposed antioxidant effect in cell membranes. Based on the suggested reduction of free radicals in wound-healing, vitamin E is usually used in high doses of 400 IU, administered twice a day, for PD therapy. Recent studies primarily examined combination therapies including vitamin E. An early study could not demonstrate a significant effect on deformity, pain or plaque change [122]. Minor adverse events include the occurrence of abdominal pain and nausea.

Pentoxifylline

Pentoxifylline, a non-selective phosphodiesterase inhibitor, is known to have anti-inflammatory properties, increase fibrinolysis and attenuate the profibrogenic effect of TGF-ß1 in PD [123]. A large study retrospectively analyzed more than

500 patients, 67% of whom received pentoxifylline, with a follow-up period of approximately 15 months. The study could show beneficial results for patients under oral therapy in terms of progression to surgical intervention (17% vs. 41%). One study compared two groups with PD with presence of a calcified plaque at ultrasound. Each group either received vitamin E or no treatment (n = 9) or pentoxifylline (n = 62) over a period of 1 year. The pentoxifylline group was more likely to achieve stabilization and to avoid disease progression. As the group sizes of both studies seem uneven, results should be interpreted with caution. The usual dose recommendation for oral pentoxifylline is 400 mg (2–3 times per day). Side effects are generally mild and comprise nausea, headaches and dizziness [123].

PDE5 Inhibitors

An antifibrotic effect of PDE-5i could be demonstrated in animal studies, showing a decrease in the ratios of collagen to smooth muscle and collagen III to collagen I and a reduction in the amount of myofibroblasts and expression of TGF-ß [124]. A prospective study evaluated a daily intake of 5 mg tadalafil in 47 patients with PD, who completed their follow-up of at least six months. PD-related pain resolved in all patients, improvement of curvature was noted in both severity groups (20–60° and >60°). A complete resolution was registered in 35% of the low severity group [125]. Another retrospective study assessed the effect of daily intake of low doses of tadalafil (2.5 mg per day) in 35 patients with plaques in the inter-cavernous septum, but no penile deformity. The authors could demonstrate a significantly higher percentage of scar resolution (69%), compared to the control group (10%) [126].

Potassium Aminobenzoate

For potassium aminobenzoate, usually abbreviated to "potaba", an anti-inflammatory and antifibrotic effect is suggested, via an increased secretion of glycosaminoglycans and activation of monoamine oxidases. Potaba is administered in frequent and high daily doses (12 g in 3–4 single doses), often causing gastrointestinal adverse events like nausea and abdominal pain. Other side effects include anxiety, sweating and pruritus. Two double-blind studies assessed the effect of potaba. In the first study 41 patients undergoing daily potaba treatment (12 g per day) for one year were observed. Results yielded positive results in terms of pain relief, but no impact on penile curvature or size of plaques [127]. The second study included a larger number of 103 patients and could demonstrate a reduction in plaque size and protection from further deterioration of curvature after a follow-up time of 12 months. However, there was no significant effect regarding pain relief in the potaba group [128].

Tamoxifen

An estrogen receptor antagonist and commonly used substance in the treatment of breast cancer, tamoxifen also has an effect on TGF-ß1 synthesis in fibroblasts. An early study reported a positive effect in PD, with regard to penile deformity, pain and plaque size, after tamoxifen therapy for three months [129]. These results could, however, not be confirmed in a later randomized, placebo-controlled trial [130]. Another study, comparing tamoxifen to treatment with acetyl-l-carnitine, observed inferiority of the first [131]. The usual daily dosage of tamoxifen is 20 mg. Side effects comprise thromboembolism, depression and alopecia. Application of tamoxifen in PD is regarded as obsolete nowadays.

Esters of L-carnitine

Inhibition of acetyl coenzyme A and an antifibrotic effect, by a negative effect on fibroblast growth and collagen synthesis, are postulated mechanisms of action of acetyl-l-carnitine and propionyl-l-carnitine. As mentioned above, the effect of acetyl-l-carnitine was assessed in a comparative trial against tamoxifen and was demonstrated as superior in terms of limitation of PD progression, penile curvature reduction and penile pain. However, these results should be interpreted with caution, as the study included mainly curvatures of mild severity [131]. Another study evaluating a combination regimen of propionyl-l-carnitine and intralesional injection of

verapamil was examined in a cohort of 60 patients. The combination therapy was associated with improvement of curvature, plaque size and disease progression, compared to the control group receiving oral tamoxifen and intralesional verapamil [132]. Esters of l-carnitine are usually taken twice a day at doses of 1 g. Regarding known side effects, abdominal pain, pruritus and skin rashes have been reported.

Colchicine

Also known for its application in gout, colchicine is proposed to have both an effect on pro-inflammatory and pro-fibrotic components in PD. A comparative, double-blind and randomized study assessed the effect of a combination regimen of daily colchicine and vitamin E in early PD. Outcomes of the study group were compared to a control group receiving 400 mg of ibuprofen daily. Significant improvement in terms of curvature and plaque size, but not regarding pain relief, could be shown for the colchicine group [133]. Another study conducted in early PD cases reported complete regression of pain in nearly the whole cohort (95%) under colchicine therapy. Improvement or stabilization of penile deformity could be observed in the majority of patients (78.3%) [134]. Applied doses range from 1.8 mg to 2.4 mg, divided into multiple intakes per day. Reported adverse events include myelosuppression, nausea and peripheral neuropathy.

- Oral medication in PD is usually applied in patients of early disease stage
- Treatment algorithms in Europe and the United States do not recommend the usage of vitamin E and tamoxifen for the reduction of deformity. They also do not recommend the administration of pentoxifylline, colchicine or esters of l-carnitine [3, 135]
- Among oral treatments, the most comprehensive evidence regarding plaque reduction, stabilization of curvature and pain relief exists for potaba
- PDE-5i may have a positive effect on associated ED, while evidence of symptom relief and improvement of curvature is limited

Intralesional Therapy

Intralesional therapy uses the direct application of substances to the site of PD. With comparison to oral treatment, higher drug concentrations can be achieved at the local site of disease. Recently, intralesional injections were subject to several studies. However, the amount of valuable evidence indicating a benefit in PD remains, similar to oral agents, limited. Possible benefits of certain agents, such as calcium channel blockers or interferons, have to be further explored in larger patient cohorts. In the following paragraph, we present a summary of the essential substance groups.

Clostridial Collagenase

Clostridial collagenase is derived from the bacterium *Clostridium histolyticum* and is often abbreviated as CCH. The proposed mechanism of action is an enzymatical degradation of collagen structures, which are essential components of plaque structures in PD. Its usage for PD therapy was approved, for the United States only, in December 2013 and has since been of great interest in clinical research. Prior to approval, two large multi-institutional, placebo-controlled phase III studies ("IMPRESS I & II") were conducted, their results are summed up in a meta-analysis [136]. Exclusion criteria were a duration of PD of less than a year, presence of ventral curvature or identification of plaque calcification upon sonography. A treatment cycle of two CCH injections (each containing 0.58 mg of collagenase), applied in an interval of 24–72 h, was followed by in-office plaque modeling. Overall, four cycles were applied, separated by six-week intervals. A significant improvement of penile curvature was reported, by 34% vs. 18% in the placebo group. PD symptoms were also more significantly reduced in the CCH group. As a notable and severe side effect, rupture of the corpora occurred in three cases. Newer studies investigated collagenase therapy in an initial disease phase, as well, with onset of PD within less than one year prior to therapy. A trial including 12 patients with initial PD showed an improvement of curvature by 20°

and enhanced life quality displayed by an improved PDQ score. Overall complications of the cohort ($n = 49$) comprised four cases of local hematoma and one case of penile fracture, which had to be surgically managed [137]. Another study compared outcomes of CCH between active and chronic disease states. Significant differences regarding a correction of curvature (by approximately 16° in both groups) or adverse events were not found. In all 162 patients, two corporeal ruptures and nine penile hematomas occurred [138]. The poor cost-efficiency of CCH therapy was pointed out in a recent study, as the procedure is more expensive by over 20.000 US dollars compared with classic plication surgery [139]. Overall outcomes of CCH therapy in both active and chronic PD seem moderately positive. In the United States, usage of CCH is recommended in a stable curvature between 30° and 90° [135]. However, existing studies are heterogeneous in terms of treatment duration and definitions of successful outcome, long-term results are entirely missing. Reported occurrences of corporeal rupture, even if only in a small percentage of patients, represents a severe adverse event. A thorough discussion of benefits, financial aspects and potential risks should be part of patient counseling before CCH treatment.

Hyaluronic Acid

A glycosaminoglycan of the extracellular matrix, hyaluronic acid is proposed to have anti-inflammatory properties and to antagonize oxygen-free radicals as well as the formation of scar tissue. It has previously found usage in orthopedics and aesthetic surgery. A multi-center study performed intralesional injections (0.8% highly purified sodium salt hyaluronic acid 16 mg/2 mL) over ten weeks, using hyaluronic acid in 65 patients with early-stage PD. Significant benefits, regarding plaque size decrease, reduction of curvature and improvement of sexual satisfaction, were reported after 2 months of follow-up. The authors reported an absence of any side effects [140]. Positive results were also described in a second single-arm study on 83 patients with inflammatory disease stage and penile curvature <45°. Therapy was performed over a course of six months. A total of 30 injections, each containing 20 mg of hyaluronic acid, were applied. Follow-up at 12 months showed significant improvement of curvature, plaque size and penile rigidity, compared to the control group [141].

Corticosteroids

The proposed mechanisms of action of steroids encompass an immunosuppressive effect as well as an inhibiting effect on phospholipase A_2 and collagen production. Reports of corticosteroid usage in PD mostly originate from small uncontrolled studies. A placebo-controlled trial using injections with betamethasone in 30 patients could not demonstrate a significant benefit for the steroid group in terms of reduction of plaque size, curvature or symptom relief after a follow-up of 12 months [142]. A more recent article pointed out technical issues with injections in calcified plaques and problems of local adverse events, such as tissue atrophy and thinning of the skin. The author suggested a benefit from systemic treatment with corticosteroids [143]. Studies on this hypothesis are still missing, local treatment with steroids nowadays seems obsolete.

Calcium Channel Blockers

A proposed effect on fibroblast function and the extracellular matrix, as well as anti-inflammatory effects, substantiate the use of calcium channel blockers in PD. A first study on the effect of verapamil has been conducted more than 20 years ago, showing a promising impact on penile curvature [144]. However, randomized and placebo-controlled trials following up on these first findings could not confirm significantly favorable results for verapamil treatment in PD [145]. A non-controlled study could show a positive effect on pain (100%) and plaque stabilization (60%) in PD patients [146]. The injection of nicardipine, another calcium channel blocker, was tested in 74 patients, randomized to either therapy or placebo groups. After 48 weeks, significant improvement of erectile function, plaque size decrease and penile curvature could be shown. However, curvature also improved in the placebo group, the results did not significantly differ from the ther-

apy group [147]. Adverse events comprise penile pain and nausea.

Interferons

Interferons are signaling proteins produced by mononuclear cells, involved in immune-modulating processes. In-vitro studies on cultured fibroblasts have shown an inhibitory effect on collagen production and fibroblast growth as well as a promotion of collagenase by interferon-α2 [148]. Earlier studies recruited small patient numbers, were non-controlled and heterogeneous in terms of dosage (ranging between 1 and 10 MU twice per week), follow-up time and outcome. A multi-institutional, placebo-controlled study of interferon-α2b described significant pain relief, plaque size reduction and curvature improvement [149]. Another study examined a potential synergistic effect of interferon-α2b and vitamin E in patients with early phase of PD, but did not yield significantly positive results [150]. A more recent study including 131 patients with PD reported a 20% improvement of curvature as well as a positive effect on penile pain, independent of plaque location. Limitations of this study include its retrospective nature and the heterogeneous treatment algorithms described [151]. Administration of non-steroidal anti-inflammatory drugs prior to interferon injection can prevent most common side effects, including myalgia, arthralgia and flu-like symptoms. More and larger placebo-controlled, randomized trials are currently warranted to evaluate the value of interferon in PD therapy.

Prostacyclin Analogues

Iloprost, a prostacyclin analogue, is known for its fibrolytic properties and is used in several conditions of vascular obstruction. The only study so far reporting the injection of iloprost in a PD cohort ($n = 38$) showed an improvement of curvature in less than a third of patients. Adverse events occurred in a majority of patients, including local dysesthesia and pain [152]. The very limited status of evidence does currently not support routine use.

- Although first results seem encouraging, further long-term studies on intralesional application of CCH are warranted to determine its clear role in PD treatment.
- Corporeal rupture following CCH therapy remains a severe side effect
- Intralesional treatment with interferons may have a positive effect on plaque size, curvature and symptoms
- Further randomized-controlled studies on intralesional treatment with hyaluronic acid are needed to confirm the preliminary positive results in active PD

Topical and Mechanical Treatments

Topical Agents

Besides injection therapy, verapamil has been examined in a topical approach in PD, in the form of a 15% gel. There is inconsistent data on whether topically applied verapamil even reaches the tunica albuginea. One study described promising outcomes after daily application over a nine-month period. The authors described positive effects on penile curvature (approximately 61% change), resolution of penile pain (100% of patients) and an enhancement of sexual function (by approximately 82%) [153]. Another topical agent, liposomally encapsulated recombinant human superoxide dismutase (lrhSOD), was examined in a double-blind and placebo-controlled trial over eight weeks in 39 patients with PD. After 12 weeks, there was pain reduction in close to 90% of cases, in nearly half of the patients a plaque size decrease could be noted. Improvement of curvature occurred only in about a fifth of patients, however, a disease progression could be prevented in more than 90% of cases [154]. H-100 is a topical compound containing superoxide dismutase, nicardipine and emu oil. A double-blind randomized-controlled study investigated its usage over three months in a cohort of eleven patients with inflammatory PD, versus a comparable control arm ($n = 11$). After three months, a significant increase of stretched flaccid penile length as well as a reduction of curvature and penile pain were registered. Cross-over patients from the placebo group also showed a significant

improvement of described parameters. Side effects included a self-limiting local rash [155].

Iontophoresis

Iontophoresis, also known as electromotive drug administration (EMDA), uses externally applied electric current to facilitate the transport of charged molecules to a target region through blocking tiers of tissue. The aim of its usage in PD is the enhanced transport of medical substances to the tunical plaque. Double-blind, placebo-controlled trials on iontophoresis in PD, for the most part using dexamethasone and/or verapamil (usually in doses of 5 mg and 8 mg, respectively) as agents, demonstrated conflicting results. Some studies report of a significant improvement of all PD-related parameters (sexual function, pain, curvature and plaque size) compared to placebo [156], other trials could not find according results [157].

Extracorporeal Shock-Wave Treatment

Analogous to the use in orthopedic calcifications and urolithiasis, mechanical energy in the form of extracorporeal shock-wave treatment (ESWT) has first been explored in PD therapy in the late 1980s [158]. A variety of devices, with different underlying technologies, are available. Goals of ESWT in PD are the disintegration of the plaque structure and the promotion of perilesional vascularization. Clinical trials on PD reported different intensity and frequency of application. Between 2000 and 4000 shockwaves were applied in multiple weekly sessions. Existing studies are also quite heterogeneous in terms of follow-up time and outcomes. Improvements of penile curvature were marginal, favorable results could primarily be observed for pain reduction and in the improvement of sexual function [159, 160]. A recent study observed a worsening of curvature after six weeks of ESWT in both treatment and placebo groups, however, pain relief was noted in a majority within the ESWT group [161]. In a double-blind, randomized trial on ESWT in PD a total of 2000 shockwaves, with an energy flux density of 0.25 mJ/mm^2, were applied once weekly over four consecutive weeks. After 24 weeks, pain relief, sexual function and patient satisfaction were significantly higher compared to the placebo group. Interestingly, improvements regarding curvature and plaque size were significantly higher in the placebo group [162]. An improvement of curvature and plaque size was reported in a smaller series of 30 patients, who were non-responders to prior conservative treatment. The investigators used a lower energy flux density of 0.09 mJ/mm^2 in weekly sessions for a total of nine weeks. The number of shockwaves per treatment was 1500. A significant improvement of the IIEF score and penile pain was described. Penile plaque reduction and improvements in cavernous artery flux were assessed by color-coded penile Doppler sonography. However, the subjective mode of evaluation with regard to deformity was not specified [163]. ESWT is recommended for the reduction of penile pain in PD, but currently not for reduction of plaque size or curvature [3, 135].

- Topical verapamil has shown favorable results in improvement of pain, sexual function and penile straightening
- Regarding alternative topical agents, more long-term results are warranted to give a clear recommendation
- Iontopheresis may be beneficial regarding symptom relief and deformity, however, study results are controversial
- ESWT in PD seems to have a comprehensible positive effect on penile pain and remains potentially applicable in early disease.
- However, evidence of an improvement of deformity and plaque size by ESWT remains inconsistent at present and needs to be followed up by further studies

Penile Traction Devices

The application of extension to the penis in PD is proposed to result in an increase of penile length and reduction of curvature. In vitro studies using traction force on tunica albuginea with PD could show an enhanced formation of smooth muscle components with comparison to healthy tissue. Mean increases of stretched penile length were described to be 1.4 and 1.7 cm in smaller series, respectively, measured after a minimum follow-

up of 3 months. Daily usage of traction devices, for at least four hours, seems to be decisive for therapy success [164, 165]. A non-randomized, controlled trial in 96 patients compared a treatment group using traction devices against a control group. After nine months, a mean reduction of penile curvature by 20° as well as significant improvement of erectile function could be noted for the therapy group [166].

Vacuum Devices

Vacuum therapy of the penis in PD is suggested, similarly to penile extension, to have a positive effect on penile length. A study in a rat model with PD, comparing vacuum therapy versus traction devices versus no treatment, showed a significant reduction of curvature after 8 weeks. The application of penile extension, however, had an even better effect on curvature. The impact on sexual function was higher for vacuum treatment. Proposed mechanisms of action are preservation of smooth muscle tissue, antifibrotic and antiapoptotic effects [167]. A preliminary human study, conducted on 31 patients, reported the effects of vacuum device application in PD. Included patients applied the device two times a day for 10 min, respectively. After a treatment duration of 12 weeks, a significant improvement of penile pain, curvature angle and penile length could be described. Penile curvature improved by up to 25° in a majority of patients (67%) [168]. A recent study describing vacuum therapy in combination with clostridial collagenase and plaque modeling for a total therapy length of 36 months showed positive results in terms of curvature and symptom reduction [169].

- Both penile traction and vacuum devices seem favorable with regard to penile length preservation
- Vacuum therapy seems to have a more beneficial effect on sexual function, penile traction a more comprehensible impact on penile deviation

Radiation Therapy

The first study on radiotherapy in PD dates back to 1948, however, the method is nowadays still used within therapy regimens [170, 171]. Randomized, controlled studies on radiation treatment in PD are missing [172]. Several uncontrolled trials described positive effects on pain, penile deformity and plaque size [173, 174]. In vitro radiation of cell cultures derived from plaque tissue and neonatal foreskin led to an increased synthesis of profibrotic cytokines by plaque fibroblasts [175]. Considerable post-radiogenic fibrosis of the cavernous bodies has been reported [176].

- Due to inconsistently reported treatment effects and the described fibrogenic potential, radiotherapy in PD should be critically discussed.

Surgical Therapy of PD

General Considerations

Surgical correction remains the gold standard in the therapy of chronic PD [3, 135]. Several operative techniques exist to correct penile deformity, listed in detail below. The primary aim of all procedures is to allow patients normal sexual activity, including penetrative intercourse. Impairment of coitus or pain in the receptive partner are clear indications for surgery. Failure of conservative therapy options or a considerable calcification of plaques justify a surgical approach, as well [177]. Patients eligible for surgery should have attained a chronic, stable state for at least three months at the time of operation, with absence of pain or progressive deformation. The preoperative discussion with patients should draw a realistic picture of expected results. Patient expectations with respect to 'complete penile straightening' should be directed towards a 'practical straightening' with a remaining curvature of 10–20°. Further, patients should be informed about a possible loss of penile length associated with all surgical procedures, particularly in plication techniques. A lack of penile rigidity may occur after surgery, due to an affection of dorsal nerve structures either by plaque infiltration or intraoperative dissection. The irritation or injury of dorsal nerve fibers and the resulting neurapraxia can also lead to impaired

sensibility of the glans penis. A reduced rigidity of the glans can occur by virtue of a decreased arterial blood supply. This may, besides general arteriosclerosis, be due to plaque infiltration of penile neurovascular structures or the urethra. Recurrence of curvature after surgery is possible and most likely due to either a non-stable phase at the time of operation or an inflammatory reactivation of disease at a later time. Early recurrences of penile deformity can also be caused by the misuse of fast-absorbable sutures on the tunica albuginea.

Choice of Surgical Approach

The type of deformity, the severity of penile curvature and the status of erectile function have all to be taken into consideration in the choice of operative strategy. Plication techniques aim to shorten the contralateral, longer side of the penile shaft in order to erect the penis. This approach is classically recommended in non-ventral penile curvatures of less than 60° and in the absence of a hinge phenomenon. More severe deformities can be addressed by an incision or excision of the plaque structures, followed by grafting techniques using different materials. In patients with concomitant therapy-refractory ED or reduced rigidity, placement of an inflatable penile prosthesis should be considered.

Surgical Procedures in PD

Plication Techniques

Plication procedures in PD have been performed for more than 50 years. The placement of plications is performed on the most convex point of the penis to shorten the longer side of the shaft with the aim to equate curvature and to ultimately straighten the penis. Surgical access is gained through penile degloving, either with or without performance of circumcision [178]. Plication is a simple operative technique and has a traditional role in the correction of penile curvatures less than 60° and with absence of indenting deformity. Recently, plication techniques have been used more flexibly and constitute nearly 75% of all surgical corrections in PD nowadays [179]. Rates of successful penile straightening using plication are generally well above 90%. A diligent preoperative discussion with the patient should cover potential penile shortening (by approximately 1–1.5 cm). While some studies report an incidence of 85% regarding penile shortening, some authors did not record any length loss at all [180]. Other side effects include loss of sensation in the glans penis (up to 36%) and ED (up to 12%) [181]. Especially a loss of penile length, although rarely causing sexual dysfunction, is often met with poor patient tolerance. Also, length loss might be overreported in general [182]. Several plication techniques exist, both with and without incision of the tunica albuginea, the current status of evidence does not suggest superiority of a specific one. The following paragraph is to give a brief overview of existing methods:

- In the classic *Nesbit* technique, first described in the 1960s, resection of a tunical wedge is followed by an adaptation of wedge margins with slowly-absorbable sutures to straighten the penile shaft [183].
- In the *tunica albuginea plication* technique, a serial sequence of parallel incisions is performed. Incision margins of adjacent incisions are then approximated.
- The *Essed-Schroeder* approach is a less invasive variant of plication. In this technique, plications with slowly-absorbable sutures are used without incision of the tunica albuginea [184].
- Variations of plication are the *16-dot and the 24-dot* techniques, respectively. In this procedure, two or three sutures are loosely placed in a parallel pattern at the maximum point of curvature. After an erection is intraoperatively caused, one suture is tied, the penile form then reevaluated. The other knots may subsequently be tied to correct a remaining deformity [185].
- The *Yachia* technique is suitable for mild variants of concomitant notching deformities. In this method, a vertical incision is horizontally reapproximated (Heineke-Mikulicz principle)

to cause penile straightening, leaving room for penile expansion [186].

Recent developments included the *Kiel's Knot Plication* procedure. In this technique eight superficial, transversal incisions along each side of the shaft are carried out. Adjacent incisions are connected by longitudinal non-absorbable sutures. Suture knots are inverted and impalpably concealed under the tunica albuginea. Intraoperative assessment of over- or undercorrection allows for easy adjustments. Patient satisfaction rates were 90% [139]. Further, *minimally invasive plication* techniques were explored by recent studies. In these trials, tunical exposure and plication was performed via a small incision of 2–3 cm at the penile base. Results showed success rates of approximately 92% and mean operation times of roughly 60 min. Both outcomes and complication rates were similar compared to plication procedures using degloving. The reoperation rate after minimally invasive surgery, due to recurrent curvature or undercorrection, was reported to be 2% [139, 180].

- Plication techniques are an established and safe surgical strategy in PD, given a chronic disease stage of at least 3 months
- Preoperative counseling should always address the possibility of penile shortening to prevent unrealistic expectations and frustration in patients

Plaque Incision/Excision and Grafting Techniques

Relaxing procedures in PD are performed on the concave side of the deformed penis. The plaque is either incised or excised, in order to cause tissue relaxation and straighten the penis. The defect is usually closed with a graft. Plaque incision/excision techniques are suitable in patients with a curvature of more than 60° and/or an associated notching malformation (e.g. an hourglass or hinge phenomenon). Complete excisions of plaques are problematic, as they are associated with an increased occurrence of postoperative ED, caused by the impaired tunical veno-occlusive function. Grafts can be of autologous (e.g. the saphenous vein or buccal mucosa), processed cadaveric (e.g. fascia lata or dermis), xenoplastic (e.g. bovine pericardium) or alloplastic/synthetic (e.g. polytetrafluoroethylene, Gore-Tex™) origin. Selection of the graft material is guided by the aim for anti-infective and hemostatic properties and by the avoidance of graft contracture and corporeal compression. At present, older alloplastic grafts are considered obsolete, as they bear an elevated risk of inflammation, fibrosis, graft rejection and contracture [187, 188]. In autologous grafting, associated side effects by tissue harvesting should be considered, such as wound healing issues, scarring, dysesthesia or swelling. By contrast, grafts manufactured by tissue engineering, including cadaveric or xenoplastic tissue, are "ready-to-use" and therefore enjoying popularity. Overall, penile shortening is less likely to occur in grafting surgery. A possible loss of length should, however, be accordingly discussed with the patient [189]. In cases of simultaneous ED, additional implantation of a penile prosthesis should be considered. Surgical exposure is, analogous to plication techniques, gained by penile degloving. Careful dissection of Buck's fascia and mobilization of the neurovascular bundle or the urethra creates the necessary exposure and prevents damage to these structures. The point of maximum deformity and intraoperative progress can be assessed by induction of artificial erection and measurement. A relaxing incision, in the form of a "double-Y" or "double-H", alternatively a partial excision of the plaque is performed, followed by placement of the graft. A persisting curvature should not be approached with additional grafting, due to an increasing risk of ED [190]. If necessary, additional plication sutures can be placed, bearing in mind the raised risk of penile shortening. The outcomes of more recent studies on penile grafting in PD reported success rates between 88% and 100% and overall patient satisfaction rates of about 75% [181, 191–193]. Reports of side effects are heterogeneous. A notable occurrence of postoperative ED was described in two recent studies using small intestinal submucosal and pericardial xenografts (53% and 35%), one of which

also mentioned a high incidence of reduced penile sensation (31%) [181, 194]. In other trials, using autologous or xenoplastic grafts, ED and decreased sensibility were reported in only up to 21% and 3% of patients, respectively. Another article reported interviews of 46 patients who had undergone grafting surgery for PD, using dermal, pericardium and small intestinal submucosa grafts. Short-term results were observed to be positive. However, after a minimum follow-up of five years, patients reported a recurrent curvature in 50–87% of cases, with the worst results for pericardium grafts. A majority of patients required PDE-5i medication due to ED, up to half of the patients noted a loss of penile length. Patient satisfaction was poor (35%) [126]. Indicators of impaired postoperative erectile function are decreased preoperative rigidity, ventral curvature and age greater than 60 years [195]. Penile straightening rates of approximately 83% could be achieved using a self-adhesive collagen fleece (TachoSil™), with only a small number of patients showing a remaining curvature of <10° postoperatively. As an advantage, the collagen fleece provides an hemostatic effect [196]. Positive results were further reported in a study of 32 patients who underwent grafting surgery with buccal mucosa. Successful curvature correction could be achieved in 96% of cases and patient satisfaction of 85% after 1 year. Among the described side effects was local pain at the site of tissue harvesting [197]. It should be pointed out that grafting procedures are generally associated with higher morbidity and longer operation times compared to plication. With respect to postoperative management, both PDE-5i and penile extension can be used to prevent graft contracture. PDE-5i are initiated ten days after the operation for a total duration of 6 weeks with the intention to promote cavernous influx of oxygenated blood to the graft. Further, a preventive effect on postoperative ED is postulated. Penile stretching can be started approximately two weeks after surgery and can either be carried out manually or using a traction device. Traction devices should be used for two hours daily for a total duration of four weeks [198].

- Reports on plaque incision/excision and grafting techniques have brought forth mixed long-term results.
- Correct patient selection seems to be key in grafting surgery. In severe notching deformities, when plication is not an option, or in patients with reduced penile rigidity, prosthetic options should be taken into consideration.
- Complications, such as postoperative ED or loss of penile sensation, can occur owing to neurovascular damage and grafting itself.
- Choice of the right material is challenging, as controversial results have been reported. Both autologous and non-autologous grafts are associated with certain advantages and disadvantages.

Implantation of a Penile Prosthesis in PD

Patients with both PD and reduced penile rigidity, who show poor response to PDE-5i, are eligible candidates for the implantation of a penile prosthesis. In this context, inflatable prostheses (IPP) were shown to be more beneficial compared to the malleable equivalent. A mere placement of cylinders is usually sufficient for the straightening of mild to moderate forms of PD-associated curvature. This is proposedly due to the loosening of fibrotic structures during dilation-related procedures. A persisting curvature of more than 30° requires additional performance of corrective manual modelling. Hereby, the penis is intraoperatively bent over the fully inflated cylinders towards the opposite direction of the curvature for 90 s. A cracking sound can often be heard during this maneuver [199]. Manual bending in ventral curvatures can result in urethral damage and should therefore be avoided. Long-term results of IPP placement and penile modeling showed an 86% success rate [200]. The aforementioned "adhesiolytic" effect of cavernous dilation was recently further explored in the "plaque scratch" method. By disrupting the plaque with a knife from inside the corpora, the method was described as an improving adjunct to the bending procedure [201]. More severe malformations or remaining curvatures after manual bending should be further corrected using relax-

ing incisions, with or without grafting, or plication techniques. Recently, length-gaining methods such as the "sliding technique" and "modified sliding technique" have been explored. In these approaches, a degloving of the penis and mobilization of both the neurovascular bundle and the urethra is performed. The corpora are then incised in a "stair-shape" fashion, connecting a proximal, ventral semicircular incision to a distal counterpart on the dorsal penis. The graduated ends are then slid over the prosthesis cylinders, the defect is closed either by grafting or reapproximation of Buck's fascia. Appropriate studies showed a 95% patient satisfaction rate and penile length gains of more than 3 cm [202, 203]. Inflatable penile prostheses are generally associated with high patient acceptance and satisfaction (95%), with regard to both aesthetics and functionality. Adverse events include an infection of the prosthesis, the risk of which is increased by simultaneous placement of a graft. Multimodal strategies in surgical therapy of PD are of current interest. A recent study on endocavernous plaque disruption, IPP insertion and postoperative vacuum therapy was associated with significant improvements of curvature and sexual function in 145 patients [204].

- IPP implantation is a suitable therapy option for patients with PD and concomitant therapy-refractory ED
- Penile modeling and endocavernous plaque disruption are used to straighten the penis
- Penile lengthening methods, such as the "sliding technique", prevent length loss and were associated with high patient satisfaction in recent studies

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Treatment of Adult Male Hormonal Disorders

22

Raul I. Clavijo

Introduction

Traditionally, testosterone has been the most important hormone for the practicing urologist to have familiarity with. Although a cursory understanding of testosterone regulating mechanisms is sufficient for most, those that treat patients regularly for conditions such as testosterone deficiency syndrome (TDS) and infertility require a more intimate knowledge of how testosterone is tightly regulated by the hypothalamic pituitary gonadal (HPG) axis. The HPG axis is comprised of the hypothalamus, the pituitary gland (comprised of anterior and posterior portions) and the testes. The hypothalamus secretes gonadotrophin releasing hormone (GnRH) in a pulsatile fashion, which enters the hypophyseal portal system in order to reach the anterior pituitary gland. This stimulates the anterior pituitary gland to secrete two hormones vital for reproduction, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The anterior pituitary gland also secretes adrenocorticotropin, growth hormone, prolactin, and thyroid-stimulating hormone (TSH). However, the roles of these hormones in reproduction and urologic diseases are poorly understood [1]. Thus, hormonal disorders a urologist may encounter and manage includes: testosterone deficiency syndrome, defects in FSH/LH production, elevated or low estradiol levels and prolactin production disorders.

Testosterone Deficiency Syndrome

Testosterone deficiency syndrome (TDS) can be characterized by a serologic laboratory value, generally total testosterone, below a certain predefined cutoff and symptoms such as decrease or loss of muscle strength, libido, memory, vitality, alterations in mood, and erectile dysfunction (ED). The epidemiology of this condition is difficult to address as rates vary widely among studies and populations depending on definitions used. Based on current evidence, however, one can confidently state that TDS becomes more prevalent as a man ages with longitudinal studies estimating a decline in total testosterone of 3.2–11 ng/dL per year and large cohort studies utilizing symptom surveys detecting an increase in TDS as men age [2, 3].

Unfortunately, there is no consensus as to how many TDS symptoms need to be present, and no practical set of objective measures outside of hormone laboratory testing, to classify a patient as having TDS. Even when utilizing total testosterone as an objective cutoff, it is notable that most professional societies that provide recommenda-

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tions on the management of TDS use a lower limit of testosterone in the range of 300–350 ng/dL below which TDS can be diagnosed, with all requiring some kind of symptom assessment and at least two separate morning time measures of testosterone [4–6]. A cutoff of 300 ng/dL is further supported by a contemporary study utilizing a central lab at the Centers for Disease Control and Prevention (CDC) to harmonize testosterone values from several large cohort studies. This study revealed that 303 ng/dL was the average fifth percentile value among healthy non-obese patients between 19 and 39 years of age [7]. Occasionally, testosterone deficiency is diagnosed during a workup of primary or secondary male infertility and treatment of TDS varies greatly in this setting compared to aging related TDS [8]. Patients suffering from infertility with low testosterone typically require treatment with clomiphene citrate or human chorionic gonadotropin (hCG), two treatment modalities that will be discussed later in this chapter.

Before starting testosterone replacement (TRT) it is advisable to discuss the risks and benefits of testosterone replacement with patients and risk stratify them appropriately based on their risk factors. The U.S. Food and Drug Administration (FDA) lists the following contraindications to initiating TRT: breast cancer and known or suspected prostate cancer (although some would argue there are exceptions in some patients on active surveillance for low risk prostate cancer). Beyond this, however, it can be difficult to assess who is at greater risk of adverse events particularly since the risk profile of testosterone is yet to be satisfactorily defined. Addressing the undefined effect of testosterone as it relates to prostate cancer risk while on TRT, it is prudent to measure prostatic specific antigen (PSA) in patients over 40 years of age who are considering TRT given a man on TRT may theoretically have an increased risk of developing prostate cancer [9]. Since TRT is associated with polycythemia and increases in estradiol, a baseline complete blood count or hematocrit level along with a baseline estradiol is warranted. An assessment of pituitary gland function is also recommended by obtaining a baseline prolactin and LH. Occasionally, medically modifiable conditions such as a prolactin secreting prolactinoma may be detected [10]. A cardiovascular risk factor assessment is also necessary before considering TRT. A history of a prior stroke, myocardial infarction or thrombotic event should alert the urologist to at least relay the possible increased risk of stroke and cardiac events in those that use exogenous testosterone, particularly since the United States Food and Drug Administration (FDA) provides explicit warnings regarding a possible risk of adverse events in patients at increased risk of these conditions. This warning stems from studies, some of which are controversial in methodology and degree of clinical impact, linking the use of testosterone products to stroke, cardiac events, and death [11–13]. Men suffering from obstructive sleep apnea and lower urinary tract symptoms attributed to benign prostatic hypertrophy (BPH) should also be warned of possible aggravation in their symptoms while on TRT. However, contemporary data points to little if any clinically discernible worsening of these conditions on TRT [14–16]. Finally, regardless of patient age, a practitioner should always relay the fact that testosterone replacement can lead to infertility by inhibiting FSH/LH production through negative feedback mechanisms, with a subsequent drastic decline in spermatogenesis [17].

Treatment of TDS

In this section, we will focus on treatment and laboratory monitoring of patients on testosterone replacement for TDS. As one can see in Table 22.1 there are many options for testosterone replacement with injections and gels being the most prevalent form of delivery. The goal of testosterone replacement (TRT) is to reach circulating testosterone serum levels as close to physiologic levels as possible.

Short Acting Injections

Testosterone injection formulations are supplied in several depot forms with the active ingredient

Table 22.1 Testosterone Replacement Options

	Major available formulations	Dosing	Advantages	Disadvantages	Monitoring
"Sperm Unsafe"					
Short Acting Injectables	Testosterone cypionate, Testosterone enanthate	50–400 mg administered every one to four weeks	Weekly or longer dosing. Less variability in absorption.	"Peak and valley" effect. Injection pain/ reactions. Polycythemia more likely.	4–6 weeks after initiation. Draw labs mid-cyle (e.g. 2–3 days if on weekly dosing).
Long Acting Injectables	Testosterone Undecanoate (Aveed)	750 mg IM initially and at 4 weeks, then 750 mg IM every 10 weeks	Less injections. After reaches steady-state, Testosterone levels are reliable.	Injection pain/ reactions. Pulmonary oil microembolism.	End of dosing interval.
Gels/Creams	Testim™ and AndroGel®	40 to 100 mg to skin daily	Non-invasive. Less likely to lead to polycythemia.	Potential to transfer from skin to skin contact. Variance in absorption. Compliance. Rash.	At least 1 week after initiation, 2–8 h after administration.
Patches	Androderm®.	Patches	Non-invasive. Less likely to lead to polycythemia.	Skin irritation in up to 1/3 of patients. Variance in absorption.	At least 1 week after initiation, 3–12 h after administration.
Pellets	Testopel®	6–14 pellets every 3–4 months	Compliance more likely. Reliable absorption.	Procedure site reactions: Infection, pellet extrusion, hematoma.	4–6 weeks after administration to evaluate peak. Alternatively, can check at end of dosing interval.
Potentially "Sperm Safe"					
Intranasal	Natesto	1 actuation (5.5 mg of testosterone) per nostril two or three times per day	Non-invasive. Possible preservation of sperm production.	Requires at least twice-a-day administration. Variable absorption levels.	At least 1 week after initiation.
"Sperm Safe"					
Clomiphene		25–50 mg every other day	Non-invasive. Inexpensive. Preservation of sperm production.	Potential estrogenic side effects. Case reports of blood clots (intracranial).	Not established. Consider 2–6 weeks post initiation.
Human chorionic gonadotropin (hCG)		2000 units every other day or BIW	Preservation of sperm production.	Expensive. May lead to decreased FSH (feedback).	Not established. Consider 2–6 weeks post initiation.
Anastrozole		1 mg two times per week	Preservation of sperm production. Inexpensive.	Low estradiol levels (low libido, decreased bone mineral density). Only suitable as monotherapy for those with high estradiol/testosterone ratio.	Not established. Consider 2–6 weeks post initiation.

being a testosterone molecule with the addition of a carbon chain (ester). The size of the carbon chain determines the solubility and hence the half-life of the testosterone molecule. Two of the most common formulations available for intramuscular (IM) injection are testosterone cypionate (TC) and enanthate (TE). These formulations have a half-life of 8–9 days and are typically given at weekly or every-other-week regimens. It should be noted that the FDA recommended doses are 50–400 mg administered every 2–4 weeks [18]. Every-other-week dosing may lead to high peaks and low valleys at the end of the administration schedule making it hard to find an ideal dose and potentially lead to adverse side effects such as polycythemia or mood disturbances [19]. For example, in one study that administered TC 200 mg IM in 11 hypogonadal men the mean peak testosterone was supratherapeutic (1112 ± 297 ng/dL) and occurred between days 4 and 5 post-injection. By day 14 the mean testosterone was noted to be around 400 ng/dL suggesting most men were therapeutic throughout most of the 2 weeks. However, these large fluctuations and exposure to supraphysiologic testosterone over at least part of the 2-week period illustrate the less than ideal kinetics of every-other-week testosterone dosing [20]. Thus, to minimize the "peak and valley" effect noted in every-other-week dosing patterns, patient self-administered testosterone IM at weekly intervals is preferred in our practice. These injectable testosterone formulations may be started at 100 mg weekly (e.g. 0.5 mL of a 200 mg/mL solution) delivered through the IM route. In an attempt to further blunt the peak and valley effect, subcutaneous administration of lower amounts of testosterone two times per week has also been studied in small patient populations but has not been evaluated by the FDA [21]. The benefits of testosterone delivered by injection include attainment of reliable levels of testosterone compared to topical formulations. Acute side effects unique to the injectable form of testosterone include injection site reactions and pain, as well as allergic reactions to the oils and preservatives used in testosterone injection formulations.

Long Acting Injections

With a half-life of about 21 days, Testosterone undecanoate (TU) is a much longer acting formulation of injectable testosterone compared to TE and TC. The typical FDA sanctioned starting dose is 750 mg of TU injected IM initially, then at week 4, and then every 10 weeks thereafter. Pharmacokinetic studies show that TU typically leads to peak testosterone levels at 7 days after each injection and steady state, where testosterone levels remain above the therapeutic range throughout the treatment period, is typically reached after the third injection administered at week 14 [22]. A successful user of TU should therefore only require about 5–6 injections per year compared to 26 or more injections in patients that use TE or TC as their injectable of choice for TRT. However, given it takes at least three consecutive injections to get to steady therapeutic levels, poor compliance or delay of even one injection can lead to testosterone levels below therapeutic levels for a portion of the treatment period. Similar to other injectable formulations TU has the side effect of pain at the injection site, which can be more prominent given the injection of 3 mL of product is required (compared to 0.5–1 mL for TE/TC). Although rare, pulmonary oil microembolism and anaphylaxis have been reported with TU use.

Transdermal Testosterone Delivery

Approximately two-thirds of men on TRT use gel or cream preparations. Although there are several testosterone gel/cream preparations available, including compounding pharmacy products, the two most common formulations encountered in the clinic setting are Testim™ and AndroGel®. These formulations typically suspend testosterone in a hydroalcoholic gel (with different types of emollients) that is rapidly absorbed into the stratum corneum of the skin which serves as a time release reservoir [23]. Typical administration sites include the shoulders, upper arms, and abdomen. Typical starting doses range from 40 to 100 mg of delivered testosterone daily. From

pharmacokinetic studies it is evident that levels tend to increase over 18–24 h after administration but individual measurements tend to vary significantly during the course of administration [23, 24]. Steady state levels tend to be reached by the third day of administration. The most obvious benefits of gels/creams are the non-invasive nature of using gels/creams and the ease of portability as no needles are necessary. The most common side effects of testosterone topicals include skin irritation, poor compliance and inability to reach physiologic testosterone levels leading to no chance of symptom improvement and subsequent discontinuation. One should also counsel patients on the potential to transfer testosterone from skin to skin contact.

A testosterone delivery system in the form a daily patch is also available and marketed as Androderm®. Pharmacokinetically, this product is advertised to mimic the normal circadian variation of testosterone as it is applied at night, leading to peak testosterone levels in the morning. Long term use data shows that patients reach average testosterone levels around 412–498 ng/dL. However, average trough testosterone levels tend to be well below 300 ng/dL [25]. Furthermore, the use of patches is plagued by patient discontinuation due to skin irritation which has been reported in up to 1/3 of patients who use patches [26].

Intra-Nasal Testosterone

One of the newer forms of TRT available on the market is intranasal testosterone gel (Natesto™). The intranasal form of administration takes advantage of the high permeability offered by nasal mucosa. The bioavailability of testosterone through this route is further enhanced by the fact the drug is not subject to first pass metabolism. The typical starting dose is 1 actuation (5.5 mg of testosterone) per nostril two or three times per day. Pharmacokinetic studies in hypogonadal men shows an average testosterone of 386 ng/dL when used three times per day with a range of 200–935 ng/dL during an administration period [27]. Interestingly, in preliminary results from a phase IV clinical trial, testosterone delivery in the form of Natesto seems to limit negative effects on LH and FSH production to a degree that preserves sperm parameters such as total motile sperm count after 3 and 6 months of use [28]. Thus, intra-nasal testosterone may soon turn out to be a reasonable choice for TRT in patients attempting to maintain their fertility potential during TRT, and at the same time would prefer to use an FDA approved TRT medication that may be covered by insurance while avoiding off label use of medications such as human chorionic gonadotropin (hCG) or clomiphene citrate.

Implantable Testosterone Pellets

Another long-acting testosterone replacement option approved by the FDA is the implantable testosterone pellet marketed as Testopel® (75 mg testosterone per pellet). These pellets are typically inserted in an office setting in the subcutaneous tissue in the upper buttocks or lower back through a small incision under local anesthesia. One retrospective multi-institutional study on the pharmacokinetics of Testopel® showed that regardless of the number of pellets implanted, mean peak testosterone levels occurred at 4 weeks post implantation. Mean total testosterone tended to be maintained above 300 ng/dL for 4 months regardless of pellet number (range 6–10). However, higher pellet numbers were associated with levels closer to mid-normal of testosterone throughout the entire treatment period of three months [29]. Determining how many pellets to insert and how often (every 3–4 months) depends on patient circumstances, individual testosterone levels during pellet therapy, and possibly BMI with more pellets likely needed for those with a higher BMI [30]. Adverse short-term events typical of testosterone pellet administration includes pain/discomfort at insertion site, hematoma, infection, skin rash and pellet extrusion. The rate of all adverse events outside of pain/discomfort are reported at <1%. The benefit of testosterone pellets lies in the fact the patient would need only four administrations of testosterone per year.

Human Chorionic Gonadotropin (hCG)

Most of a man's endogenous testosterone is produced by Leydig cells in the testicle as a result of direct stimulation by LH, which is controlled by the pulsatile secretion of GnRH. Human chorionic gonadotropin (hCG), which has a pharmacological action similar to LH, has the capacity to be used to stimulate endogenous testosterone production. Most of what we know regarding the ability to treat patients with TDS with hCG comes from treatment of patients with hypogonadotropic hypogonadism. In these patients, hCG has been shown to be able to stimulate spermatogenesis as a direct result of increasing intra-testicular testosterone [31]. Early studies in men with normal testosterone levels revealed that a 1500 IU dose of hCG can increase testosterone levels by about 2×, on average, 48 h after administration [32]. A more contemporary study on patients with TDS suggests hCG can be as effective as other forms of TRT in reaching testosterone levels with the difference being hCG does not seem to have a negative effect on semen parameters or testicular volume [33]. There are no standard doses or intervals for hCG administration in TDS treatment. Low dose hCG divided into several doses (300 IU over 5 days) may be more effective at producing an optimal testosterone to estradiol ratio compared to a single larger dose (1500 IU × 1 dose) [32] Another study shows that hCG induces a biphasic response in testosterone production resulting in a peak at 2–4 h and a higher one at 48–72 h after one administration of hCG [34] This would indicate that every third or fourth day dosing is ideal. In our practice we typically start with 2000 IU of hCG administered in an intramuscular or subcutaneous fashion two times per week. Outside of adverse reactions related to injection and higher testosterone levels (e.g. polycythemia), no unique side effect profile has been attributed to hCG administration. However, no large prospective studies exist evaluating the efficacy of hCG for the treatment of TDS to glean a side effect profile from, and thus, it is used off-label (not FDA approved) for this purpose.

Clomiphene Citrate

For most andrologists, clomiphene citrate (Clomid) serves as an option in the treatment of TDS, although it is used off-label for this purpose as well. Clomiphene is a selective estrogen receptor modulator (SERM) that is found in a racemic mixture of two isoforms (enclomiphene and zuclomiphene) with both antagonism and agonist activities. It works to increase testosterone by competitively binding to estrogen receptors in the hypothalamus and pituitary gland decreasing the negative feedback estrogen provides. As a result, LH production by the pituitary increases, eventually leading to an increase in testosterone. Given clomiphene's potential to preserve LH and FSH production, and as a result spermatogenesis, it has mostly been studied in younger men (<50 yo) for its potential to replace testosterone. One study in 86 healthy young men (mean 29 years of age) taking clomiphene at either 25 mg or 50 mg every other day showed an increase in total testosterone from a mean of 192 to 485 ng/dL after 6 months of treatment. Interestingly this study did not reveal any major side effects and no patient ceased treatment because of adverse reactions [35]. The optimal dosing of clomiphene citrate (CC) is patient specific, however, taking into account clomiphene's half-life is estimated to be 10–14 days, we prefer to start at 25 mg two times per week and titrate up as needed to achieve desired testosterone levels. Side effects attributed to clomiphene include headaches, gastrointestinal symptoms, hot flushes, nausea, dizziness, visual disturbance, weight gain and fluid retention. Rare cases of central retinal vein occlusion in a man with factor V Leiden and a case of intracranial venous thrombosis presenting as a severe headache have been reported [36]. Theoretically, the enclomiphene isomer of clomiphene (Androxal) may have less chances of precipitating these side effects given it has mostly estradiol antagonist properties. Although it has been shown to reliably increase testosterone levels in those with TDS, enclomiphene has not received FDA approval [37].

Oral Testosterone Formulations

Oral formulations of TU are currently not available in the United States and as of January 2018 have not been approved by an FDA advisory panel due insufficient data on short and long term risks. Oral TU is available in Europe and some parts of Asia however and is marketed as Andriol® Testocaps®. Most studies on oral TU date back to the 1970–1980 and show that oral TU typically only modestly increases testosterone levels with difficulty achieving therapeutic levels in most study participants [38].

Monitoring

Checking testosterone levels regularly in those on testosterone replacement is advocated by most professional medical society guidelines. Typically, a testosterone level is drawn at the 4 week to 3 month mark for an initial measurement that facilitates titration. Table 22.1 lists typical time-points in an administration cycle as to when testosterone should be drawn to aid in testosterone titration.

The risk of polycythemia from TRT is troublesome due to a potential to exacerbate vascular diseases (coronary, peripheral, cerebral). Injections are associated with the greatest risk of erythrocytosis compared to topical formulations [39]. In one study, testosterone enanthate given at weekly doses of 25–600 mg lead to hemoglobin and hematocrit increases in a linear, dose-dependent fashion in both young and older men [40]. Thus, routine monitoring of hemoglobin/hematocrit is strongly advised particularly with injectable regimens. To simplify regimens it is typically recommended that a hematocrit be checked every time a testosterone level is checked unless it is to monitor response to a phlebotomy session. Strategies in patients who develop polycythemia include decreasing the testosterone dose or prescribing regular phlebotomy sessions.

Hepatotoxicity is currently thought to be limited to steroids which are designed for oral administration [41]. Unless an oral testosterone formulation is prescribed, liver function monitoring is not routinely recommended for patients receiving testosterone. Similarly, routine monitoring of lipid profiles is not strongly recommended. This is supported by studies that do not show any discernible changes in cholesterol levels, outside of a possible mild decrease in HDL, even with supraphysiologic testosterone levels [42, 43].

As previously alluded to, although evidence linking testosterone replacement with a higher risk of prostate cancer development is weak, PSA and DRE checks at 3–12 month intervals are supported by most society guidelines on testosterone replacement [5, 44].

Lastly, while someone is on testosterone replacement therapy, particularly early on, it is important to monitor symptoms to ensure the patient is deriving at least subjective improvement. Questionnaires such as the Androgen Deficiency in the Aging Male (ADAM) questionnaire may prove useful for this purpose [45]. It should be emphasized that the goal should be to achieve physiologic levels of testosterone and only continue therapy if patients do experience improvement in symptoms attributed to low testosterone.

Estradiol

The importance of normal estradiol levels in men is exemplified by studies conducted on men receiving exogenous testosterone with aromatase inhibitors, as well as congenital cases of aromatase deficiency. In one unique study assessing the role of estradiol in men researchers used goserelin acetate to suppress endogenous testosterone and estradiol production. Men were then treated with exogenous testosterone and randomly assigned to administration of aromatase inhibitors (AI) to prevent the conversion of androgens to estradiol by blocking the action of the enzyme aromatase. Interestingly, significant estradiol deficiency in those treated with AI lead to a decline in sexual desire and more undesirable fat distribution [46]. More extreme cases of low estradiol levels can be found in patients with aromatase deficiency. These men tend to develop osteopenia, above-average height due to delay in fusion of the epiphyses, abnormal lipid profiles and infertility. Interestingly, treatment of these patients

with exogenous estradiol can lead to improvement in some of these abnormalities [47]. Given the association of low estradiol with osteopenia, measurement of bone mineral density may be needed only in those with low estradiol levels. On the other hand, cases of aromatase excess usually present as men with gynecomastia, accelerated growth and premature bone maturation [48]. Anastrozole (Arimidex) represents a common AI used by andrologists. This medication is typically used to decrease iatrogenic excess in estradiol that may accompany testosterone replacement. In men using anastrozole to treat an iatrogenic excess of estradiol a typical starting dose is 1 mg every other day given its half-life of 50 hours. Although difficult to define a normal range for men, a range of 20–60 pg/mL is typically targeted in men on TRT. Anastrozole and other AIs have also been studied as monotherapy in the treatment of TDS, especially in patients with a low testosterone to estradiol ratio. Typically, AI therapy tends to increase testosterone levels to well within the therapeutic range (>350 ng/dL) consistently. However, estradiol levels fall to levels that may precipitate symptoms such as loss of libido and impact bone mineral density in a negative manner [49]. Thus, AIs are rarely used as monotherapy for TDS and it should be noted that AIs are not FDA approved for this purpose.

Prolactin

It is known that an excess of prolactin, typically as a result of a productive prolactin secreting adenoma in the pituitary gland, can contribute to a decline in GnRH secretion and thus a subsequent decrease in LH production. Without adequate stimulation, Leydig cells in the testicle stop producing adequate amounts of testosterone leading to TDS. On the other hand, low prolactin levels have also been associated with derangements in the following areas: metabolic, psychological, erectile and ejaculatory [50, 51]. Currently, there is no practical way to supplement or increase prolactin levels and, given the weak evidence that hypoprolactinemia leads to clinically relevant disease, it is questionable how much weight should be put on an isolated finding of hypoprolactinemia . Hyperprolactinemia, however, is a well established condition. The first decision a clinician has to make is when to check prolactin. Professional society guidelines generally advise checking prolactin in any patient diagnosed with TDS, particularly if LH is low or normal. Some studies further suggest the need for a pituitary MRI in patients with a testosterone of <150 ng/dL and low/normal LH levels regardless of prolactin levels [39]. However, a more recent study suggests one is unlikely to detect significant pituitary findings until prolactin levels are at least two times above normal levels [52]. If a pituitary abnormality is found, an endocrinology referral is warranted unless the urologist is experienced in managing prolactinomas.

Conclusion

Adult male hormonal disorders typically encountered by urologists involve the hormones testosterone, estradiol and prolactin. Unfortunately, there are no definitive recommendations on the symptoms and laboratory value ranges attributed to derangements in these hormones and the practitioner should alert the patient of the ambiguity of what defines conditions such as testosterone deficiency. It should be emphasized that close laboratory and symptom monitoring is necessary to avoid potential side effects in patients being treated for these hormonal derangements. A guide on the evaluation, treatment, and monitoring of patients with symptoms and laboratory values consistent with abnormal testosterone, estradiol, and prolactin levels are provided in this chapter. However, this should not be interpreted as a delineation of strict protocols and treatment should always be individualized to the patient and his co-morbid conditions and symptoms.

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Metabolic Evaluation and Medical Management of Stone Disease

23

Russell S. Terry and Glenn M. Preminger

Epidemiology

Nephrolithiasis has a high worldwide prevalence with rates which range from 7 to 13% in North America, 5 to 9% in Europe, and 1 to 5% in Asia according to recent reports [1]. This prevalence appears to be increasing, with recent data from the National Health and Nutrition Examination Survey (NHANES) in the United States showing a 63% relative increase from 6.3% in 1988–1994 to 10.3% in 2007–2010 [2]. Also changing is the gender gap in the prevalence of stone disease. While historically nephrolithiasis has been considered to be a male-predominant disease, a reanalysis of the NHANES over the time period 2007–2012 showed no difference in stone prevalence between men and women under 50 years of age [3]. Similarly disproportionate increases affecting demographic groups historically considered to be at lower risk for nephrolithiasis, including children, African Americans, and Hispanics, have been documented recently as well [2, 4].

These increases in overall and gender-specific prevalence of nephrolithiasis have been linked to systemic conditions such as obesity, diabetes, and metabolic syndrome. Moreover, the magnitude of increased kidney stone risk conferred by obesity appears to disproportionately affect women [5]. Based in part on the high degree of geographic variability of stone disease prevalence in the United States as well as internationally, studies have hypothesized and subsequently demonstrated that weather related variables such as increasing ambient temperature and sunlight exposure constitute risk factors for nephrolithiasis as well [6]. These findings have led to concerns that progression of global warming in the coming decades could further contribute to increasing stone disease prevalence [7, 8].

The economic burden of nephrolithiasis is tremendous. As of 2000, the estimated annual cost attributed to urolithiasis in the United States was $2.1 billion dollars, representing a 50% increase since 1994 [9]. More contemporary estimates are as high as $10 billion dollars annually [10]. As a consequence of an increasing stone prevalence, it is predicted that the overall expenses related to nephrolithiasis will continue to increase over time [7].

Stone Types and Associated Metabolic Conditions

Stone classification is traditionally divided into two groups: calcium based and non-calcium based stones (Table 23.1). Calcium based stones are the most frequently encountered and include

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Table 23.1 Stone Types and Frequency [11, 12]

Stone type		Frequency (%)
Calcium (80%)	Calcium oxalate monohydrate	35–55
	Calcium oxalate dihydrate	20–30
	Calcium phosphate	10–15
Non-calcium (20%)	Struvite	5–10
	Uric acid	5–10
	Cystine	1–2
	Urate (Ammonium acid, Sodium)	<1
	Xanthine	<1
	Drug-induced	<1

calcium oxalate monohydrate (35–55%), calcium oxalate dihydrate (20–30%), and calcium phosphate (10–15%) [11, 12].

Non-calcium stones are less commonly encountered and include struvite (magnesium ammonium phosphate, 5–10%), uric acid (5–10%), cystine (1–2%), urate (ammonium acid urate, sodium urate, <1%), xanthine (<1%), and medication-related stones (indinavir, ephedrine, triamterene, silicates, ciprofloxacin, sulfa medications) [13].

Calcium-Based Urolithiasis

Calcium Oxalate Stones

While calcium oxalate is the most common stone type, the formation of calcium oxalate stones has been associated with a large number of different metabolic defects [14], and therefore stone analysis alone in these patients may not be specifically revealing into the potential underlying disorder [15]. Metabolic defects which have been associated with calcium oxalate stone formation include hypercalciuria (absorptive and renal), hypocitraturia, hyperuricosuria, hyperoxaluria, gouty diathesis (low urine pH), and low urine volume. On comprehensive metabolic evaluation over 97% of patients will have an identifiable metabolic derangement, and many patients will be discovered to have multiple of these risk factors in combination.

Calcium Phosphate Stones

Calcium phosphate stone formation, in contrast to calcium oxalate, is more likely to be associated with a specific metabolic disorder such as distal renal tubular acidosis (RTA 1) or primary hyperparathyroidism [14, 15].

Uric Acid Urolithiasis

At a urine pH of less than 5.35, uric acid exists predominantly in its free form which has exceedingly poor solubility in urine and therefore crystallizes to form uric acid stones [16]. Low urine volume and only occasionally hyperuricosuria can contribute to the development of uric acid stones, but these factors play a secondary role to low urine pH [17]. Low urine pH, defined as a pH lower than 5.5 and also known as "gouty diathesis," has been associated with systemic insulin resistance [18, 19] and increased body weight [20] through a postulated mechanism of impaired ammoniagenesis in the renal tubules. The most common cause of hyperuricosuria is dietary purine excess. Other medical conditions which may cause hyperuricosuria include gout, certain myeloproliferative and hematologic disorders with rapid cell turnover, and rarely hereditary errors in purine metabolism or urate transport. In the setting of hyperuricosuria without pH <5.5, formation of microscopic uric acid crystals in the urine has been demonstrated to form a nidus that can seed heterogeneous nucleation of calcium oxalate stones and lead to hyperuricosuric calcium urolithiasis (HUCU) [21, 22].

Infectious Urolithiasis

Infectious stones are composed of magnesium ammonium phosphate, more commonly referred to as struvite, which may be present purely or in mixed composition with other stone types, often carbonate apatite and hydroxyapatite [23]. These calculi occur secondary to urinary tract infection by urease-splitting bacteria [24]. Common uropathogenic organisms associated with urease

production include *Proteus*, *Klebsiella*, *Providencia, Morganella, Corynebacterium, and Ureaplasma* species [25]. *Staphylococcus* and *Pseudomonas* species may occasionally produce urease, however *E. coli* does so only exceedingly rarely. Bacterial urease catalyzes the conversion of urea to ammonia and carbon dioxide, which promotes the formation of alkaline urine (pH > 7.2) and creates a milieu conducive to the formation of struvite or mixed struvite stone [23]. Struvite growth may be enhanced in the setting of concurrent chronic infection and obstruction [26]. Women are twice as likely to have struvite stones than men due to their higher incidence of urinary tract infections [27].

In the past it was believed that struvite stones composed the majority of staghorn calculi. More recent series, however, suggest that stones with staghorn configurations more commonly have a metabolic etiology, specifically calcium phosphate [28].

Cystine Urolithiasis

Cystinuria is a hereditary condition, usually with an autosomal recessive inheritance pattern, which is characterized by defective resorption of the dibasic amino acids cystine, ornithine, lysine, and arginine within the proximal renal tubule [29]. While urinary concentrations of all four of these amino acids are elevated, only cystine forms renal stones due to its very poor solubility in urine at physiologic temperature, pH, and concentration [30]. Notably, even though cystine stone formers all have definitive genetic derangements, they often also demonstrate other metabolic abnormalities such as hypocitraturia, hyperuricosuria, and hypercalciuria [31].

Other Non-Calcium Urolithiasis

Ammonium Acid Urate Stones

Ammonium acid urate (AAU) stones are rarely encountered in industrialized nations, with an incidence of less than 1% in North America [32]. Risk factors for the development of these stones, in order of prevalence, include morbid obesity (40.6%), recurrent UTIs (36.4%), inflammatory bowel disease (25%) with or without ileostomy diversion (22.7%), recurrent uric acid stones (20.5%), and a history of laxative abuse (13.6%) [33].

AAU stones are more classically encountered endemically in the composition of pediatric bladder stones in the developing world, where they are thought to occur in areas where diets are poor in phosphorus content, rich in purine-containing cereal grains, restricted in access to abundant clean water, with a high incidence of diarrheal illness [34].

The proposed mechanism for formation of AAU stones in the setting of the above-listed risk factors involves dehydration from chronic GI fluid and sodium loss leading to intracellular acidosis and concomitant increased urinary ammonium and decreased urinary sodium. These changes, coupled with low urinary pH and hyperuricosuria, create an environment in which AAU stones may form.

Medication-Induced Stones (Table 23.3)

Direct Promotion of Stone Formation

Several drugs are known to directly promote stone formation via concentration and direct precipitation in the urine [13]. These medications include but are not limited to indinavir (as well as newer generation protease inhibitors used to treat HIV [35]), ciprofloxacin, triamterene, silicates, guaifenesin/ephedrine, and sulfa medications. The diagnosis and treatment of these stone types can be very difficult as many of them are quite radiolucent, even on CT.

Indirect Promotion of Stone Formation

Several other medication classes promote stone formation indirectly by altering urine parameters that increase stone risk. Loop diuretics (e.g. furosemide) and corticosteroids cause hypercalciuria. Carbonic anhydrase inhibitors (e.g. acetazolamide), certain anti-convulsants (topiramate and zonisamide), and thiazides can produce intracellular acidosis, hypocitraturia, and overly-alkaline urine in the long term which increases risk for calcium phosphate stones. As previously men-

tioned, laxative abuse has been associated with ammonium acid urate stone formation. Vitamin C supplementation, in excess, has been linked to hyperoxaluria and increased stone formation rates [36, 37].

Metabolic Evaluation of Stone Disease

Goals

Prospective studies have shown that first time stone formers are estimated to have a 27–50% risk for stone recurrence within 5 years of their initial stone episode [38, 39]. Because urinary stone disease carries significant morbidity, discomfort, and cost, patients and physicians alike are motivated to reduce recurrence as much as possible. The goal of the metabolic evaluation therefore is to identify any specific metabolic derangements which may contribute to the formation of new stones or the growth of existing stones.

Specific dietary therapy made on the basis of a comprehensive metabolic evaluation has been shown to be superior to generalized dietary recommendations in preventing stone recurrence [40]. Additionally, targeted medical therapy based on the findings of a comprehensive medical evaluation has been shown to reduce stone growth and new stone formation compared to empiric treatment [41, 42].

Who Needs Metabolic Evaluation?

Recent recommendations from the American Urological Association Nephrolithiasis Guidelines Panel suggest that metabolic testing should be performed in recurrent stone formers and in high risk or interested first time stone formers [43]. Patient populations considered to be at high risk for stone recurrence include those with a family history of stone disease, inflammatory or other malabsorptive bowel disease, recurrent urinary tract infections, obesity, renal tubular acidosis type 1, primary hyperparathyroidism, osteoporosis, gout, or diabetes mellitus type 2 [44].

There is controversy regarding whether non-high risk first-time stone formers should undergo metabolic evaluation or be treated empirically. There is ample evidence that stone recurrence is greatly reduced in first-time calcium-based nephrolithiasis patients by increasing fluid intake with or without general dietary modification, suggesting that the recurrence risk for these patients can be reduced without undergoing the cost and inconvenience of metabolic testing [38, 45]. However, there is also evidence that recurrent stone formers and first-time stone formers have similar types and frequencies of metabolic abnormalities on 24-h urine testing [46], and since we know from several randomized controlled trials that directed medical therapy for specific urinary abnormalities can reduce stone recurrence [47], this finding suggests that first-time stone formers may in fact benefit from comprehensive metabolic evaluation and selective medical treatment.

Stone formers with stone types that are associated with increased likelihood of metabolic derangements should undergo metabolic evaluation. Uric acid and cystine stone formation have been demonstrated to coincide with gouty diathesis and cystinuria metabolic derangements, respectively, in nearly all cases [15], and therefore metabolic evaluation in these patients is justified. For many years, pure struvite stones were believed to have a low likelihood of being associated with specific intervenable metabolic derangements and therefore metabolic evaluation was not routinely recommended for these patients [48]. However, more contemporary reports have identified metabolic abnormalities in pure struvite stone formers to be more common than previously believed and suggest that these patients would benefit from comprehensive evaluation and directed medical therapy [49].

There is controversy regarding whether or not all children with urolithiasis require a comprehensive metabolic evaluation following a stone episode. While the overall incidence of pediatric nephrolithiasis has rapidly increased over the past few decades in the United States [50], this increase appears to be occurring disproportion-

ally in school-aged children older than age 8 and is hypothesized to be related to increases in the prevalence of pediatric and adolescent obesity during the same time period [51]. Augmenting this epidemiologic data, a recent retrospective multi-institutional study of pediatric 24 h urine studies demonstrated that children older than age 10 are significantly less likely than younger children to have an identifiable metabolic abnormality on evaluation and their most common abnormalities were low urine volumes and hypocitraturia [52]. Conversely, children aged 10 or younger were significantly more likely to have metabolic disorders, specifically hyperoxaluria, hypercalciuria, and elevated calcium phosphate supersaturation. Taken together, these findings suggest that perhaps older children may be evaluated and treated with or without comprehensive metabolic evaluation in a manner similar to adult first-time stone formers, whereas younger children should be treated as high risk patients and encouraged to complete a full evaluation.

What Are the Components of the Metabolic Evaluation?

Medical History and Physical Examination

The metabolic evaluation should begin with the performance of a physical examination and the taking of a detailed medical history. The history should include careful probing for medical conditions, prior surgeries, family history, medications, and dietary/bowel habits that may predispose to urolithiasis (see Table 23.2).

Particular focus should be given to a history of gastrointestinal diseases or surgery. Patients with a history of bariatric surgery or bowel resection are at increased risk of developing kidney stones [53]. Patients with a history of chronic diarrhea or inflammatory bowel disease are at increased risk for low urine volumes and altered oxalate and/or citrate metabolism. Excessive laxative use has been associated with ammonium acid urate stone formation.

Dietary history should evaluate approximate daily fluid intake as well as obtain a general

Table 23.2 Risk factors for urolithiasis from medical history

Risk factors for urolithiasis from patient history	
Medical history	Primary hyperparathyroidism
	Renal Tubular Acidosis (RTA) Type 1
	Gout
	Metabolic syndrome/diabetes mellitus Type 2
	Obesity
	Inflammatory bowel disease
	Chronic diarrhea/malabsorptive gastrointestinal disorder
	Osteoporosis
	Spina Bifida or Other Neurologic Disorder
	Personal or family history of nephrolithiasis
	Recurrent urinary tract infections
Surgical history	Bariatric surgery
	Gastrointestinal reconstruction
	Urinary diversion
	Prior urologic surgery
Dietary history	Low fluid intake
	High salt intake
	High animal protein intake
	Low fruit and vegetable intake
	Very high or very low calcium intake
	High oxalate intake
	Special Diets (i.e. Low Carbohydrate/High Protein)

Table 23.3 Stone-inducing medications

Stone-inducing medications		
Medications	Direct stone promotion	Indinivir (and other antiretroviral protease inhibitors)
		Ciprofloxacin
		Triamterene
		Silicates
		Guaifenesin/Ephedrine
		Sulfa Medications
	Indirect stone promotion	Carbonic anhydrase inhibitors (Acetazolamide, Topiramate, Zonisamide)
		Long term loop diuretics
		Chronic corticosteroid use
		Vitamin D and Calcium Supplements
		Vitamin C Supplements
		Chemotherapy

assessment of protein, calcium, sodium, high-oxalate or high-purine, and fresh fruit and vegetable intake. Medication history should be obtained and should include information on over-the-counter supplements, especially Vitamin C.

Serum Chemistry

Serum chemistries should be obtained at the time of metabolic evaluation [43]. These should specifically include basic electrolyte panel, calcium, creatinine, and uric acid measurement. An elevated serum calcium should raise concern for possible primary hyperparathyroidism and serum levels of intact parathyroid hormone (PTH), Vitamin D, and phosphate should be measured [54]. Hyperchloremia and hypokalemia could indicate the presence of a metabolic acidosis possibly secondary to distal RTA. Hyperuricemia can be suggestive of a defect in purine metabolism such as gout.

Stone Analysis

When a stone is available, clinicians should obtain a stone analysis at least once [43]. Stone type is correlated with urinary supersaturation levels [55], which are frequently monitored on serial 24-h urine testing as an endpoint of success with medical therapy. Therefore, knowing the stone type can provide valuable information to help guide prevention. Moreover, certain stone types correlate tightly with specific metabolic abnormalities [15]. Calcium phosphate stones can be associated with primary hyperparathyroidism or distal RTA with routinely alkaline urine. Pure uric acid stones are strongly associated with an acidic urine (patients with gouty diathesis). Calcium oxalate stones may result from a variety of metabolic derangements, and therefore the finding of CaOx stone composition alone is not necessarily predictive of any specific metabolic abnormality.

Urine Evaluation

Urinalysis

Urinalysis (UA) should be obtained at the time of metabolic evaluation and should include both a dipstick and microscopic examination [43]. The sample should be assessed for pH, evidence of possible infection, and the presence of stone crystals. Low urine pH of less than 5.5 is diagnostic of gouty diathesis and may indicate the possibility of uric acid stone formation. High urine pH greater than 7 can be indicative of the presence of urea-splitting bacteria and can indicate the presence of struvite stones, or suggest the finding of distal RTA.

Urine Cultures

Urine culture should be obtained in patients with a UA that is suggestive of infection or in patients who are symptomatic or have a history of recurrent UTIs [43]. Urinary tract infections should be treated, especially if the patient is planned to undergo surgical intervention.

24-h Urine Collections

The urine constituents most commonly assayed during 24-h urine collections include: Total volume, pH, calcium, phosphorus, oxalate, citrate, sodium, magnesium, potassium, uric acid, and sulfate. Whereas most of these parameters are self-evident, sulfate is measured in order to assess the amount of animal protein ingested, which may increase the risk of certain stones. Urine creatinine is measured to evaluate the adequacy of urine collection. 24-h urine creatinine values lower than 500 mg/day should be considered as incomplete collections whereas creatinine values >3000 mg/day in normal-sized individuals suggest an "over collection" of urine. Cystine values should be requested when cystinuria is suspect. It is our routine to have the patient collect two 24-h urine samples on two different days (either consecutive or separate) with the patient on their "normal routine" (normal diet, fluid intake, medications, physical exercise, etc.).

In the past, a third 24-h urine collection on a calcium-restricted diet was performed to differentiate between the various causes of absorptive hypercalciuria—Absorptive hypercalciuria Type I or Type II. Moreover, the previously used calcium fast and loading urine collections were used to differentiate between absorptive and renal leak hypercalciuria. However, discrimination of specific causes of hypercalciuria, while important

for physiologic discrimination, has little importance presently as thiazide diuretics are the only medications available to treat patients with either absorptive or renal leak hypercalciuria.

When Should Metabolic Evaluation Be Performed?

Metabolic evaluation should not be performed during an acute stone episode. Ideally patients should wait at least one month following stone passage or surgical intervention prior to initiating evaluation in order to allow the return to normal diet, work, and daily routine. Often, the metabolic evaluation will begin with stone analysis from a recent stone episode. Afterwards, or if the patient is a recurrent stone former who has not necessarily had a recent acute stone episode, evaluation may be initiated immediately.

Medical Management of Urolithiasis

The primary goal of medical stone management is to prevent urine crystallization and hence the formation or growth of stones. This goal can be achieved either by conservative or by selective medical management.

Conservative Management

Conservative management may be effective as initial treatment for first time stone formers and for those patients without significant risk factors for recurrent stone formation. It may also be applied as a baseline measure to patients with specific metabolic derangements who are also undergoing selective medical therapy.

Increased Fluid Intake

The most important recommendation that can be offered for the prevention of kidney stones is to increase fluid intake. Increased fluid intake produces a dilute urine with a decreased propensity for stone crystallization [56]. A generally accepted hydration goal is 3 L of ingested fluid, resulting in 2.5 L of urine output daily [43]. High fluid intake (>2 liters daily) has been shown in a randomized trial to decrease stone recurrence rates from 27% to 12% in idiopathic calcium stone formers at 5 years [38]. Encouraging high fluid intake and avoidance of dietary excess alone has been shown to prevent stone recurrence in 58% of idiopathic calcium stone formers at 5 years [45].

General Dietary Recommendations

Several dietary parameters have been investigated in terms of their relationship to kidney stone formation. However, our understanding of this complex topic remains somewhat limited because the majority of these studies have not been prospective, randomized, controlled trials, and they most frequently compare several individual dietary interventions simultaneously—making it difficult to draw conclusions about the stone risk conferred from each individual dietary component in isolation.

Increasing dietary sodium has been demonstrated to increase urinary calcium and decrease urinary citrate [57]. Therefore, a low sodium diet of ≤2300 mg/day is often recommended to help reduce hypercalciuria.

Diets which are high in animal protein (e.g. a high acid-ash diet) increase stone formation risk by lowering urine pH, thereby contributing to hypercalciuria and hyperuricosuria [58, 59]. Concordantly, prospective studies have shown that restricting animal protein intake (0.8 g/kg per day) increases urinary citrate and decreases urinary calcium, uric acid, and oxalate levels [60, 61].

Perhaps the highest quality evidence that we have on the topic of dietary prevention of kidney stones is from Borghi et al who were able to demonstrate in a prospective, randomized trial that a multicomponent diet consisting of normal calcium, reduced animal protein, and reduced salt intake significantly decreased 5 year stone recurrence rates from 38% to 20% relative to a low calcium diet in patients with idiopathic hypercalciuria and recurrent nephrolithiasis [62]. Subsequent large cohort studies have further correlated adherence to a DASH diet—which also emphasizes fresh fruits and

vegetables and limited sodium—with reduced risk for kidney stones [63].

Based on the results of the Borghi trial as well as large observational studies showing an increase in kidney stone risk for patients with low dietary calcium [64], a moderate daily calcium intake of 1000–1200 mg is recommended (2–3 dairy servings per day). For patients who take a daily calcium supplement for a justifiable medical reason, 24-h urine calcium content and calcium salt supersaturation should be monitored.

Oxalate Restriction

Dietary oxalate can account for 24–42% of urinary oxalate. This percentage correlates positively with the amount dietary oxalate consumed, and it correlates negatively with the amount of dietary calcium consumed [65]. Therefore, it is reasonable to recommend dietary oxalate restriction in patients with hyperoxaluria, and this recommendation may be particularly helpful in patients with enteric hyperoxaluria secondary to GI reconstruction or malabsorptive/inflammatory bowel conditions. A number of current websites list the oxalate content of various foods [66].

Citrus Supplementation

Natural citrus juices such as lemon juice and orange juice as well as artificial products such as citrus flavored drink mixes and carbonated beverages contain appreciable amounts of citrate. In one study, the highest citrate concentrations were found in grapefruit, lemon, orange and pineapple juice, along with reconstituted lemonade and lemonade flavored Crystal Light® [67]. Their effects on urinary chemistry and calcium salt supersaturation are variable. Lemonade and orange juice have both been shown to raise urinary citrate in hypocitraturic calcium stone formers [68, 69], however orange juice produces a notable urinary alkalinization whereas lemonade does not impact urine pH [70]. The high sugar content of orange juice however may increase the risk of stone disease [71].

Grapefruit juice also provides a significant citrate load which translates to increased urinary citrate levels, however it also appears to increase urinary oxalate and therefore no net change in calcium salt supersaturation in produced [72]. In addition to this lack of efficacy, grapefruit juice is known to interact with several major classes of commonly prescribed medications through its inhibition of the hepatic cytochrome P450 enzyme pathway, a fact which makes it even less desirable as a routine dietary recommendation.

Selective Medical Therapy

Our ability to perform sophisticated testing in high risk stone formers is only as useful as our ability to treat the specific abnormalities which that testing reveals. The goal of selective medical therapy, therefore, is to reduce the risk of future stone formation by correcting specific metabolic derangements as identified in the comprehensive metabolic evaluation. Interestingly, while selective medical therapy has been shown to be superior to placebo [47], there has never been definitive randomized trial evidence demonstrating the superiority of selective medical therapy over conservative management. The following sections are organized by specific metabolic derangement and discuss the selective medical therapy options for managing them.

Hypercalciuria

The two main subtypes of hypercalciuria are absorptive and renal leak. Although the underlying pathophysiology of these two entities differs, they are currently treated similarly. In absorptive hypercalciuria (AH), the underlying defect is over absorption of calcium from the gastrointestinal tract. AH is further subdivided into Type I and Type II, with Type I being the more severe defect and Type II being a milder, dietary responsive variant. Renal leak hypercalciuria is due to impaired tubular reabsorption of calcium.

Primary hyperparathyroidism is associated with hypercalcemia and hypercalciuria, and it is implicated in approximately 5% of nephrolithiasis cases [73]. Excess parathyroid hormone produces increased gastrointestinal calcium absorption and increased bone resorption. First line therapy for primary hyperparathyroidism is surgical excision.

Thiazides

Thiazides do not directly address the underlying physiologic defect in AH. Nonetheless, thiazides are widely used in the treatment of AH because they are effective in lowering urinary calcium by stimulating calcium resorption in the distal renal tubules. The effectiveness of thiazides versus placebo in preventing calcium stone recurrence has been demonstrated in several randomized trials and confirmed in at least two meta-analyses [47, 74]. Interestingly, because many of the patients in these studies did not have documented hypercalciuria, the benefit of thiazides in preventing calcium stone recurrence may not be restricted to hypercalciuric patients. Thiazides have traditionally been contraindicated in primary hyperparathyroidism because of concern for potential severe hypercalcemia, although that dogma has recently been called into question [75].

Thiazide dosing regimens used in the aforementioned trials include hydrochlorothiazide 25 mg twice daily, chlorthalidone 25–50 mg once daily, and indapamide 2.5 mg once daily. Importantly, a significant proportion of patients on thiazide therapy will develop hypokalemia with the risk of secondary intracellular acidosis and hypocitraturia. Therefore, potassium supplementation must always be a consideration when starting a thiazide. Potassium citrate (20 mEq twice daily) is often a reasonable choice since it will address both the hypokalemia and potential hypocitraturia without causing hypochloremia or metabolic alkalosis [76]. Moreover, the choice of potassium citrate co-administration with thiazides in patients with recurrent calcium stones and either no identifiable or adequately addressed metabolic abnormality is recommended with a grade B strength of evidence in the most recent AUA guidelines on the medical management of kidney stones [43]. Potassium chloride may be used if elevated urine pH is a concern since KCl will not have an alkalinizing effect.

Hyperoxaluria

Hyperoxaluria, defined as greater than 40 mg/day of urinary oxalate excretion, can be categorized as primary, enteric, or dietary [35]. Primary hyperoxaluria occurs as a result of an autosomal recessive genetic defect in the oxalate metabolism pathway, and its severe forms require liver transplant to correct the underlying problem. Enteric hyperoxaluria is more common and occurs in the setting of fat malabsorption and rapid GI transit whereby fatty acids bind enteric calcium and therefore increase the amount of oxalate available for absorption and eventual urinary excretion. This finding can be a result of prior GI resection or reconstruction, inflammatory bowel disease, or other GI disorders. Dietary hyperoxaluria results from overindulgence in oxalate-rich foods, the effect of which can be substantial since half of urinary oxalate derives from the diet [77].

Enteric hyperoxaluria can be treated with selective therapy to address the underlying defect [78]. Oral administration of over-the-counter calcium salts three times daily with meals may be used to bind dietary oxalate within the gut lumen. Bile acid binding resins such as cholestyramine may be used to decrease the amount of irritant bile acid that gets delivered to the colon and causes mucosal irritability with secondary hyperabsorption of oxalate.

Pyridoxine supplementation has been shown reduce urinary oxalate in patients with primary hyperoxaluria as well as in stone formers with idiopathic hyperoxaluria [79, 80]. The presence of Oxalobacter formigenes gut colonization has been correlated with decreased urinary oxalate excretion [81], but the results of interventional studies whereby probiotic preparations are delivered in an attempt to reduce oxalate excretion have been mixed [82].

Gouty Diathesis

The primary goal in the management of gouty diathesis is to increase the urinary pH above pH 5.5, preferably between 6.0 and 6.5. Potassium citrate is often the treatment of choice for this purpose, and it should be given at dose sufficient to maintain urinary pH at approximately 6.5 (30–60 mEq per day in 2–3 divided doses). Sodium bicarbonate may also be used for urinary alkalinization; however, its concomitant sodium load raises concern for the risk of causing hypercalciuria and potentially secondary calcium stones

[83]. Alkalinization of the urine to a pH greater than 7.0 should be avoided due to the risk of increasing calcium phosphate supersaturation in this elevated pH range [84].

Importantly, patients with uric acid stones should not be offered allopurinol as first-line therapy [43] because improvement in hyperuricosuria is futile in these patients unless their low urine pH is treated first. For patients who continue to form uric acid stones despite adequate urinary alkalinization, then allopurinol treatment may be considered.

Hyperuricosuria

Hyperuricosuria, defined as greater than 600 mg per day of urinary uric acid excretion, is often secondary to dietary excess and is associated with increased risk of calcium oxalate stones [85, 86]. For hyperuricosuric calcium oxalate nephrolithiasis (HUCU), allopurinol (300 mg once daily) is the physiologically meaningful drug of choice because it inhibits uric acid production and therefore lowers serum and urine uric acid levels. Allopurinol has been shown in a randomized controlled trial to decrease calcium oxalate stone recurrence and lengthen time elapsed between recurrences in recurrent stone formers with hyperuricosuria and normal urine calcium [87]. These results have been confirmed in a recent meta-analysis [74].

For hyperuricosuric patients with gouty diathesis or who form uric acid stones, urinary alkalinization should be pursued with an agent such as potassium citrate with a goal pH of 6.0–6.5 such that the urinary uric acid will remain dissolved and unavailable to either crystallize into uric acid stones or seed calcium oxalate stone formation. As discussed in the previous section, treatment of hyperuricosuria with allopurinol should only be pursued after adequate urinary alkalinization has been established.

Hypocitraturia

Urinary citrate functions as an inhibitor of calcium stone formation via several different mechanisms [35]. Hypocitraturia has been associated with increased risk of calcium stone formation and is reported to be present in up to 50% of stone formers [88, 89]. Systemic acid-base balance is the most important determinant of urinary citrate excretion [90], but there are other notable conditions which can cause it as well which are discussed herein.

For most causes of hypocitraturia, the mainstay of treatment is potassium citrate to address the frequently underlying metabolic acidosis as well as to replete urinary citrate levels. Notably, many of the underlying pathophysiologic states which contribute to hypocitraturia are not correctable, and patients may require potassium citrate therapy for life. Fortunately, long-term potassium citrate therapy appears to maintain its safety and efficacy over the long term [91].

Distal Renal Tubular Acidosis

Distal renal tubular acidosis (Distal or Type I RTA) occurs when the distal nephron is defective in its ability to secrete hydrogen ions into the urine, and therefore the urine cannot be acidified. Clinically this syndrome results in a chronic hypokalemic, hyperchloremic metabolic acidosis with alkaline urine pH (>6.5) and profound hypocitraturia (<100 mg/day) [92]. Incomplete forms of the syndrome exist as well which may present with normal serum electrolytes and mildly alkaline urine pH with impaired ability to respond to an acid load.

Potassium citrate therapy is effective in treating the hypokalemia and hypocitraturia associated with distal RTA, although large doses (up to 120 mEq per day in divided doses) may be required to correct the underlying metabolic acidosis [93].

Chronic Diarrheal States

Patients with chronic high volume gastrointestinal fluid losses are characterized by low urine volumes, metabolic acidosis from bicarbonate loss in the stool, low urine pH, and hypocitraturia. Unlike patients with inflammatory bowel disease, these patients are not necessarily at risk for enteric hyperoxaluria.

Potassium citrate therapy is useful in this population to address the hypocitraturia and the underlying metabolic acidosis. The dose of potassium citrate will be dependent on the severity of

hypocitraturia. A liquid preparation of the medication is preferable as the usual slow-release wax matrix form of the medication may be poorly absorbed in the case of rapid GI transit. Furthermore, the liquid preparation needs to be dosed several times per day (every 6–8 h) due to its short duration of bioavailability.

Thiazide-Induced Hypocitraturia

Thiazide therapy may induce hypocitraturia due to hypokalemia with resultant intracellular acidosis. Co-administration of potassium citrate to patients receiving thiazide for treatment of hypercalciuria is often advisable as this treatment has been shown to correct thiazide-induced hypokalemia as well as hypocitraturia [94].

Cystinuria

The treatment goal for cystinuria is to reduce the urinary concentration of cystine to below its solubility limit (200–300 mg/L). A number of techniques are available to achieve this goal. Initial treatment should include high daily fluid intake to produce urine output of at least 3 L per 24 h [95]. Next, a low sodium diet should be instituted as sodium both in dietary and sodium alkali forms has been demonstrated to increase urinary cystine excretion [96–98].

Once an adequate dietary regimen has been established, the urine should be alkalinized with potassium citrate [98] to a goal pH of 7.0–7.5. Unlike with uric acid stones, however, urinary alkalinization for cystinuria is often met with limited success due to the high pKa of cystine around 8.3 and the dangers of attempting to alkalinize the urine to that level. Moreover, increasing urine pH to this degree presents a very real risk of promoting calcium phosphate stone formation.

Despite institution of the above measures, many cystinuric patients will continue to have urinary cystine level above the solubility limit and will therefore require additional therapy with cystine-binding thiol drugs, which have the effect of converting cystine to cysteine, which is 200 times more soluble in the urine than cystine. D-penicillamine and alpha-mercaptopropionylglycine (tiopronin) are two such medications, with tiopronin being used more frequently due to decreased frequency of adverse events compared to D-penicillamine and similar efficacy [99]. Dosing of tiopronin typically starts at 800 mg daily (in 2–3 divided doses) and is titrated up to achieve the desired decrease in urinary cystine levels.

Infection Lithiasis

The initial step in the management of struvite calculi is maximal surgical stone removal whenever possible [100]. Any remaining stone or stone debris within the renal collecting system can potentially harbor persistent bacteria which represents risk for recurrent infection and stone recurrence [101]. Effort should be directed toward decreasing risk for recurrent urinary tract infections as much as possible by maximizing bladder health and adequate urinary drainage. Urinary tract infections should be monitored for and treated aggressively. In addition, suppressive antibiotics should be considered.

Acetohydroxamic acid (AHA) is a medication which inhibits bacterial urease and may reduce the urinary saturation of struvite and inhibit struvite stone formation. When given at a dose of 250 mg three times per day, AHA has been shown to prevent recurrence of new stones and inhibit the growth of stones in patients with chronic urea-splitting infections [102, 103]. However, 30% of patients receiving chronic AHA therapy have experienced minor side-effects, and 15% developed deep venous thrombosis [102], so close monitoring of this cohort is imperative while on AHA therapy.

Follow-up

Follow-up Metabolic Evaluation

All patients who are at high risk for stone recurrence or who have discrete metabolic abnormalities requiring treatment should be followed. After all, the purpose of performing the metabolic evaluation and prescribing selective medical therapy is to alter the urinary parameters in a way that will decrease risk for future stone formation, so

follow-up evaluations are necessary both to ensure normalization of lithogenic urinary parameters as well as to make periodic adjustments in therapies and dosing as necessary.

In patients who are being started on a medication with the potential to cause electrolyte imbalances—such as hyperkalemia with potassium citrate or hypokalemia with thiazides—a basic metabolic panel including serum electrolyte measurements should be obtained within two to three weeks of therapy initiation so that dose adjustments can be made if necessary.

After initiating medical therapy, it is reasonable to repeat another 24-h urine collection within three to four months to assess for adequacy of response and patient compliance. If all is well and the patient appears to be metabolically quiescent, longitudinal one-year follow-up with updated 24-h urine is appropriate. If concerns persist or if medication doses or therapies are changed, closer follow-up at four to six months with a repeat 24-h urine could be considered.

If a patient on long term medical therapy develops active stone issues following a period of metabolic inactivity, a stone analysis should be repeated if possible. Additionally, periodic blood work should be performed for patients on long term medical therapy to assess for adverse effects of the medication [43].

Follow-up Imaging Evaluation

Despite the importance of longitudinal monitoring of stone-forming risk factors and treatment response with periodic 24-h urine collections, stone activity—defined as the formation of new stones or the growth of existing stones—can only be determined with imaging studies [104].

There is no universal standard for the optimal frequency of surveillance imaging for stone activity, however, and these decisions must be tailored to each individual patient based on their history of stone activity and response to therapy. An annual imaging interval is a reasonable starting point for many patients, with the recognition that unstable patients with active stone formation may ultimately require more frequent imaging pending better medical and/or surgical control of their disease. Conversely, patients who have demonstrated stone inactivity and metabolic quiescence for a number of years may be reasonably spaced out to biennial imaging.

As with imaging frequency, there exists no established optimal imaging modality for the surveillance of stone activity. Plain abdominal films with or without digital tomosynthesis [105–107], renal ultrasound, and unenhanced CT all may play valuable roles when used appropriately. Patient factors such as stone type and anatomic variants, as well as concerns for radiation dosimetry, cost, availability, and the potential need to evaluate for other non-stone conditions should be taken into consideration when making such determinations.

Summary

Urinary stone disease is an increasingly prevalent and expensive condition as a result of many complex human and geographic factors. The foundation of successful long term management and risk reduction is the comprehensive metabolic evaluation and judicious application of appropriate dietary counseling and medical therapy. Crucial to the process is comprehensive physician-patient communication and reliable long term follow-up for this lifelong disease.

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Innovations in the Surgical Management of Nephrolithiasis

24

Christopher Haas, Marla Wardenburg, and Ojas Shah

Introduction

Innovations in technology and surgical approach have rapidly changed the landscape of endourology, which has been a discipline particularly adept at advancing the status quo. In this chapter we present an overview of recent developments in the surgical management of nephrolithiasis including new laser technologies, the emerging role for disposable ureteroscopes, percutaneous nephrolithotomy (PCNL) positioning, percutaneous access technology, endoscopic combined intrarenal surgery, and "miniaturized" PCNL. It is our hope that the reader may apply some of these innovations and approaches in a practical manner to their current practice as well as gain an appreciation for what the future may hold.

Laser Technology

The newest generation of holmium: yttrium-aluminum-garnet (Ho:YAG) laser lithotripters allow the operator to control parameters including pulse energy, frequency, and pulse width in order to achieve optimal stone dusting or fragmentation during retrograde ureteroscopy and PCNL. Retropulsion and stone migration to difficult locations are common challenges during holmium laser lithotripsy. Recently, Lumenis has developed a new technology for the Lumenis Pulse 120H laser system designed to mitigate these issues [1]. Moses Technology (Lumenis, Yokneam, Israel) is a pulse modulation mode that improves holmium laser energy transmission through water. The wavelength of Holmium laser, 2100 nm, is near the 1940 nm absorption peak of water and in traditional pulse mode most of its energy forms a vapor bubble which generates pressure waves upon collapse [2]. With the "Moses effect", first described almost 30 years ago [3], the laser-induced vapor bubble created during an initial pulse "parts the water", allowing the subsequent pulse to be more efficiently delivered to the stone or tissue for enhanced ablation [4].

The effects of Moses Technology (delivery of a short, low-energy pulse to create a vapor bubble before delivery of a longer, higher energy pulse) were first investigated in a preclinical study by El Hilali and associates [5]. They found that stone movement in vitro was reduced by 50 times at a setting of 0.8 J and 10 Hz ($p < 0.01$), and observed a clear reduction in retropulsion with both fragmentation settings (high energy) and dusting settings (low energy, high frequency). In addition, stone fragmentation tests showed that the Moses modes resulted in a significantly higher ablation

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volume when compared with the regular mode at all settings tested. A subsequent in vitro study by the same investigators showed higher efficiency of stone fragmentation with the Moses mode compared to standard mode [6]. Recently, using an automated in vitro dusting model, Winship and colleagues demonstrated that the Moses Ho:YAG laser technology provided more efficient ablation of soft stones compared with standard long-pulse lithotripsy, both with the laser tip in contact with the stone surface and at a distance of 1 mm [7].

The thulium fiber laser is currently being explored as an alternative lithotripter to the gold standard Ho:YAG laser. This experimental fiber laser is not to be confused with the Thulium:YAG laser that has been in use for BPH procedures for over a decade. With fiber lasers, a chemically doped silica optical fiber is used as the gain medium instead of a bulk solid-state crystal (as used in Ho:YAG and Thulium:YAG). The light originates within the core of a small optical fiber and is pumped by another laser source, such as a diode laser, and then the light emitted from the fiber laser can be coupled into a separate, conventional, disposable silica surgical fiber [8].

The primary advantage of fiber lasers in general is their ability to deliver high power output from a small fiber core, resulting in high intensity or brightness [9]. The spatial beam profile of the thulium fiber laser is much smaller than the beam profile typically produced by Ho:YAG laser, allowing it to be coupled to a silica working fiber as small as 50 μm [10]. The thulium fiber laser emits light at a wavelength of 1940 nm, which more closely matches the water absorption peak in tissue and calculi than Ho:YAG (2100 nm), leading to higher ablation efficiency at the same power [11]. Several in vitro studies have supported this property. Using Begostone phantoms, Chiron et al. demonstrated that with a single impact, for an equivalent delivered energy, the area destroyed by the thulium fiber laser is four times higher than the effect of Ho:YAG laser [12]. Thulium fiber laser has also been shown to produce twice as much stone dust as Ho:YAG laser with Moses technology at the same settings [13]. Studies describing initial clinical experiences with thulium fiber laser suggest that it is safe and effective for use in retrograde ureteroscopy [14] and PCNL [15], however, to date there are no clinical studies with direct comparison to the Ho:YAG laser. Thulium fiber laser is currently not approved for clinical human use in the U.S. or Europe with the exception of Russia where the initial clinical investigations have taken place. Further clinical studies are needed to validate the performance and safety of this new technology.

Advances in Ureteroscope Technology

Since the first description of therapeutic flexible ureteroscopy for stone extraction in 1987 [16–18], there has been a revolution in the treatment options for stone disease. In one population based cross-sectional time series analysis, Ordon et al. showed a significant increase in the use of ureteroscopy between 1991 and 2010 (25–59% of all stone procedures, $p < 0.0001$) and a reciprocal decrease in the use of shock wave lithotripsy (69% to 34% of all procedures, $p < 0.0001$) [19]. The versatility of the ureteroscope in both percutaneous and retrograde stone intervention is attributable to incredible technological developments over the past decades such as the introduction of the digital ureteroscope and its improved image quality in 2008 [20].

Single-use (disposable) flexible ureteroscopes represent not only a new innovation in endourology but a paradigm shift in operating room workflow and efficiency, bypassing the issues of sterilization and the need for repair of fragile, costly instruments. The Polyscope (Polydiagnost, Germany) was the first single-use system described in the literature by Bader et al. in 2010 [21]. This 8F, fiber optic ureteroscope had a syringe-like handle to allow for one-sided deflection, and required both a reusable image fiber and light source connected outside of the sterile field. In this series, a stone-free rate of 87.5% was achieved in the completed cases, however in 5 out of the 40 cases the instrument broke. Single-use ureteroscope technology has continued to

evolve and as of 2017 there had been seven devices developed [22]. Only two of these devices are approved by the U.S. Food and Drug Administration for use in patients - the LithoVue (Boston Scientific, Massachusetts, USA) and the Uscope UE3022 (Zhuhai Pusen Medical Technology Co, Ltd., Zhuhai, China).

The LithoVue is a single-use flexible digital ureteroscope with a similar structure to reusable digital ureteroscopes as well as a built-in LED light source and camera (Fig. 24.1). The device has a 7.7F tip and 9.5F shaft, 3.6F working channel, 270° deflection in both directions, and connects with a built-in cable to its own touchscreen monitor or to an operating room screen through DVI connection [23]. Since the LithoVue was introduced to the U.S. market in 2015 there have been numerous clinical studies comparing its performance to reusable digital ureteroscopes.

The Pusen Uscope was approved by the FDA in 2017 and is a single-use, flexible digital ureteroscope with a 9F tip and 9.5F shaft, 3.6F working channel, and an advertised 270° deflection in both directions [24]. Like the LithoVue, it has an integrated fixed camera that is connected using a cable to its own monitor or to an operating room screen. To date, there is minimal published clinical data on Uscope performance. In a recent case series, Emiliani et al. described successful completion of standard ureteroscopy and laser lithotripsy using the Uscope in four out of five procedures, with scope replacement required in one procedure due to leaking at the handle-shaft junction [25]. In another series of 71 procedures (with no comparison group), Salvadó et al. reported no device failure and clinical outcomes comparable to ureteroscopy with reusable instruments [26].

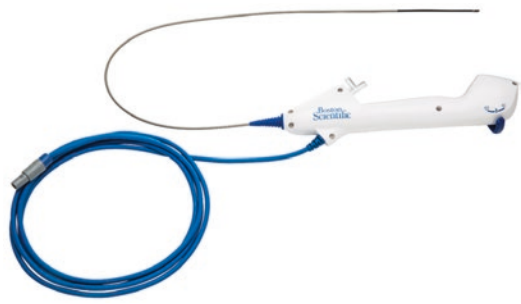


Fig. 24.1 LithoVue (Boston Scientific, Massachusetts, USA)—single use (disposable) ureteroscope

Image quality of digital single-use flexible ureteroscopes, critical to the success and efficiency of endoscopic procedures, has been demonstrated to rival that of reusable digital instruments. Talso et al. compared image resolution and quality of seven different flexible ureteroscopes by filming standardized grids and stones of different composition in a simulated fluid setting and showing the videos to 103 subjects (51 urologists and 52 non-urologists) who rated image quality on a 5-point scale. Image quality of the LithoVue was rated as better than that of the two fiberoptic ureteroscopes (Olympus URF-P6 and Storz Flex-X2) as well as two of the digital ureteroscopes (Wolf Cobra Vision and Olympus URF-V2), but inferior to image quality of the reusable digital ureteroscopes Storz Flex-XC and Olympus URF-V [27]. Additionally, in a blinded ex-vivo study using porcine kidneys, 13 experienced endourologists rated the image quality of the LithoVue as significantly better than that of six commonly used reusable flexible ureteroscopes (Storz Flex-X2, Storz Flex-Xc, Olympus URF-P5, Olympus URF-P6, Olympus URF-V2, Wolf Cobra), and similar to the image quality of the Wolf Boa [28].

Deflection properties of the LithoVue have been shown to meet or exceed those of conventional ureteroscopes. Dale et al. examined performance characteristics and found that with an empty working channel, the LithoVue had bidirectional maximal deflection of 276°, compared to 263° for the Flex-Xc and 253° for the Cobra fiberoptic ureteroscope. Furthermore, the LithoVue ureteroscope had minimal loss of deflection, only 2–5°, with the 200 μm laser fiber, 1.9F nitinol basket, and 2.0F and 2.4F nanoelectric pulse lithotripsy probes in the working channel. The Flex-Xc and Cobra ureteroscopes showed loss of deflection ranging from 2 to 27°, depending on the instrument placed [29]. In a study using human cadavers, Proietti et al. found no significant differences between the LithoVue, Olympus URF-P5, and Olympus URF-V in lower pole access and deflection angle. Surgeons

participating in the study also rated the overall maneuverability of the LithoVue as higher than the reusable ureteroscopes [30].

The overall clinical performance of the LithoVue was recently assessed by Usawachintachit et al. in prospective case–control study [31]. Study cases included 115 consecutive flexible ureteroscopic procedures in which the LithoVue was utilized over a 6 month period at a single institution, and study controls included 65 consecutive cases in which reusable fiberoptic flexible ureteroscopes (Olympus URF-P6) were utilized over a previous six month period. There were no significant differences in indication for procedure (stone removal, diagnostic, urothelial carcinoma), total stone burden, and lower pole stone burden treated between the two groups. Scope failure occurred in 4.4% of LithoVue cases and 7.7% of reusable cases ($p = 0.27$). The overall mean procedure duration was 10.4 min shorter in the LithoVue cohort (64.5 vs. 54.1 min, $p < 0.05$) compared with the reusable ureteroscope cohort. For stone removal cases only, mean procedural duration was also significantly shorter in the LithoVue cohort (70.3 vs. 57.3 min, $p < 0.05$) compared to the reusable ureteroscope cohort. Stone-free rates were higher in the LithoVue cohort (60% vs. 44.7%), but not significantly ($p = 0.36$). The authors speculate that the decreased procedure time in the LithoVue cohort may be explained by better image quality than the fiberoptic reusable ureteroscopes as well as by ergonomics and operator fatigue—the LithoVue (with integrated light source and camera) weighs only 277.5 g, while the combination of the URF-P6 scope plus camera head and light cord weighs between 838 g and 1378 g, depending on which camera and light cord model is attached [32].

It is debatable at this time whether the cost of a disposable instrument will mitigate the significant costs associated with sterile processing and maintenance of reusable flexible ureteroscopes. In addition to the initial expense of acquiring the reusable instruments ($23,000–$58,000), there is the cost of repair, which has been shown to be necessary approximately every 5–22 cases [33, 34]. Tosoian et al. calculated that at a large-volume academic center, the cost of flexible ureteroscope repair averages to $605 per case [35]. Recently, Martin et al. developed an algorithm to evaluate the potential economic cost of single use, flexible digital ureteroscopes compared to reusable flexible digital ureteroscopes. All cases using the Storz Flex-XC digital ureteroscope were prospectively recorded over a 12 month period, and cost assessment was performed based on the original purchasing cost and repair-exchange fees divided by the number of cases. Ureteroscopes required repair after an average of 12.5 cases. Excluding original purchasing costs, the analysis revealed an average cost of $848 per case. Based on an approximate cost of $1500 per disposable ureteroscope, after 99 ureteroscopy cases the cost-benefit analysis favored reusable ureteroscopes. The authors included that exclusive disposable ureteroscope use may be cost beneficial at only at centers with a lower case volume per year [36]. In contrast, in a prospective, single-center micro-costing analysis, Taguchi et al. demonstrated comparable overall cost per case between disposable and reusable flexible ureteroscopes [37]. This study accounted for the initial cost of reusable ureteroscope acquisition (Olympus URF-P6) in addition to costs of sterile processing and repair costs per case. Of note, the authors included the labor costs for disposal of used LithoVue ureteroscope and recycling of the packaging in this analysis.

The environmental impact of single-use ureteroscopes is another factor to consider. Davis et al. recently quantified this cost in an analysis of the typical life cycle of the LithoVue compared to the Olympus URF-V. To measure the carbon footprint, data were obtained on manufacturing of single-use and reusable flexible ureteroscopes, repairs and processing of reusable scopes, and ultimate disposal of both ureteroscopes. The authors found that environmental impacts of the LithoVue and the reusable ureteroscope were similar; 4.43 kg vs. 4.47 kg of CO2 per endourologic case [38].

As endourologists decide what role single-use instruments will play in their practices, one approach might be to use them selectively for cases in which a high chance of ureteroscope damage is possible. Overdeflection has been shown to be responsible for the majority of damage to reusable digital ureteroscopes, particularly

Table 24.1 High-wear cases for preferential use of disposables

(1) Large stone burden (≥1.5 cm)
(2) ≥3 lower pole stones
(3) Extensive ureteral/renal urothelial carcinoma with expected operative duration (≥1 h)
(4) Bilateral ureteroscopy
(5) Stones within complex/tortuous renal anatomy
(6) Placement of ureteroscope through a trocar during robotic or laparoscopic procedures

when it leads to laser fiber breakage and firing inside the working channel [34]. A recent large multi-institutional prospective cohort study, which included both digital and fiberoptic reusable ureteroscopes, demonstrated that use of a ureteral access sheath is also associated with significantly greater need for ureteroscope repair (OR = 2.53, $p = 0.005$, 95% CI = 1.31–4.87) [39]. Tsui et al. recommended an algorithm whereby a single-use flexible ureteroscope would be used for complex cases with anticipated high-wear scenarios (Table 24.1) in order to preserve the life of reusable flexible digital ureteroscopes.

Following implementation of the algorithm at their institution, the number of annual ureteroscope repairs decreased from 47 to 35 (despite an overall increase in number of cases), for a direct cost savings of 21%. The authors also noted that the LithoVue was used in 26 additional procedures where an acceptable reusable digital ureteroscope was not available in order to prevent surgery delay or cancellation [40].

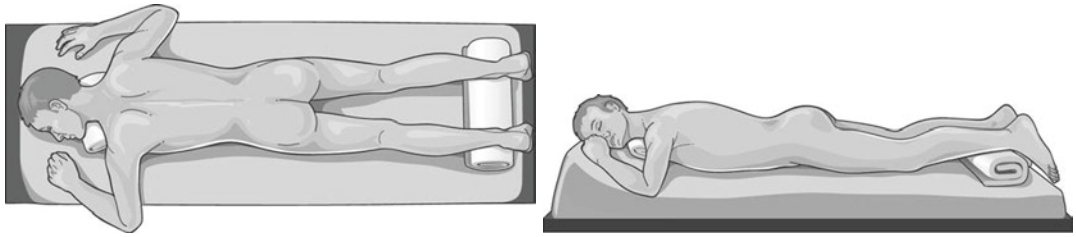
In conclusion, current data suggests that single-use flexible ureteroscopes provide an acceptable alternative to conventional ureteroscopes in terms of performance, may help avoid damage to reusable ureteroscopes, and will help increase patient access to ureteroscopy in situations where sterile, reliable reusable equipment is not readily available.

Innovations in Percutaneous Nephrolithotomy

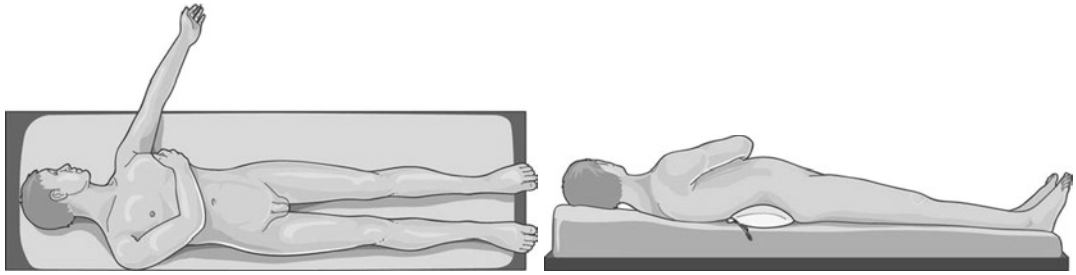
Prior to the 1970s, open stone surgery was the standard treatment for patients with renal calculi [41]. In 1955, Goodwin et al. described the first successful nephrostomy tube placement and in 1976 Fernström and Johansson described the first extraction of renal calculi through a percutaneous nephrostomy tract under radiologic guidance in three patients unfit for open surgery [42]. Initially described as a procedure that occurred over several days of serial dilation with risk of high morbidity [43], PCNL can now be performed with a short hospitalization, or in select cases, as an outpatient. Continuous innovation and refinement in renal access, radiology, instruments, and lithotripsy techniques have all contributed to improving the safety and efficacy of the modern day PCNL. Even after the advent of less invasive treatment modalities such as shock wave lithotripsy and flexible ureteroscopy, PCNL remains the gold standard treatment for large or complex renal stones and a mainstay of modern endourology. Despite these advances, PCNL still remains a challenging procedure and the most morbid procedure performed by endourologists, with opportunity for continued improvement. The goal of this section is to discuss established advances that led to the modern PCNL as well as some experimental technologies that have the possibility to impact what PCNL may look like in the future.

Patient Positioning

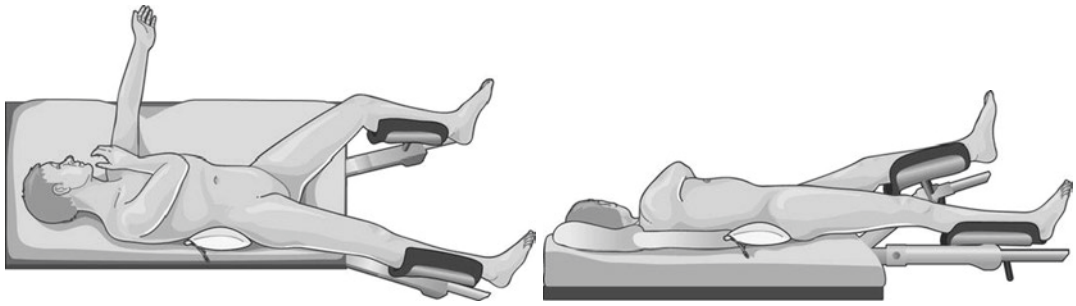
While PCNL has classically been performed with the patient in the prone position, there has been renewed interest in alternative patient positions, namely the supine position and its variations. Advantages of the supine position include less risk of positioning-related injuries, reduced operative time related to patient positioning, and ability to simultaneously access the urethra for retrograde access. Disadvantages include a restricted working space, difficulty in performing an upper pole puncture, and an awkwardness in manipulation of the rigid nephroscope created by the downward angle of the access tract. Since the original description of supine PCNL in 1990 by Valdivia Uria and colleagues in a series of 287 patients [44], there have been numerous modifications to the basic supine position including the split-leg [45], flank [46], oblique supine lithot-



Prone decubitus – frontal and lateral view (© Carole Fumat)



Supine decubitus (Valdivia position) – frontal and lateral view (© Carole Fumat)



Galdakao-modified supine Valdivia decubitus – frontal and lateral view (© Carole Fumat)

Fig. 24.2 Common Positions for PCNL. Prone decubitus—frontal and lateral view (© Carole Fumat). Supine decubitus (Valdivia position)—frontal and lateral view (© Carole Fumat). Galdakao-modified supine Valdivia decubitus—frontal and lateral view(© Carole Fumat)

omy [47], and prone flex [48], to name a few (Fig. 24.2). Modifications to the supine position were primarily borne out of the need to make the position more comfortable for the surgeons whilst still ensuring access to the urethra.

The advantage afforded by the supine position most readily observed in clinical practice is decreased operative time. A recent randomized controlled trial comparing 101 oblique supine lithotomy PCNLs vs 102 prone PCNLs, while observing no differences in stone free rates or complications, found that operative parameters improved in the oblique supine lithotomy position: mean hemoglobin loss (1.03 vs. 2.18 g/dL), mean operative time (86 vs. 112 min), and mean hospital stay (50 vs. 21 h) favored the modified supine position [47]. A meta-analysis by Yuan et al. reviewing 13 studies comparing prone to supine PCNL found that the average operative time was reduced by 18 min ($p = 0.04$), while also having a lower incidence of blood transfusion (OR 0.73, $p = 0.02$) [49]. In contrast, another meta-analysis by Falahtkar et al. found no difference in operative times, but still supported the finding of decreased blood transfusion [50]. After sufficient surgeon familiarity with the supine approach, it stands to reason that operative times would decrease as the added time of repositioning the patient in the prone position after induction of anesthesia is eliminated.

Theoretical advantages of the supine position that have not borne out in practice include decreased pulmonary and cardiovascular stress in co-morbid and obese patients along with improved stone-free rates secondary to the downward direction of the access tract that would allow for spontaneous drainage of stone fragments. Although it has been suggested that obese patients stand to benefit most from the supine approach because of their decreased respiratory reserve [44], one study comparing the peak inspiratory pressure of 50 obese patients with 51 non-obese patients in the supine and prone positions noted that while obese patients had higher peak inspiratory pressures than non-obese patients in general, there was no change in peak inspiratory pressure from the supine to the prone position in either cohort [51]. Some anesthesia studies have found the prone positions associated with a decreased cardiac index related to obstruction of the IVC which has in turn been found to potentially exacerbate bleeding in spine surgery [52]. Also not to be underestimated, supine position affords the anesthetist easier access to the airway in case of airway emergency and lessens the risk of endotracheal tube displacement or kinking. Furthermore, the supine position avoids the risk of prolonged prone position complications such as increased optic nerve pressure which has, in rare cases, resulted in blindness [53, 54].

Despite the proposed advantage of allowing gravity to aid in passage of stone fragments in the supine approach, the evidence has generally shown decreased stone free rates with the supine position. In a study utilizing the multi-institutional Clinical Research Office of the Endourology Society Study (CROES) that examined 1079 PCNLs of which 232 were performed in the supine position, the authors found significantly shorter operative time and higher stone-free rates (both $p < 0.001$) for patients in the prone position with no differences seen in complications [55]. While Falahtkar's meta-analysis of 2110 supine cases and 5623 prone PCNLs did not show difference in stone-free rates, Yuan's meta-analysis did demonstrate an advantage with the supine approach (77.7% vs. 74.3%, OR 0.74, $p < 0.001$). These meta-analyses also show similar complication rates with no increased concern for bowel injury in the supine approach. With slightly decreased operative time at the expense of slightly decreased stone-free rates seen in the supine approach, there is no clear superior position and the decision which approach to take is largely driven by surgeon training and familiarity. Likely because of this, performing PCNL in the prone position remains the most common approach, with the CROES database and surveys revealing the prone position preferred in 78% of cases and 86% of urologists, respectively [56, 57].

Percutaneous Access

Gaining safe and adequate access into the collecting system remains one of the most critical and challenging aspects of performing PCNL. Fluoroscopic guidance was the first method described and remains the most popular access technique, comprising 63.6% of the global approach according to the CROES PCNL global study [56]. In an effort to improve the success rate of obtaining access and to limit radiation exposure, alternative access techniques utilizing endoscopic and ultrasonic guidance have been developed. The radiation exposure to patients during fluoroscopically guided PCNL is not trivial, with some studies suggesting that approximately 400 s of fluoroscopy or a mean effective dose of 8 mSv during PCNL exposes patients to roughly double the radiation exposure of a non-contrast renal computerized tomography (CT) [58]. While still less common than fluoroscopic access alone, there is evidence to suggest that use of ultrasound guided access has been increasing, with a combined fluoroscopic and ultrasound approach used in 15% of cases and an ultrasound only approach used in 10.4% [57]. Endoscopic guided access, both from a retrograde and antegrade approach, can be used to facilitate either imaging modality.

While ultrasound's use has increased with the improved image quality/cost ratios of modern machines and with efforts to reduce radiation exposure to the patient and operating room staff, its widespread adoption may be hindered by the

learning curve to become adept at this approach. Despite this, there have been studies showing that an experienced urologist can surpass the learning curve after 20 cases [59]. Moreover, a trial that randomized urology trainees into obtaining access for 64 PCNLs either with ultrasound (with minimal fluoroscopy for confirmation or adjustment as needed) or fluoroscopy alone found that both techniques were safe with no differences in time to puncture, number of puncture attempts, or intraoperative and post-operative parameters. Fluoroscopy time was significantly lower in the puncture phase for the ultrasound group (9 vs. 44 s, $p < 0.001$) and overall (204 vs. 240 s, $p = 0.04$) [60]. Other studies have shown far greater reduction in fluoroscopy use from 182 to 17 s [61] and from 157 to 22 s [59]. Phantom models are currently in development for teaching urology trainees ultrasound access technique and early studies have shown promise in increasing resident accuracy and efficiency in obtaining successful access needle positioning [62]. Importantly, use of ultrasound for obtaining access has not shown any inferiority in outcomes of stone-free rates or complications when compared to the traditional fluoroscopic approach in several randomized trials [63–65] and a large case match control study from the CROES database [66].

Endoscopic guided assistance (EGA) has been a relatively new development to augment the safety and efficacy of image guided access. Initial reports of EGA made use of the patient in the prone split-leg position (Galdakao-modified supine Valdivia position) [67] which allowed subsequent retrograde ureteroscopy access to confirm accurate antegrade puncture [68]. In 2003, Kidd and Conlin then described grabbing the wire and bringing it out through the urethra in order to secure "through and through" access [69]. Subsequently, Khan et al. used EGA with URS to visualize the puncture site in real time and reported less use of fluoroscopy with a safer calyceal puncture [70]. Potential advantages of EGA include shorter fluoroscopy time, shorter operative time, less bleeding, and fewer tracts needed while providing a similar stone-free rate [71]. Some studies also report decreased need for secondary stone surgery and decreased risk of early termination of the PCNL [72]. Nearly all studies demonstrate reduction in fluoroscopy time with the most impressive reduction demonstrated in Alsyouf and colleague's cohort in which only 9 s of fluoroscopy time was used in the EGA approach vs. 1028 s in the traditional fluoroscopic approach equating to 99% reduction [73]. This study made use of ultrasound to detect deflections of the ureteroscope after placing the tip of the ureteroscope in the ideal calyx for puncture. Further enhancing the use of concomitant retrograde access in targeting antegrade access, Lima et al. developed a novel navigation system that makes use of an electromagnetic sensor inserted through the working channel of a ureteroscope to enhance target accuracy with spatial 3D images of the needle in real-time. In a recent phase I trial, they demonstrated an impressive 10/10 successful first-time punctures without use of fluoroscopy [74]. A recent web-based survey found that a not-insignificant percentage of providers utilize a retrograde (19%) or a combined approach (12%) for obtaining access; however the degree to which endoscopic assistance was used to assist in antegrade puncture could not be assessed [57].

The future of percutaneous access is exciting, with many novel techniques being developed to further improve both the safety and accuracy of percutaneous access. Amongst the most promising developments are 3D reconstructions and real-time puncture needle tracking technologies. The Uro Dyna CT is an operating room cone beam CT that can generate interventional 3D images in less than 2 min [75]. Combining this technology with proprietary software adds the capability of mapping out the ideal c-arm position and puncture site in addition to superimposing fluoroscopic imaging over the 3D CT images, allowing for the needle to be traced in real-time for more accurate puncture. Ritter and colleagues demonstrated the feasibility of this approach for complex punctures with an initial puncture success rate of 22/25 (88%) but noted an increased radiation exposure when compared with conventional fluoroscopy [76]. Barriers to adoption of this approach are primarily the added cost and

expertise required to obtain and operate the system. To overcome some of the drawbacks of cost and increased radiation exposure, Rassweiler and colleagues developed a computer-assisted puncture approach utilizing an iPad and laptop [77]. This system makes use of pre-rendered images from a CT and fiducial markers with overlaid fluoroscopic images displayed on an iPad. While incurring less radiation exposure than traditional fluoroscopy with improved time to puncture for novices in phantom models, this method lacked accurate reproduction of depth and did not translate into improved time to puncture for experts. Studies of 3D real-time puncture tracking systems in human patients remain limited and experimental [78]. A Japanese group recently developed a system to perform real-time virtual sonography in which a magnetic detector is able to trace ultrasound movement into a virtually enhanced previously obtained CT image in real time. They successfully performed this technique in 15 patients and noted a decreased mean number of puncture attempts(1.6 vs. 3.4) compared to standard ultrasound-guided puncture [79]. These futuristic systems, while compelling, require additional in-depth knowledge of equipment, set-up, and software application, and have not yet become commercially available.

Endoscopic Combined Intrarenal Surgery

After successful use of a combined retrograde approach to assist antegrade access, the logical evolution of the technique was to utilize the ureteroscope and nephroscope simultaneously for lithotripsy in a technique called endoscopic combined intrarenal surgery (ECIRS). This is a synergistic and non-formulaic approach that requires coordination, with two urologists performing simultaneous maneuvers, and allows for modification of the approach that best suits the patient's stone burden and anatomy. For example, in a maneuver coined as *pass the ball* by Undre et al., larger stones that are unable to be reached by the nephroscope and unable to be extracted via a ureteral access sheath are instead basketed using the ureteroscope and relocated near the access tract where they can then be extracted using the rigid nephroscope [80]. Potential advantages of ECIRS are listed in Table 24.2 [81].

Table 24.2 Potential advantages of endoscopic combined intrarenal surgery

(1) Ability to endoscopically evaluate the patient's anatomy, stone location and composition for optimal planning of the entry site.
(2) Added safety advantage of performing renal puncture, tract dilation, and sheath application under visual control.
(3) Ease of establishing safety wire access down the ureter for full field endoscopic control.
(4) Increased likelihood of avoiding the need for multiple tracts in order to fully clear the stone burden.
(5) Improved ease of final endoscopic evaluation to decide need for ureteral stent or a second stage procedure.
(6) Reduction in the overall radiation exposure and operative times.

In one of the early series of ECIRS in 2008 of 127 patients, Scaffone et al. found that in 33% of cases, retrograde ureteroscopy was essential for attaining complete stone clearance. They achieved a stone-free rate of 81.2% using a single access in 98.4% with a mean operative time of 70 min starting from positioning of the anesthetized patient [67]. In a separate comparative study, 60 ECIRS cases with a single small tract of 18F were compared to 82 conventional PCNLs and found to have a higher stone free rate (81.7% vs. 45.1%) with a lower incidence of bleeding [82]. Despite these proposed advantages and promising case series, a distinct disadvantage is the added cost and expertise needed for operating two simultaneous endoscopic systems by two qualified urologists. Furthermore, the technique is not applicable for patients with retrograde access challenges such as ureteral strictures, urinary diversions or large stones that obstruct the UPJ, and also comes with the added risk of ureteral manipulation and need for ureteral stenting if a ureteral access sheath is used. The stone may also obstruct the desired target calyx, making prolonged holmium laser lithotripsy required if puncture and access sheath insertion is to be visualized.

Miniaturized Percutaneous Nephrolithotomy

In effort to reduce the morbidity of access-related complications and tissue trauma of PCNL, urologists have investigated the use of smaller caliber instruments than the traditional nephroscope that utilizes a 26–30fr tract. Jackman et al. first described a new miniaturized technique in infants and children in which an 11F peel-away vascular access sheath was used to accommodate a 7F rigid cystoscope and 9.5F flexible ureteroscope [83]. Since then, investigators have experimented with miniaturized PCNL all the way down as small as 5F in which the entire procedure was performed through the sheath of an all-seeing needle [84]. Terminology has yet to be standardized with different nomenclature used for different tract sizes such as mini-PCNL for ≤22F [85], ultra-mini PCNL (UMP) for 10–13F [86], Super-mini PCNL (SMP) for 10–14F [87], mini-micro PCNL for 8F [88], and micro-PCNL for <5F [84]. To help clarify terminology and simplify comparative analysis, Tepeler proposed simply using superscripts after PCNL to signify the size of the tract [89]. Later, Schilling et al. proposed a system for accommodating a range of sheath sizes as XL ≥25F, L 20–24F, M 15–19F, S 10–14F, XS 5–10F, and XXS <5F [90]. The authors suggest using this terminology would contribute to better comparability in the literature.

Studies comparing miniaturized PCNL to conventional PCNL have generally found similar stone-free rates with the primary benefit of less bleeding complications. Initial proponents of mini-PCNL believed that it would have less nephron scarring compared to conventional PCNL; however, a study by Traxer et al. refuted this hypothesis, demonstrating in a pig study a non-significant difference in scar tissue between 11F and 30F tracts that represented 0.63% and 0.91% of the renal parenchyma, respectively [91]. The benefit of a reduction in bleeding was first clearly seen in a single-institution randomized trial of 69 patients who underwent mini-PCNL vs. 111 patients who underwent standard PCNL. The authors found similarity in regards to length of hospital stay, postoperative pain, rates of post-op fever, and stone-free rates, but found a lower rate of bleeding requiring transfusion in the mini-PCNL group (1.4% vs. 10.4%). The only downside they found to the mini-PCNL technique was a 12–15 min longer operative times depending on stone burden [92]. Besides longer operative times seen with mini-PCNL over conventional PCNL, another potential drawback noted by other investigators is the higher intrarenal pressures observed in downsized systems [93, 94], which may have the implication of higher rates of postoperative fever and sepsis.

The results of this randomized trial have been supported by two meta-analyses that found similar stone-free rates with less bleeding events at the price of longer operative times. The meta-analysis by Zhu et al. included eight comparative studies for which the mini-PCNL tract size fell between 10 and 18F for a total of 749 patients and found significantly less drop in hemoglobin with a mean difference of 0.47 g/dL and less blood transfusion with an odds ratio of 0.18. Stone free rates were similar (OR 1.06 95% CI 0.71–1.58) while operative time was longer for mini-PCNL (mean difference 15.5, 95% CI 4.2–26.8). In addition, this meta-analysis found a shorter hospital stay of 1.3 days and less pain in the mini-PCNL cohort [95]. A more recent meta-analysis in 2017 by Ruhayel et al. included all mini-PCNL tract sizes from 4.8F to 22F for a total of 18 studies and had similar conclusions [96]. These meta-analyses are limited in their strength of conclusions, however, because the majority of studies included are retrospective comparisons or case series which invariably are subject to selection bias and outcome-reporting bias (the first meta-analysis was comprised of three randomized trials while the second used only two). We believe the bias is significant enough to hesitate designating mini-PCNL as a less morbid procedure than conventional PCNL. Moreover, even a simple parameter such as the stone-free rate is difficult to compare across studies because of the different imaging modalities used, with KUB and ultrasound less sensitive than CT, in addition to the differing definition of what size stone left behind represents a “clinically insignificant” fragment, since

any residual fragment is theoretically clinically significant.

Identifying the optimal indication for use of mini-PCNL remains an area of investigation in which more data is needed. The heterogeneous nature of the published studies with different stone characteristics and different access sheath sizes makes drawing conclusions for optimal use of mini-PCNL difficult. Some studies suggest that mini-PCNL seems to be more effective for smaller rather than larger renal stones >20 mm [97, 98]. Other specific-use case scenarios that may favor mini-PCNL may be management of stones in a calyceal diverticulum, pediatric patients, or for patients with a particularly small collecting system [94], but these uses require further investigation. Some urologists have questioned the benefit of obtaining percutaneous access with miniaturized systems for stones 15–20 mm when these stones usually can be treated with the less morbid procedure of SWL or URS. A recent meta-analysis by De et al. compared PCNL with URS and found a higher stone-free rate and higher complication rate in PCNL [97]. A subgroup analysis was then performed between mini-PCNL and URS with the surprising finding that URS actually resulted in a higher stone-free rate than mini-PCNL (OR 1.7, $p = 0.0002$) [97]. Their conclusion was that URS should be recommended over minimally invasive PCNL for stones sized <20 mm because of the generally lower morbidity of retrograde access. Other authors have noted a particular advantage of mini-PCNL over URS in cases of challenging lower pole stones or stones in a difficult-to-access calyx [99]. The mini-PCNL technique has shown promise in providing similar success rates compared to conventional PCNL at the expense of longer operative times; however, further quality randomized trials are needed to prove its potential lower morbidity and specific indications.

Conclusions

To summarize, regarding laser technology, the Moses Ho:YAG laser has made significant improvements over prior Ho:YAG laser technology in reduction of retropulsion and increased ablation volume while the Thulium laser has shown great promise in preliminary studies and may become the laser modality of the future. The disposable (single use) ureteroscope, which has demonstrated similar usability characteristics to reusable ureteroscopes, gives the urologist an additional tool for which to tackle complex stone cases that could compromise longevity of re-usable ureteroscopes and may also bring ureteroscopy to providers with less volume who cannot afford the upfront cost of a re-usable ureteroscope. In PCNL, there has been a renewed interest in the supine position and its variations because of its potential time-saving and physiologic advantages, in addition to allowing for endoscopic combined intrarenal surgery. Utilizing a combined retrograde and antegrade approach may facilitate access and improve stone clearance ability at the expense of increased cost. As perhaps the most difficult and dangerous component of performing PCNL, innovations in access technology is a ripe area for new technology to make a significant impact. Combined used of ultrasound with other modalities is becoming increasingly popular with early trials of live tracking of 3D reconstructed images showing promise. It remains to be seen when a user friendly and commercially available system will become available. Finally, miniaturized PCNL systems are becoming increasingly popular with some results showing reduced morbidity and similar efficacy compared to conventional PCNL; however, well designed trials are lacking and their specific use-case scenarios remain to be well defined. There has never been a more exciting time in endourology as technology continues to evolve practice and may change it in ways that are now unforeseen.

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Reconstruction of the Renal Pelvis and Ureter

25

Jennifer G. Rothschild

Abbreviations

TUU	Transureterostomy
UNC	Ureteroneocystotomy
UPJ	Ureteropelvic junction
UU	Ureteroureterostomy

Overview of the Management of Renal Pelvis and Ureteral Strictures in Adult Patients

Ureteral strictures can be classified into extrinsic or intrinsic, benign or malignant, iatrogenic or non-iatrogenic. The potential etiology of ureteric stricture includes congenital, infection (Tuberculosis or Schistosomiasis), iatrogenic (ureteroscopy, gynecological or other pelvic surgery), radiation, malignancy, lymphadenopathy, urolithiasis, penetrating trauma, or retroperitoneal fibrosis. Iatrogenic injury at time of pelvic surgery could be due to crush injury, burn, or complete transection.

Conservative option for management of strictures can be placement of double J ureteral stent, either plastic or metallic. However this requires routine stent exchanges every 6–12 months with or without anesthesia. Unfortunately, there are high occlusion rates for ureteral stents in the subset of patients with extrinsic ureteral compression due to malignancy [1]. The etiology is thought to be due to the idea that urine flows around the stent preferentially, and not through the stent. Therefore, with external compression around the stent from the extrinsic compression, urine is forced through the stent and can get more easily obstructed by debris. For these patients, some physicians advocate to leave larger bore stents or stiffer stents or even placing two parallel stents simultaneously [2]. For the patients who do not want to manage their stricture with routine stent exchange or a permanent nephrostomy tube, reconstructive surgery is an option.

The reconstructive surgical management of renal pelvis and ureteral strictures depends on the location and length of the defect as well as the quality of adjacent tissues. For short, uncomplicated ureteropelvic junction (UPJ) obstruction and proximal ureteral strictures, pyeloplasty and ureteroureterostomy are the gold standards. For short defects involving the upper or mid-ureter, a ureteroureterostomy (UU) or transureterureterostomy (TUU) is appropriate. A short defect involving the lower ureter is usually managed by uretero-neocystotomy with or without a psoas hitch and/or Boari Flap (Table 25.1). For long ureteral defects, options include renal auto transplantation, TUU, or ureteral reconstruction using

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Table 25.1 Ureteral reconstruction options

Ureteral stricture location	Anatomic location	Reconstructive options	Length of ureteral defect (cm)
Proximal ureter	Above the sacroiliac joint to the ureteropelvic junction	Ureteroureterostomy Transureteroureterostomy	2–3 >10
Mid ureter	Overlying the sacroiliac joint	Ureteroureterostomy Transureteroureterostomy +/− Boari flap	2–3 >10 12–15
Distal ureter	Sacroiliac joint to the ureterovesical junction	Ureteroneocystosomy +/− Psoas hitch +/− Boari flap	4–5 6–10 12–15

bowel segments such as an ileal ureter. Although nephrectomy is always an option (and should be included in consent and patient discussion), renal preservation is the reconstructive goal to avoid the potential long-term risks associated with chronic kidney disease. In the dire trauma case or emergency situation when ureters need to brought to the skin with the goal to return at some point, cutaneous ureterostomy is an option—however this is not a good long term plan as they are difficult to manage. Surgical incision for options for ureteral repair include mid-line incision or subcostal (proximal ureter), Gibson (mid ureter), and low midline or Pfannensteil (distal ureter).

When conceptualizing reconstructive surgery of the renal pelvis and ureter, the goal is to preserve renal function by the restoration of non−obstructed drainage of the affected kidney in a dependent fashion. Classic urologic surgical standards are presumed with reconstructive techniques such that an anastomosis not under tension and dissection should be done in a fashion to preserve blood supply to the ureter and adjacent tissues.

The functional anatomy of the ureter is important to keep in mind when dissecting the ureter and planning reconstruction. The ureter is between 25 and 30 cm in length from the renal pelvis to the bladder. As the ureter crosses over the pelvic brim, it is divided anatomically into the abdominal and pelvic segments, each approximately 12–15 cm in length. Above the pelvic brim, the blood supply of the ureter is derived from medial vessels such as gonadal arteries and aorta, whereas more distally, the blood supply originates laterally. Thus, above the pelvic brim, dissection and mobilization of the ureter should be approached laterally and distal to the pelvic brim, medially. Maintaining blood supply is vital to the anastomotic success and to diminish the risk of future stricture.

When deciding which reconstructive option to pursue, consideration of the length of the stricture, the degree of peripelvic and ureteral fibrosis, degree of redundancy of renal pelvis, and the ability to mobilize the ureter and recipient target are all important factors. Usually a ureteral double J stent is placed through the repair anastomosis. The advantage of placing a stent across the anastomosis is to curtail the associated edema, allowing the healing of tissues to occur while minimizing anastomotic leak and to maintaining patency. The anastomosis is completed using fine, 4-0 or 5-0, non-reactive, monofilament, absorbable suture in an interrupted or running fashion. The sutures are placed in a watertight manner over an internal double J ureteral stent. A closed suction drain is usually placed near the anastomosis for a limited time and removed when appropriate. An indwelling Foley is also left in place when indicated.

Renal Pelvis Reconstruction

The ureteropelvic junction (UPJ) is the most common site of obstruction in the upper urinary tract [3]. UPJ obstructions can be caused by a congenital condition (most common in children), scar tissue, infection, or kidney stones (Image 25.1). UPJ obstruction causes a restriction to flow of urine from the renal pelvis to the ureter, which, if left uncorrected, can lead to gradual renal deterioration and pain. UPJ obstruction can be

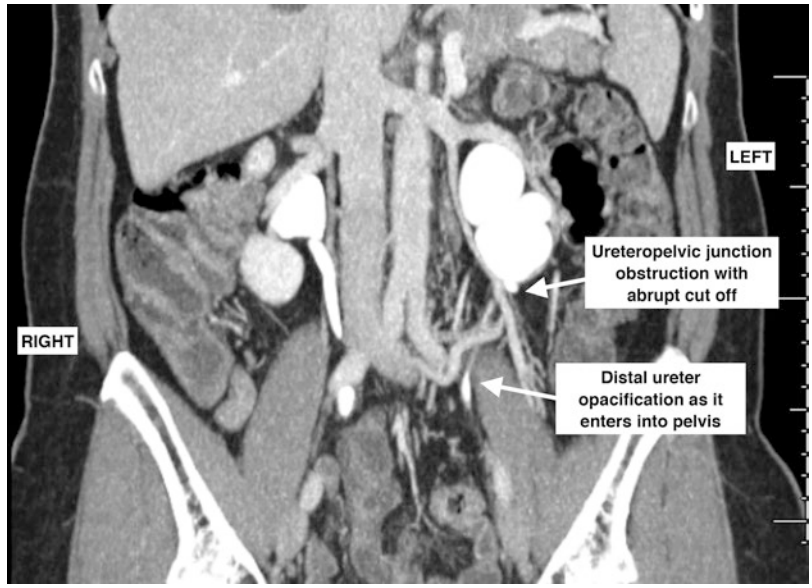

Image 25.1 Left ureteropelvic junction obstruction with moderate left hydroureteronephrosis. The kidneys enhance symmetrically. The left proximal ureter is dilated and tortuous, with an abrupt cut off that then returns to expected opacification as it enters the pelvis

managed with different techniques such as endopyelotomy, open pyeloplasty, laparoscopic pyeloplasty, or robotic pyleoplasty.

Open procedures for the treatment of UPJ obstruction include the Anderson-Hynes dismembered pyeloplasty [4] which is the gold standard of pyeloplasties: the strictured portion of ureter is excised and the healthy, patent ureter is spatulated and anastomosed to a dependent position of the renal pelvis. However if the renal pelvis is small or the ureteral length is inadequate, then dismembered pyeloplasty is not ideal and a non-dissmembered pyeloplasty should be considered. Non-dissmembered pyeloplasty options include the Culp de Weerd spiral flap procedure [5] and the Foley Y-V technique [6], which are ideal for long segment UPJ strictures. The latter is also ideal for high insertion ureters. Other options for long UPJ strictures include the vertical (Scardino –Prince) flap pyeloplasty [7]. Because of its relative simplicity, the preferred method for open pyeloplasty is the Anderson-Hynes dismembered pyeloplasty with or without reduction of the redundant pelvis [4]. This method provides lasting improvement in function (79%) and drainage in most patients (96%) [8]. Most series reports success rates of open dismembered pyeloplasty ranging from 72 to 100%, with an average of 90% success rate [9].

Although open pyeloplasty does have high success rates, it does have its inherent post-operative complications [10]. In contrast, improved patient tolerance is one of the principal benefits of minimally invasive approaches. Endoscopic methods to treat UPJ obstruction include antegrade endopyelotomy, retrograde endopyelotomy (Acucise™) and balloon dilation. All three of these endoscopic methods have been shown to be tolerated significantly better that open pyleoplasty as assessed by post-operative pain, length of hospital stay, and recovery time. Specifically, Acusize was found to be the best tolerated [10]. The success rate for antegrade and Acusize pyelotomy appear to have similar success rates at approximately 78% [10]. Additionally, endoscopic approach is commonly recommended for patients who have failed open operative repair [11].

For simple UPJ or proximal ureteral strictures, these can be managed surgically with pyeloplasty or UU. However for the more complex UPJ or recurrent strictures, the technique can be challenging. Salvage reconstructive options include TUU, ureterocalicostomy, renal autotransplantation, or an ileal ureter replacement, described in detail below. When the renal pelvis is relatively inaccessible, fibrotic, or has an intrarenal pelvis, an alternative option for reconstruction is the ure-

teroocalicostomy [12]. There are reports of ileocalicostomy as ureteral substitution as well [13]. These later two options may be useful for recurrent failed repairs with insufficient ureteral length such that the healthy portion of ureter is anastomosed to lower calyx parenchyma. Also, if all reconstructive options are not feasible, simple nephrectomy may be the only option for a patient who's goal is to live free of stent or percutaneous nephrostomy tube. These options should be fully discussed with the patient and included in the surgical consent.

First described in 2001 [14], robotic-assisted laparoscopic pyeloplasty is a minimally invasive option for the correction of UPJ obstruction. Both laparoscopic or robotic pyleoplasty have been shown to have decreased length of stay, less post-operative opioid requirements, and similar success rates of 88–100% as compared to open pyeloplasty [15]. Robotic pyeloplasty results in long-term improvement in subjective symptoms and resolution of obstruction for patients with success rates reported at 96% [16].

Ureteral Reconstruction

Repair of ureteral injuries can pose significant challenges depending on the location and length of the ureteral stricture as well as quality and health of the surrounding tissues. The location of ureteral stricture are divided, per se, into the proximal ureter (above the sacroiliac joint to the ureteropelvic junction), mid ureter (overlying the sacroiliac joint), and distal ureter (sacroiliac joint to the ureterovesical junction) (Table 25.1). Briefly, options for repair include primary anastomosis of ureter to ureter or ureter to bladder with or without psoas hitch and/or Boari flap. These approaches can also be done laparoscopically or robotically, with the robotic option providing for increased dexterity of intracorporeal suturing and improved visualization when compared to laparoscopic approaches. Most ureteral injuries that are short in length can be repaired with debridement and ureteroureterostomy in the proximal and mid-ureter or ureteroneocystostomy in the distal ureter [17].

Options for proximal and mid ureteral reconstructive repair of simple and short (2–3 cm) ureteral strictures are ureteroureterostomy (UU) or trans-ureterureterostostomy (TUU) (Table 25.1). Ureterouretosomy is done such that the proximal ureter and distal ureter is mobilized, the defect is excised and the remaining healthy tissues are widely spatulated and re-anastomosed together in a non-tension, end-to-end fashion. Prior to completion of the anastomosis, a double J stent should be placed. If possible, omentum or retroperitoneal fat is mobilized to surround the repair, and a drain is placed in the retroperitoneum near the anastomosis. A Foley catheter is left indwelling.

The complication rate after repair of traumatic ureteral injuries is 25%, with the most common complication being prolonged urinary leakage at the anastomotic site, which can lead to urinoma, abscess, or peritonitis. Placement of a closed suction drain in the retroperitoneum at the time of initial repair can minimize the risk of these complications [17]. Other less common complications include recurrent stricture leading to hydronephrosis, abscess, fistula formation, and infection.

TUU was first described by Higgins in 1935 [18]. The idea of the TUU is to bring the injured ureter from one side of the body, across the midline under the mesentery of the intestine to the healthy ureter on the opposite side, such that a contra-lateral UU anastomosis is reconstructed following the same surgical principals as the UU. If TUU is chosen, decision should be made intra-operatively whether or not the ureter will cross above or below the inferior mesenteric artery between the levels of L4 to S2. The anastomosis is made into a Y formation in an end-to-side or end-to-end fashion with a widely spatulated donor ureter. Double J ureteral stent or pediatric feeding tube (which will provide more length) should be placed such that it course through the donor ureter across the anastomosis and through the distal portion of the recipient ureter to the bladder. When considering a TUU, preference should always be given to direct reimplantation into the bladder if possible [19]. Contraindications for a TUU include any disease which might involve both kidneys or ureters (TB,

papillomatosis, recurrent stone formation) or retroperitoneal fibrosis. The accepting ureter and kidney must be normal due to the fact that after the TUU is performed, any disease process that affects one ureter or kidney puts the contralateral ureter and kidney now at risk. Also, if the ureter is chronically dilated and atonic, TUU should not be considered as it can lead to persistent, poor drainage [20].

Distal ureteral strictures can be managed by ureteral re-implantation into the bladder, or ureteroneocystotomy (UNC). This option should always be selected if the distal ureter can reach the bladder easily (up to 3–5 cm length) as it has a high success rate of approximately 85% [19]. For correction of ureteral defects that are longer than 5 cm, options for modification include psoas hitch and/or a Boari flap.

Ureteral reimplantation with a psoas hitch was first described by Zimmerman in 1960 [21] and is a way to tack the posterior bladder wall to the psoas muscle to allow the bladder to be repositioned closer to ureter, tension free. Briefly, the steps for the psoas hitch should include [22]: bladder mobilization with development of the space of Retzius, freeing of the peritoneal attachments, and division of contralateral obliterated umbilical artery to provide enough mobility for the bladder to reach the ureter of injury for a tension-free anastomosis. If the contralateral superior aspect of the bladder is mobilized well, it should allow for the bladder to reach the ipsilateral psoas muscle tendon. The addition of a downward nephropexy can further increase the gap length to be spanned. A vertical, oblique, or horizontal-closed-vertically cystotomy on the low anterior surface of the bladder is made, manually displacing the bladder toward the ipsilateral ureter. The incision should not include the bladder dome, so the surgeon can insert fingers into the bladder and facilitate fixation to the ipsilateral psoas tendon, avoiding the genitofemoral or femoral nerves. Non-absorbable or delayed absorbable suture (PDS) is used to place with several interrupted sutures. Preplacing psoas hitch sutures prior to ureteral anastomosis, allows the surgeon to verify that the anchoring sutures are not inadvertently placed too deep through the bladder mucosa. It is also preferred to do this prior to anastomosis so the reimplanted ureter can lay in place in an unkinked, dependent fashion. The ureter is then implanted in a non-refluxing submucosal tunnel or a refluxing-type direct anastamosis. Indwelling stents are left in place for 1–3 weeks post operatively. Cystotomy is closed in two layers with absorbable suture. In review, successful UNC should be made in a fashion to be a tension free anastomosis with debridement and spatulation of the ureter and include a post-operative closed suction drainage system. The success rate of ureteral reimplantation with a psoas hitch exceeds 85% in both adults and children [23].

Modifications of this technique with the addition of the submucosal tunnel to prevent reflux has also been described [24]. Although the advantage of a non-refluxing ureteral anastomosis is a significant concern for the pediatric population over concerns for pyelonephritis and renal insufficiency secondary to chronic reflux and infection, these risks in the adult population are less clear [22]. Antireflux procedures offer no advantage over refluxing ureteric reimplantation in adults [25]. However, the advantages of a refluxing-type ureteral anastomosis include: technically simpler, offer a shorter operating time, decrease the risk of distal ureteral stricture, and provides an additional 2–3 cm of ureteral length that would have been devoted to a submucosal tunnel [22].

Ureteral defects proximal to the pelvic brim usually require more than a simple psoas hitch alone. Therefore sometimes an additional modification with the Boari flap in addition to the psoas hitch provides for extra length up to more 5 cm to bridge the ureter to bladder. First described in 1947 [26], the Boari flap is a surgical maneuver in which the bladder is tubularized into a flap to extend from the bladder to the ureter [27]. In fact, the Boari flap can be selected for injuries to the ureter with defects up to 14 cm in length [19].

The initial approach to the Boari flap is the same as that for the psoas hitch such that the contralateral bladder pedicle is mobilized. The base of the flap should be at least 4 cm in width, and the flap is extended obliquely across the anterior

bladder wall, with the tip of the flap at least 3 cm in width. The base of the flap is secured to the psoas tendon as described previously. The ureter is delivered through cystotomy in the posterior flap, and a primary mucosa-to-mucosa anastomosis or a submucosal tunnel can be created if a nonrefluxing anastomosis is preferred. After the ureteral anastomosis, the tube is rolled anteriorly and closed using absorbable suture. The ureteral adventitia may be anchored to the flap and the repair can be wrapped in omentum or peritoneum [28]. Post-operatively, CT cystogram is convenient to verify watertight anastomosis prior to stent and Foley catheter removal (Image 25.2).

Contraindications to UNC, psoas hitch, or Boari flap are those patient's with small contracted bladders, limited tissue mobilization, poor bladder compliance, or patients with dysfunctional voiding. For these reasons, if the reconstructive surgeon is considering work up for a lengthy ureteric defect, urodynamic evaluation should precede the operation to determine bladder capacity and compliance. Additionally, performing reconstructive techniques with irradiated bladder or ureter can also lead to post-operative complications such as urine leak and anastamotic and/or wound breakdown.

Ideally, ureteral defects should be bridged by tissue lined with urothelium and available tissue of the urinary tract should be used for ureteral repair whenever possible. This includes UU, TUU, UNC, psoas hitch, and/or Boari flap when feasible. However, unfortunately some patients are not amenable to these reconstructive options and suffer with routine exchanges of permanent nephrostomy tubes due to irreparable ureteral defects. For patients with complete ureteral injury in which JJ ureteral stent is not feasible, limited options exist such as chronic nephrostomy tube, ileal ureter, autotransplant, or nephrectomy.

First described by Shoemaker in 1906 [29] and popularized in 1959 by Goodwin [30], the use of ileum as a ureteral substitution to restore functional integrity of the upper urinary tract may be appropriate for unique cases. The surgical techniques include key elements such as isolating 20–25 cm of ileal segment proximal to ilealcecal valve, performing the ileal substitution in an isoperistaltic, refluxing fashion with tension-free anastomosis to the renal pelvis and to the bladder [31] (Image 25.3). Use of bowel segments such as ilium can pose some long-term problems which patients should be aware of. Ileal ureter is known for risk of electrolyte abnormalities, most notably hyperchloremic metabolic acidosis [32]. However in carefully selected patients who have good renal function preoperatively, the risk of worsening uremia and hyperchloremic metabolic acidosis is low with reports of 75% patients having stable or improved serum creatinine [33, 34].

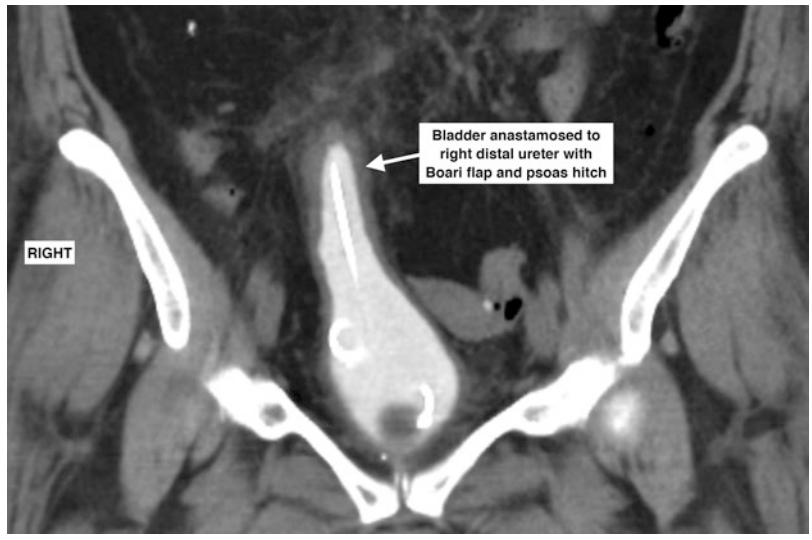

Image 25.2 CT cystogram of Boari flap and psoas hitch. Imaging demonstrates a Foley catheter and bilateral ureteral stents. The patient is 3 weeks postoperative from right ureteroneocystotomy with psoas hitch and Boari flap and left ureteroureterostomy. The right side of the bladder is pulled up and anastomosed to the right distal ureter. No evidence of contrast extravasation is seen

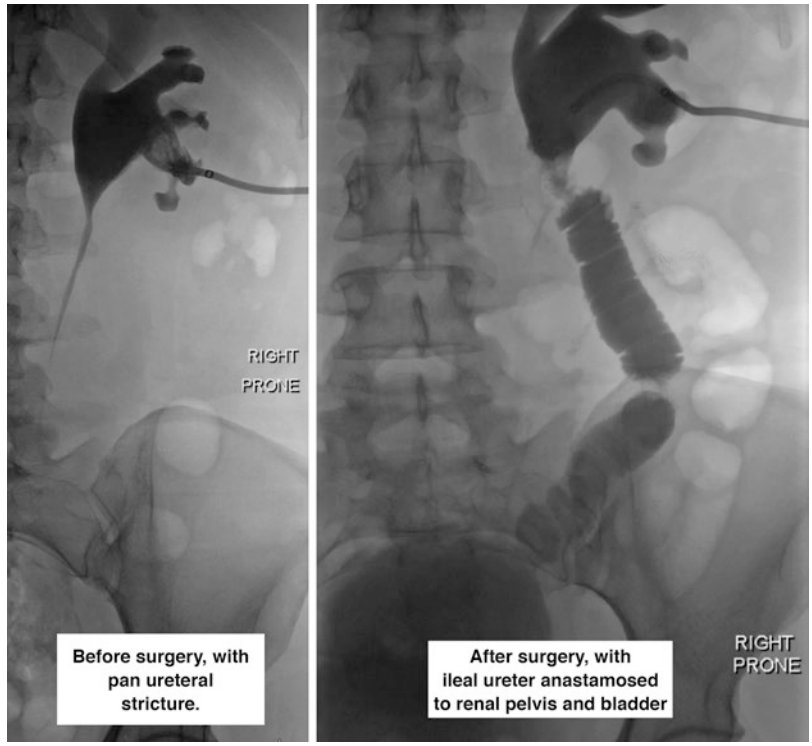

Image 25.3 Before and after antegrade nephrostogram images of pan ureteral stricture repaired by an ileal ureter

In summary, there are many options for UPJ and ureteral stricture repair. It is helpful to explain to the patients pre-operatively that sometimes, the definitive option isn't decided until intra-operative assessment is done. Therefore, surgeons should be prepared to do whichever reconstructive option the patient's anatomy allows with the least morbidity and best possible outcomes. Patients should also be prepared for this prior to surgery, with multiple options included on the surgical consent.

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Current Trends in Urethral Stricture Management

26

Christopher R. Chapple

Introduction

The ICUD consultation 2010 [1] confirmed that a urethral stricture is defined as a narrowing of the urethra consequent upon ischaemic spongiofibrosis and as distinct from sphincter stenoses and urethral disruption injuries. Whenever possible an anastomotic urethroplasty should be used because of the higher success rate as compared to augmentation. There is some debate currently regarding the critical stricture length at which an anastomosis procedure can be used, but clearly the extent of the spongiofibrosis and individual anatomy are important. The limiting factor for this being extension beyond the peno-scrotal junction and the production of chordee. More recently there has been a debate over whether to excise and anastomose or to carry out a stricturotomy and re-anastomosis using a heineke-micilicz technique. Augmentation urethroplasty has evolved towards the more extensive use of oral mucosa grafts as compared to penile skin flaps.

It is important that the reconstructive surgeon is well versed in the full range of available techniques, as no one technique is suitable for all cases, thereby providing them with the opportunity to deal with any condition of the urethra that is discovered intraoperatively.

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Urethral stricture disease can result from a multitude of aetiological factors. Once predominantly inflammatory in origin, the causality has now shifted towards iatrogenic and traumatic factors.

An anatomical and aetiological understanding of the underlying disease process is essential to offer patients the best treatment options and the lowest possible stricture recurrence rates. The current understanding of the underlying factors resulting in stricture formation will be discussed here.

Anatomy

The male urethra is approximately 20 cm in length and is composed of the short posterior urethra and the longer anterior urethra. The posterior urethra comprises of the prostatic and membranous sections. The anterior urethra is formed by the bulbar and the penile segments and terminates at the external urethral meatus at the tip of the glans penis. The bulbar urethra is located at the dorsal aspect of the corpus spongiosum, having a thick ventral covering, whereas towards the distal penile urethra, the urethra is located ventrally. The configuration of the corpus spongiosum surrounding the urethra varies considerably and is absent in the posterior sphincteric portion with significant variation as one progresses along the length of the urethra (Fig. 26.1). It is important

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Table 26.1 Stricture aetiology by location [5]

	No. Penile (%)	No. Bulbar (%)	No. Panurethral (%)	No. Posterior (%)
Prostatectomy	0	3 (2.33)	1 (2.78)	5 (12.5)
Perineal trauma	0	6 (4.65)	0	0
Urethral catheterization	9 (14.29)	13 (10.08)	9 (25)	0
Idiopathic/unknown	13 (20.63)	62 (48.06)	5 (13.89)	0
TUR	7 (11.11)	32 (24.81)	9 (25)	4 (10)
Hypospadias	18 (28.57)	5 (3.88)	2 (5.56)	0
Pelvic fracture	0	0	1 (2.78)	29 (72.5)
Urethritis	1 (1.59)	6 (4.65)	3 (8.33)	0
Lichen sclerosus	10 (15.87)	0	3 (8.33)	0
Cystoscopy	0	1 (0.78)	2 (5.56)	0
Tumor	3 (4.76)	0	1 (2.78)	0
Penile fracture	2 (3.17)	1 (0.78)	0	0
Brachytherapy	0	0	0	2 (5)
Totals	63	129	36	40

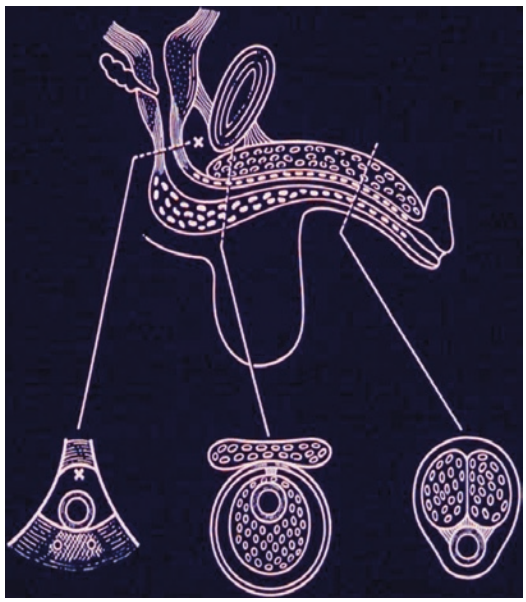

Fig. 26.1 The differing anatomy along the length of the urethra demonstrating posteriorly a sphincter active urethra with very little corpus spongiosum (if any) and showing the configuration of the corpus spongiosum more distally. The corpus spongiosum is thickest ventrally in the bulbar urethra and is very thin circumferentially in the penile urethra

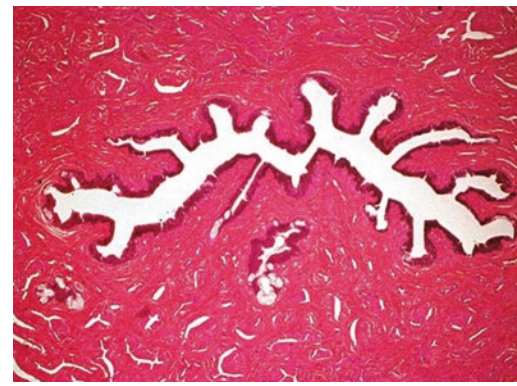

Fig. 26.2 The very vascular nature of the bulbar urethra

to realize that the corpus spongiosum is a very vascular organ (Fig. 26.2) and it is ischemic damage to this which leads on to urethral stricture disease (Fig. 26.3).

The absence of an outer corpus spongiosum at the posterior urethra has important implications in stricture terminology and treatment. Being the only urethral segment lacking any fixed supportive tissue, the membranous urethra is vulnerable to external injury and importantly the distal urethral sphincter is located at this level.

The distal urethral sphincter mechanism, supplied by nerves from the S2 to S4 level provides voluntary control of urinary flow. The anterior urethra acts as a conduit for the passage of urine. Lined by stratified epithelium, the anterior urethra differs from the transitional epithelium lined posterior urethra.

The female urethra measures 4 cm in length. It consists of both smooth muscle layers and striated muscle along its length, with the outer striated muscle critical in maintaining continence.

Pathophysiology

Strictures form as a result of ischaemic scarring of the spongy tissue of the corpus spongiosum (spongiofibrosis). The area of disease appears white or grey in contrast to the pink appearance of healthy urethral tissue (Fig. 26.3).

As a result of epithelial insult, the underlying vascular spongy tissue is exposed which heals by fibrosis. As voiding occurs, urine further irritates this process. Stenoses form in the posterior urethra due to direct trauma to the urethral epithelium or in the bulbar urethra due to external injury; so called pelvic distraction injuries associated with a pelvic fracture or fall astride injuries as seen in the bulbar urethra respectively, both of which are not associated with significant loss of urethral length (Fig. 26.4).

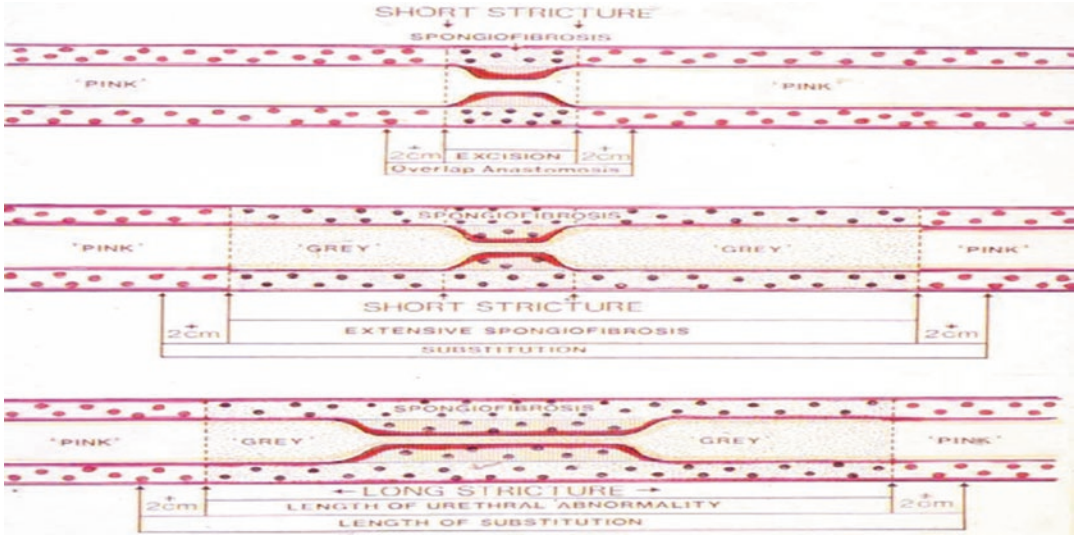

Fig. 26.3 The anatomical abnormality of a true urethral stricture showing the impact of ischemic spongiofibrosis

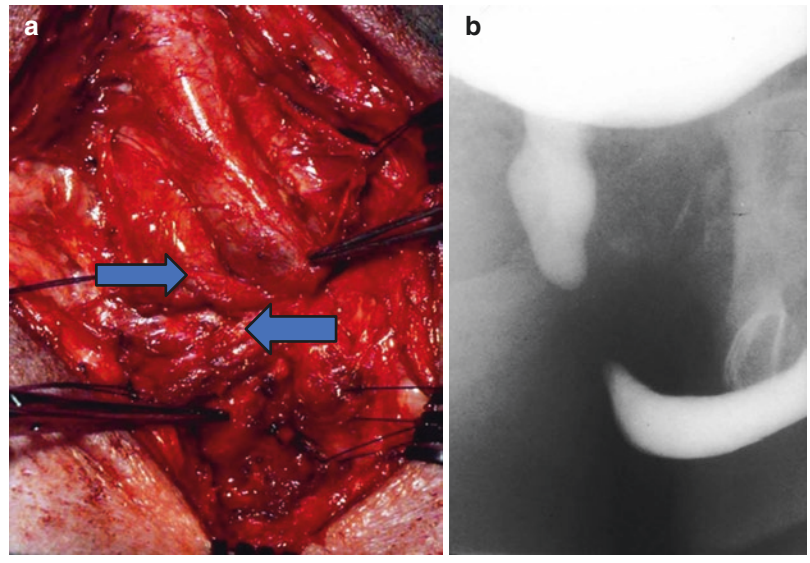

Fig. 26.4 Urethral distraction injuries. (**a**) A fall astride injury, (**b**) A pelvic fracture distraction injury

Lichen sclerosus (LS), formerly known as Balanitis Xerotica Obliterans is responsible often for complex strictures of the anterior urethra. First described by Stuhmer in 1928 [2], it is an inflammatory condition of unknown aetiology affecting the stratified epithelium of the anterior urethra. For this reason, it does not affect the posterior urethra, lined by transitional epithelia. Urethral involvement by LS was first described by Laymon in 1951 [3]. Histologically, excess dermal collagen is present with a hyperkaratotic epidermal layer. It has a progressive tendency, leading to significant rates of recurrence in urogenital epithelium.

Aetiology

The aetiology of stricture disease is a fundamental consideration in planning treatment. In contemporary practice most urethral strictures encountered are idiopathic, traumatic, inflammatory or iatrogenic.

Although the term posterior urethral stricture is still used, it generally encompasses the terms bladder neck stenosis (or vesico-urethral anastomotic stenosis following prostatectomy) and the pelvic fracture urethral injury (PFUI) affecting the membranous urethra or the bulbomembranous junction [4]. This distinction is important, as the pathogenesis and surgical options differ significantly. Following a radical prostatectomy, a stenosis may form at the vesicourethral anastomosis proximal to the distal urethral sphincter. This can also be seen in posterior urethral stenoses that occur in men following TURP. In this case, the sphincter mechanism is intact and the urethra, although stenosed remains in continuity.

In pelvic fracture urethral distraction disorder (PFUDD), the two urethral ends are distracted relative to one another, even though the gap between the ends may be significant there is minimal loss of length. In approximately 60% of cases the distal sphincter mechanism is involved in the injury and continence depends on the integrity of the bladder neck mechanism.

The idiopathic abnormality of the bulbar urethra which gives rise to the short strictures identified in young men without an identifiable cause represents a significant proportion of cases. Being short and soft in composition, these can be successfully treated by a single direct vision internal urethrotomy (DVIU) in a proportion of patients. Proximal bulbar strictures can also occur following perineal trauma due to distracting forces between the protected bulbar urethra and the vulnerable membranous urethra.

Lichen sclerosus, as previously discussed, tends to be responsible for long anterior urethral strictures and may affect other areas of genital epithelia. For example prepucial skin and the urethral meatus.

Hypospadias, although not directly associated with stricture formation itself, can result in spongiofibrosis as a result of the surgery used to correct it in childhood.

Occasionally strictures can occur following genitourinary infections, although with the advancement of antibiotic therapy, causative organisms such as Gonorrhoea and Chlamydia represent much less of a burden on stricture formation.

The two major types of stenosis are shown in Figs. 26.3 and 26.4.

Evaluation

Basic Investigations

Most men with urethral stricture disease will present with voiding lower urinary tract symptoms. There may be a feeling of incomplete emptying as obstruction slowly develops, with or without haematuria or urinary tract infection as a consequence.

Uro-flowmetry characteristically shows a plateau pattern with a low Qmax. However it must be remembered that the effective diameter of the unobstructed male urethra is in the order 11Fr [6] and until the stricture narrows beyond this point there would not necessarily be interference with flow. Indeed, patients who have a known diagnosis of a stricture, but have a flow rate greater than

10mls/sec, normal bladder thickness and no features of recurrent urinary tract infection do not necessarily require treatment. In the face of recurrent urinary tract infections or features of obstruction, either biochemically or radiologically, treatment should be considered.

Urethrography

Retrograde urethrography (RUG) is regarded as the gold standard investigation in urethral stricture assessment. When performed correctly, it can give the investigating clinician information regarding the stricture location, length and any other pathology affecting the urethra (diverticulum, fistula, false passages).

A synchronous combination of RUG with voiding cystourethrogram or a combined cystoscopy and urethroscopy (retrograde or antegrade) is recommended to assess posterior urethral strictures and importantly identify the function of the bladder neck. This has particular implications and is certainly recommended in patients with pelvic fracture urethral injury (Fig. 26.4b).

Cystoscopy

Standard retrograde flexible or rigid cystoscopy is recommended to assess the location and degree of spongiofibrosis. It is also suggested as a method of follow up for patients undergoing uroflowmetry, as uroflorometry alone may not indicate recurrence of disease until the urethral calibre diminishes significantly. Nevertheless, the stricture calibre is often impossible by standard cystoscopic techniques.

Cystoscopy can also be utilized in the context of early catheter realignment in the acute management of high grade PFUDD.

Further Imaging

Although ultrasonography is helpful in assessing stricture length and extent of spongiofibrosis, its use is not recommended for the sole assessment of strictures and should be combined with urethrography given its anatomical limitations. Other imaging modalitites, such as CT or MRI can provide useful information particularly in those patients with PFUDD and can be helpful in identifying diseased segments of urethra.

Posterior Urethral Stricture

Management of PFUI

With PFUDD the treatment aim is to restore continuity of the diseased urethra. This can either be achieved in the acute setting, opting to perform early catheter realignment in an attempt to achieve an early time to spontaneous voiding, or to perform a suprapubic cystostomy and accept delayed stricture repair at a later date. In recent years with advances in endoscopic equipment there has been a great deal of interest in the use of early endoscopy at an early stage (within 2–3 weeks) to evacuate blood clot and introduce a catheter across the defect. In view of the rarity of this injury in most clinicians' experience, it is advisable to limit this to specialized centres with the expertise; bearing in mind the other co-existing injuries and medical problems in these patients, acute transfer of these patients is rarely appropriate, hence the reliance on a two stage approach of introducing a suprapubic catheter and a secondary repair.

Stenosis occurring at the bulbomembranous junction following PFUI can be successfully reconstructed using a bulbomembranous anastomotic urethroplasty. To obtain sufficient length, one relies on the elasticity of the bulbar urethra following mobilization. When sufficient length cannot be achieved, either due to excision of a long stricture or where there is significant gap following a PFUDD, several manoeuvres can be undertaken in a step-wise fashion with the aim of reducing the natural curve of the bulbar urethra. These include separation of the crura at the penile base, a wedge pubectomy, or failing this, urethral re-routing until the bulbar urethral course from the apex of the prostate to the peno-scrotal junction is a straight line. Webster and Ramon, using

a perineal approach incorporate these steps in bulbomembranous anastomotic urethroplasty [7]. In clinical practice however, the latter steps are seldom practiced given that optimal length is often gained by the initial steps, although it is recommended that surgeons should be well versed in these practices as the need arises.

Repair of the majority of defects can be achieved by a perineal approach due to the defect commonly being short. Long-term patency rates for most bulbomembranous anastomotic urethroplasty procedures are in the region of 90–98% [8, 9]. The success rates for re-do procedures are similar to primary repair (87% vs. 90%) [10].

Treatment of Bladder Neck Stenosis and Vesico-Urethal Anastomotic Stenosis

Bladder neck stenosis, the term encompassing those strictures of the posterior urethra (when the prostate is in situ and there is absence of PFUI) results from iatrogenic trauma. Vesico-urethral anastomotic stenosis (VUAS) is the term given to the stenosis occurring following a radical prostatectomy. The potential mechanisms involved in VUAS include tension at the anastomosis, inflammation, extravasation of urine and ischaemia. A stepwise treatment approach in VUAS is recommended, initially with dilation and direct visual internal urethrotomy (DVIU) demonstrating success rates of 58–92% [11, 12]. Open reconstruction is challenging and can jeopardize continence, while stent procedures are limited by migration and tissue regrowth.

Transurethral resection of the prostate (TURP) can give rise to bladder neck stenosis, particularly in the resection of smaller prostates. Here, dilatation is rarely beneficial and bladder neck incision demonstrates relative success.

Similarly, posterior urethral stenoses can be observed following external beam radiotherapy (EBRT) or brachytherapy (BT) as part of the treatment of prostate cancer. Outcomes of DVIU/dilation are similar to those observed for the treatment of VUAS.

Anterior Urethral Stricture

DVIU/Dilation

Originally introduced by Sachse in 1974, the intention of dilatation is to progressively stretch the stricture restoring a normal calibre urethral lumen. In DVIU, the stricture is incised, following which a catheter is left to splint the urethra open allowing re-epthelialisation before contracture can occur. This, however, is largely dependent upon blood supply and any underlying pathology, e.g. LS.

For patients with short, soft bulbar strictures, stricture free rates in the region of 50–70% can be achieved. Whilst this is significantly lower than that demonstrated by excision and primary anastomotic urethroplasty (EPA) (90–95%), it is not unreasonable to attempt a single DVIU in those patients with single bulbar urethral strictures <1 cm. Indeed, a second DVIU can be offered to those patients with recurrent disease >6 months following initial treatment [13]. The optimal duration of post-operative catheterization following DVIU is unclear.

There is no evidence that balloon dilatation of a sphincter is any way different in outcome to a urethrotomy and there is no evidence to suggest that a laser incision is in any way different to a cold knife urethrotomy.

It is recommended in healthy patients with stricture recurrence within 3 months of initial DVIU/dilation or indeed failing a second DVIU that urethroplasty should be offered. Repeat DVIU/dilation is not recommended except in those either unfit or unwilling to undergo reconstructive surgery.

In cases with a distal sphincter stricture, often seen in patients following TURP or radical prostatectomy, it is best to avoid a urethroplasty as there is no functioning bladder neck mechanism. In these cases after a urethrotomy it is best to rely upon regular intermittent self-dilatation of the stenosis.

There has previously been some interest into the use of urethral stents, both temporary and permanent for the treatment of anterior urethral

strictures. Unfortunately, however these were associated with significant complications including migration, encrustation and infection. Moreover, it seems their use does make reconstruction technically more difficult in the case of a failed stent. This is particularly true in terms of bulbar urethral strictures, where the morbidity associated with encrustation is significant.

In recent years a number of studies have evaluated the efficacy of agents injected into the scar tissue at the site of stricture area as an internal urethrotomy procedure to decrease recurrence rates by preventing recurrent spongiofibrosis. In this context, Mitomycin C has been used for anterior urethral stricture [14]. Authors have reported that after 15 months mean follow-up urethral stricture recurred in 10% of patients in the mitimycin-C treated group and in 50% of patients in the untreated group [15, 16]. Another study evaluated the use of triamcinolone injection and showed a significant decrease in recurrence rate [17, 18].

Excision and Primary Anastomosis

The gold standard for the treatment of short bulbar urethral strictures is the excision and primary anastomotic urethroplasty. This allows the diseased length of urethra to be excised and the two healthy ends to be spatulated and anastomosed. Success rates are reported as high as 98.8% in 260 patients with a stricture length of 0.5–4.5 cm (mean 1.9 cm) followed up for 50 months [19]. Barbagli [20], in a study with 153 patients followed up for a mean duration of 68 months demonstrated success rates of 90.8%. Interestingly, those who underwent either a single treatment prior to urethroplasty or no treatment at all showed success rates of 92.1–100% whereas in those whom had undergone multiple previous treatment modalities stricture free rates were lower.

There is much debate over the critical stricture length to be managed by EPA. It is generally considered that the stricture length should not exceed 2 cm and Guralnick and Webster [21] suggest a limit of 1 cm. The rationale behind this is that after the 1 cm stricture length is excised and 1 cm of proximal and distal healthy urethra are spatulated and anastomosed, the deficit is 2 cm. This can result in shortening and chordee. On the other hand, it is argued that by freeing up the urethra and separating the corpora, several centimetres more may be gained in length. Morey [22] reports that in young men with proximal bulbar strictures of up to 5 cm, a 91% success rate can be achieved. Clearly, local factors play a vital part in the anastomotic repair of long bulbar urethral strictures.

In 2012, Andrich and Mundy [23] in a preliminary report, described a non-transecting anastomotic technique, relying upon a dorsal stricturotomy following mobilization of the urethra, leaving the ventral spongiosum intact. The rationale behind this is to limit the neurovascular damage resulting from urethral transection with subsequent improved healing and ED rates at the cost of incomplete stricture excision. They used this technique in 22 patients. In the 16 patients who had been followed up for a minimum of 1 year, success rates were 100%.

Substitution Urethroplasty

Those strictures considered to be too long (>2 cm) for EPA, particularly in the presence of an inflammatory process such as LS, substitution urethroplasty is recommended. This can be undertaken as part of a one or two stage procedure. A two-stage procedure involves stricture excision with the formation of a roof strip of graft, which is then allowed to heal prior to closure. With a single stage procedure, there are two options:

(a) Stricture incision with an onlay patch (Onlay augmentation urethroplasty)
(b) Stricture excision with urethral anastomosis augmented with a roof or floor strip and patch (Augmented anastomotic urethroplasty)

Tube grafts are very currently rarely performed due to unacceptable stricture recurrence rates.

Bulbar Urethral Strictures

The treatment of bulbar urethral strictures differs slightly from that of penile strictures due to the inability to reconstruct the urethra using a flap technique. The treatment of bulbar urethral strictures and penile urethral strictures are therefore considered separately here.

Augmentation Urethroplasty: Bulbar Urethra

For longer urethral strictures (>2 cm in length), success rates greater than 90% can be achieved with stricturotomy and onlay augmentation urethroplasty using a buccal mucosa graft (BMG). It is useful when the peri-urethral spongiofibrosis is relatively limited and the urethra is patent [24]. Both Andrich et al. [25] and Bhargava et al. [26] have found success rates in excess of 90% with the technique.

Recently, the equally popular dorsal approach and ventral approach to augmentation urethropasty have demonstrated similar stricture free rates [27] with the advantage of the ventral onlay graft being ease of approach and limited mobilization of the urethra. The disadvantage to the ventral approach is that of bleeding when one performs incises the stricture on the thicker ventral aspect as compared to the dorsal urethra. There is evidence to support the ventral onlay graft in proximal bulbar strictures [28] and dorsal onlay graft technique in distal bulbar strictures [29].

Palminteri et al. suggested that in addition to the placement of a dorsal inlay graft via a ventral sagittal approach, a ventral onlay could be applied as well with high success rates [30].

Augmented Anastomotic Urethroplasty: Bulbar Urethra

When considering the treatment of longer, denser strictures of the bulbar urethra, particularly those associated with blunt perineal trauma, the augmented roof strip anastomosis may be of benefit. This allows complete excision of the diseased segment with anastomosis using a graft to avoid chordee. This procedure can be performed, again, using a transecting or non-transecting approach. Recent systematic reviews of graft augmentation anastomotic urethroplasty has demonstrated no significant difference between the dorsal or ventral onlay in the bulbar urethra [31].

El-Kassaby et al. [32] report the largest series of augmented anastomotic procedures with a mean follow up of 36 months. The success rates were 93.7% in 233 patients using a ventral onlay BMG.

Using a non-transecting technique, a dorsal urethrotomy is performed until healthy mucosa is encountered. At this point the decision to perform a dorsal onlay substitution graft or an augmented anastomotic repair with BMG without completely transecting the urethra is determined by the degree of urethral patency. Success rates in excess of 90% were demonstrated in a study of 44 patients, 23 of whom underwent substitution urethroplasty, whilst 21 underwent augmented non-transecting anastomotic urethroplasty. After median follow up of 2.3 years, there was no significant difference between the two groups [33].

Penile Urethral Stricture

The treatment options for penile urethral strictures depend very much on the underlying disease process. Here, it is not possible to simply excise the stricture and undertake an end-to-end anastomosis due to risk of chordee. Instead, one must perform either a single or multi-stage procedure using either a flap or graft. With similar stricture free results, the choice here very much depends on the presence of LS and availability of tissue for transfer.

Flap Urethroplasty

In those patients with a normal penis, i.e. the penile skin, urethral plate, corpus spongiosum and dartos are available for tissue transfer, a one stage reconstruction is worldwide the procedure of choice.

Orandi [34] first described the reconstruction of the anterior urethra using a pedicled skin flap in 1968. The principles of this single stage procedure remain the gold standard in the treatment of non-obliterative penile urethral strictures not due to LS. More recently, McAninch [35] described the use of a circular faciocutaneous skin flap in a single stage reconstruction of complex penile urethral strictures. Whitson and colleagues [36] reported

on the long-term stricture free rates of distal penile circular fasciocutaneous flaps in 2008. A total of 124 patients with complex anterior urethral strictures were followed up for a median duration of 7.3 years (1 month to 19.5 years) with a median stricture length of 8.2 cm (0.5–24 cm). At 1,3,5 and 10 years, the overall success rates were 95%, 89%, 84% and 79% respectively.

Graft Urethroplasty: Penile

The use of free grafts has evolved since Snodgrass originally described a repair technique in 1994 [37], with Hayes and Malone performing an onlay of BMG onto the incised urethral plate in failed hypospadias repair [38]. This technique was taken further in 2001, when Asopa and colleagues developed a similar technique for stricture repair utilizing a ventral sagittal urethrotomy and a dorsal inlay graft.

Although it is preferable to use a flap in patients with a narrow, rigid urethral plate and fibrous spongiosum tissue, in those with a wide urethral plate without fibrous spongiosum tissue a graft is preferred. Both BMG or preputial skin grafts can be used with equal success [39]. Except in a carefully selected subset of patients [40], a two-stage penile augmentation urethroplasty is preferred.

Andrich et al. [41] reported a success rate of 98% in a study of 58 patients. Follow up, however was limited to 6 months. Conversely, Kulkarni reported success rates of 73% at 56 months using oral mucosa [40].

Penobulbar Strictures

With complex panurethral strictures commonly due to Lichen sclerosus, repeated instrumentation or previous failed hypospadias repair, it is not unreasonable to discuss the option of permanent perineal urethrostomy with such patients. Although one-stage procedures are possible, the original Johanson approach involving marsupialization of the urethra followed by tubularization of a strip 3–6 months later is still an option for complicated strictures.

In view of the often grossly extensive disease, the length of graft required is often long and may often necessitate bilateral BMG harvest. In the absence of LS, various other tissues as described above can be utilized. Of note, tunica albuginea, bladder or colonic mucosa. Xu et al. [42] in a study of 36 patients followed up for 53.6 months demonstrated an 85.7% success rate using colonic mucosa graft in a single stage procedure. These however are not advocated as alternatives to BMG given their donor site morbidity and difficulty to harvest. Kulkarni and colleagues [29] demonstrated a 92% success rate in a study of 12 patients followed up for 22 months using oral mucosa grafts in a single stage procedure. The approach in this case was a one-sided anterior dorsal BMG urethroplasty, preserving the lateral vascular supply. Their experience using this technique in 117 men with panurethral strictures followed up for 59 months gave a success rate of 86.5% for primary urethroplasty and 61.5% in those whom have previously undergone a failed procedure. Of note, recurrences developed at the proximal end of the graft.

Andrich et al. [41] utilized a two-stage procedure using BMG or full thickness skin graft. They report a success rate of 91.7% in 24 patients followed up for 6 months.

Tissue Engineering

The role of tissue engineering in reconstructive urology is rapidly progressing. Given potential donor site morbidity with using grafts there is a niche for tissue engineering, particularly with lengthy strictures or in patients with reduced mouth opening. An ideal tissue should be easy to handle, take well and not undergo contraction, fibrosis or indeed rejection.

Engineered grafts include acellular grafts obtained from cadaveric or animal tissue. These are then decelluarised with the resulting biological matrix being implanted. Cellularized grafts consist of cultured autologous cells in matrix. These cells are obtained from a biopsy before the cells are expanded in vitro.

With regards to acellular grafts, Fiala et al. [43] reported an 80% success rate at 31 months follow up with small intestinal submucosa grafts. The failures here occurred early (6 months) and

were more common in reconstruction of penile urethral strictures. Palminteri et al. [44] described failure rates of 24% in 25 patients undergoing urethroplasty using SIS followed up for 71 months. All cases where a graft in excess of 4 cm was used, failed.

Engineered oral mucosa urethroplasty outcomes were first reported in 2008 [45], where oral fibroblasts and keratinocytes obtained from patient biopsy were seeded onto de-epidermised cadaveric dermis and expanded in vitro. The five patients involved in the study had complex strictures secondary to LS. Initially 100% graft take was demonstrated, however 1 patient the required complete excision of the graft due to scarring whilst another required partial excision due to a hyperproliferative reaction. Of the remaining three patients, all required some form of instrumentation at 3 year follow up. Furthermore, in recent study by Ram-Liebig et al. [46], 10 patients with short strictures (1–3 cm) received tissue engineered buccal mucosa graft. Three weeks following urethroplasty, urethrography demonstrated in five patients a wide, watertight urethra with no donor site morbidity. One patient suffered early recurrence at the graft site. Clinical co-workers allied to this group expressed potential enthusiasm for this new material [47]. They cited the results of this initial study in support of this view. In this initial series of patients ($n = 21$) with a median follow up of 18 mo (range 13–22) the success rate reported was 80.9%. This study represents the most important step in the clinical use of tissue-engineered material for urethral reconstruction [48]. Barbagli and Lazzeri concluded 'that by following strict protocol criteria, it is possible to move tissue-engineering technology from the laboratory bench to the bedside'. They did however emphasise the importance of an appropriate subsequent study and were justified in taking a cautious approach. As the subsequent larger prospective observational multicentre clinical study of 99 patients from 8 centres from this group [49]. They reported success with a heavy reliance on subjective measures and flow rates that at 2 years in 98 patients. There was significant variation in the results in different centres, with two low volume centres reporting success rates of 0 and 50% respectively at one year with an overall success rate of 67.3% and a two year success rate of approximately 60%. From a careful review of this paper in my view it is likely that if urethrography or urethroscopy had been carried out in all of the cases then the success rate is likely to have been lower than this. This is clearly less than the success rates noted in a systematic review of more than 2000 anterior urethroplasty procedures described in the literature. For bulbar urethral strictures there was no significant difference between the average success rates of the dorsal and the ventral onlay procedures, 88.4% and 88.8% at 42.2 and 34.4 months in 934 and 563 patients, respectively [31].

From the above data, it is clear that although acellular grafts are available 'off the shelf' they are associated with recurrence in terms of longer strictures and have issues with failure of cell ingrowth. Cellularized grafts on the other hand do show promise in longer strictures, however, this does still require a biopsy that carries morbidity and requires cell expansion for several weeks. There are also no current long-term follow up studies to show support for this technique.

Female Urethral Strictures

Female urethral stricture (FUS) is a rare and challenging clinical entity. Several new surgical techniques have been described for the treatment of FUS, although with the limited number of reports, there is no consensus on best management. The pathogenesis of FUS is poorly understood, although factors such as trauma, infection and prior instrumentation/surgery make the condition more likely.

Given the relative rarity of the condition, there is no accepted definition not to mention no accepted diagnostic criteria. Urethral calibration in general would be <20F. Indicators of disease would be suggested by a high pressure, low flow pattern in the voiding phase of a video-urodynamic assessment along with a strictured urethral segment radiologically. An MRI scan may demonstrate a diverticulum or fistula.

Dilation is recommended in the first instance and Romman and colleagues [50] in a study of 93

patients followed up for a mean duration of 46 months reported an overall success rate of 51%. Here, the urethra was dilated to 41F and a proportion of the patients ($n = 26$) had undergone previous dilatation. No post-op ISC was performed. Urethrotomy for female urethral strictures is potentially harmful and along with bladder neck incision, should not be used in women.

Urethroplasty for female urethral strictures can be performed using a variety of reconstructive techniques and the approach employed relative to the position of the urethra can be dorsal, ventral or circumferential. The advantages of a ventral approach are reduced urethral mobilization at the expense of theoretical risk of fistula formation. The dorsal approach carries the risk of injury to the sphincter mechanism or the neurovascular supply to the clitoris resulting in sexual dysfunction. The vaginal mucosa, in addition to being locally accessible, it naturally wet and hairless. It is generally well tolerated with minimal donor site morbidity, however, may not be ideal in conditions such as vaginal atrophy or fibrosis.

In a systematic review of the literature classifying the results by surgical technique and type of graft in the case of graft augmentation urethroplasty for female urethral stricture disease [51] a total of 221 patients were reported on with outcome measures after intervention for FUS. The mean age of women was 51.8 yr. of age (range: 22–91). All studies were retrospective case series. There was no consistent definition of FUS nor unified diagnostic criteria. Most studies used a combination of diagnostic tests. Where aetiology was defined, idiopathic and iatrogenic stricture were the two most common causes. Ninety-eight patients underwent prior intervention for FUS, mostly urethral dilatation or urethrotomy. Success was defined as the lack of need for further intervention. Urethral dilatation, assessed in 107 patients, had a mean success rate of 47% at a mean follow-up of 43 months. Fifty-eight patients had vaginal or labial flap augmentation, with a mean success rate of 91% at 32.1 months of mean follow-up. Vaginal or labial graft augmentation had a mean success rate of 80% in 25 patients at a mean follow-up of 22 months. Oral mucosal augmentation, performed in 32 patients, had a mean success rate of 94% at 15 months of mean follow-up. No instances of de novo stress incontinence were reported, which is most unusual in these circumstances and has not as yet been explained based on our understanding of urethral function. The conclusion of this review was that the techniques of urethroplasty all have a higher mean success rate (80–94%) than urethral dilatation (<50%), although with shorter mean follow-up. Urethroplasty in experienced hands appears to be a feasible option in women who have failed urethral dilatation, although there is a lack of high-level evidence to recommend one technique over another.

Conclusions

It is perhaps unwise to make sweeping statements with regard to the treatment of urethral stricture disease on the basis of the above. This is due to the vast differences in each individual patient, not only in terms of the location of the stricture, but the availability of tissues for reconstruction, previous interventions and disease aetiology.

It can be deduced that for strictures due to PFUDD, bulbomembranous anastomotic urethroplasty can yield success rates in excess of 90%. It is associated with high rates of erectile dysfunction, which may be attributable to the original trauma process. For short bulbar urethral strictures it is not unreasonable to attempt a single DVIU, however, following failure, an anastomotic bulbar urethroplasty can be associated with success rates in the region of 90–100%. Although what is considered a ‘short’ stricture is up for debate, clearly local factors in the individual patient can influence whether an anastomotic technique is successful.

Onlay augmentation bulbar urethroplasty versus an augmented anastomotic approach can yield similar results in experienced hands, their utilization largely dependent upon experience, urethral patency and stricture density. The ventral and dorsal approaches both come with their individual risks and benefits but in general show similar success rates. BMG has become the first

choice of most practicing urologists, given its relative ease of harvest, however the debate on whether the graft should be placed dorsally or ventrally continues. Some surgeons are adopting a non-transecting approach to avoid the neurovascular complications associated with transection of the urethra.

Flaps are generally preferred to grafts in the treatment of penile urethral strictures, with the Orandi technique and derivatives remaining the gold standard for non-obliterative strictures of the penile urethra. The penile circular fasciocutaneous flap as described by McAninch does have high stricture-free rates. A two-stage substitution urethroplasty using BMG has become popular for the treatment of penile urethral strictures and is particularly recommended for the management of patients who have undergone previous failed hypospadias repairs or in the case of LS.

Whilst perineal urethrostomy is regarded as a reasonable option for those patients who are either not suitable for urethoplasty or refuse such treatment, the management of panurethral strictures represents a challenge. The Johanson technique provides adequate results as a staged procedure, whereas, there is growing popularity of the use of substitution urethroplasty using BMG as a one stage procedure in a select group of patients.

Urethral dilatation for female urethral strictures is associated with high failure rates. Urethroplasty on the other hand confers a high stricture free rate with minimal risks of urinary incontinence. Of the several reconstructive approaches, there is no strong evidence to suggest a significant benefit of one over the other. Given the relative rarity of female urethral strictures, it is recommended that the treatment is undertaken at a centre with experience in the disease.

We advocate the use of short term flexible urethroscopy follow up at 6 months and 12 months, given that in the absence of progressive disease processes, such as LS, most stricture recurrences are evident at 6 months. These would be missed using urofluorometry alone. It is our opinion that endoscopic surveillance provides the most reliable information in terms of the presence of stricture, location and state of the urethra. It is often easier to interpret than other available methodologies such as urethrography and certainly more sensitive than symptom scores or flow rate.

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Contemporary Management of Urinary Incontinence

27

Sophia Delpe Goodridge and Roger Dmochowski

Introduction

Urinary incontinence is defined by the international continence society as the complaint of involuntary leakage of urine [1]. It can be broken down into two categories: urgency urinary incontinence (UUI) and stress urinary incontinence (SUI). Urgency urinary incontinence is defined as the observation of involuntary leakage form the urethra synchronous with the sensation of sudden, compelling desire to void that is difficult to defer. Stress urinary incontinence is defined as the involuntary loss of urine on effort or physical exertion [2]. Wu and associates estimate that the prevalence of urinary incontinence in U.S. women is about 17.1%. This is associated with a significant cost burden to both the healthcare system and individual patients [3]. The annual cost related to urinary incontinence is estimated at 27.8 billion in the US [4, 5]. Compounding this is the significantly diminished reported healthcare related quality of life in these patients [6]. The goal of this chapter is to review the contemporary treatment options for the management of urinary incontinence.

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SUI

SUI is experienced by approximately 35% of women >18 in the US [4, 5]. Fifty percent of women reporting urinary incontinence, report SUI. The main risk factors for developing SUI include parity, obesity and increased age [7]. It is more commonly seen in non-Hispanic, white women and is worsened with chronic medical conditions such as asthma, diabetes and physical inactivity [7–9]. Briefly, we will review the diagnosis and contemporary treatment options for SUI.

Diagnosis

SUI can be broken down into two subcategories: midurethral hypermobility or intrinsic sphincter deficiency (ISD). Midurethral hypermobility results in a lack of support of the urethral sphincter which does not allow it to close during moments of high intraabdominal pressure [10]. This can be diagnosed by performing a Q-tip test in which a cotton swab is placed in the urethra and the patient is asked to strain. If there is greater than a 30-degree change from the original position of the cotton swab, hypermobility is present. In contrast, ISD is a failure of the sphincter mechanism of the urethra to function without the presences of hypermobility. Difficulties arise more often in management of ISD than hypermobility [11].

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If urodynamics is done and the urethral pressure profile (UPP) is obtained, ISD can be diagnosed if the maximal urethral closing pressure (MUCP) is below 20 cm H_2O. To date, there is not a cut-off point of the MUCP which is a predictor for success with surgical management [12, 13]. Valsalva leak point pressure (VLPP) measures the intraabdominal or intravesical pressure required to overcome urethral resistance ultimately leading to urinary incontinence. McGuire described that VLPP <60 was often associated with ISD [14]. It is uncertain what the clinical significance is by distinguishing between the two different forms of SUI.

It is important to obtain a thorough history and physical exam when evaluating a patient with SUI. In history taking, it is crucial to assess if there are components of UUI associated with leakage and which symptoms are predominant as 20–36% of patients experience mixed urinary incontinence (MUI) [15]. Supplemental information may be obtained via a voiding diary, imaging, cystoscopy or urodynamics depending on the clinician's index of suspicion.

A thorough physical exam is necessary to support the medical history. Inspection of the external genitals for signs of pelvic organ prolapse, vaginal atrophy, urethral hypermobility, and abnormalities in the urethra (patulous, prolapse etc.) is a crucial part of patient assessment [16]. Additionally, SUI should be confirmed with a negative Marshall/Booney test (urine leakage on straining or coughing with a moderately filled bladder.) This test can be done in supine position and standing if leakage is not visualized in supine position.

Pelvic organ prolapse is an essential part of the physical exam as it may influence the treatment plan. There are several ways to quantify the degree and location of prolapse with the Pelvic Organ Qualification score (POP-Q) being one of the most common tools used [16]. This scoring system assesses the level of anterior, posterior and apical prolapse as it relates to the hymenal ring. If there is concomitant anterior prolapse or significant apical prolapse, assessing SUI with reduction of prolapse should be done. This can be done with manual reduction or with use of a pessary.

As an adjunct to the history and physical exam, pad weight testing and voiding diaries can offer valuable information though is only obtained by <10% of urologist evaluating patients for SUI. While patients are more compliant with shorter testing periods (1-hour for pad test), the longer the testing (48–72 h), the more reproducible the results [17]. Validated questionnaires can be another source of supplemental information.

Urodynamics (UDS) seemed to be commonly performed before surgery for SUI without much evidence supporting its use. Nager et al. performed a study randomly assigning women to undergo office evaluation with UDS versus office evaluation only in women with uncomplicated SUI. They found treatment success at 1 year was 76.9% in the UDS testing group versus 77.2% in the evaluation only group. They concluded that in women with uncomplicated, demonstrable SUI, office examination alone was not inferior to evaluation with UDS [18].

Management

Non-Invasive Management of SUI

Management options for SUI range widely from conservative to invasive. Treatment options include physical therapy, weight loss, vaginal estrogen cream, urethral inserts, pessary, periurethral bulking, midurethral sling, burch colposuspension, and autologous pubovaginal sling.

As stated earlier in the chapter, obesity is significantly associated with SUI [7, 19]. Subak and associates demonstrated that 8.0% weight loss had a significant impact on decreasing SUI episodes in obese women in comparison to women who did not lose weight [6]. Given these findings, lifestyle modification aimed at weight loss is recommended in obese patients as an initial treatment option for SUI [20].

It stands to reason that a decrease in fluid intake will result in decreased urine production and thus a decrease in volume or overall incontinence episodes however no clinical trials have confirmed the effect of fluid management on SUI [21]. It is recommended that patients maintain fluid hydration.

Pelvic floor physical therapy (PFPT) is often recommended as a first line treatment for patients with SUI. The oldest form of PFPT for SUI is kegel exercises consisting of sets of 8–12 contractions of the pelvic floor sustained for 10 s. This should be repeated multiple times per day for 4–5 months to assess efficacy [22]. Several studies have looked at the efficacy of PFPT on SUI. Dumoulin et al. after reviewing the outcomes of 18 studies found that following PFPT, 56% of patients are cured in the treatment group compared to 6% in the non-treatment group [23].Long term follow up is not available on PFPT and the rate of adherence to treatment has been demonstrated to rage from 10 to 70% [24]. A randomized control trial in which women were randomized between PFPT and midurethral sling surgery (MUS) showed that initial surgical treatment gave significantly higher objective (77% vs. 59%) and subjective cure rate (85% vs. 53%) at one-year follow-up. When patients crossed over to the MUS group, no additional benefit was found from undergoing PFPT beforehand [25]. Initial treatment with PFPT is a Grade A recommendation by the European Urologic Association (EUA) as a first line therapy given its non-invasive nature, safety and cost-effectiveness [20].

While some studies have demonstrated that vaginal estrace cream or oral conjugated estrogen can result in improvement or cure of SUI in postmenopausal women, the data is lacking and recent publications indicate no difference in improvement between placebo and estrogen supplementation groups.

Several urethral inserts exist on the market as a non-surgical alternative to management of SUI. The Reliance Insert was the first FDA approved urethral insert designed to function as an occlusive device. It is composed of an external meatal tab, a rigid stem and a proximal balloon inflated with 3 cc. Varying sizes are available ranging from 3.0 to 5.0 cm. It is not a reusable device and must be changed after voiding [26]. Statskin et al. studied this device in 135 women with SUI or mixed incontinence and found that at 4 months 80–95% of patients reported complete dryness to significant improvement of their symptoms [27]. Similarly Miller and associates reported at 1 year follow up 79% of women were completely dry and an addition 16% reported significant improvement [28].These types of devices are intended for use in highly motivated patients who do not desire surgery, have good manual dexterity and are tolerate of a urethral device. Other urethral inserts include the Viva Plug, FemSoft Insert, Relax, Influence and AutoCath® 100 [26]. The latter three are valve activated prosthetics that require surgeon application and exchange every month to several months.

Commercially available vaginal devices such as the Impressa® is another conservative treatment source for SUI that can be used in patients desiring control of incontinence without medical or surgical intervention. Unfortunately, too few studies have been done to assess the efficacy of this device [29].

Pessaries are classically used for the management of pelvic organ prolapse (POP) however certain pessaries are designed with the intent of reducing POP and controlling SUI. Ring pessaries with knobs and Mar-land pessaries are used for concomitant management of Stage I/II prolapse and SUI. They are designed to decrease urethral hypermobility by compressing the urethra against the posterior pubic symphysis. The contraindications to using these devices include pelvic/vaginal infection, vaginal ulcerations and poor patient compliance [30]. The Uresta® is a bell shaped pessary recently introduced into the market. A short term randomized control trial was done assessing the efficacy of the device. A total of 36 patients were enrolled into the study with 18 patients in each arm. Treatment success was defined as ≥50% decrease in pad weight following placement of device. Success was achieved in 66.7% of the Uresta® group and 22.2% of the placebo group, ($p = 0.01$) [29]. A follow up study showed that at 12 months, 76% of participants successfully fitted in the treatment group continued use, while 50% of overall fitted participants continued use [31].

Minimally Invasive Management of SUI

Minimally invasive procedural treatment options include urethral bulking agents (UBAs). UBAs are injectable natural or synthetic substances that are

injected to the periurethral space for treatment of bothersome SUI. They work by increasing the resistance of the urethra and increasing urethral support [32]. Most bulking agents consist of a biodegradable carrier gel which is degraded by the body allowing scar tissue to form around the particles yielding a lasting effect. The effect diminishes over time, however, due to the degradation of the gel. Though minimally invasive, efficacy has not been shown to be great with UBAs. There is a lower success rate compared to surgical procedures and their long term effect is limited often requiring reinjections [33, 34]. Complications associated with UBAs include bleeding, tissue migration, allergic reactions and formation of sterile abscess [34]. UBAs can also be mistaken on cross sectional imaging for bladder stones. No bulking agents has been proven to be superior to another [33]. The preferred location for injection is the mid urethra [35]. Although widely skewed ranging from 10 to 83%, this can be a valuable treatment options for older patients and patients who are not good surgical candidates [36, 37].

Stem cell injection therapy has been considered for the potential regenerative repair of ISD. Scientist postulate that autologous stem cell transplantation may persist longer than injected foreign substances given that the cell based therapy will not cause an immunogenic or allergic reaction [38]. A recent study published by Carr et al. demonstrated the injection of high dose autologous muscle derived cells for 12 or more months resulted in a >50% improvement in pad weight and >50% reduction in diary reported stress leaks. No major treatment related adverse events were reported in this study [39]. This is still largely under investigation but provides an interesting concept and shows promise for the management of SUI in the future.

Surgical Management of SUI

Colposuspension

Surgical management of SUI should be considered after failure of conservative and minimally invasive options have been exhausted or as a primary treatment option once an informed discussion is held between the patient and provider. Traditional surgical treatment options consisted of Marshall-Marchetti-Krantz (MMK), Burch colposuspension and the pubovaginal sling modified and improved by McGuire in the late 1970s [40]. In the late 1990s the synthetic midurethral sling (MUS) was introduced into the market radically changing the treatment of SUI. Since then, the mini-sling and single incision sling have been introduced into the market.

The MMK procedure is a bladder neck colposuspension designed to stabilize the urethra and reposition the bladder neck and proximal urethral intra-abdominally restoring original anatomy using absorbable or non-absorbable suture to tack the aforementioned tissue to the periosteum of the pubic bone. This was first described in 1949 [41]. Complications following this procedure were noted in 20% of patients and included bladder neck obstruction, worsening SUI and osteitis pubis occurring in 0.9–3.2% of patients [42]. These results lead to modification of the procedure and development of the Burch colposuspension.

The Burch colposuspension first described in 1961, the paravaginal fascia is attached to coopers ligament in lieu of the pubic symphysis. Cure rates using this procedure approach 70–90% with the effects diminishing down to 85% at 1 year and 70% at 5-year follow-up [43].

Pubovaginal Sling

The pubovaginal sling has undergone many iterations with the most accepted technique described by McGuire in 1970 [40]. Traditionally, it was not considered a first line treatment, but an option after treatment failure of colposuspension or MUS. It is now considered a treatment option for index SUI patients. Materials for PVS can be autologous, allograft, xenograft or synthetic. Fascia lata and rectus fascia are the most common autologous materials used and are typically 8 cm × 2 cm in size. The graft material is placed at the bladder neck, in contrast to the mid-urethra. Tensioning of the sling is clinician dependent, however the general rule is to allow a two-fingerbreath space between the suture and the fascia when tensioning [44]. Cystourethroscopy is recommended following passing trocars and sling placement to assess

for bladder perforation. The literature suggests a cure rate of 46–97% in patients undergoing autologous fascia slings [43]. It is unclear what the cure rates are for non-autologous PVS. Several studies suggest that PVS and Burch colposuspension have similar cure rates [45]. Schimpf et al. showed evidence to the contrary suggesting PVS had a superior cure rate compared to Burch colposuspension [46]. Short term complications include wound infection, seroma, hematoma and urinary retention. Long term complications associated with PVS include sling erosion or extrusion, followed by de novo urgency and UUI.

Midurethral Sling

The goal of the midurethral sling is for it to be placed at the highest pressure part of the urethra to mimic the function of the pubourethral ligament [47]. Most tapes consist of polyprolene in contrast to the polyethylene and polytetrafluoroethylene materials which were associated with erosion. MUS are macropourous with pore size of >75 μm resulting in better incorporation into native tissue.

In comparison to the PVS, operating time tends to be shorter for this procedure accompanied by a shorter recovery with similar clinal outcomes. Documented cure rates of retropubic tape range from 71 to 97% at 1 year and 51 to 88% at the 5- year mark [48].

Complications following this procedure include mesh erosion, extrusion, urinary retention and perforation of the bladder. The most common intraoperative complication is bladder perforation (6.6%) Cystourethroscopy is required following MUS placement to assess for bladder perforation. Post operatively, retention was noted at 16.6% [49].

Transobturator tapes (TOT) were created in an attempt to decrease rates of bladder perforation and vascular injury associated with retropubic tape. The TOT is midurethral and tension free similar to retropubic tape however the arms of the sling are fixed in the obturator foramen. The subjective cure rate following TOT is 62–98% at one year follow-up and 43–92% at >5 years [48]. Groin pain and sexual dysfunction are more commonly seen after TOT [50].

Following failure of any type of MUS, it is recommended that if mesh is to be used again, a retropubic route be done [51].

Transobturator Versus Retropubic MUS

Richter et all compared the transobturator approach to the retropubic approach and demonstrated an objective equivalence in treatment outcomes. Subjectively, there was a slight increase in efficacy with the retropubic sling (62.2%) versus the transobturator (55.8%). The complication seen more commonly in the retropubic group was voiding dysfunction while neurologic symptoms were more often experienced in transobturator group neurologic symptoms [52].

Single Incision Slings

Single Incision Mini Slings (SIMS) were introduced into the market in 2006 to provide a less invasive, less morbid means of managing SUI. This required no blind passage and one single incision to the midline of the vagina. Initial review of efficacy demonstrated clear inferiority to the traditional MUS. Recent reviews of newer products have demonstrated similar efficacy between SIMS and MUS [53]. An adjustable SIMS which was introduced in to the market in 2009. This allows for anchoring of one arm of the sling while adjusting tension and securing the tape only after adequate tensioning is achieved. SIMS-adjust was compared to TVT-O and TVT and no significant difference in cure rates was appreciated [54]. The main advantage for SIMS over TVT-O/TVT was the shorter operative time. Long term outcomes are still not known and not enough data exists to reliably compare SIMS to MUS [55].

Urethral Compression

The artificial urinary sphincter (AUS) may be considered for management of SUI in patients who have failed all other treatments and should be considered a last resort. This is a three-piece device that has an intraabdominal pressure regulating balloon, a urethral cuff and a labial pump. It is estimated that 1% of women with refractory SUI have AUSs implanted. There are many different approaches to placement of the AUS including

transvaginal, abdominal/retropubic, laparoscopic, and robotic. The most commonly accepted approach is the retropubic approach [56]. The overall cure rates are reported at 76–89%. One long term study showed that after 20 years, 32.4% of women still had durable success [57]. Explant of the device can be necessary secondary to infection, erosion or device failure [58, 59]. Urethral atrophy does occur frequently in male patients, however there is lack of data on the incidence of atrophy in female patients. If this is a surgical consideration for a patient, they should be referred to a specialized center for placement.

Several European countries have adopted the use of external compression devices. The Adjustable Continence Therapy (ACT®) was designed as a minimally invasive mechanisms to manage refractory SUI in patients with ISD who were previously operated on while avoiding the retropubic space and abdominal cavity. Its major advantage is the ability to adjust the periurethral balloon fluid to fine tune the balance between incontinence and obstruction [60]. The ACT kit contains two silicone elastomer balloons connected to a titanium port along with a syringe and a puncture needle used to inflate the device. Balloons are placed alongside the bladder neck at the 5–7 o'clock position under fluoroscopy and flexible cystoscopy. The balloons are then filled with a radiopaque solution to 0.6 mL. A urethral catheter is left in place for 12 h. This is done as an outpatient procedure. The balloon can be filled 0.6 mL at a time until maximum efficacy is achieved with a maximum fill of 7 mL [58, 60, 61]. A single center retrospective trial focusing on patients with ISD compared ACT® with the AUS in 61 women, 25 undergoing ACT and 36 undergoing AUS. Those in the ACT group had prior history of pelvic radiation, more comorbidities and were older. Overall, the operative time and length of hospitalization were lower in the ACT group ($P < 0.001$). A higher rate of intraoperative complications were noted in the AUS group (47% vs. 8%, $p < 0.001$). The rate of postoperative complications did not differ between the two groups. Two members of the ACT group required explant due to vaginal erosion associated with device infection in comparison to seven explants required in the AUS group. The decrease in stress urinary incontinence subscore was significantly greater in the AUS group (−7.6 vs. −3.2; $p < 0.01$) as was the decrease in mean number of pads per 2 h (−4.6 vs. −2.3; $p = 0.002$). The patient global impression of improvement was better in the AUS group ($p < 0.001$). While the AUA does not mention use of the ACT in their treatment algorithm for complicated SUI, the EUA considers that it might play a role, however recommend a secondary sling, autologous PVS or colposuspension as first line in complex patients [20, 62].

Urgency Urinary Incontinence

Urgency urinary incontinence (UUI) impacts 17% of women over the age of 45 in the US and 27% of all women over the age of 75 in the US [63]. UUI can have a significant impact on quality of life with the clinical manifestations depending on the severity of detrusor instability, integrity of the external sphincter and patients functional status [64]. The vast majority of treatment options are aimed at management of detrusor instability. Much like SUI, UUI can be managed conservatively, followed by more invasive measures. We will review the diagnosis and contemporary treatment options for the management of UUI.

Diagnosis

As with diagnosis of most medical conditions, a thorough history and physical exam in a crucial component. History taking should encompass past medical history, surgical history, gynecologic history, duration of symptoms, frequency of symptoms, and current medications. Providers may obtain a post void residual to rule out overflow incontinence however this is not mandated and is a Grade B/C recommendation. A pelvic exam encompassing a perineal and rectal exam is necessary. Providers should also assess for pelvic floor muscle strength. Voiding diaries can also be used to assess storage and filling and to determine functional bladder capacity [20]. The presence of

an active urinary tract infection may worsen urinary incontinence, thus a urinalysis is recommended ± urine culture if indicated [65]. Urodynamics may influence clinical decision making, however the evidence suggests that it does not change treatment outcomes therefore is left to the discretion of the treating clinician [66]. Little evidence exists to suggest that imaging contributes to improved clinic outcomes thus routine imaging is not recommended (Grade A) [20].

There is weak evidence suggesting that taking alpha-blockers in women may precipitate or worsen urinary incontinence [67]. Additionally, systemic estrogen doubles the prevalence of UI in previously continent women, and worsens UI in 30% of women [68]. Diuretics given to elderly patients do not worsen or cause UI however central nervous system agents, may cause UI [69, 70].

Minimally Invasive Management UUI

Unlike pelvic floor physical therapy in SUI, there is little evidence to suggest that PFPT improves UUI in patients with primary UUI or mixed incontinence. When comparing PFPT to use of anticholinergics, there was no benefit to PFPT alone or in conjunction with oral agents [71].

Pelvic floor physical therapy addresses both the external sphincter and, theoretically, detrusor instability. Clinicians suggest the use of "quick-flicks" to inhibit bladder contractions when they start addressing the detrusor instability component of UUI. The quick flick exercise involves taking slow deep breaths, while contracting the pelvic floor muscles rapidly 3–5 times when the sudden urge to void is felt. This has been found to suppress the urge to void [72]. Additionally, kegel exercises aimed at pelvic floor strengthening assist in improving external sphincter resistance during involuntary bladder contractions [64].

Medical Management UUI

Antimuscarinics are widely used for the management of overactive bladder and UI aimed primary at decreasing detrusor activity via cholinergic blockade. Acetylcholine (ACh) is released from cholinergic nerves and stimulates muscarinic receptors. Five subtypes of muscarinic receptors exist and two, M_2 and M_3, have a predominance in the bladder. Stimulation of these receptors result in detrusor contraction [73–75]. Several formulations of anticholinergic medications exist with two of the most commonly used anticholinergics being Tolterodine and Oxybutynin.

Oxybutynin is offered in several different formulations and can be distributed orally, transdermal, rectally or intravesically. Oral oxybutynin is distributed in two forms: Controlled release (CR) and immediate release (IR). Studies have found that both forms lead to a reduction in 24-h incontinence episodes by 84–88% in the controlled and immediate release treatment groups, respectively. In either regimen, total continence was found to be achieved in 40% of patients. Dry mouth, however is more frequently reported in the IR group (87%) than the CR group (68) $p = 0.04$ [76].

A systematic review of the literature performed by Harvey et al. compared tolterodine 1–2 mg twice per day to oxybutynin 2.5–5 mg three times per day. Both drugs were found to have similar rates of decreased micturition in 24-h period. Oxybutynin, however, was found to have a marginally decreased rate of incontinence episodes over 24 h and an increased mean voided volume per micturition. The study noted that fewer patients experienced dry mouth with the use of tolterodine. While there was a statistically significant increase in improvement seen in the oxybutynin group, this was not clinically relevant and patients overall tolerated tolterodine better [77].

Potential adverse effects of this drug class include urinary retention, constipation, pruritus, erythema, dry mouth and blurred vision. The central nervous system (CNS) is largely unaffected by anticholinergic agents, however, in elderly patients, due to the increase in the blood brain barrier, they should be prescribed with caution [78]. The M1 selectivity of oxybutynin together with its high permeability for the BBB results in higher CNS effects than quaternary amines such as trospium and non-selective anthicholinergics such as tolterodine [79, 80].

Several studies have been published addressing patient adherence to anticholinergics. Medical claims studies have shown that within 30 days of prescription, 43–83% of patients discontinue use of medications. These studies also show that over half of patients never refill their medications. This low level of compliance lead clinicians and researchers to development of treatments with fewer side effects and similar or improve efficacy.

β3 adrenergic receptors are expressed on nerve fibers in the mucosa and muscular layers of the bladder and are predominant in the human detrusor muscle. They are activated by adrenergic stimulation resulting in detrusor relaxation [81, 82]. This knowledge lead to the development of the β3 agonist mirabegron for the management of frequency, urgency and UUI.

In a pooled analysis of three clinical trials, Chapple et al. compared placebo to mirabegron 50 mg and 100 mg. Compared to 59.6% of patients in the placebo group, 69.5% of patients in the 50 mg group and 70.5% of patients in the 100 mg group reported ≥50% reduction in incontinence from baseline ($p \leq 0.001$) [83].

Studies have reported the adverse events associated with mirabegron treatment, however the reported rate of serious events is low. The DRAGON investigator group found that the incidence of treatment related adverse events in patients receiving mirabegron doses ranging from 25 to 100 mg was comparable to placebo with serious adverse effects reported at a rate of <2% [84]. HR was found to increase in a dose dependent fashion and only in patients receiving mirabegron doses 100 mg or higher. Special attention should be noted when administering this drug to patients with chronic kidney disease and advanced liver disease. The accepted dose recommendations in the US are 25 mg and 50 mg based on balance between efficacy and side effect profile.

While monotherapy with either drug is efficacious in patients with OAB, combination therapy provides increased improvement in symptoms. Side effects are appreciated in all groups with no greater side effects noted in the combination group compared to mirabegron alone [85, 86].

Treatment compliance to mirabegron in comparison to anticholinergics differs depending on patient experience. In patients with ≥1 prior treatment for OAB at 12 months compliance was noted in 39% in mirabegron group vs. 14–35% in the anticholinergics group. In treatment naïve patients, adherence at 12 months was 30% in mirabegron group, vs. 14–21% anticholinergic group [87]. Anticholinergics and mirabegron appear to have similar efficacy in the treatment and management of OAB. Overall, there is a higher reporting of AEs in the anticholinergic groups.

Burglo et al. assessed whether combining drug therapy with behavioral training compared to drug therapy alone would achieve a sustainable reduction in incontinence after discontinuation of medications and found that the addition of behavioral training to drug therapy reduced incontinence frequency during treatment but this was not sustained following discontinuation. This suggests combination therapy has a beneficial impact on patients. Seventy percent of patients who received combination therapy vs. 58% had a reduction in UUI episodes at ten weeks [88].

Third Line therapy UUI

Posterior Tibial Nerve Stimulation and Sacral Neuromodulation

While there are many minimally invasive measures to address OAB and UUI, patients who are treatment refractory may elect to proceed with third line treatment.

Bladder innervation is controlled by the sympathetic and parasympathetic nervous systems. Under normal circumstances, excitation of the parasympathetic system results in effective bladder wall contraction and complete bladder emptying. Conversely, excitation of the sympathetic system enables bladder wall relaxation and subsequent storage of urine via activation of β -adrenoceptors.

Posterior tibial nerve stimulation (PTNS) is another treatment option for UUI. The posterior tibial nerve has both motor and sensory function and arises from the same spinal segment as the

nerves which innervate the bladder and pelvic floor [72]. The stimulation of the posterior tibial nerve results in retrograde stimulation of the sacral nerve plexus with neuromodulatory effects that can result in improvement in bladder overactivity. The exact mechanism of action of neuromodulation is unclear. In a randomized control trial (RCT) comparing PTNS to sham therapy, 54.5% of patients reported moderate to marked improvement from baseline compared to 20.9% of sham subjects. ($p < 0.001$) (Peters) Another randomized controlled trial comparing the anticholinergic tolteridine to PTNS, 79.5% of patients undergoing PTNS and 54.8% of patients undergoing oral treatment considered themselves cured or improved ($p = 0.01$). The study found that both groups experienced similar improvements in UI, urgency, frequency and quality of life [89].

Sacral neuromodulation (SNM)is also considered a third-line therapy for patients with overactive bladder [62]. InterStim® therapy was introduced after approval by the FDA in 1997 for the use of treatment of refractory UUI. It is a permanent implanted neuromodulator device that is placed via the sacral foramen along the sacral nerve, typically S-3. It is a staged procedure with the first stage attaching the lead to a temporary test stimulator and the second stage attaching the lead to an implanted pulse generator if patients achieve a >50% improvement in their symptoms during the first stage. The InSite study was a multicenter, prospective, RCT comparing standard medical treatment to SNM. The study found that at 6 months, OAB therapeutic success was 49% in the medical therapy group and 76% in SNM group ($p = 0.002$). The SNM group also showed significant improvement in quality of life compared to medical therapy ($p < 0.001$). Adverse events were noted in 30.5% of SNM group and 27.3% of medical therapy group demonstrating the superiority of SNM to medical management of OAB [89].

Several studies have been published reporting the rate of adverse events following SNM. Seigel et al. report a revision rate of 32% with 33% of patients requiring revision for battery replacement. He also reports a permanent removal rate of 13% compared to the 8.6% rate reported in the Rosetta trial [90]. While the Rosetta trial reports that 58% of patients will require re-programming at 24 month follow-up, they only report a revision rate of 3%. The authors postulate that this stark contrast may be secondary to improved clinical technique with lead placement. Following SNM, the Rosetta trial reports a UTI rate of 11%.

OnabotulinumtoxinA (Botox A®) is a neurotoxic protein produced by the bacterium Clostridium botulinum. It functions by preventing the release of acetylcholine neurotransmitter from the axon endings at the neuromuscular junction causing flaccid paralysis [91]. When used in the bladder, this causes detrusor relaxation. It was first described for use in patients with detrusor hyperreflexia following spinal cord injury in 2000. Patients were injected with 200–300 units of OnabotulinumtoxinA. Nineteen out of 21 patients were evaluated 6 weeks following injection. Of those patients, 89% were completely continent, the patients that were found to have persistent incontinence received the 200 unit dose. There was an overall decrease in mean voiding pressures ($p < 0.016$) and an increase in cystometric bladder capacity 296.3 ± 145.2 to 480.5 ± 134.1 ($p < 0.016$) The mean PVR increased from 261.8 ± 241.3 to 490.5 ± 204.8 ($p < 0.016$). Duration of treatment lasted for at least 9 months following initial injection. Safe and effective treatment was proven in SCI patients with incontinence refractory to anticholinergics with a dose of 300 units providing the best chance at counteracting incontinence episodes. Three patients with tetraplegia experienced autonomic dysreflexia and were responsive to treatment [92].

The use and efficacy of this drug have been studied in the neurogenic and idiopathic OAB group. A double-blind, placebo-controlled, randomized dose ranging trial was done assessing safety and efficacy of Botox A® on idiopathic OAB patients with UUI experienced eight or more times per week and eight or more micturitions daily at baseline. Subjects received doses ranging from 50 to 300 units or placebo. The primary end-point was determining improvement in weekly urinary incontinence episodes. Durable efficacy was found in all patients using doses of

100 units or higher. Efficacy was noted as early as week 2. Minimal additional benefit was seen in patients treated with doses greater than 150 U. A dose dependent increase in PVR was noted with the greatest increase in PVR at the 200 U dose, with peak PVR reached at 2 weeks post treatment. Patients with PVRs >200 cc were associated with increased risk of UTI and need for CIC. The authors conclude that 100 U may be the recommended starting dose for idiopathic patients where they may see the ideal balance between efficacy and side effects [93]. Patients with neurogenic detrusor overactivity have chronic conditions requiring life-long treatment. Kennelly and associates demonstrated that long-term use of Botox A® in this patient population is both efficacious and well tolerated when treated with 200 units of onobotulinumtoxinA [94].

The rate of urinary retention following Botox injection is highly variable largely due to how retention is defined by clinicians, the patient population and units administered. Osborne et al. sought to determine the true rate of post-Botox urinary retention defining retention as any patient started on daily intermittent catheterization or had an indwelling catheter placed following Botox injection [95]. In this retrospective study with a median follow up of 12.5 months, patients were excluded if they had pre-operative PVR >200, history of neurogenic bladder or neurologic disorder known to affect voiding, history of urinary retention, had less than 4-week follow-up following Botox injection, received Botox at an outside institution and received more than 200 units during their first treatment. Seventy-six percent of the patients were female with a mean age of 64 ± 13.2 years. Post-operatively, 35% of patients experienced urinary retention requiring catheterization for a mean duration of 16 weeks. They found that patients who received 100 units and had preoperative PVR of <100 mL had a 21% rate of retention. The authors also reported a postoperative urinary tract infection rate of 16% and an efficacy rate of 74%. This is in contrast to the Rosetta trial 6-month follow-up which reported a urinary retention rate of 8% with the median duration of catheterization being 37 days. Additionally, they reported a urinary retention rate of 35% with 39% of patients who did have an infection having multiple infections within a 6-month follow-up period [90].

Botox Versus SNM

Botox and SNM are well accepted as third line therapy options for refractory OAB [62]. The Rosetta trial was a randomized control trial comparing the two treatment options and evaluating for efficacy. The study defined success as ≥50% improvement in symptoms and found that SNM and Botox 200 Units had similar rates of efficacy at 84 and 83%, respectively at two-year follow-up [91]. No difference was found in the mean episodes of urgency urinary incontinence episodes (−3.88 vs. −3.50; $p = 0.2$). While the 6 month follow up showed an increase in cure rate in the Botox group versus the SNM group, at 24 months both groups had a cure rate approaching 5%. The Botox group did report a higher rate of treatment satisfaction ($p < 0.001$) and treatment endorsement ($p < 0.002$). Interestingly, while the Botox group had a higher rate of urinary retention following a second treatment (6%), this rate is lower than that reported in the literature (0–30%). Additionally, patients undergoing the 200 Unit Botox treatment had an median interval from first and second injection of 350 days suggesting a higher dose may correspond to longer duration of efficacy. This study confers that both treatment options are effective and sustainable in the management of OAB.

Fourth Line Therapy UUI

Augmentation Cystoplasty

While most patients with overactive bladder and associated urinary incontinence may be managed with the treatment measures detailed above, a small subset of patients are refractory. In patients with low compliance, low capacity, unstable bladders who fail third line treatments, augmentation cystoplasty (AC) may be considered.

This technique was first described in 1888 by Foggi and Tizzoni and later gained popularity in

the 1950s with Couvelaire [96, 97]. Traditionally ileum, stomach, cecum, ascending colon and sigmoid colon have all been used in differing forms to augment the bladder [98]. Other tissues have been used for augmentation however are associated with a high failure or complication rate. Synthetic materials including Teflon, polyvinyl sponge, silastic and collagen have also been used without great success rates and are associated with complications including stone formation, UTI's, contracture and fistulae [99, 100].

Contraindications to augmentation cystoplasty include patient unwillingness to intermittent catheterize, chronic bowel disease, exposure to radiation with result compromised bowel segments, or short bowel syndrome. In patients with compromised bowel, gastrocystoplasty or autoaugmentation with bladder may be considered. Autoaugmentation has not had long term follow-up and has been reported to have moderate success ranging from 50% in neurogenic detrusor hyperreflexia to 70% in idiopathic DO [101]. While renal insufficiency is not a contraindication, it is a relative contraindication and should be considered as patients who undergo augmentation cystoplasty may have slightly worsening renal function following the procedure [102–104].

Success rates following AC are higher in neurogenic patients (92%) than they are in idiopathic detrusor overactivity patients (53–58%). There is a wide failure rate ranging from 5to 42% [105–107].

AC is a major abdominal surgery and as such has significant short-term complications including wound infections, prolonged ileus, urine leak, small bowel obstruction, hemorrhage VP shunt infections and common complications seen with all major abdominal surgeries. Long term complications include, but are not limited to, metabolic disturbance, stone formation, renal impairment, bacteriuria, need for intermittent catheterization, perforation, vesicoureteric reflux, and nighttime incontinence. Malignancy has been reported in up to 30 patients to date following AC [108].

In rare instances, cystectomy and urinary diversion can be offered in patients with severe, refractory, complicated OAB with no other treatment alternatives [62].

Mixed Incontinence

Mixed urinary incontinence, defined by a combination of involuntary leakage of urine secondary to urgency and exertion, occurs in 30% of all women who report incontinence [109–112]. Accurately defining the cause and pathophysiology of MUI is difficult resulting in challenges in patient management [113]. Historically, management of urgency component was done primarily, followed by potential surgical management of SUI component if conservative measures failed [114]. Management of the SUI component primarily has the potential of treating both issues or causing de novo or worsening lower urinary tract symptoms. Ultimately the treatment plan is designed based on the degree of bother of each individual component and shared decision making.

Diagnosis

The diagnosis of MUI relies on clinical judgment as well as diagnostic tools. UDS should be considered given the complex nature of these patients however, it should be noted that not all patients who report UUI in their day-to-day life will experience detrusor overactivity with or without leakage on UDS [115]. Detection of DO on UDS in patients who report UUI can be as low as 8%. UDS may be used as a tool but should be supplemented with patient history, physical exam, validated questionnaires and voiding diaries.

Non-Surgical Treatment of MUI

Some effective first-line treatment options for MUI include behavioral modification, PFPT and weight loss. Timed voiding, double voiding and fluid restriction may offer patients with significant improvements in quality of life [113]. PFPT was found to be better than no treatment in a Cochrane review on management of MUI [23]. A study done by Subak et al. demonstrated that weight loss had a significant impact on the number of weekly incontinence episodes with resul-

tant improved patient satisfaction compared to no weight loss [6].

Medical Management of MUI

The Mixed Incontinence Effectiveness Research Investigation Tolterodine (MERIT) trial was a double-blinded, randomized, multicenter control trial which recruited 854 women with MUI to assess the impact on tolterodine ER on MUI. The study found that after eight weeks of treatment while there was no improvement in SUI episodes, there was a statistically significant reduction in UUI episodes compared to placebo (−12.3 vs. −8.0; $p < 0.0001$). Additionally, the tolterodine ER group experienced statistically significant improvements in quality of life domains and overall reported improvement in their bladder condition [116]. Similarly, Dmochowski et al. reported use of 3.9 mg of transdermal oxybutynin in patients with MUI versus placebo resulted in significant improvements in urinary frequency, mean voided volume, quality of life and weekly incontinence episodes [117].

As mentioned above, high quality studies for the impact of estrogen on the management of UUI and SUI is lacking. To date, studies have shown that estrogen supplementation in post-menopausal women for the management of urinary symptoms demonstrates similar outcomes to treatment with placebo [113].

Surgical Management of MUI

Surgical management of MUI can be challenging owing to the complex pathophysiology of the disease process. Traditionally, there were concerns that management of SUI without prior management of UUI could result in worsening or de novo symptoms. Langer et al. reported following colposuspension in women with MUI, DO decreased to 33.3% from 73.3% [118]. Other studies looking at 2-year outcomes give rise to concern that presents of DO at the time of SUI surgery could lead to decreased surgical efficacy as patients with pre-existing DO have a cure rate of 75% compared to 95% appreciated in women with pure SUI [119]. Studies have also shown that 45–69% of patients experience resolution of UUI following pubovaginal sling [120–123]. Caution should be taken when interpreting these studies given the variation in defining "cure". Similar studies have found some improvement in DO in women with MUI undergoing MUS placement with 60% subjective cure rates reported at 4-years by Holmgren at al compared to 85% subjective cure rates in patients with pure SUI [124].

When assessing how anti-incontinence procedures measure against each other in women with MUI, Gamble et al. found that women who underwent bladder neck sling had the lowest rate of post procedural, UDS proven, DO in comparison to those women undergoing transobturator sling and retropubic sling [125].

Ultimately, the management of MUI is complex and can be approached in many different ways. It is crucial to carefully evaluate the patient and have an informed discussion regarding possible treatment options and outcomes with patients. Initial management may be conservative, surgical or medical depending on patient presentation and clinical factors.

Future Potential Treatment Modalities

There has been a lot of discussion regarding laser treatment of the vaginal epithelium for treatment of genitourinary syndrome of menopause (GSM). GSM encompasses post-menopausal lower urinary tract symptoms including urinary urgency and dysuria. As such, several studies have looked at the effect of vaginal laser therapy on lower urinary tract symptoms including stress urinary incontinence. Gambacciani et al. conducted a prospective, longitudinal study in postmenopausal women suffering from GSM. The study identified 19 post-menopausal women who had mild to moderate SUI. Participants were treated with vaginal erbium laser (VEL) with a wavelength of 2940 nm once monthly for three months. The control group was treated with vaginal gel containing estriol 50 mg twice weekly for

three months. Treatment with VEL resulted in significant improvement in ICIQ-SF scores from baseline ($p < 0.01$) up to 24 weeks from initial treatment [126]. Fistonic et al. similarly used the Er:YAG laser at a wavelength of 2940 in women with SUI and found a statistical and clinically significant improvement in ICIQ-UI questionnaires compared to baseline. Several devices have been marketed for treatment of urinary incontinence however, the vaginal laser is not specifically indicated by the FDA for treatment of urinary incontinence at this time [127].

Urinary incontinence is highly prevalent and has be shown to significantly impact quality of life. Khurt and associates found that UUI impacts quality of life more so than SUI or mixed urinary incontinence [128]. This chapter outlines contemporary treatment options for the management of urinary incontinence.

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Neurogenic Bladder

28

Altaf Mangera

Introduction

The lower urinary tract comprises the bladder, bladder neck and smooth muscle sphincter which are under autonomic control and also the rhabdosphincter which is somatically controlled. This provides a unique function allowing the switch between involuntary storage and voluntary voiding control. There is no agreed definition of a neuropathic bladder but a broad definition would be "lower urinary tract symptoms due to a responsible neurological lesion". Thus a wide range of pathologies may be responsible for the neuropathic bladder. In this chapter, we categorise these lesions according to their influence on lower urinary tract function and then discuss their management.

Neuro-anatomy

It needs to be understood that the bladder spends 99% of its time storing urine in what is called the storage phase. The detrusor muscle component of the bladder is composed of smooth muscle. The urinary sphincter is composed of inner smooth muscle and outer striated muscle components [1, 2]. The urinary sphincter should not be confused with the bladder neck sphincter, which may be absent in some women. In men, it is primarily a genital sphincter with the chief role of preventing retrograde ejaculation [3]. However, it is sufficient to maintain urinary continence on its own.

Storage

During storage the bladder needs to; transmit sensation and appreciation of bladder volume to higher centres, accommodate urine without pressure change i.e. receptive relaxation and maintain continence. The healthy bladder accomplishes this with key spinal reflexes which are influenced by higher centres.

Stretch sensations from the bladder and bladder neck/urethra are transmitted to the spinal cord by the pelvic/hypogastric nerves. Bladder afferent fibres synapse in the dorsal root ganglia of S2-4 and T11-L2. Here, they synapse with interneurons that project to higher centres and to nerves involved in the "**micturition reflex**" which are in the sacral micturition centre. The former travel via a delta fibres to the lateral nucleus of the pontine micturition centre (PMC) and to the peri-aquaductal grey [4]. Quiescent C-fibre afferents are part of the micturition reflex [5]. Bladder afferents containing nitric oxide synthase, glutamate, and a variety of neuropeptides enter the dorsal horn of the spinal cord where second-order neurons project rostrally to

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supraspinal sites including the hypothalamus, thalamus, and pons. The hypothalamus is known to coordinate autonomic activity. The thalamus processes nociceptive information. The pons is specifically involved in micturition [6].

Functional MRI studies have shown that the prefrontal cortex is active during bladder storage signifying its role in inhibition of micturition [7]. Thus during storage the efferent action is to inhibit detrusor contraction via inhibition of the parasympathetic muscarinic nerves and promote **receptive relaxation** via activation of B3 adrenergic sympathetic nerves. The pons is seen as the control centre for this. Stimulation of the dorsolateral pons (designated the urine storage centre) increases sphincteric activity and inhibits bladder contraction. Other brain regions implicated in bladder control include the hypothalamus, central nucleus of the amygdala, bed nucleus stria terminalis, paraventricular nucleus, and locus coeruleus indicating why stress and alertness could affect bladder function [8].

Receptive relaxation is proposed to be a spinal reflex that suppresses intrinsic bladder activity to permit bladder compliance. The sympathetic output also stimulates the alpha adrenergic receptors in the urethra and bladder neck which maintain smooth muscle tone in the bladder outflow thus preserving continence. Throughout storage, with increased filling, the striated sphincter is progressively contracted to maintain continence due to the **guarding reflex** [9]. The neurons innervating the external urethral sphincter and the pelvic floor arise from the anterior horn of S2-4 (eponymously termed Onuf's nucleus) and travel in the pudendal nerve.

Voiding

Successful voiding needs to be voluntary and for the bladder to empty completely. Initiation arises in the PMC and involves input from the periaqueductal gray, inferior frontal gyrus and hypothalamus [10]. Parasympathetic nerves mediate bladder contraction through the M3 and M2 muscarinic receptors via the sacral micturition centre. Detrusor contraction needs to be sufficiently powerful and prolonged to overcome outlet resistance and to ensure near complete bladder emptying. During voiding, co-ordination is required between bladder contraction and sphincter relaxation (by switching off the guarding reflex). The smooth and striated components of the urinary sphincter are relaxed by nitric oxide and alpha adrenoreceptors respectively.

Thus it can be concluded that there are three spinal reflexes under higher centre control. The micturition reflex (parasympathetic S2-4) is inhibited during storage, receptive relaxation (sympathetic T11-L2) and the guarding reflex (parasympathetic S2-4) are active during storage. A reversal is required for voiding. These spinal reflexes are under the control from the pontine micturition centre which in turn is influenced by multiple higher centres.

In predicting the impact of neurological conditions on urinary control, it is helpful to envision a hierarchical scheme divided into suprapontine, pontine, suprasacral, sacral/peripheral and polyneuropathy.

Investigations

It is imperative that a patient with neurogenic bladder is assessed in the context of a detailed neurological history and examination. A neurologist can be invaluable in this context. Having in depth neurological information can be helpful in predicting bladder behaviour, safety of the upper tracts and determining what further urological investigation and long term follow-up is needed. The rectum is analogous to the bladder in its neurological supply and thus a neuropathic bladder is often accompanied by a neuropathic bowel which in turn can reciprocally affect the bladder. Remember the adage "a happy bladder is an empty bladder, but a happier bladder is an empty rectum!" The urologist will also be interested in the neuropathic effect on sexual function and it is worth recognising the patients' mobility and hand function in case intermittent self-catheterisation needs to be considered in the management algorithm.

Imaging

Imaging of the neuropathic bladder necessitates imaging of the upper tracts when they are deemed at risk of high pressures; and hydronephrosis is most often easily noted on ultrasound scanning. This is relatively non-invasive and imparts no radiation and therefore has become the investigation of choice for serial assessment of the upper tracts. Due to the long term risk of renal impairment in patients at risk of high bladder pressures annual or at least biennial ultrasound assessment is recommended.

Renal scans may occasionally be required to differentiate between obstruction and a dilated renal drainage system. A diuretic renogram may be useful in this regard and in some circumstances if this is equivocal, a Whitaker test (upper tract urodynamic study) is also needed. Due to the higher than average incidence of stone formation in this cohort of patients, a plain KUB X-ray and/or CT scan may be warranted when required for monitoring and planning treatment for urinary tract calculi. The regular routine use of X-rays in patients with a neuropathic bladder, to screen for urinary tract stones, is no longer advocated due to the risks posed by the cumulative effects of radiation.

Video-urodynamics

Video-urodynamics is also crucial in investigating structural and functional abnormalities. Vesico-ureteric reflux may transfer the high pressures associated with the neuropathic bladder back to the kidneys and affect their drainage and function. In this scenario the reflux may also absorb the pressure rise in the bladder and this would not become apparent on the cytometric pressure recording and therefore concomitant cystography is obligatory to come to a correct conclusion in such patients. Video fluoroscopy also provides information on the level of obstruction, whether it be at the bladder neck, external sphincter, internal sphincter or urethra.

Fill rate is often reduced to 20 mL/min for patients with a neuropathic bladder in order not to falsely stimulate poor compliance or a detrusor contraction. Sensations may be absent and the voiding phase may be non-existent. Classic patterns such as seen in detrusor sphincter dyssynergia (saw tooth pattern of the pdet) and poor compliance (upward slope of the Pdet line) should be considered and the circumstances surrounding them (Figs. 28.1 and 28.2). For instance DSD is considered to pose a high pressure risk to the kidneys but if it is not prolonged and occurs

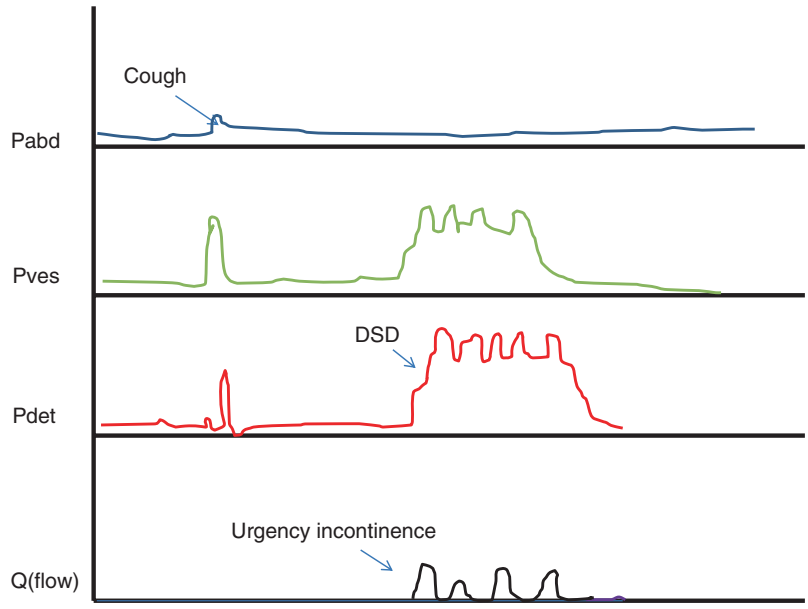

Fig. 28.1 Simplified cystometrogram demonstrating detrusor sphincter dyssynergia (DSD) and urinary incontinence. NB- the rectal line is dampened which is often the case in spinal cord injured patients

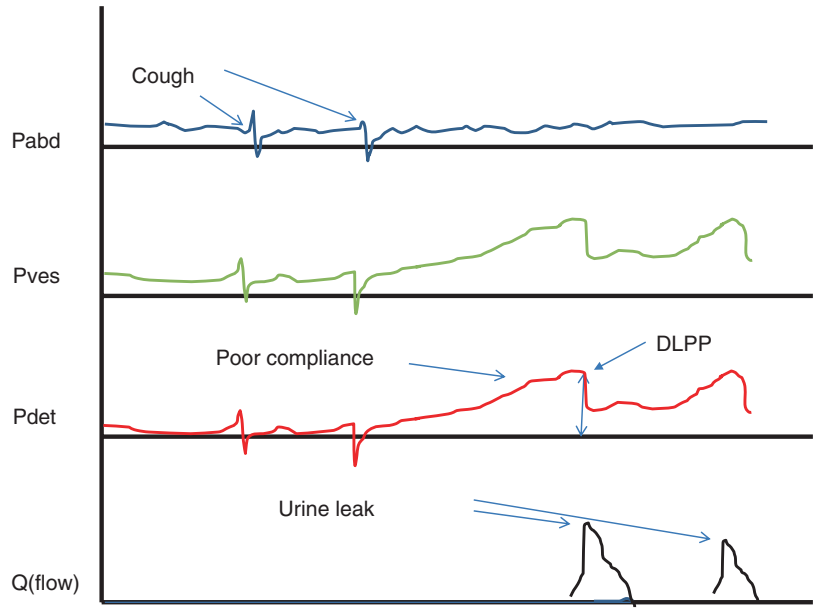

Fig. 28.2 Simplified cystometrogram demonstrating poor compliance and the detrusor leak point pressure (DLPP)

late in the storage phase when the bladder is very full then the risk is lower. Similarly, a poorly compliant bladder where the compliance only starts to increase after the bladder contains more than 600 ml or where the detrusor leak point pressure is low would be relatively safe.

A low detrusor leak point pressure prevents the bladder from transferring pressure onto the kidneys but it usually means the patient will leak urine relatively easily and therefore when considering a procedure to reverse this leak, consideration needs to be given to what will happen to the bladder pressure should the detrusor leak point pressure rise. Thus the urodynamics study should also simulate a higher detrusor leak point pressure (by occluding the urethra) and ensure the bladder pressure does not rise after this. If it does rise then a concomitant bladder procedure is also indicated. Data from children with meningomyelocele suggests that a detrusor leak point pressure greater than 40 predicts long term renal impairment [11].

Urethral pressure profilometry and electromyography are technically difficult, not standardised and their need is currently limited as they do not impact treatment choice. Thus these are mostly limited to research studies.

Suprapontine

Suprapontine lesions such as cerebrovascular accident, Alzheimer's, brain tumours etc. can lead to a loss of voluntary initiation and if cognition is affected, social incontinence ensues where the bladder is emptied without voluntary control. The pontine micturition centre is intact and therefore voiding efficiency is usually not compromised. There is little to no risk of poor compliance or detrusor sphincter dyssynergia and thus the bladder is considered "safe" from renal impairment. The majority of these patients are able to void spontaneously [12]. Disruption to the brains inhibitory effect on the PMC leads to neurogenic detrusor overactivity leading to urgency incontinence.

After a cerebrovascular event 29% will report incontinence which reduces to 14% at 6 months [13]. Immediately after a cerebrovascular accident, urinary retention may be evident. Later on, it is often noted that, there may be detrusor overactivity which in some cases may have been pre-existing (idiopathic) or may develop due to activation of C-fibre afferents [14]. A urodynamic study of 106 patients with incontinence found 56% to have detrusor overactivity, 15% had

detrusor underactivity, 15% both detrusor overactivity with impaired contractility with the remainder having normal studies [15].

One in three patients with Parkinson's disease (PD) have incontinence [16]. This is secondary to detrusor overactivity in 2/3 of them [17]. Nocturia is the most prevailing symptom in Idiopathic PD. Antimuscarinics are often helpful but should be used with caution due to their risk of worsening cognitive function [18]. Voiding dysfunction with incomplete bladder emptying is less common in PD and may be due to a multitude of factors including concomitant BPH, anticholinergic use and bradykinesia of the striated urethral sphincter [19, 20].

Multiple system atrophy (MSA) initially presents with similar symptoms to PD. The finding of an open bladder neck (suggestive of sphincter denervation) is suggested as a hallmark finding of MSA and differentiates from PD. [21] In addition, these patient have a lax anal tone. Other findings, which occur with greater frequency in MSA are detrusor sphincter dyssynergia and higher post void residuals. The life expectancy of those with MSA and higher post void residuals has also been shown to be worse [22]. Men with MSA who undergo a de-obstructing procedure such as a transurethral resection of the prostate are at a higher risk of post-operative incontinence than men with PD. [23] Therefore men considered for a de-obstructing procedure with symptoms of PD should have video urodynamic studies to assess for an open bladder neck and confirm bladder contractility.

With normal pressure hydrocephalus the ventricles are seen to be dilated and typical features such as gait disturbance, memory impairment and urinary incontinence are seen, with the majority (up to 95%) demonstrating detrusor overactivity [24]. A shunt will improve the symptoms in the majority of patients.

Pontine

Pontine lesions are uncommon and therefore only case reports describing bladder function after pontine injury are reported in the literature [25]. In one 5 year old with a pontine pilocytic astroctoma, urodynamic studies showed both storage and voiding dysfunctions, with detrusor overactivity, normal bladder compliance, open bladder neck and detrusor sphincter dyssynergia [26]. No recommendations can be made regarding management of such disorders as it would depend on the symptoms and urodynamic findings.

Suprasacral Spinal Cord Injury

Complete Injury

A completely transected spinal cord that leads to a cranial spinal cord segment and a caudal spinal cord segment leads to a particular lower urinary tract picture. In effect, the caudal spinal cord segment becomes autonomous and is known as the "distal autonomous cord". Thus, muscles supplied by this segment of the cord lead to spasticity, increased tone and hyperreflexia known as upper motor neurone effects. The spinal bladder reflexes therefore also become autonomous and lose pontine co-ordination. Therefore, as the bladder fills and pressure rises it contracts automatically leading to involuntary urination. The guarding reflex (which contracts the urethral sphincter on urine entering the bladder neck) is no longer synchronised with voiding (as this is co-ordinated by the pons). This leads to neurogenic detrusor overactivity and detrusor sphincter dyssynergia i.e. concomitant contraction of the urethral sphincter during involuntary bladder contraction (Fig. 28.1). As a consequence, the bladder may not empty well.

In this group of patients, video urodynamic assessment is essential and the upper tracts are potentially at risk of high pressures. The cytometry will inform if the pressures are high and prolonged and when in the cycle they occur and if the bladder empties well or not. In a patient with non-prolonged high detrusor pressure and good bladder emptying, reflex voiding into a convene sheath may be appropriate but requires long term monitoring.

In patients with prolonged high pressures, the principle would be to ablate the pressure and

make the bladder safe. Therefore the options for this include to either reduce the sphincteric resistance or reduce detrusor contractile pressure. The former is achieved with a sphincterotomy and the latter with the use of antimuscarinic agents, b3 agonists, botulinum toxin or augmentation cystoplasty [27, 28]. With a sphincterotomy, the patient needs to be prepared to wear a lifelong convene sheath and will be rendered totally incontinent. Conversely, when artificially diminishing detrusor contractility, the bladder will not empty as reliably and so another method of bladder emptying is required such as intermittent or indwelling catheterisation.

An emergency feature of this type of spinal cord injury is autonomic dysreflexia. With lesions above T6 and a distal autonomous cord, a painful stimulus below the level of the lesion leads to an aberrant sympathetic response. The painful stimulus, such as a distended bladder or impacted bowel, leads to vasoconstriction, piloerection and sweating below the level of injury. There is dumping of blood from the areas of vasoconstriction into the areas above the lesion leading to significant hypertension. Compensation occurs in the region above the lesion with vasodilatation and bradycardia. However this may be insufficient if the lesion is high (>T6) and hypertension may lead to stroke or myocardial infarction. Early recognition of the signs is essential and elimination of the painful stimulus is the first step in the management, along with use of a vasodilator such as glycerine tri-nitrate.

The crede expression manoeuvre (pressing firmly on the bladder with a fist) was previously advocated to increase bladder pressure to cause expulsion of urine. However, this technique carries a high risk of complications and can lead to renal failure due to the imbalance of pressure being applied to the bladder compared to the rest of the abdomen [29]. Also, only 2% of patients have been shown to have urethral sphincter relaxation during the manoeuvre making it grossly inefficient [30]. Voiding by Valsalva manoeuvre and tapping of the abdomen are also potentially dangerous and require long term follow up [31, 32].

Incomplete Injury

The type of injury and the amount of damage to spinal tracts can be variable and thus leads to a mixed picture. If the dorsal columns are affected then bladder sensation may be impaired [33]. The risk of neurogenic detrusor overactivity and detrusor sphincter dyssynergia is still present as is the risk to the upper tracts [34]. The management of this type of lower urinary tract dysfunction follows the same principles of those with a complete injury. A phenomenon sometimes seen with incomplete injury is neuropathic bladder pain. Urological interventions are often not helpful for this pain and instead neuropathic painkillers such as amitriptyline and gabapentin are recommended.

Sacral/Peripheral

Complete Sacral Lesions

This occurs when the conus medullaris (cauda equine) is completely destroyed resulting in lower motor neurone lesions in the distribution of the affected nerves and absent conus reflexes. Thus there is no distal autonomous cord. A high spinal lesion where the whole distal spine is damaged can also lead to this picture. The muscles usually supplied by the damaged nerves assume a flaccid state and become areflexic. This is also the case with peripheral nerve injuries.

Thus a bladder with complete sacral injury (complete cauda equina) will lead to an areflexic bladder. The sacral micturition reflex and guarding reflex are absent. Receptive relaxation will only be present in injuries below the L1 level and with injuries above this level the bladder is more likely to develop poor compliance (which is a lack of receptive relaxation). Normal bladder sensation is lost.

With an absent micturition reflex, the bladder does not contract, instead it fills and the compliance is lost gradually and eventually this overcomes sphincteric resistance leading to overflow incontinence (Fig. 28.2). Due to denervation of the urethral rhabdosphincter, stress incontinence

is present and the detrusor leak point pressure is dependent on the smooth muscle component of the urethral sphincter.

Managing this type of bladder requires an in depth video urodynamic study. With a low detrusor leak point pressure, incontinence can be managed with pads or convene drainage. More commonly, the low detrusor leak point pressure is corrected with a procedure to increase outlet resistance such as an autologous sling in females or an artificial urinary sphincter in males. When doing this it is essential to ensure the bladder will be safe afterwards and can hold a good volume without a pressure rise. If not then a concomitant bladder procedure, such as a cystoplasty, is necessary [35]. With a high detrusor leak point pressure, bladder drainage prior to the development of high pressure is required and thus intermittent or indwelling catheterisation is considered.

Incomplete Sacral Lesions/Peripheral Nerve Injury

With cauda equina syndrome, patchy nerve damage to the conus may occur. Likely causes of cauda equina include disc herniation, lumbosacral fracture, tumour, spinal abscess and spinal surgery. Depending on the insult, some nerve recovery is possible over time. The likely problems in this form of nerve injury include a lack of bladder sensation (afferent nerve injury), acontractile bladder (efferent nerve injury), stress incontinence (sphincter denervation) [36]. Peripheral nerve injury or injuries may also lead to similar problems and are most commonly iatrogenic. Due to the variability in nerve damage, there are difficulties in predicting bladder behaviour and thus a video-urodynamic study is useful.

Spinal dysraphism (Spina bifida) is a congenital disorder due to failure of closure of the neural tube and non-fusion of vertebrae, most commonly affecting the lumbosacral vertebrae and nerves [37]. Of 350 individuals with spinal dysraphism, 61% described having urinary incontinence [38]. Urodynamic assessment of 36 infants with myeldysplasia revealed sphincter dyssynergia in 50% and an incompetent sphincter in 25% [39]. Most importantly, 72% of those with dyssynergia later developed hydronephrosis which only improved with better bladder drainage. Management is guided by symptoms and urodynamic findings and these patients require lifelong follow up within a multidisciplinary team [40].

Pudendal nerve neuropraxia is a recognised complication of delivery and emergency caesarean section, of which the majority of lesions recover by six months [41]. Of 14 multiparous women followed for five years after delivery, it was found five had stress incontinence with neurophysiological evidence of partial denervation of the urethral sphincter and pudendal neuropathy [42]. It should be noted, that this is not the only mechanism responsible for stress incontinence post-partum [43].

The above patients are managed by inserting a tension free vaginal tape beneath the mid urethra [44]. If there is a high degree sphincteric deficiency (which may be assessed on urodynamic studies) then a pubovaginal sling of autologous rectus fascia placed with tension beneath the bladder neck is advisable [45]. A third option is the insertion of an artificial urinary sphincter if the sphincter is significantly incompetent [46]. Conversely in men, stress incontinence is rare post surgery due to a more developed bladder neck sphincter unless the patient has had a radical prostatectomy. The artificial urinary sphincter is the gold standard and the sub-urethral sling is considered to have poorer outcomes [47].

Urinary retention has been reported to occur in <0.5% of patients undergoing rectal and uterine surgery [48]. The postulated mechanism is peripheral nerve injury and bladder de-afferentation and in these patients intermittent catheterisation is first instituted but sacral neuromodulation may be beneficial if the injury is incomplete [49]. A meta-analysis of one RCT and 13 observational studies revealed sacral neuromodulation led to increased voided volume by 299 mL and reduced residual volume by 236 mL in women with mixed non-obstructive urinary retention [50]. It is not clear from the analysis what proportion of these women had a peripheral nerve injury. If sacral neuromodulation is not feasible then the mainstay of management will be intermittent catheterisation. With

Table 28.1 Urodynamic classification adopted by ICS

Bladder	Sphincter outlet
Overactive • Neurogenic detrusor overactivity • Poor compliance	Increased resistance • Detrusor sphincter dyssynergia • Dysfunctional voiding
Underactive • Impaired contractility • Detrusor areflexia	Reduced resistance • Uninhibited sphincter relaxation • Intrinsic sphincteric deficiency • Urethral hypermobility

peripheral nerve injury, long term risk to the kidneys is negligible if the patient manages their bladder sensibly.

Polyneuropathy

Multiple sclerosis (MS) occurs due to demyelination of white and grey matter in the central nervous system [51]. Autonomic dysfunction may be a consequence of lesions in regions responsible for autonomic regulation such as the pons [52], or due to cervical spinal cord atrophy [53]. Altogether, 97% of patients with MS will describe a urinary symptom during the course of the disease [54].

In a study of 52 patients with MS, 25% were found to have detrusor overactivity and 27% detrusor sphincter dyssynergia, whereas 65% had urinary urgency [55]. In another study when urodynamics was repeated in 22 patients, it showed worsening change in 12 and this was not associated with worsening of their MS symptoms [56]. A recent systematic review showed that 14 studies had reported on renal impairment occurring in MS patients [57]. Although this is uncommon, the mean maximum detrusor pressure, detrusor sphincter dyssynergia in men and a post void residual greater than 30% of bladder capacity were reported as risk factors for renal impairment [58, 59].

Management in MS patients is based on symptoms and urodynamics. The above reports of renal impairment have argued the case for regular follow up. Intermittent self catheterisation is recommended when there is incomplete emptying but there is no strong evidence for cut off for a post void residual but 100 mL has been suggested [57, 60]. Where antimuscarinic agents fail botulinum toxin has good success at relieving detrusor overactivity [28].

Amyotrophic lateral sclerosis causes degeneration of motor neurons responsible for skeletal muscles. Bladder and bowel function typically remains intact until the terminal stages of the illness [61]. Onuf's nucleus is affected to a lesser degree than the other anterior horn cell groups [62]. Thus urinary problems tend to be managed conservatively with catheterisation in this group of patients as they are often at a debilitated stage when they occur.

Classification and Management

Due to the large variability of neurological insults to affect anywhere between the brain and the peripheral nerves supplying the lower urinary tract and the complex interplay between the bladder and sphincters it has been difficult to have a fully comprehensive classification system. Classification can be made according to the neurological insult, anatomical site of injury, symptoms the patient displays or urodynamic findings. The International Continence Society (ICS) has adopted an urodynamic classification scheme looking at the sphincter outlet and bladder separately as being either overactive or underactive (Table 28.1).

Strategies to treat an overactive bladder include; antimuscarinic agents, b3 agonists, botulinum toxin, sacral neuromodulation and augmentation or substitution cystoplasty. Occasionally a diversion may be in the patients' best interest. The above treatments may predispose to inefficient bladder emptying and this may need to be addressed at the same time. Strategies to make the bladder more active are currently lacking. Sacral neuromodulation may have a role and a number of drugs are being investigated to improve bladder contractility. Therefore with an underactive detrusor patients may need to intermittently catheterise, have an indwelling catheter or have a urinary diversion.

To increase sphincteric resistance, in our armoury we have duloxetine, bulking agents, tape procedures, sling procedures, compressive devices such as artificial urinary sphincter or the bladder outlet can be surgically closed. Alternatively, a containment device may be appropriate such as a convene sheath. To reduce sphincteric resistance alpha antagonists, botulinum toxin to the sphincter, sphincterotomy, sphincteric stents and transurethral resection of the bladder neck may be used.

The urodynamic findings should match the neurological and anatomic findings and explain the patients' symptoms. Conventional wisdom would suggest that an overactive bladder or sphincter should be made less overactive and the converse reasoning should be applied for an underactive bladder and sphincter. However, treating an urodynamic abnormality on its own is not fruitful and it should always be placed in the context of how the patient is managing their bladder and the risk posed to the upper tracts. A safely managed bladder does not impart prolonged high pressures onto the kidneys. Interventions we employ to treat incontinence should not place the kidneys at risk of this pressure. So, despite being able to assess the sphincter outlet and bladder separately we should consider the effect of our intervention on both.

For instance, in a T5 paraplegic man wearing a convene sheath, reducing or ablating neurogenic detrusor overactivity will only serve to increase his residual volumes and place his kidneys at risk and thus his DSD needs addressing too. Similarly, an incontinent woman with spina bifida with a weak sphincter who has an artificial urinary sphincter inserted can return later to have bilateral hydronephrosis and renal failure despite the artificial urinary sphincter having worked very well for her incontinence. Thus a comprehensive approach is necessary when managing neuropathic patients.

Conclusions

The lower urinary tract is a window into the nervous system. The concluding message is to relate the patients lower urinary tract symptoms to their underlying neurology, bladder diary and urodynamic findings. A holistic approach is required when assessing and managing the neuropathic bladder. Therapy must be planned to preserve upper tracts, avoid urinary infections, and maintain an acceptable quality of life. Such planning may be complex in view of the social, economic, cognitive, functional and urodynamic deficits that patients with neurogenic bladder present with. A stepwise approach to management with periodic surveillance offers a good strategy to the urologist.

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Pelvic Organ Prolapse

29

Thomas G. Gray and Stephen C. Radley

Prevalence and Effects of Pelvic Organ Prolapse

The true prevalence of pelvic organ prolapse (POP) is not known, this is partially because POP is an under-reported condition. Barriers to seeking treatment include embarrassment, lack of awareness of effective treatments and feeling that POP is a normal part of ageing and to be accepted [1].

It is estimated that up to half of all women who have had children may be affected by a degree of POP [2–5]. Large, well-designed epidemiological studies have consistently demonstrated the prevalence at rates of around 50% [2–5]. In older parous women (aged over 68 years) up to 97% have been demonstrated to have prolapse on clinical examination [5]. There is, however, a large difference between the number of women objectively demonstrated to have POP on clinical examination and those who experience bothersome symptoms. It have been shown that POP when defined by symptoms may have a prevalence as a low as 6% [6].

The lifetime risk of surgery for prolapse in women was been shown to be around 11–12% [7, 8] and these numbers have been quoted in many studies. However, more recent studies have suggested that by the time women reach their ninth decade, rates of up to 19% in Australia [9] and 20% in the United States have been reported [10]. Despite heterogeneity in these types of studies, including different patient populations, indications for surgery and type of healthcare system, this still makes POP one of the most common indications for surgery in women.

Symptomatic pelvic organ prolapse has been demonstrated to have a significant impact on quality of life [11, 12], as it can impair both physical and social activities, as well as impacting on relationships and sexual function [13, 14].

Women with POP may reduce physical activities as a result of prolapse symptoms, or for fear that such activity may cause the POP to worsen or progress. POP may contribute to social isolation and withdrawal from physical exercise.

The relationship between prolapse and sexual function is now well understood. Both women and their partners have been shown to avoid sexual activity due to POP. Affected women may be aware of 'something coming down' or 'in the way' during sex as well as reduced sensation and reduced overall satisfaction with sex. A large systematic review showed that sexual function generally improves following prolapse surgery [15].

The relationship between prolapse and body image is a newer area of research. Prolapse has been shown to impact negatively on body image in a number of studies [12, 16–18] and prolapse surgery has been shown to improve body image [19].

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Assessments of the impact of prolapse symptoms on quality of life, sexual function and body image are important in the evaluation of women with POP.

Aetiology of Pelvic Organ Prolapse

A simple understanding of functional pelvic anatomy is useful for understanding both the aetiology and pathophysiology of POP.

Three levels of support of the pelvic organs are described [20]. These are the endopelvic fascia, the muscles of the pelvic floor and the ligaments attaching the cervix to the pelvis (Table 29.1). The female organs sited in the pelvis, namely the bladder, uterus and rectum, are supported by the endopelvic fascia, which provides attachment of the pelvic organs to the muscles of the pelvic floor. The largest and most important of this thin sheet of muscles is the levator ani. The muscles of the pelvic floor have their origin and attachment to both the bony pelvis and to the perineal body. The perineal body is a central site of insertion for the muscles of the pelvic floor and is located between the anus and the posterior fourchette of the vagina. The uterus itself, and with it the upper vagina, is supported by fibromusclular ligaments attached to the cervix (the uterosacral and lateral cervical ligaments).

Table 29.1 Delancey's three levels of pelvic support from DeLancey JO. Anatomie aspects of vaginal eversion after hysterectomy. American journal of obstetrics and gynecology. 1992 Jun 1;166(6):1717–28

Level 1: The uterosacral and lateral cervical ligament complex provides attachment of the uterus and the vaginal vault to the bony sacrum. This means that uterine prolapse occurs when this ligament complex breaks and becomes detached or becomes thinner and weakened.
Level 2: The arcus tendineous fascia of the pelvis and the facia lying over the levator ani muscles provide support to the middle part of the vagina. Damage to this fascia- a fascial defect- contributes to the formation of pelvic organ prolapse of the bladder, bowel and uterus.
Level 3: The urogenital diaphragm formed of the perianal muscles and the perineal body into which they insert provide support to the lower part of the vagina. Damage to these muscles, and particularly the point of insertion at the perineal body contributes to the formation of pelvic organ prolapse.

The principal cause of pelvic organ prolapse is damage to the endopelvic fascia, pelvic floor muscles or ligamentous supports of the uterus. Primary damage usually happens to these support structures during pregnancy and childbirth, both through stretching and distension due to the mass effect of pregnancy and the trauma of delivery. Perineal trauma can result in injury of the endopelvic fascia, levator ani muscles and their insertions. Studies using MRI and 3D ultrasound have helped to establish the relationship between levator ani defects, including avulsion, and pelvic organ prolapse, but this remains an understudied area [21]. Significant perineal trauma including third and fourth degree perineal tears, shoulder dystocia and large birth weight are all shown to be independent risk factors for pelvic organ prolapse [22]. Studies showing that caesarean section is protective against pelvic organ prolapse also support parturition being the leading risk factor for development of pelvic organ prolapse [4].

The other primary cause of POP is connective tissue disorders, including Ehlers-Danlos and Marfan's syndromes. These conditions affect the strength of the structures involved in pelvic organ support and often lead to development of pelvic organ prolapse at a younger age, or when pregnancy has not occurred. POP in a patient who is nulliparous and has normal connective tissue is, however, unusual.

Following initial damage to the supports of the pelvic organs following childbirth or due to connective tissue disorders, increasing age is the best-evidenced risk factor for POP, which has been shown to approximately double with each decade of life [23].

The mechanism for this is thought to be increased laxity and weakness in the pelvic ligaments and musculature. The hypo-oestrogenic environment of the menopause is also likely to be a risk factor for the development of POP, though evidence is conflicting and hormone replacement therapy has not been shown to be protective against POP [24].

Finally, any condition which causes a continual or regular increase in intra-abdominal

pressure may contribute to the development of pelvic organ prolapse. This is due to direct pressure on the pelvic floor exacerbating damage caused by childbirth, connective tissue disease or ageing. Obesity, chronic constipation, heavy lifting and chronic cough are all risk factors. Occupations which require frequent heavy lifting or exercise regimes involving heavy weight lifting are known causes. Further lifestyle risk factors include smoking and low socioeconomic status [22]. It has been shown that regular low-impact physical exercise is protective against pelvic organ prolapse [25].

Anatomical Classification of Pelvic Organ Prolapse

POP can involve the anterior, apical or posterior compartments of the vagina (Table 29.2). Anterior compartment prolapse involves urethra and bladder and is termed cystourethrocoele. The posterior compartment involves the rectum and the small bowel causing a rectoenterocoele (Fig. 29.1). Apical compartment prolapse is the descent of the uterus downwards into the vagina. The uterus may be absent following previous hysterectomy, in which case the vaginal cuff forms the apical portion. When this descends into the vagina this is termed vault prolapse.

Anterior compartment prolapse is most common, followed by uterine prolapse and posterior compartment prolapse. In the Women's Health Initiative study, of the 41% of women aged between 50–79 years who had POP; 34% had a cystocoele, 19% had a rectocoele and there was uterine prolapse in 14% [2].

Table 29.2 Types of pelvic organ prolapse

Anterior compartment
• Urethrocoele- prolapse of the urethra into the vagina
• Cystocoele- prolapse of the bladder into the vagina
• Cystourethrocoele- prolapse of both urethra and bladder into the vagina
Apical compartment
• Uterine prolapse- descent of the uterus and cervix into the vagina
• Vaginal vault prolapse- following hysterectomy, descent of the vaginal cuff scar into the vagina
Posterior compartment
• Enterocoele- prolapse of the Pouch of Douglas containing small bowel (ileum) into the vagina
• Rectocoele- prolapse of the rectum into the vagina

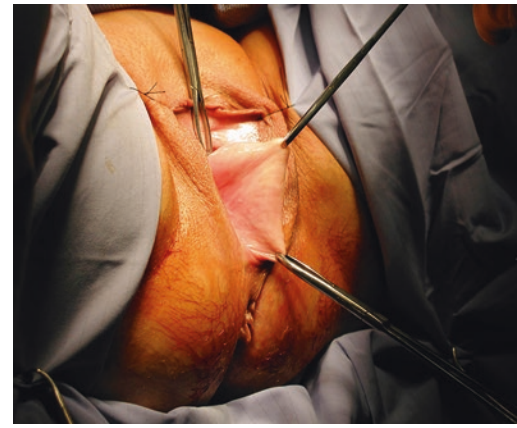

Fig. 29.1 Posterior compartment prolapse (rectoenterocoele) , seen prior to surgery. The leading edge of the prolapse is grasped with a Littlewood's forceps and is descending to 2 cm beyond the hymenal ring

Symptoms of Pelvic Organ Prolapse

POP is often asymptomatic and may be an incidental finding, for example at smear testing or cystoscopy. Symptoms of POP depend on the anatomical site of the prolapse, with different symptoms for anterior compartment POP (bladder) compared to posterior compartment prolapse (rectum). As POP causes symptoms which are embarrassing or taboo in nature, woman may not readily disclose these symptoms during a consultation [26]. Therefore, the use of patient reported outcome measures to assess patient's symptoms and concerns is invaluable to helping to accurately ascertain the patient's symptom profile [27–30].

Vaginal Symptoms

The primary symptom of POP is vaginal bulge. Affected women usually see or feel a bulge, lump or 'something coming down' inside the vagina or out through the introitus. The bulge may only be felt on direct palpation by the patient, rather than

being visible, or may typically protrude on straining, physical activity or at the end of the day. Symptoms are impacted on by the effect of gravity and long periods of standing or physical exercise.

Pelvic pressure with a sensation of heaviness or dragging over the suprapubic area is another common symptom. Crampy low back pain, typically worse at the end of the day or after physical activity is also often reported. If the leading edge of the prolapse is protruding from the vagina and rubbing on underwear or incontinence pads, the vaginal skin on the prolapse may become sore and bleed, in cases of prolonged trauma ulceration may occur. This is a common cause of postmenopausal bleeding and also of microscopic haematuria. Patients with prolapse may well be referred for an urgent cystoscopy yielding an opportunity to identify vaginal trauma or ulceration as a source of bleeding.

Bowel Symptoms

If the prolapse affects the posterior compartment, then problems with evacuation and tenesmus can be bothersome symptoms. Some women use a finger to support the perineum to defecate effectively (perineal splinting), some need to manually evacuate using a finger inserted into the anus or the vagina (digitation). Some will complain of faecal soiling and difficulty getting clean due to trapping of faeces caused by the posterior compartment POP.

Urinary Symptoms

Similarly, voiding problems may occur with anterior compartment prolapse, particularly third degree or severe cases, with women needing to press on their perineum with a finger or press on the anterior vaginal wall to achieve voiding. Patients may find that they need to lean forward on the toilet to void urine effectively and some may complain of a spraying stream. Incomplete emptying and retention of urine may also occur. It is important to consider however, that mild and moderate degrees of prolapse do not usually cause obstruction so resolution of prolapse through surgery or pessary may not improve LUTS in this context.

Overactive bladder symptoms of urgency, frequency and nocturia may also occur. De novo overactive bladder symptoms can occur due to anterior wall prolapse, although the relationship between overactive bladder and anterior wall prolapse is non-linear. Some studies have demonstrated that anterior repair does produce significant improvement in overactive bladder symptoms [31, 32]. This is thought to be due in part to improvements in voiding post cystocoele repair [33]. Not all patients with overactive bladder symptoms in the context of prolapse will improve post-surgery.

Sexual Symptoms

Pelvic organ prolapse has been clearly demonstrated to have a significant negative impact on sexual function. POP can cause dyspareunia, obstructed intercourse, vaginal laxity and resulting loss of or decrease in libido [34–36]. Improvements in sexual function following intervention have been clearly demonstrated [15].

Examination and Classification of Pelvic Organ Prolapse

If a woman presents to a urologist with lower urinary tract symptoms or haematuria which are through to be related to POP, or if a prolapse is found on clinical examination, the patient should be referred for urogynaecological review.

The purpose of examination in a woman with POP symptoms is to assess for the presence of prolapse, assess which compartment(s) are affected and to assess the stage of the prolapse and the strength of the pelvic floor muscles. All of these findings will, along with the woman's symptom profile, direct the management strategy.

In order to assess POP, initial examination should be undertaken with the woman supine with legs flexed. Firstly, the perineum should

be inspected and signs of oestrogen deficiency, such as thin, dry or inflamed skin noted. In order to demonstrate the prolapse, the woman should be asked to cough hard and to strain or 'bear down'. Reproducing prolapse in a clinical environment can be challenging and examination may be usefully carried out with the patient standing if an obvious prolapse cannot be demonstrated supine. During this assessment, leakage of urine on coughing/straining may also be noted. Treatment should be aimed at dealing with the symptoms the patient finds to be most bothersome; again, the use of self -completed validated questionnaires may be of value in this context.

Usually the woman is then examined in the left lateral position using a Sims' speculum to visualise the anterior and posterior vaginal walls separately (Fig. 29.2). It is helpful to have a chaperone to support the patients right leg to aid visualisation of the anterior and posterior vaginal compartments. A Sims' speculum is used for this. Both metal and single use plastic Sims' speculums are available. Sim's speculum is inserted along the posterior wall to assess anterior compartment prolapse and along the anterior wall to assess posterior compartment prolapse. Sponge holding forceps are long round ended forceps, which can be utilised to gently reduce anterior or posterior compartment prolapse to effectively visualise the cervix or vaginal cuff in order to assess descent of the apex (Fig. 29.2). Grasping the cervix or vaginal cuff with a pair of toothed tenaculum forceps is another way to demonstrate prolapse descent, but can cause discomfort and should be undertaken with consent and caution (Fig. 29.2).

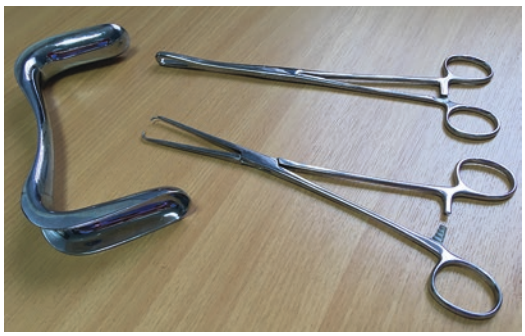

Fig. 29.2 From left to right: Sim's speculum, round ended sponge holding forceps, sharp tooth-ended tenaculum forceps

As part of routine assessment, pelvic floor muscles strength should be measured. This is recorded using the Modified Oxford Score (Table 29.3) [37].

There are two widely-used prolapse grading systems. The POP-Q or pelvic organ prolapse quantification system describes the descent of the anterior, posterior and apical segments of the vaginal walls relative to a fixed anatomical point-the hymen (Table 29.4) [38]. Ideally the POP-Q system requires the use of a measuring stick to accurately record the extent of prolapse on maximal straining. In reality, using the POP-Q system is complicated, as it can be difficult to understand and practically hard to measure. However, it has

Table 29.3 The modified Oxford Score from Laycock J, Jerwood D (2001) Pelvic floor muscle assessment: the PERFECT scheme. Physiotherapy 87(12):631–642

Oxford Score	Signs
0	No contraction
1	A flicker
2	Weak
3	Moderate with some lift
4	Good contraction with lift, against some resistance
5	Normal muscle contraction, strong squeeze and lift

Table 29.4 The POP-Q staging system for prolapse∗ Bump RC, Mattiasson A, Bø K, Brubaker LP, DeLancey JO, Klarskov P, Shull BL, Smith AR. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. American journal of obstetrics and gynecology. 1996 Jul 31;175(1):10–7

Stage 0: No prolapse
Stage I: The most distal portion of the prolapse is >1 cm above the level of the hymen
Stage II: The most distal portion of the prolapse is ≤1 cm above the level of the hymen
Stage III: The most distal portion of the prolapse is >1 cm below the level of the hymen but protrudes to no further than 2 cm less than the total length of the vagina
Stage IV: Complete eversion of the vagina

Table 29.5 The Baden-Walker staging system for prolapse (Baden WF, Walker TA. Surgical Repair of Vaginal Defects. Philadelphia: Lippincott; 1992. pp. 161–174)

Stage 0: Normal position for each respective site, no prolapse
Stage 1: Descent halfway to the hymen
Stage 2: Descent to the hymen
Stage 3: Descent halfway past the hymen
Stage 4: Maximum possible descent for each site

advantages for objective assessment of prolapse, as the scoring system should be the same when assessed by different observers, making it a useful tool for research [39].

The Baden-Walker prolapse classification system predates POP-Q and is still widely used in clinical practice (Table 29.5) [40]. This system is more subjective and less accurate, but is simpler to use in clinical practice.

Conservative Management of Pelvic Organ Prolapse

Lifestyle Modification

Lifestyle modifications may be beneficial in addressing prolapse symptoms and preventing progression of the prolapse, though are unlikely to reduce the stage of the prolapse per-se. Recommending weight loss for those who are overweight or obese with referral to appropriate community weight loss services will have wider health benefits as well as reducing prolapse progression [41]. Causes of chronic cough should also be addressed. Smoking cessation or a switch to vaping have been shown to be beneficial for reducing chronic cough and prolapse progression [42]. Avoidance of heavy lifting during exercise or occupation may also help to both reduce symptoms of prolapse and also prevent progression.

It is clear that prolapse stage correlates poorly with prolapse symptoms [2]. So, if a woman has minimal or no prolapse symptoms, employing watchful waiting, especially in the presence of advanced age or multiple co-morbidities, would be a very reasonable management strategy.

Physiotherapy: Pelvic Floor Muscle Training

There is extremely robust level A evidence for the role of pelvic floor muscle training (PFMT) in the treatment of pelvic organ prolapse. At least three randomised controlled trials have shown that one-to-one PFMT with a women's health physiotherapist, undertaken for 16 weeks to six months, is highly effective in the reduction of POP symptoms [43–45]. PMFT in these studies was also shown to reduce the POP-Q scores.

As well as training patients how to contract their pelvic floor through examination and teaching, women's health physiotherapists can utilise adjuncts such as biofeedback (using a device in the vagina which tells the woman how effectively she is contracting her pelvic floor) and electrical stimulation (where an electrode device in the vagina aids contraction of the pelvic floor, allowing the patient to replicate this as they learn to contract their pelvic floor more effectively).

It is important to be aware that self-directed PFMT using instruction sheets has not been shown to reduce either prolapse symptoms or grade. It is essential that women have an opportunity to have one-to-one directed PFMT under the care of a women's health physiotherapist. It is not enough to provide women with information sheets or details of websites about how to do self-directed PFMT themselves. It is reasonable to refer women with prolapse of grade I-II for PMFT and most women with this magnitude of prolapse should expect an improvement in symptoms. Patients should be informed that PMFT may provide sufficient improvement in symptoms to negate the need for surgical intervention. However, for patients with grade III and IV prolapse, this is less likely to be successful. Urologists seeing patients with POP in their clinical practice could reasonably refer such patients with stage I-II POP to a women's health physiotherapist for assessment and PMFT prior to urogynaecological review.

Pessaries

Pessaries are devices, usually made from silicon or plastic, which can be inserted into the vagina to restore and support the prolapse into its normal anatomical position. There are many such devices available for use (Fig. 29.3). A Cochrane database systematic review from 2013 demonstrated that there is actually a paucity of good evidence for the use of pessaries for pelvic organ prolapse and no clear consensus for the type of pessary to use, or regarding the frequency of changing the device or appropriate period of follow-up [46]. Pessaries do, however, remain a popular first line treatment for pelvic organ prolapse and may be used with good effect in the long term. In 2000, a survey of 360 urogynaecologists in the USA and Canada demonstrated that 98% used vaginal pessaries for treatment of POP [47].

Pessaries function as either 'support' pessaries or 'space filling pessaries'. The most commonly used support pessary is the ring pessary, although there are many other types. Ring pessaries have the advantage of being widely available, including in primary care, are relatively easy to change, by GPs and often the patient themselves. Space occupying pessaries are utilised for more advanced prolapse or following failure of a support pessary. These include shelf and Gellhorn pessaries.

Pessaries are generally safe if fitted and followed up by an experienced practitioner- this may be a urogynaecologist, specialist nurse or general practitioner. Complications include vaginal discharge, vaginal irritation or ulceration due to rubbing of the pessary. Pessaries becoming entrapped in the vagina and requiring surgical removal is rare. There are case reports of fistulas, more commonly rectovaginal fistula, resulting due to displacement of the pessary [48]. This is more of a risk with the peg of the shelf or Gellhorn pessary if this rotates anteriorly or posteriorly. Occult stress urinary incontinence previously masked by a kinked urethra due to the effect of a cystocoele can also occur when the urethra is straightened out by using the pessary.

It is possible to have sexual intercourse with ring pessaries, but not with space occupying pessaries. This is a very important consideration for women with pelvic organ prolapse who are sexually active when considering management options. Women with prolapse who have not yet completed their family may also use pessaries instead of having surgical intervention until their family is complete.

Well-motivated patients can be shown how to fit and change their own ring or support pessaries and this is standard practice in several UK units which have set up services to train and support women in this. High patient satisfaction rates and significant cost-savings have been demonstrated from employing this strategy [49]. Further larger studies are currently underway to evaluate this approach.

Fig. 29.3 Different types of pessary. From left to right: shelf pessary, Gellhorn pessary, ring pessary

Surgical Management of Pelvic Organ Prolapse

Surgical treatment is not necessary for all women with POP. Women should have all options for management discussed with them, including the options of no treatment, PMFT and pessary, as well as all surgical options available to them and the attendant risks of each. Many women with pelvic organ prolapse will choose surgery for definitive treatment of their prolapse.

The types of surgical intervention for prolapse are summarised in Table 29.6.

The mainstay of pelvic organ prolapse where there is descent of the uterus from the apical com-

Table 29.6 Surgical management of pelvic organ prolapse

Type of prolapse	Surgical procedure
Anterior compartment	Anterior colporrhaphy- the prolapse sac caused by prolapse of the bladder and/or urethra is excised from the vaginal skin and sutures used to plicate native fascia in order to reduce the prolapse sac and prevent recurrence. Partial colpocliesis- vaginal closure
Posterior compartment	Posterior coloporrhaphy- the prolapse sac caused by prolapse of the rectum and/or small bowel is excised from the vaginal skin and sutures used to plicate native fascia in order to reduce the prolapse sac and prevent recurrence. Partial colpocliesis- vaginal closure
Uterine prolapse (apical compartment)	Vaginal hysterectomy- removal of the uterus and cervix using a vaginal approach. Sacrohysteropexy- uterine preserving surgery- the uterus is attached to the sacrum using mesh. This can be done through an open abdominal incision or laparoscopically. Sacrospinouscervicopexy- uterine preserving- the cervix is attachment to the sacrospinous ligament. This is done via a vaginal incision. Total colpocliesis- vaginal closure
Vaginal vault prolapse (prolapse of apical compartment follow a vaginal hysterectomy)	Sacrospinous fixation- sutures between the top of the vaginal vault and the sacrospinous ligament. This can be used both to treat vaginal vault prolapse or be done prophylactically to prevent it happening at the time of a vaginal hysterectomy Sacrocolpopexy- attachment of the vaginal vault to the sacrum using mesh. This can be done abdominally through an open incision or laparoscopically Partial colpocliesis- vaginal closure

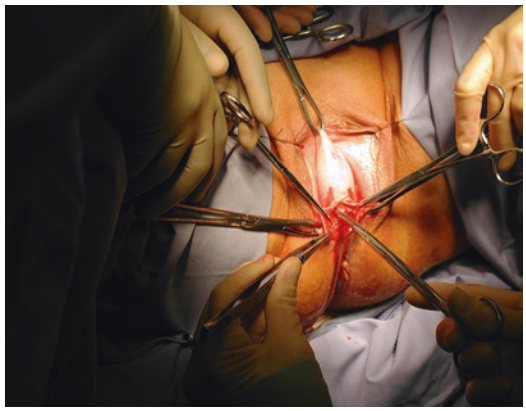

Fig. 29.4 Surgical management of rectoenterocoele showing initial perineal incision over the prolapse

partment is a vaginal hysterectomy, usually in combination with a repair of the anterior wall (anterior repair or anterior coloporrhaphy- these terms are interchangeable) or a posterior repair/posterior colporrhaphy (Fig. 29.4). Alternative procedures for uterine prolapse where the patient wishes to retain their uterus include a Manchester repair, where the cervix is amputated via the vagina and the uterosacral ligaments plicated or a sacrohsyteropexy, where the uterus is attached to the sacral promontory using a type 1 polypropylene mesh. Sacrocervicohysteropexy is an alternative procedure which attaches the cervix to the sacrospinous ligament using sutures. This operation is rarely performed as it has a very high recurrence rate of uterine prolapse. Uterine conserving prolapse surgery is not typically done to retain fertility, as resulting pregnancies are likely to lead to recurrence of the uterine prolapse. Advice generally favours conservative measures, including the use of ring pessaries until child-bearing is complete.

The use of mesh in prolapse repair was previously widespread. Type 1 polypropylene mesh inlays were designed for use in both anterior and posterior compartment prolapse. A large number of manufacturers produced such ‘mesh kits’. However, it rapidly became apparent that a significant number of complications including mesh erosion, fistula, chronic pain and early recurrence of prolapse could all occur when synthetic non-absorbable mesh was employed. These findings were supported by the PROSPECT study and synthetic mesh for prolapse repair is no longer a recommended treatment outside a research setting [50, 51]. The use of synthetic mesh, placed abdominally (either via laparotomy, or more commonly laparoscopically) is however recommended in the context of recurrent prolapse, particularly apical prolapse following hysterectomy, when preservation of vaginal capacity is important.

For patients with stage III and IV prolapse, too frail to undergo prolapse repair, particularly hysterectomy, closure of the vagina or colpocliesis is an alternative operation. This can be done in those with a uterus or who have had a hysterectomy. It consists of excising a rectangle of tissue from both anterior and posterior vaginal walls and then suturing these together, reducing the prolapse inside the vagina and closing the vaginal space. It is only suitable for those who no longer wish to be sexually active. Body image and satisfaction are shown to improve following colpocliesis [52, 53].

The risks of surgery for POP are infection, bleeding, pain and injury to abdominal viscera; particularly the bladder and ureters in the case of vaginal hysterectomy and anterior repair and the rectum in the case of posterior repair. Deep vein thrombosis and pulmonary embolus are other associated risks. Urinary incontinence can present de novo post op, either stress incontinence due to straightening out a previously kinked urethra or an overactive bladder causing urgency and urge incontinence. Recurrence of the prolapse may carry up to a one in three lifetime risk depending on factors such as weight, age and the extent of the prolapse. Pre-operative stage of the prolapse is the main risk for prolapse recurrence with women who have a more advanced prolapse more likely to experience recurrence [54].

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Urologic Trauma

30

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Introduction

Trauma can be defined as any physical injury to living tissue caused by an extrinsic agent. It is the sixth leading cause of death worldwide, accounting for 10% of all mortalities [1]. Injury is most often related to car accidents and personal injury. Trauma has a male predominance. Geographic and socioeconomic variation greatly impacts the causes and effects of traumatic injuries [2].

Urologic injuries may occur during severe trauma, requiring a multidisciplinary approach for management. The Urologist remains an important consultant to the trauma team, ensuring accurate radiographic evaluation of urogenital structures and acting as the steward for preserving genitourinary function. In the context of urotrauma patients, urologists must be familiar with open and minimally invasive surgical techniques in order to control bleeding and/or obtain timely urinary drainage [3].

Isolated urologic injuries are rare because the kidneys, ureters and bladder are well protected. While the penis and testicles are mobile, they are also rarely affected. More commonly, urologic injuries are concomitant with major abdominal trauma events; urologic organs are involved in 10% of abdominal traumas [4].

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Classification of Trauma

The World Health Organization classifies traumatic injuries into intentional (violence related, war related or self-inflicted injuries) and unintentional injuries e.g. motor vehicle collision, falls and other domestic accidents (Table 30.1) [1]. Traumatic injuries are classified according to their basic mechanism into penetrating and blunt injuries. Penetrating is when an object pierces the skin. Objects, depending their origins (projectile, stab), may lead to a substantial range of tissue effects.

Penetrating trauma is also classified according to the velocity of the projectile into:

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Table 30.1 WHO classification of injuries

Type of injuries	
Intentional	Self—Inflicted
	Interpersonal violence
	War-related
Unintentional	Road traffic
	Poisoning
	Falls
	Fires
	Drowning

High-velocity (rifle bullets) inflict severe damage due to extreme shear forces.

Medium velocity (handgun bullets) damage is usually confined to the projectile tract.

Low velocity (knife stab) inflict focal trauma without heat effects.

Blast injuries combines both blunt and penetrating trauma, and also may be accompanied by a burn injury [5]. Because of varied tissue effects, understanding the mechanism of the trauma, type and caliber of weapon impacts management. Blunt injuries occur through different mechanisms such as crush, transmission of a stress wave via compressive forces, or shear injury due to deceleration. These mechanisms explain multiple intra-abdominal organ injuries that are not in close proximity to each other [6].

Initial Management

The Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach is a systematic way to immediately assess and treat injured patients [7]. Initial evaluation must include hemorrhage control, basic stabilization of the patient, intravenous fluids, and drainage catheters. As much information about the mechanism of trauma and the patient's medical history should be collected. Abdominal and genital palpation as well as searching for bruises and hematomas may reveal a lesion in the retroperitoneum or pelvis. Lower rib fractures should lead to suspicion of renal injuries. Pelvic fractures may be related to bladder and urethral injuries. Diffuse abdominal pain could be related to intraperitoneal organ perforation, bleeding or intraperitoneal urine extravasation. In males prior to insertion of a urinary catheter, check for the presence of blood at the meatus [8].

Renal Trauma

Renal trauma accounts for approximately 1–5% of all trauma and approximately 10% of abdominal trauma [9]. The kidney is protected by lumbar muscles, ribs and Gerota's fascia/peri/para nephric adipose tissue. Blunt trauma to the abdomen or back is the most common cause of renal trauma, accounting for 80–85% of all renal lesions [5]. Additionally, a direct blow to the flank during sports activities can cause renal trauma. This occurs most frequently in biking (31%), baseball and softball (9.3%) and football injuries (6.5%) [10].

Sudden deceleration or a crush injury may result in a contusion or laceration of the parenchyma and renal hilum, but renal vascular injuries in blunt trauma are rare (<5%). Isolated renal artery injury is also rare, but renal artery occlusion is associated with rapid deceleration [11]. Penetrating trauma includes gunshot and stab wounds as the most representative causes and are less predictable and more severe than blunt trauma. Projectiles and bullets can cause more parenchymal destruction and compromise multiple organs [12].

Classification

The AAST is the most commonly used classification scheme (Table 30.2). It has proven clinical relevance and classification predicts the need for intervention, morbidity, and mortality [13]. There are proposals for minor changes to grade 4 and 5 classifications to further delineate non-operative management of more complex lesions (Table 30.3). This has come to pass given the advent of better imaging and treatment technologies such as endovascular management [14, 15].

Authorized from: The Journal of Trauma and Acute Care Surgery," Revision of Current American Association for the Surgery of Trauma Renal Injury Grading System".

Table 30.2 1989 AAST OIS Classification

Grade	Injury description
I	
Contusion	Microscopic or gross hematuria, urological studies normal
Hematoma	Subcapsular, nonexpanding without parenchymal laceration
II	
Hematoma	Nonexpanding perirenal hematoma confined to renal retroperitoneum
Laceration	<1.0 cm parenchymal depth of renal cortex, without collecting system rupture or urinary extravasation
III	
Laceration	>1.0 cm parenchymal depth of renal cortex, without collecting system rupture or urinary extravasation
IV	
laceration	Parenchymal laceration extending through the renal cortex, medulla, and collecting system
Vascular	Main renal artery or vein injury with contained hemorrhage
V	
Laceration	Completely shattered kidney
Vascular	Avulsion of renal hilum which devascularizes kidney

Advance one grade for multiple injuries to same organ
Authorized from: The Journal of Trauma and Acute Care Surgery

Table 30.3 Revised Injury Scaling Classification

Grade	Injury definition
I	
Parenchyma	Subcapsular hematoma and/or contusion
Collecting system	No injury
II	
Parenchyma	Laceration <1 cm in depth and into cortex, small hematoma contained within Gerota's fascia
Collecting system	No injury
III	
Parenchyma	Laceration >1 cm in depth and in medulla, hematoma contained within Gerota's fascia
Collecting system	No injury
IV	
Parenchyma	Laceration through the parenchyma into the urinary collecting system
	Vascular segmental vein or artery injury
Collecting system	Laceration, one or more into the collecting system with urinary extravasation
	Renal pelvis laceration and/or complete ureteral pelvic disruption
V	
Vascular	Main renal artery or vein laceration or avulsion main renal artery or vein thrombosis

A renal unit can sustain more than one grade of injury and should be classified by the higher grade of renal injury

Diagnostic Tools

Blunt trauma to the back, flank, lower thorax or upper abdomen may involve the kidneys. Flank pain, ecchymoses, abrasions, fractured ribs, abdominal distension or palpating a mass may raise the suspicion for renal compromise. In penetrating injuries, entry and exit wounds should be found. Wounds in the lower thoracic back, flanks or upper abdomen may involve the kidneys. Be aware that for a stab wound, the extent of the entrance wound may not accurately reflect the depth of penetration [5]. Moreover, blast injury may extend beyond the entry and exit points, and the route of bullets may be unpredictable.

Labs, Imaging

Initial laboratories required are hematocrit, baseline creatinine and urinalysis. Major injuries such as disruption of the UPJ, pedicle injuries, segmental arterial thrombosis and stab wounds may not present with hematuria [16]. While urine dipstick is a rapid test to screen for hematuria, the rate of false negatives are 3–10% [17]. Serial measurement of hematocrit is part of continuous trauma evaluation along with the response to resuscitation; a decrease in hematocrit and requirement of blood transfusions may indicate a major renal injury. Serum creatinine on presentation usually reflects renal function prior to the injury; an increased level usually reflects pre-existing renal pathology as creatinine is a lagging indicator of renal health [5]. New markers of acute renal injury such as cystatin-C, cysteine-rich protein-61 (CYR-61), ELISA, Interleukin-18 (IL-18) may have an

increasing role in diagnosing acute renal compromise [18].

When a renal lesion is suspected the aims of imaging are: grade the injury, identify injuries to other organs, confirm presence of the contralateral kidney, and document pre-existing renal pathology. Renal imaging should be undertaken in patients with blunt trauma, visible and non-visible hematuria and hypotension (systolic blood pressure <90 mm Hg) [3, 5]. Imaging is recommended in patients with rapid deceleration injury, direct flank trauma, flank contusions, lower ribs fractures and lesions to the thoracolumbar spine, and in penetrating trauma with or without hematuria [19–21].

Computed tomography (CT) with immediate and delayed phases is the imaging modality of choice and can identify and grade renal lesions. Arterial phase images allow assessment of vascular injuries and extravasation of contrast, while the delayed phase identifies collecting system or ureteral injury [22]. Although the AAST system of grading is primarily based on surgical findings, a good correlation with CT appearance has been demonstrated [23].

The intraoperative pyelography, or "One-shot", consists of a bolus of intravenous contrast media (2 mL/kg) followed by a single plain film taken after 10–15 min. This remains a useful technique to confirm the presence of a functioning contralateral kidney, in particular for patients too unstable to undergo a CT. Utility of this exam can be hampered by the presence of warming blankets, retractors or laparotomy sponges; also, under resuscitation leads to poor contrast excretion [24, 25].

Ultrasonography is not considered appropriate in the initial evaluation due to poor sensitivity. Studies have demonstrated that ultrasonography may be inaccurate in detecting solid organ trauma. Usually in the blunt trauma scenario, Focus Assessment with Sonography for Trauma (FAST) exam in an unstable patient is negative [26]. Magnetic resonance imaging (MRI) accuracy is similar to CT, but the logistical of moving a trauma patient, the length of time to scan, and the need for MRI-safe equipment make its routine use impractical. Radionuclide scans also do not play a role in the acute evaluation of renal trauma.

Management

Blunt injuries: Non-surgical treatment is the recommendation of choice. All grade 1, 2 and 3 injuries can be managed non-operatively. In stable patients primary conservative management consists of supportive care with bed rest, hemodynamic observation, blood transfusion as needed, and is associated with lower rate of nephrectomies and preservation of renal function [27]. Patients with grade 4 and 5 injuries with concomitant major injuries usually undergo exploration and sometimes require nephrectomy. Despite the variability in different medical centers and the comfort level with the management of renal trauma, the conservative approach is still favored. As it is stated in the AUA Guidelines, there is Grade B Evidence regarding the observational management of hemodynamically stable patients. Grade 5 vascular injuries should be managed with immediate nephrectomy in cases of hypotension refractory to transfusion to stem the risk of exsanguination [28]. Approximately 25% of blunt injuries are high-grade injuries, meaning grade 4 or 5. Actual data indicates that many of these patients can be treated with observation, especially in hemodynamically stable patients regardless of injury grade [29]. A conservative approach in these patients is not associated with prolonged hospital stay [30].

Angioembolization has a central role in the non-surgical management of stable patients who continue to bleed. It has been utilized in all grades of trauma and most beneficial in grades 4 or greater [31]. The criteria for angiography and embolization in a patient with renal hemorrhage include persistent bleeding from a renal segmental artery with or without parenchymal laceration, hemodynamic instability with grade 3–4 injury, arteriovenous fistula or pseudoaneurysm, persistent gross hematuria and/or rapidly decreasing hematocrit requiring 2 units of blood [32]. This procedure can be as successful in up to 94.9% grade 3, 89% grade 4 and 52% grade 5 injuries [31].

Penetrating injuries: In all grade 1 and 2 injuries management is non-operative as outlined above. Traditionally penetrating injuries have

been treated surgically based on a full evaluation of clinical, laboratory and radiological factors. In selected stable patients, non-operative management has been successful, and treatment depends on the extent and grade of injury. Gunshot injuries must be explored if the renal hilum is involved, in the presence of ureteral lesion, or renal pelvis lacerations [5]. Low-velocity gunshot and stab wounds can be managed conservatively, conversely tissue damage in high-velocity gunshot may ultimately require a nephrectomy. Non-surgical management has been documented with successful outcomes between 50 to 100%, with rates of nephrectomy of 24%, that can increase to 72% if the retroperitoneum is explored [33].

Surgical management: Treatment of renal injuries may be influenced by the decision to explore associated abdominal injuries. Hemodynamic instability and unresponsiveness to aggressive resuscitation due to renal hemorrhage is an indication for surgical intervention. Moreover, finding an expanding or pulsatile perirenal hematoma during an exploratory laparotomy performed for associated injuries is an indication to act [5]. The main objective of surgical intervention is control of bleeding and renal preservation. A transperitoneal approach is recommended and access to the pedicle may be obtained through the posterior parietal peritoneum, which is incised over the aorta, medial to the inferior mesenteric vein. Alternatively, initially dissect the psoas muscle fascia adjacent to the great vessels with blunt dissection and upon identification of the aorta, the dissection is continued superiorly until the renal vein is identified. Once identified the artery is occluded, if bleeding persists the vein is then clamped. Once vascular control is achieved, the colon is reflected to incise Gerota's fascia laterally and evacuate the hematoma. The entire kidney must be exposed to examine the renal pelvis, parenchyma and vessels [5, 9, 34].

The reconstruction process starts with debridement; all non-viable tissue should be removed. Parenchymal vessels must be closed with absorbable sutures; veins can be ligated freely. While ligation of arteries may lead to renal infarction, persistent bleeding usually stops when the parenchymal defect is closed. Watertight closure of the collecting system must be done. Re-approximation of the capsule will close the defect and prevent urinary extravasation. When this is not possible, a pedicle flap of omentum is an excellent alternative, secured over the defect with absorbable sutures. Lesions to the upper or lower pole may be treated with partial nephrectomy, with the same principles of bleeding control, collecting system and capsule closure if possible. Lesions to the mid portion follows the same principles above described, and instead of omentum, placement of Gelfoam can improve hemostasis [9]. When a contained hematoma is founded several authors recommend to avoid Gerota's fascia exploration, the supporting theory is that given their confined retroperitoneal location and Gerota's protection, it functions as an innate tamponade mechanism to control excessive bleeding and urinary extravasation. When Gerota's fascia is opened, the hematoma is no longer contained and may lead to more bleeding and need for nephrectomy [35].

Follow up in trauma patients includes physical examination, serial blood pressure measurement, urinalysis and serum renal function. Radiological studies must be individualized, depending on the degree of trauma. As mentioned, grades 1–3 do not require imaging follow up as long as they remain clinically well. The usefulness of frequent CT scan has never been proved. Guidelines recommend repeat imaging 2–4 days after trauma to minimize the risk of missed complications [5]. This should always be done in patients with fever, unexplained decrease of hematocrit, significant flank pain, suspicion of a urinoma or fistula. If fistula or urinoma is detected, immediate urinary drainage with a ureteral stent and/or percutaneous drainage of urinoma or percutaneous nephrostomy may be considered [3].

Ureteral Trauma

Ureteral injuries are rare, accounting for 1–2.5% of genitourinary trauma. Acute ureteral injury is most likely to occur in an iatrogenic fashion (80%) vs. occurrences related to violent trauma like stab wounds or gunshots (20%). Exposure to

an agent (ureterolithiasis or recurrent instrumentation) or a treatment (radiation) can also be considered a cause of ureteral trauma [36, 37]. Procedures involving the ureter or near the ureter are frequent, so iatrogenic ureteral injuries are relatively common.

Gynecological surgery accounts for over half of all iatrogenic ureteric injuries [38]. Colorectal operations such as abdominoperineal resection or low anterior resection may particularly increase the risk of injury given the complexity of resection [39, 40]. Common types of injuries in order of frequency include: ligation, kinking by suture, transection/avulsion, partial transection, or crush and devascularization with delayed necrosis/stricture. The pelvic ureter is compromised in 80% of these injuries, and this has not been shown to be prevented by placing a preoperative stent [40]. Routine prophylactic stenting is generally not cost effective and does not decrease the rate of injury [5, 41], but may improve detection of the ureter and identify the injury [38]. In acute trauma, a high degree of clinical suspicion is required for ureteral injury. In particular with deceleration injury, ureteral injury may occur in 10% of cases, most frequently proximally or mid-ureter. The likelihood of distal ureteric injury is low because this region is protected by the bony pelvis [5, 37, 41].

There are no typical symptoms and signs of ureteral trauma; a high index of suspicion should be maintained. Lesions may be identified during any primary procedure using intravenous dye agents (indigo carmine) [5]. Of note, penetrating trauma is associated with vascular and intestinal injuries and low blood pressure which may reduce the effectiveness of dye agents and contribute to a delay in diagnosis. Gross hematuria has been reported to be present in 40–50% of patients in some series but is not a pathognomonic sign of ureteral trauma Table 30.4.

In a delayed scenario, iatrogenic trauma usually is detected when there is evidence of urinary obstruction, urinary fistulae formation or sepsis. There are clinical signs characteristic of a delayed diagnosis: flank pain, vaginal drainage, urinary leakage, hematuria, fever, urinoma or urinary incontinence [5, 37]. When possible, a sample of draining fluid can be sent to the laboratory for a fluid creatinine level to confirm urinary fistula. Early recognition facilitates immediate repair and provides better outcome [42].

Table 30.4 Ureter injury scale

Grade	Injury definition
I	
Hematoma	Contusion or hematoma without devascularization
II	
Laceration	<50% transection
III	
Laceration	>50% transection
IV	
Laceration	Complete transection with <2 cm devascularization
V	
Laceration	Avulsion with >2 cm of devascularization

Advance one grade for bilateral up to grade III
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CT with 10-min delayed images is the diagnostic tool of choice both in iatrogenic and penetrating stable patients. Findings suggestive of ureteral injury may include contrast extravasation, delayed pyelogram, hydronephrosis and lack of contrast in the ureter distal to the injury [3, 5].

Reconstructive options for the ureter depend on the location and length of injury. A key principle for reconstruction is a lack of tension on the repair. Proximal ureter injuries shorter than 3 cm may be managed with a uretero-ureterostomy. When that seems ill advised, an uretero-calycostomy may be considered. If the lesion is extensive, a transuretero-ureterostomy is a valid option. In extended lesions or complete ureteral injury, a segment of intestine, appendiceal or fallopian tube could be considered as replacement. Also, auto transplantation may be considered. For injuries in the mid ureter, uretero-ureterostomy or a Boari flap would be options. Distal injuries should be managed with ureteral re-implant (uretero-neocystostomy). Due to the vascular compromise of the distal ureter a primary anastomosis is not recommended as the primary surgical approach. The use of stents in the repair has been controversial related to stricture formation, inflammatory reaction and discomfort, but others advocate for their use in that benefits outweigh the risks [41].

In trauma patients with suspected ureteral injury that requires a laparotomy, direct inspection must be performed. This is especially true in cases during which a proper radiological study has not yet been performed. If a lesion is founded, immediate repair must be done. In unstable patients temporary urinary drainage and delayed definitive management is recommended [3]. The ureter can be clipped or tied off and percutaneous nephrostomy tube planned.

Bladder Trauma

Bladder trauma is considered the most frequent of the lower urinary tract injuries. The major cause of bladder injury is blunt trauma accounting for 85% [41] and is most often related to motor vehicle collisions, falls, industrial trauma/pelvic crush injuries and blows to the lower abdomen [5]. Pelvic fractures are associated with bladder trauma in 3.6% of cases, of those intraperitoneal varies from 14 to 50% and extraperitoneal 44–68% among series [43, 44]. Penetrating trauma accounts for 14–49% of bladder trauma; gunshot wounds comprise 88% of all bladder trauma [40]. Also, iatrogenic injuries during abdominal surgery can cause bladder trauma.

Classification

The AAST classification of bladder trauma (Table 30.5) is based on the extent and location of the injury, and it is important as it will guide management [13]. Location is classified into (Table 30.6):

Pelvic fractures cause distortion of the pelvic ring, with associated shearing of the anterolateral bladder wall near the bladder base. In some cases the bladder is perforated directly by a bony fragment [5, 45]. Intraperitoneal ruptures are related to compression of a distended bladder with a sudden rise in intravesical pressure. Usually this is secondary to a blow to the pelvis or lower abdomen. The bladder dome is closely related to the peritoneum and is considered the weakest point where most ruptures occur [45].

Table 30.5 Bladder injury scale

Grade	Injury definition
I	
Hematoma	Contusion, intramural hematoma
Laceration	Partial thickness
II	
Laceration	Extraperitoneal bladder wall laceration <2 cm
III	
Laceration	Extraperitoneal (>2 cm) or intraperitoneal (<2 cm) bladder wall laceration
IV	
Laceration	Intraperitoneal bladder wall laceration >2 cm
V	
Laceration	Intraperitoneal or extraperitoneal bladder wall laceration extending into the bladder neck or ureteral orifice (trigone)

Advance one grade for multiple lesions up to grade III
Authorized from: The Journal of Trauma and Acute Care Surgery

Table 30.6 Bladder injury different classifications

Location	Intraperitoneal
	Extraperitoneal
	Combined
Non-iatrogenic	Blunt
	Penetrating
Iatrogenic	External
	Internal
	Foreign body

Iatrogenic bladder injury risk factors include prior surgery, inflammation and malignancy [46]. In endoscopic procedures like Transurethral Resection of Bladder Tumor (TURBT) internal bladder trauma may occur with risk factors such as large tumors, older age, location of the lesions and previous intravesical therapy. In these cases extraperitoneal perforations are more frequent than intraperitoneal [5, 41].

Diagnosis

Bladder injuries are rarely isolated injuries Guttmann et al. describes a triad of clinical symptoms: hematuria (may not be present in all cases),

suprapubic or abdominal pain and difficulty voiding. Clinicians should suspect bladder involvement for any trauma patient based on clinical history and physical exam; in particular, those with pelvic fracture, suprapubic tenderness or fullness, low urine volumes, lower abdominal bruising or swelling and abdominal hematoma (Table 30.7) [3, 41].

Cystography or CT cystogram for hemodynamically stable patients with hematuria, pelvic ring fracture or a trauma mechanism concerning for bladder injury must be performed [45, 47]. This procedure ideally involves retrograde gravity filling of the bladder with 300–350 mL of diluted contrast material until the patient reaches a fully distended bladder with a minimum of two views: first at maximal filling and second after bladder drainage [3, 41].

Table 30.7 Clinical signs and symptoms

Location	Clinical signs
Bladder injury	Hematuria
	Inability to void
	Abdominal tenderness
	Suprapubic bruising
	Abdominal distension
	Entrance/exit wounds at: lower abdomen, perineum, buttocks (penetrating injuries)

Findings indicative of bladder injury include contrast material visible outside of the bladder. In intraperitoneal injury contrast material is visible outlining the bowels, while extraperitoneal injuries contrast extravasation may be visualized in the prevesical space, anterior peritoneal space and can be associated with flame-shaped areas. A good drainage image is imperative to identify these findings [5, 41, 44, 45] (Images 30.1 and 30.2).

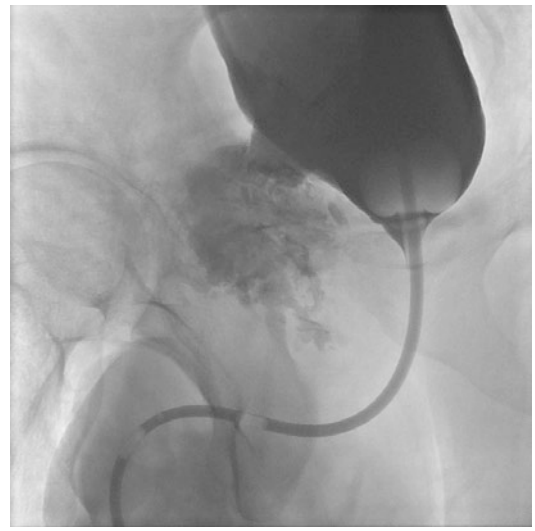

Image 30.2 Extraperitoneal rupture

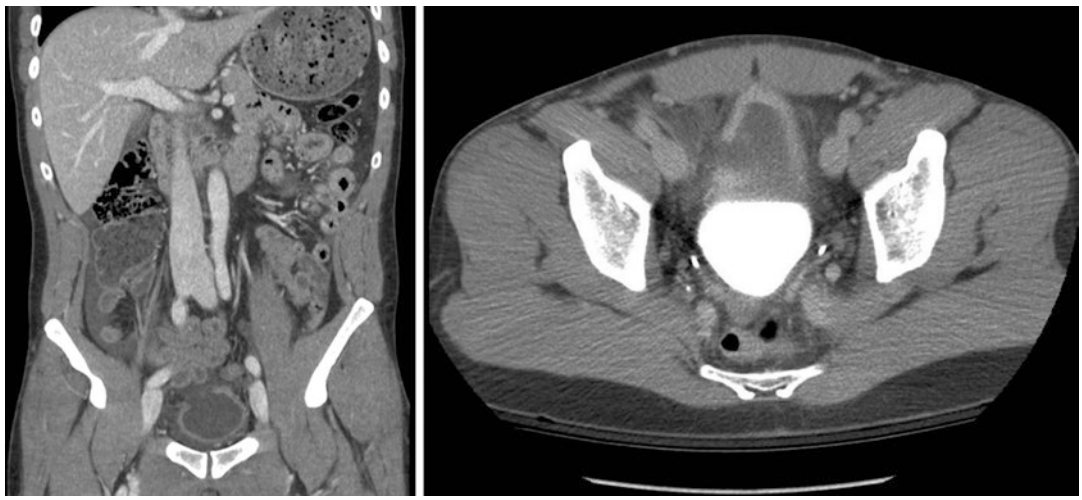

Image 30.1 Intraperitoneal rupture

Treatment

In patient with non-complicated blunt trauma and extraperitoneal injuries, treatment of choice is bladder drainage. Follow up cystography should be considered to confirm that the bladder injury has healed. If leakage is persistent surgical repair should be considered [3, 5, 41, 44, 45, 47].

Complicated extraperitoneal injuries should be surgically repaired to avoid sequelae from the injury. Complex settings include: bony fragments in the bladder, concurrent rectal or vaginal lacerations, or bladder neck injuries. Hematuria leading to challenges in catheter drainage is another relative indication for repair. One may consider repair of bladder ruptures if the patient is already undergoing a surgical procedure where repair is facilitated, even if uncomplicated [3, 5, 41, 44, 45, 47].

Blunt intraperitoneal rupture should always be managed by formal surgical repair. Injuries located at the dome of the bladder are unlikely to heal spontaneously with catheter drainage alone. Failure to repair can result in translocation of bacteria from the bladder to the abdominal cavity, resulting in peritonitis, sepsis and rarely death. Integrity of the bladder neck and ureteral orifices should be confirmed during the surgical repair [3, 5, 41, 44, 45, 47]. This can be done with direct visual inspection but is often aided by use of methylene blue. Any hematuria seen emanating from a ureter requires further investigation and may indicate concomitant ureteral injury. Likewise, no urine output visualized could indicate rare bilateral ureteral injury or under-resuscitation.

In penetrating non-iatrogenic trauma, emergency exploration is the treatment. As previously mentioned, the integrity of the bladder neck and ureters must be noted. For gunshot wounds in particular, there is a strong association with intestinal or rectal injuries, sometimes requiring fecal diversion. These injuries are also associated with entry and exit injuries so the bladder must be checked for those two lesions [3, 5, 41, 44, 45, 47].

If iatrogenic trauma is noted during a surgical procedure, exploration with repair is the standard treatment. If intraperitoneal trauma is noted during TURBT, the bowel must be inspected to rule out concomitant injury. Extraperitoneal surgical exploration is only needed for large lesions complicated with extra-vesical fluid collections. Drainage of the collection with or without closure of the bladder injury may be successful. In perforations during mid-urethral sling or transvaginal procedures, re insertion and prolonged urethral catheterization should lead to good clinical outcomes [3, 5, 41, 44, 45, 47, 48].

Urethral Trauma

Urethral injuries are infrequent in trauma patients, accounting for approximately 4% of genitourinary trauma in several series [40, 41, 49]. Nonetheless, such injures lead to substantial long-term morbidity such as: incontinence, impotence, infertility and intractable stricture disease. Of injuries involving the urethra, 65% are complete disruptions and 35% partial tears. Given the anatomical longer length and reduced mobility, urethral injuries are approximately five times more common in men than women [40, 41]. Lesions to epithelial tissue can occur from external blunt or penetrating trauma, ranging from a mild contusion with preservation of epithelial continuity to a partial tear of the urethral epithelium or full urethral transection [49]. Urethral injuries are rarely life threatening but can be related to major pelvic fractures or multiple organ injuries. There are several types of classification schemes in the literature, depending of the origin of trauma, anatomical localization and concomitant injuries. There is no reliable clinical method to distinguish between partial and complete injuries. Anatomically, urethral injuries can be either anterior or posterior (Diagrams 30.1 and 30.2).

The anterior urethra includes the fosa navicularis, the penile or pendulous urethra, where injuries are frequently related to penis fractures, and the bulbar urethra, which is more vulnerable to crush injuries (straddle). In some cases injuries are not recognized immediately and present later as a stricture (Table 30.8) [40, 41, 44, 49].

The posterior urethra consists of the prostatic and membranous urethra, which is surrounded by the urogenital diaphragm. Injuries are associated with major trauma, most due to pelvic fractures. Road traffic accidents are the most common cause of pelvic fracture and account for four times as

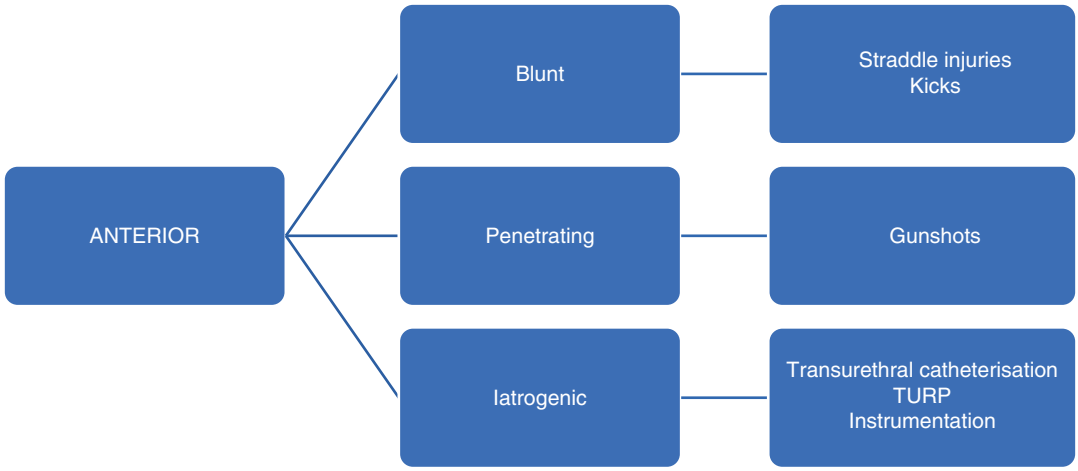

Diagram 30.1

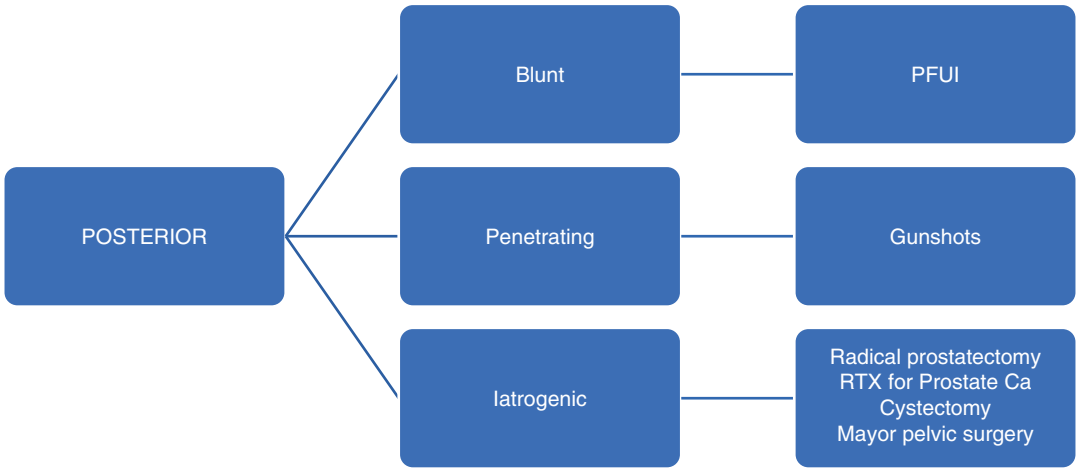

Diagram 30.2

Table 30.8 Causes of anterior urethral injuries

Causes of anterior injuries	
Blunt trauma	Fall astride, kicks in the perineum, saddle horn injuries, skateboarding
Penetrating trauma	gunshot, stab wounds
Iatrogenic	Urethral catheters, penile surgery, endoscopic instrumentation
Other	Penile fractures, foreign bodies, constriction bands

Table 30.9 Causes of posterior urethral injuries

Causes of posterior injuries	
Blunt trauma	Pelvic fractures, e.g. road traffic accidents, falls from height, industrial accidents
Penetrating trauma	gunshot, stab wounds
Iatrogenic	Complication of endoscopic surgery (TURP), radical prostatectomy

many lesions than the second most common cause: falling from a height. Pedestrians are more likely to have a urethral lesion rather than the occupants of a car involved in a motor vehicle collision (Table 30.9) [50]. Depending of the magnitude of trauma, the urethra is initially stretched and then partially or completely disrupted at the bulbomembranous junction [40, 49]. Studies have dem-

onstrated straddle fracture (fracture of all four ischiopubic rami) combined with diastasis of the sacroiliac joint had the greatest risk of urethral injury, almost 25 times greater than other pelvic fractures [50, 51]. Despite these findings, pelvic fracture is not always associated with urethral injuries, only 3–25% in most studies [49, 52].

Diagnosis

The cardinal sign in any type of urethral trauma is blood at the meatus, present in 20–100% of patients, accompanied by an inability to void and a distended bladder. Depending on the mechanism of trauma and location, other signs such as penile or perineal swelling and ecchymosis can be found. Extension of penile bruising beyond the shaft is caused by the rupture of Bucks fascia. In these cases, the Colles fascia acts as a limiting tissue resulting in a bruise in the perineum. (Table 30.10) Usually these clinical signs appear >1 h after the trauma.

Digital rectal exam must be performed in all patients in order to detect a rectal injury, failure to detect a rectal injury my lead to fatal consequences. In women vaginal injuries must be evaluated [3, 40, 44, 50, 53].

All patients with suspected urethral trauma should undergo a retrograde urethrogram, considered the standard diagnostic tool [3, 5, 45, 51, 53–55]. The urethrogram is performed by inserting a Foley catheter in the fosa navicularis, with the balloon occluding the meatus. Next, a clinician injects 20–30 mL of undiluted contrast material, with the patient in a 30-degree oblique angle position if possible, with the bottom leg flexed at the knee and the top leg kept straight. A Christmas tree or other cylindrical device attached to a syringe and gauze around penis to place it on stretch is also effective. In severe pelvic or spine fractures, leaving the patient in supine and stretching the penis to acquire the images is appropriate [3, 5, 47, 49]. The aim of the urethrography is to identify the site of the injury and assessment of its extent. The distinction between partial and complete lesion is not always clear. In a partial lesion extravasation is observed during bladder filling, and in a complete lesion extravasation is seen without any bladder filling. (Images 30.3, 30.4, 30.5, and 30.6) Diagnosis is challenging for partial inju-

Table 30.10 Clinical signs and symptoms

Location	Clinical signs
Male urethral injury	Blood at the meatus
	Hematuria and dysuria
	Scrotal, perineal or penile swelling
	Inability to void
	Difficulty/inability to insert a catheter
	High-riding or impalpable prostate
Female urethral injury	Blood at the meatus and/or vaginal introitus
	Inability to void
	Labial swelling
	Vaginal laceration
	Hematuria

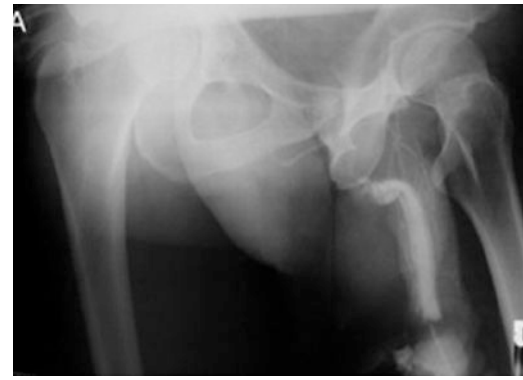

Image 30.3 Straddle injury penis off stretch

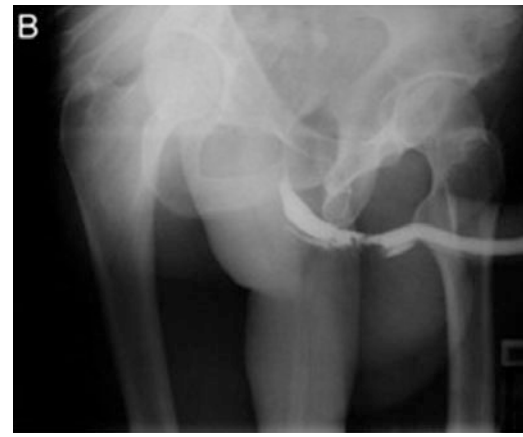

Image 30.4 Straddle injury penis on stretch

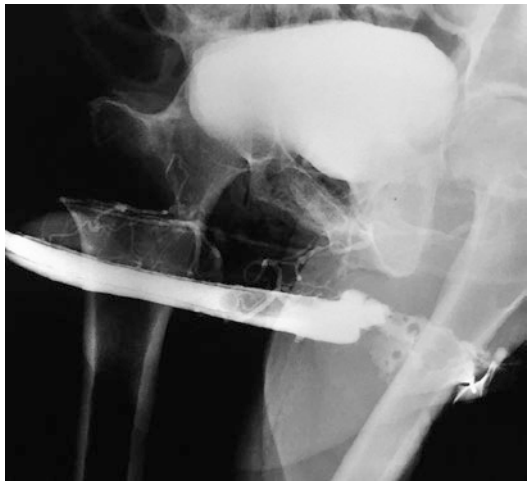

Image 30.5 Complete urethral laceration

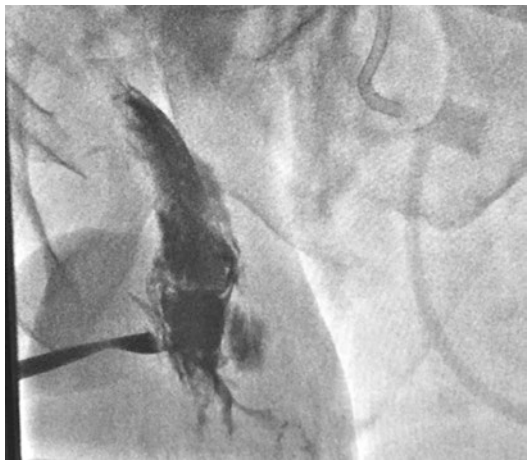

Image 30.6 Complete urethral laceration

ries, as the spasm of the sphincter may mimic a complete disruption [5, 44].

The AAST classification is based on retrograde urethrography (Table 30.11).

Table 30.11 Urethral injury scale

Grade	Injury Definition
I	
Contusion	Blood at urethral meatus; urethrography normal
II	
Stretch injury	Elongation of urethra without extravasation on urethrography
III	
Partial disruption	Extravasation of urethrography contrast at injury site with visualization in the bladder
IV	
Complete disruption	Extravasation of urethrography contrast at injury site without visualization in the bladder; <2 cm of urethra separation
V	
Complete disruption	Complete transection with >2 cm urethral separation, or extension into the prostate or vagina

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Treatment

Anterior urethral lesion treatment depends on the mechanism of injury. In blunt lesions associated with spongiosum contusion, the limits of the lesion can be difficult to determine related to the indistinct nature of the injury. As such, immediate urethroplasty is not recommended and urinary suprapubic tube diversion and follow up studies such as uroflowmetry, retrograde urethrography or cystoscopy are indicated. Endoscopic realignment, if preformed, must be performed by well-trained urologist, the goal being to allow a luminal re canalization in partial ruptures in up to 68% of cases. In patients with penile fracture immediate repair is recommended in order to preserve erectile function. This is done by closing the cavernosal tunica albuginea concomitant with the urethral tear. Penetrating injuries must be immediately treated, first by debriding devitalized tissues. Depending on the length, attempts to spatulate urethral ends and primary anastomosis must be made. In bulbar injuries defects up to 2–3 cm, and in penile urethra up to 1.5 cm may be repaired in this manner. In longer defects or with risk of infection (bite wounds) a staged repair and suprapubic drainage is recommended [3, 5, 49, 54, 56].

Posterior blunt urethral lesions must be treated in a sequence of timing into two steps:

1. Immediate: <48 h after injury
2. Deferred: >3 months after injury

The initial management is a suprapubic tube that must performed in the first hours of trauma, with the aim of monitoring urinary output and preventing urine extravasation. The insertion of the suprapubic tube depends on the condition of the patient. In stable patients, suprapubic tube can be easily placed, but there are circumstances such as displaced bladder, empty bladder, or a concomitant bladder rupture, which require ultrasound guidance or placement via open surgery. In unstable patients, urinary diversion must be performed during laparotomy or treatment of other injuries in the OR [3, 5, 44, 47]. Immediate endoscopic realignment is an option for stable patients, and the aim of realignment is to diminish stricture rate. If scarring and subsequent stricture is produced, the correction may be easier in terms of surgical planes, and if a urethroplasty is ultimately required it may be technically easier following alignment. This area is controversial. Urethroplasty outcomes may be improved in such patients due to biased patient selection in available studies on realignment. The technique for realignment includes using a flexible scope and passing a wire under direct visualization into the bladder. Over this, a catheter is placed in the bladder. The catheter remains between 4 and 8 weeks [3, 5, 44, 47]. Immediate open realignment or urethroplasty is not recommended for posterior injury because the high incidence of impotence, incontinence and strictures. Poor visualization and the inability to accurately assess the degree of the lesion make immediate posterior urethroplasty challenging [3, 5, 44, 47].

Delayed treatment has been attempted, with the aim to treat the stable patient between 2 and 14 days post injury. The primary objective of the delayed treatment approach is to perform a endoscopic realignment with the same objectives as the immediate treatment; open primary urethroplasty is not recommended due the lack of documented experience [44].

Deferred treatment is the treatment of choice for posterior lesions, usually recommended after 3–6 months of suprapubic diversion when the pelvic hematoma and other associated injuries have resolved. The objective is to perform a tension free anastomosis between two urethral health ends. The incidence of re-stenosis is about 10% [3, 5, 44, 47].

Penetrating Posterior Injuries

Immediate exploration via a retropubic route is indicated, and depending on the condition of the patient primary realignment can be performed. Also, bladder neck injuries must be treated, and if there is a concomitant rectal injury a colostomy is necessary. In life threatening injuries, bladder neck injuries must be treated, and urinary diversion for a delayed urethroplasty can be done [3, 5, 44, 47].

Iatrogenic Injuries

The conventional treatment is temporary stenting with an indwelling catheter; in complex cases, catheterization assisted by cystoscopy and guide wire placement is recommended. A suprapubic tube always remains an alternative treatment. In prostatic injuries, endoscopic management with incision or resection can be a successful. Given a requirement for complex procedures for a lesion associated with radiation, referral to a specialized center is recommended in such cases [5, 44].

Genital Trauma

External genital trauma accounts for 28–68% of all urological injuries and is much more common in males than females. Due to the external location of the male genitalia, they are relatively more exposed and vulnerable to trauma. The mobility of the scrotum and its contents is protective against severe injury. As described previously, trauma can be classified as blunt or penetrating [40, 44]. The most common injuries are penile fracture, testicular rupture and penetrating testicular end penile injury. Always consider urethral trauma when there is blood at the urethral meatus [47]. These lesions incur significant sexual, reproductive, physiologic and psychological consequences [40].

Blunt injuries account for 80% of all genital trauma, and frequently occurs unilaterally to the scrotum. The most common cause are sports related injuries, frequently due to inadequate use of protective aids. Use of bicycle is the most common cause of trauma, due to collision with the top tube or the handlebars, followed by baseball and softball injuries. In patients between 16 and 18 years, the most common cause is football, followed by basketball and bicycling [10, 44].

Penetrating injuries account for the remaining 20% of genital trauma, most frequently related to gunshot injuries. Other rare causes are self-mutilation (psychotic patients), genital burns (industrial flame or chemicals) or bites (human, animal) [44, 54, 56].

Penile Trauma

Blunt penile trauma in the flaccid penis usually does not cause tearing or lesions to the tunica albuginea, but subcutaneous hematoma may be seen. In an erect penis the most important presentation is penile fracture. The most common cause is sexual intercourse, forced flexion, masturbation or roll over. The mechanism of injury is typically when the penis slips out of the partner and crashes against the symphysis pubis or perineum. Fracture is caused by rupture of the cavernosal tunica albuginea and is associated with subcutaneous hematoma and lesions of the corpus spongiosum or urethra. The patients report a cracking or popping sound associated with pain and detumescence. When the diagnosis is uncertain, or the patient does not have the typical signs, an ultrasound or MRI may be done. Ultrasound is the most commonly used imaging due to availability, low cost and rapid examination times. Once diagnosed, surgical repair should be performed. The repair is performed exposing the injured corpus cavernosum and suturing tunica albuginea with absorbable suture. Urethral injury should always be evaluated [55] and must be repaired in the same setting [3, 44, 47] (Images 30.7 and 30.8).

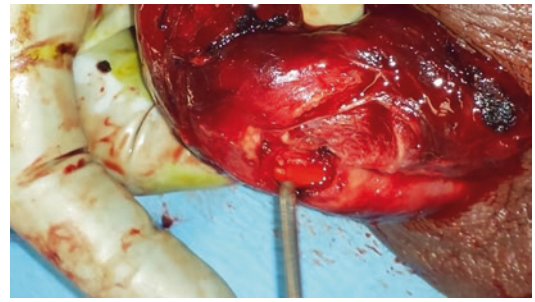

Image 30.7 Penile fracture with urethral trauma

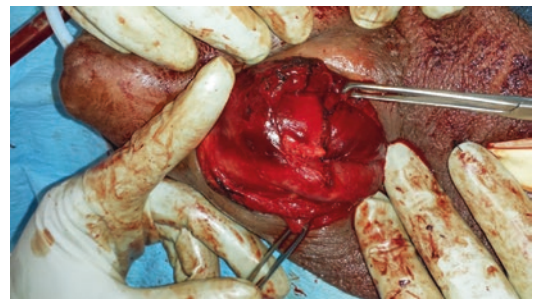

Image 30.8 Penile fracture with urethral trauma repaired

Scrotal Trauma

Hematocele is an intratesticular hematoma without rupture of tunica albuginea. In any hematocele smaller than three times the size of the contralateral testis, conservative management is recommended. In larger hematoceles, a delay in surgical management can lead to testicular loss in 45–55% of cases, therefore these cases should be treated surgically.

Testicular rupture after blunt or penetrating scrotal injuries may be suggested by scrotal ecchymosis and swelling, or difficulty in palpating the contour of the testicle. Testicular rupture is found in approximately 50% of cases of direct blunt scrotal trauma. It is produced by intense pressure against the testicle that produces a rupture of the tunica albuginea. Suffering patients present with pain, nausea, vomiting and sometimes fainting. Ultrasonography is recommended as a diagnostic tool but is not necessary for diagnosis. Nonetheless, ultrasound findings include

loss of testicular contour and heterogenous echotexture of parenchyma. Management consists of surgical exploration, debriding non-viable tissue and closing the tunica albuginea when possible. A tunica vaginalis flap could be a helpful tool for tunica albuginea closure when needed. The health of the testicle remaining can be assessed visually or with handheld Doppler. When reconstruction cannot be achieved or is unwise, orchiectomy is indicated [3, 44, 56, 57].

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Urinary Tract Fistula

31

Andrew C. Margules and Eric S. Rovner

Introduction

A fistula is defined as an extra-anatomic communication between two or more epithelial or mesothelial lined body cavities or the skin surface. Fistula can occur as a result of congenital anomalies, malignancy, inflammation or infection, tissue trauma, or iatrogenic causes, such as surgical injury or radiation. There have been reports of fistula formation since ancient times, involving connections from the urinary tract to a myriad of bodily cavities and organs. Organ systems immediately adjacent to the urinary tract are the most commonly affected, specifically the reproductive and gastrointestinal systems. Presenting signs and symptoms of urinary fistula are dependent on the termination point of the fistula, the fistula size, concomitant infection or inflammatory processes, and associated malignancy or other medical conditions.

The principles of general fistula management are applicable to all urinary tract fistulas and should be addressed prior to any planned intervention. Issues of nutrition, infection, and malignancy can significantly alter risk factors for initial fistula formation, the approach to repair, and the risk of recurrence following a given intervention. As many urinary fistulas in the industrialized world are iatrogenic, prevention of fistula development is paramount. Intraoperative and early postoperative identification of urinary tract injury allows for immediate management and minimizes the possibility of a fistula.

Once the diagnosis is established, the etiology of the fistula is determined, and complications such as skin breakdown are addressed, definitive therapy is pursued. Although some fistula might respond to conservative management, surgery is often necessary for definitive repair. The principles of management and surgical intervention are outlined in Table 31.1. Surgical repair of urinary fistula is associated with a high rate of success. The finding of a persistent fistula following surgical intervention

Table 31.1 Principles of treatment and surgical repair of a urinary tract fistula

Nutritional optimization
Elimination of infection
Evaluation for malignancy
Adequate exposure of the fistula tract
Debridement of devitalized or ischemic tissue
Careful dissection to maintain separation of involved organ cavities and hemostasis
Removal of foreign bodies or synthetics
Repair with well-vascularized healthy tissue flaps
Multiple layer closure with non-overlapping tension-free suture lines
Removal of distal obstruction
Maintain adequate urinary tract drainage
Awareness of medicolegal implications

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may suggest the existence of other complicating host factors such as malignancy, nutritional deficiency, poor tissue quality, or surgical factors such as inadequate urinary drainage or relief of obstruction, or technical problems with the actual operation.

Urologic fistulae are nearly always unexpected occurrences with potentially life-altering implications. The diagnosis is often accompanied by significant distress and frustration. Patients should be approached in a forthright manner, with great care taken to validate their concerns and to present a multimodal treatment strategy that addresses these concerns. Treating physicians must also be mindful of the potential medicolegal implications of the diagnosis, taking great care to set appropriate expectations and documenting meticulously.

Urogynecologic Fistula

Vesicovaginal Fistula

Vesicovaginal fistula (VVF) are the most common acquired fistula of the urinary tract [1]. It is defined as a communication between the bladder and vagina, resulting in continuous urinary leakage. Descriptions of vesicovaginal fistulas have been well documented since ancient times, although early attempts at repair met with little success. In 1852, Sims published his method for the surgical treatment of VVF using a transvaginal approach, followed by Trendelenburg in 1888, who successfully performed a transabdominal VVF repair [2, 3].

Etiology and Risk Factors

The etiology and prevalence of VVF differ in various parts of the world. In the industrialized world, the most common cause of VVF is iatrogenic injury during gynecologic, urologic, or other pelvic surgery, accounting for greater than 75% of cases [2, 4, 5]. Hysterectomy is the most common procedure associated with lower urinary tract injury, with most of the remainder a result of general surgical pelvic procedures, urogynecological procedures such as anterior colporrhaphy, cystocele repair, or incontinence surgery, or other urologic procedures [6]. In a study of 207 VVF repairs by Eilber et al., the cause was reported as 83% from abdominal hysterectomy, 8% from vaginal hysterectomy, 4% from radiation, and miscellaneous in 5% [7].

A review of 25,998 obstetric and gynecologic procedures performed in a Turkish center over 3 years found that bladder injuries were reported in −0.49% of gynecologic operation and 0.18% of obstetric operations [8].

The overall rate for iatrogenic bladder injury at the time of hysterectomy is between 0.5% and 1.0%, while the incidence of fistula is approximately 0.1–0.2% [9, 10]. The primary risk factor for the development of VVF following hysterectomy appears to be intraoperative injury. Iatrogenic cystotomy, tissue necrosis from cauterization injury, or suture placement through both the bladder and vaginal wall can predispose to postoperative fistula formation. Tissue ischemia and necrosis lead to fibrosis and inflammation between the bladder and vagina, eventually allowing formation of an epithelialized tract. This most commonly occurs at the apex of the vagina at the level of the vaginal cuff [11]. Preoperative risk factors include prior cesarean section or uterine surgery, endometriosis, infection, diabetes, arteriosclerosis, pelvic inflammatory disease, and prior pelvic radiation [12]. Additionally, abdominal hysterectomy is three times more likely to result in bladder injury compared to vaginal hysterectomy.

In the industrialized world, radiation is also a significant cause of complicated urinary tract fistula. The incidence of radiation-induced fistula is dependent on the type, dose, and location of radiation, as well as the specific malignancy undergoing treatment. Urinary fistula rates of 1.6% have been reported following radiation treatment for cervical carcinoma [13]. VVF from radiation may occur as long as several decades following treatment [14]. Biopsy of the fistula tract in such cases should be strongly considered prior to any definitive therapy to exclude recurrence of the primary malignancy. Malignancy-induced VVFs

can occur with locally advanced cervical, vaginal, and endometrial carcinomas and account for approximately 3% of fistulas [15]. The management of malignant fistulas may be very different from the benign type combining extirpative surgery with subsequent reconstruction and/or complete urinary diversion.

In the developing, non-industrialized world, VVF most commonly results from complications of childbirth. The incidence of obstetric fistula in developing countries is approximately 0.3–0.4% of deliveries, or between 1 and 4 per 1000 vaginal deliveries [16, 17]. In a study surveying 14,070 reproductive age women in Ethiopia, 1% experienced obstetric fistula in their lifetime. Women who gave birth ten or more times were far more likely to develop a fistula than those with four or fewer childbirths [18]. Routine prenatal and perinatal obstetrical care is limited, as is access to general healthcare. Additionally, pelvic size may be small due to poor nutritional status and/or an early age of marriage and conception [19]. Prolonged obstructed labor due to cephalopelvic disproportion can cause pressure necrosis of the anterior vaginal wall, bladder, bladder neck, and proximal urethra. The "obstructed labor injury complex" which occurs in such individuals includes variable degrees of urethral loss, stress incontinence, renal failure, vesicovaginal fistula, rectovaginal fistula, rectal atresia, anal sphincter incompetence, vaginal stenosis, osteitis pubis, and foot drop [20]. Obstetric fistulas tend to be larger than iatrogenic gynecological VVF, with necrosis of large parts of the anterior or posterior vaginal wall and/or urethra, distally near the true pelvis and pubis. Repair can be exceedingly complicated due to the large areas of necrosis and poor adjacent tissue quality due ischemia and/or inflammation as well as trophic skin changes due to large volume urine loss.

Evaluation and Diagnosis

The most common presentation for vesicovaginal fistula is persistent, continuous urinary drainage from the vagina. The amount of drainage is variable and may be directly related to the size of the fistula tract. Pain is uncommon but can be present in cases with extensive skin irritation or prior radiation. VVF should be distinguished from urinary incontinence due to other causes including stress, urge, and overflow incontinence, as well as ureterovaginal or urethrovaginal fistula.

Iatrogenic VVF from surgical intervention most commonly present 1–3 weeks following the initial procedure or following removal of the foley catheter. Radiation-induced VVFs can present months to years following therapy. While patients may experience clear or serous vaginal drainage following pelvic procedures, if fistula is suspected, the prolonged discharge can be tested for creatinine and urea. The diagnosis can be established from a thorough history and physical examination, incorporating pelvic examination, endoscopic, and radiologic methods to evaluate the presence, size, and location of the fistula tract (Fig. 31.1).

Pelvic Examination A bimanual pelvic exam and bivalve speculum evaluation should be performed in cases of suspected VVF. Relevant vaginal anatomy, including depth, prolapse, atrophy, and introital size can affect the choice of surgical approach (Fig. 31.2). The visual and manual assessment of tissue quality, scarring and inflammation can inform important decisions about the repair. The presence of acute inflammation and infection at the vaginal cuff typically mandates a delayed repair, allowing time for affected tissues to heal and regain strength. Vaginal atrophy should be documented and treated with estrogen cream prior to definitive repair, optimizing the quality of potential vaginal wall flaps. Identification of prior abdominal, perineal, thigh, or vaginal scars are necessary to evaluate for tissues that would provide less favorable reconstructive flaps.

The location of the post-hysterectomy VVF is most commonly on the anterior vaginal wall, near the vaginal cuff. Visualization can occasionally be difficult, as there can be many dimples or folds in the area of the vaginal cuff. Instillation of a vital blue dye, such as indigo carmine or methylene blue, can assist in identification small or occult fistula tracts (Table 31.2) [21]. Double dye or tampon tests may confirm the diagnosis of a

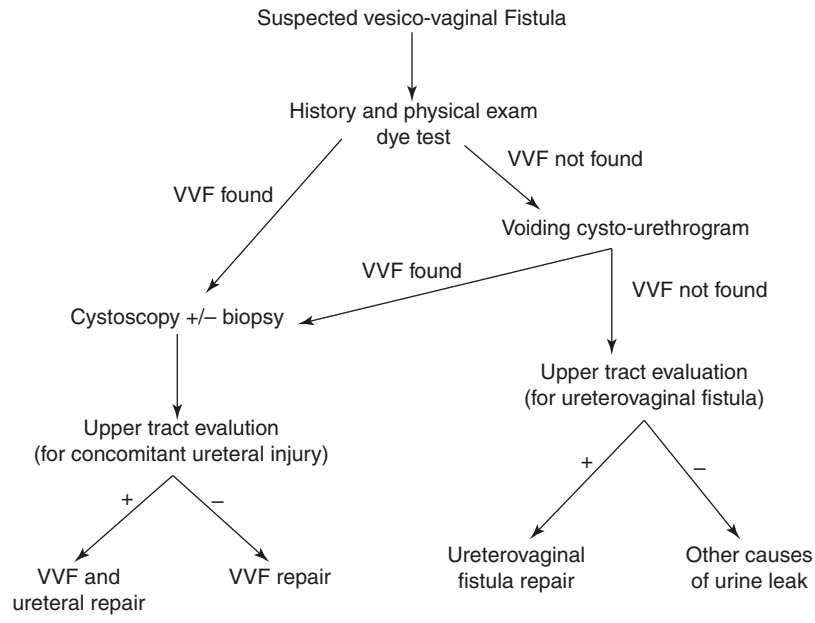

Fig. 31.1 Algorithm for diagnosis and management of vesicovaginal fistula (*VVF* vesicovaginal fistula, *UVF* ureterovaginal fistula)

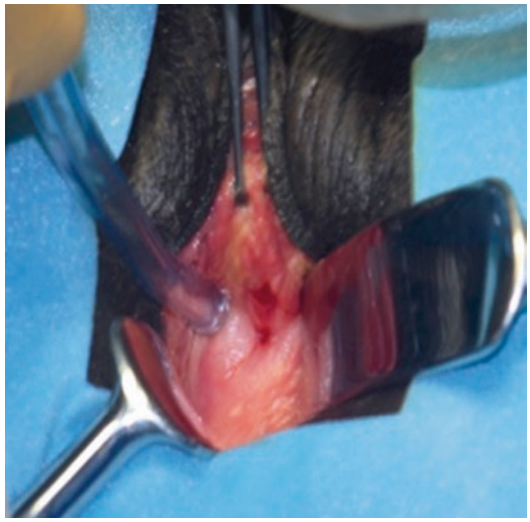

Fig. 31.2 Proximal vesicovaginal fistula. Such a proximal location in a deep vagina can make the transvaginal approach to repair challenging. A transabdominal approach or laparoscopic/robotic approach can be considered in such cases. See later discussion

urinary fistula and indicate the possibility of primary/concomitant ureterovaginal or urethrovaginal fistula [22, 23].

Cystoscopy An endoscopic evaluation should be performed in all patients with suspected VVF. Immature fistulas are often surrounded by bullous edema and do not have a distinct ostium. Mature fistulas are variably sized with smooth, distinct margins. In many cases, especially from iatrogenic VVF, the fistula site will be located on the posterior bladder wall, at or just above the intertrigonal ridge, frequently with multiple pits present, making it difficult to localize the specific tract. In cases where identification of the fistula is difficult, cystoscopic passage of a guide wire via the fistula tract can confirm the exact location of the fistula within the bladder and the vagina simultaneously.

Imaging Evaluation of VVF should include both bladder and upper tract imaging. A voiding cysto-urethrogram (VCUG) may objectively determine the presence and location of the fistula tract. With bladder filling, the contrast will opacify the vagina, usually best seen in a lateral image projection. Voiding images are occasionally necessary to visualize small VVF, as the increase in intravesical pressure will facilitate fistula drainage. A complete VCUG in the evaluation of VVF includes filling, voiding, and drainage films in multiple projections (A-P, lateral, and oblique). CT or a specialized CT cystogram may be utilized for the evaluation of VVF in certain centers [24].

Ureteral injury or ureterovaginal fistulas can be present in up to 12% of postsurgical VVF;

Table 31.2 Commonly utilized procedures during patient examination for the evaluation of stress urinary incontinence, vesicovaginal fistula, and urethrovaginal fistula

Test	Vaginal packing	Dye	Provocative maneuvers	Diagnosis
Marshall-Bonney	No	Intravesical indigo carmine/ methylene blue	Cough	Visualize leak with cough through the urethral meatus = stress incontinence
Intravaginal Pad Test	Yes	Intravesical indigo carmine/ methylene blue/Uribel	None	Distal pad blue = stress incontinence or urethrovaginal fistula
Double Dye Test	Yes	Intravesical indigo carmine/ methylene blue And oral phenazopyridine	none	Proximal pad blue = VVF Distal pad blue = stress incontinence or urethrovaginal fistula Middle/proximal pad blue = VVF Upper pad orange = Uretero-vaginal fistula

therefore, upper-tract evaluation is obtained routinely [25]. This can be accomplished easily and successfully with intravenous urography, CT urography, or MR urography. Retrograde pyelograms may be utilized if the distal ureter is not well visualized, and a concomitant ureterovaginal fistula is suspected but has not been demonstrated [1, 12]. Delayed visualization of contrast within the vagina on CT urogram or direct contrast extravasation into the fistula tract on CT cystogram provides alternate means of evaluation, with the added ability to detect additional intra-abdominal pathology [26].

Treatment

The goal of treatment of VVF should be the timely and complete cessation of urinary leakage with minimal effect on normal urinary and genital function.

Conservative Management

Conservative measures can be considered for small fistulas, typically less than 2–3 mm in diameter. This consists of continuous bladder drainage with an indwelling catheter along with anticholinergic medications to manage symptoms. In properly selected patients, fistula closure can occur after 2–3 weeks [27]. Pooled data suggest a 13% spontaneous closure rate for fistulas managed with initial catheterization [28]. Ongoing drainage of urine from the vagina after placement of a foley catheter indicates a persistent fistula tract and other methods should be considered for treatment as appropriate. Prolonged foley catheter drainage in a persistent fistula will cause considerable patient discomfort and is doomed to fail.

Cystoscopic electrocoagulation of the epithelialized fistula tract in conjunction with bladder catheterization may provide some additional benefit. Stovsky et al. reported successful ablation in 11/15 patients with fistula tract diameters less than 3.5 mm [29]. Fibrin sealant has also been utilized with some success to plug the fistula tract, presumably until tissue ingrowth occurs [30]. Again, if persistent leakage is noted with indwelling urethral catheterization following electrocoagulation, other methods should be considered in the short term.

Surgical Management

The timing of intervention for VVF is a contentious issue. Classic teaching advocates delaying repair several months after diagnosis to allow for stabilization of inflamed or necrotic tissue and recovery from the inciting event. More recently, however immediate intervention has become the preferred approach, at least in uncomplicated iatrogenic fistula. Early repair can minimize patient discomfort and anguish without compromising surgical repair [12, 31, 32, 33–35]. In complex cases, however, such as those involving continued infection, obstetric etiology or radiation, a waiting period of anywhere from 1 to 12 months may be necessary to allow demarcation of inflamed or devascularized tissues [20, 36, 37].

Table 31.3 Surgical management of vesicovaginal fistula; comparison of transabdominal and transvaginal approaches to repair

Approach	Transabdominal	Transvaginal
Timing	Delayed (3–6 months)	Immediate/delayed
Ureteral involvement	Reimplant possible if indicated	Reimplant not possible
Sexual function	No change in vaginal depth	Risk of vaginal shortening
Flaps	Omental, peritoneal	Labial, peritoneal, gluteal, gracilis
Indications	Large fistula, high fistula in narrow vault, radiation, failed vaginal approach, other procedures (augment)	Low fistulas, failed transabdominal repair
Morbidity	High	Low

During any such waiting period, special attention should be paid to skin protection (incontinence pads, barrier creams) and to nutritional status.

Once the decision to pursue definitive repair has been made, thoughtful surgical planning is essential to maximize chances of success. The first attempt at VVF repair is typically offers the best opportunity for success, free from some of the scarring, anatomical distortion and revascularization that often complicate salvage procedures.

VVF can be repaired via a transvaginal or transabdominal approach. There is no "correct" approach, and each option has advantages and disadvantages. Whereas vaginal repairs are typically outpatient procedures that can be done immediately and regardless of surgical history, abdominal repairs introduce the potential complications involved in abdominal surgery, often in patients who have recently had a complicated abdominal surgery. Transabdominal repairs are associated with greater blood loss and longer hospital stay [25]. Transvaginal surgery may be challenging in treating fistulas located high at the vaginal cuff in a deep vagina, or in patients with a narrowed vagina due to radiation, and in patients who are unable to be placed in a high-lithotomy position. In such patients, an abdominal or minimally invasive approach (laparoscopic/robotic) can be considered. An abdominal approach is necessary in patients requiring a concomitant ureteral reimplantation or in the case of complex fistulas involving adjacent organs. Regardless of the approach taken, ureteral catheter placement should be considered in the case of any fistula located close to the ureteral orifices to avoid inadvertent injury to these structures.

While each case has specific factors that inform the decision, ultimately surgeon experience and comfort should be the primary factor determining the optimal approach to repair. Most iatrogenic fistulas can be repaired transvaginally by a surgeon trained to do so. Regardless of approach, the intraoperative technical goals remain the same: (1) mobilization of well vascularized flaps, (2) separate water-tight closure of the urinary and genital tract with non-overlapping suture lines and (3) interposition of a well vascularized tissue flap when deemed clinically necessary. When these principles are followed, either approach should yield high rates of successful fistula closure, usually greater than 90% (Table 31.3) [7, 38–41].

It should be noted that in certain extreme cases where repair is not feasible or not possible, urinary diversion should be considered. This is most common in situations involving active pelvic malignancies, multiple failed repairs, severe radiation damage or other cases of extreme tissue loss [42–44].

Transabdominal Repair

The classic transabdominal VVF repair was described by O'Conor in 1980 [45]. Transabdominal approaches for fistula repair include supravesical or transvesical approaches, and laparoscopic/robotic techniques. The O'Conor transabdominal VVF repair has been well described [45]. The patient is positioned in a low lithotomy position, with access to the vagina and abdomen. Ureteral catheters may be placed and are recommended if the fistula is near the ureteral orifices or the trigone. A lower midline

incision is performed and the bladder is mobilized. The bladder is then bivalved vertically to the level of the fistula, and dissection is continued distally to open the vesicovaginal space, 2–3 cm distal to the fistula site. Following mobilization of the vaginal wall from the bladder wall distal to the fistula tract, the fistula tract is excised, and the vaginal wall is closed with running synthetic absorbable suture (SAS). The bladder is closed in multiple layers with running SAS. An additional layer of tissue can be placed between the suture lines utilizing an omental interposition flap or peritoneal flap. It is important to secure the interpositional flap distally beyond the fistula.

A later adaption, known as the transvesical approach, mitigated some of the morbidity associated with the complete bivalving of the bladder. Instead, the bladder is opened via an anterior wall midline cystotomy. The VVF tract is visualized on the posterior wall, were it is then circumscribed and excised. Following mobilization of the vesicovaginal space surrounding the fistula site, the vaginal and vesical tissues are closed separately. A flap of adjacent bladder tissue may be advanced to avoid overlapping suture lines as described by Gil-Vernet [46].

Interest in minimizing the morbidity of transabdominal VVF repair led to the advent of minimally invasive approaches. First reported in 1994 by Nezhat et al., laparoscopic VVF repair has been described in several case series in both transvesical [47–49] and extravesical [50] approaches, with various modifications, with or without the utilization of omental or peritoneal flaps. A literature review found success rates across multiple case series to be 93.5%, comparable to open repair, with a complication rate of 2.3% [51]. Advantages of minimally invasive surgery, such as improved visualization, decreased blood loss, shorter length of stay and decreased convalescence are well established. One particular advantage of minimally invasive transvesical techniques is the use of a limited posterior cystotomy, typically less extensive than anterior cystotomy in typical open cases and, as such, is likely less morbid than the formal bivalving of the bladder required in the classical O'Conor procedure [52]. Potential drawbacks of laparoscopic VVF repair include the longer operative time, potential injury to intraabdominal structures (as compared to the transvaginal approach) and the advanced laparoscopic skill necessary to successfully complete the procedure.

The advent of robotic surgery helped to overcome some of the perceived drawbacks of pure laparoscopy, most notably a steep learning curve pertaining to dissection and suturing. By the mid-2000s series of robotic-assisted laparoscopic VVF repair began to appear in the literature. The largest series to date by Bora et al. described robotic assisted laparoscopic repair of 30 VVF. Average fistula size was 10.3 mm and 11 of the 30 fistulas were characterized as "complex" (prior failure, prior radiation, obstetric cause). Their technique involved cutting down posteriorly directly on to the fistula, guided by manipulation of a traversing open-ended catheter. Eighteen patients underwent interposition flaps (epiploic, omental, peritoneal). They reported two recurrences, with an overall success rate of 93.3%. No complications were reported [52]. A recent review performed by the same group of smaller published cases and case series of robotic VVF repair corroborated the impressive success rate [53]. However, it must be cautioned, that such an approach should not be attempted by those who are unskilled in robotic techniques.

Transvaginal Repair

The transvaginal approach for fistula repair is shown in Fig. 31.3 [7, 54, 55]. The patient is placed in the dorsal lithotomy position, and a rectal pack is placed. Labial retraction sutures are placed as well as a weighted speculum. A self-retaining ring retractor with hooks aides in visualization. Cystoscopy is performed to localize the fistula tract, and a guide wire is placed though the fistula into the vagina. A 10–12 French foley catheter should be placed though the fistula site, using the previously placed guide wire. This catheter provides traction of the fistula toward the introitus throughout the case. Ureteral stents are placed if the fistula is in close proximity to the ureteral orifices. A urethral catheter is placed, and a supra-pubic catheter may also be utilized for bladder drainage. An

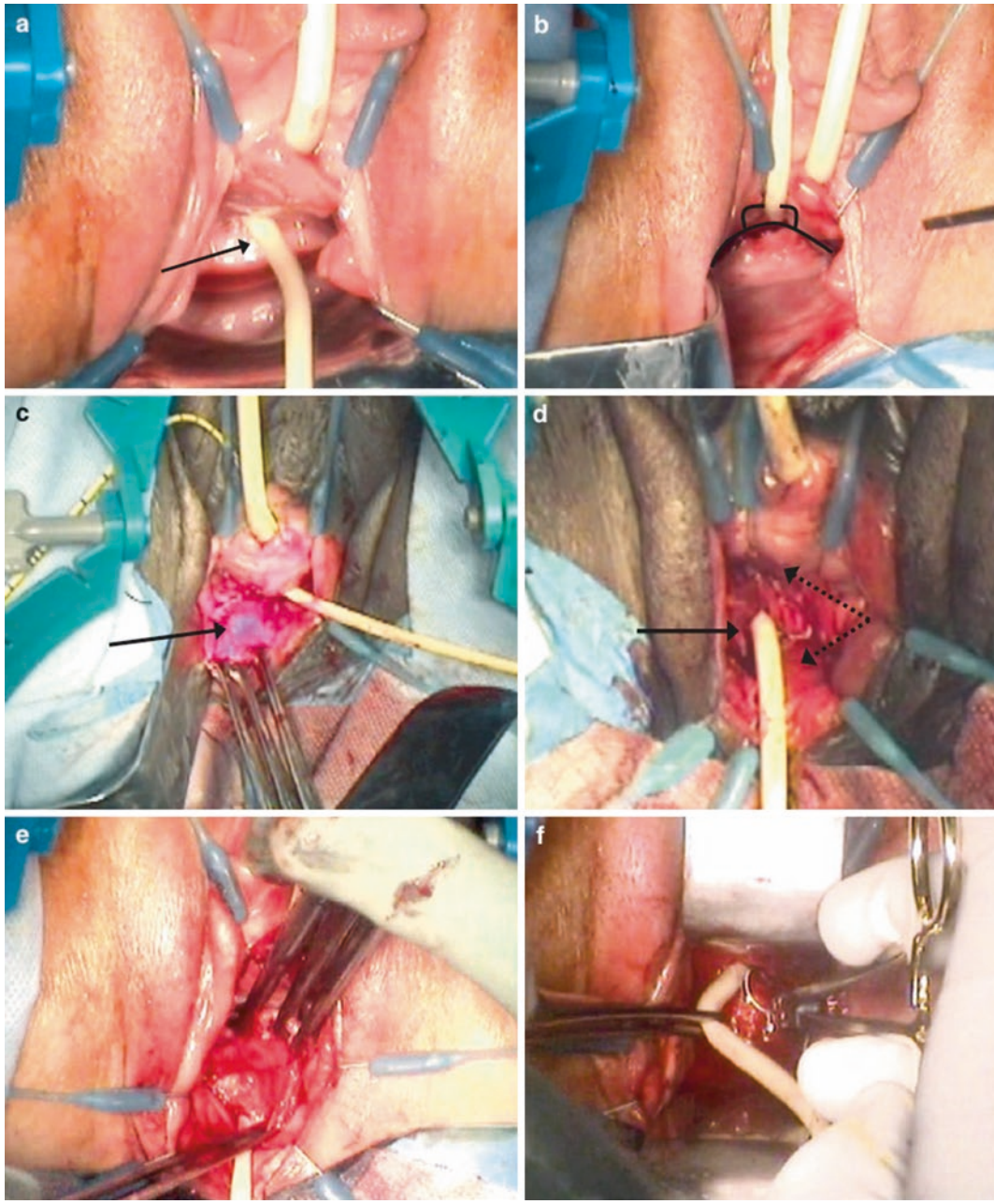

Fig. 31.3 (**a–j**) Transvaginal repair of vesicovaginal fistula. (**a**) Foley catheter within the urethra and vesicovaginal fistula (*arrow*). (**b**) anterior curvo-linear vaginal wall incision (*black line*) incorporating the fistula site. (**c**) Dissected posterior vaginal wall flap (*arrow*) retracted inferiorly. (**d**) Perivesical tissue (*solid arrow*) and retracted superior and inferior vaginal wall flaps (*dashed arrow*). (**e**) Dissection of perivesical tissue from the underlying detrusor muscle to provide an additional layer of closure. (**f**) initial suture placement, closing the detrusor and bladder mucosa. (**g**) Sutures retracted to visualize the initial layer of closure. The foley catheter is then removed from the fistula, and the sutures are tied. (**h**) Second line of closure with imbricated interrupted sutures to reinforce the initial layer of closure. (**i**) Third tissue layer of inter- rupted sutures, bringing together the previously dissected perivesical fascial layers. *Arrows* identify the perivesical tissue flaps. (**j**) Closure of the vaginal wall (reprinted from Chapple)

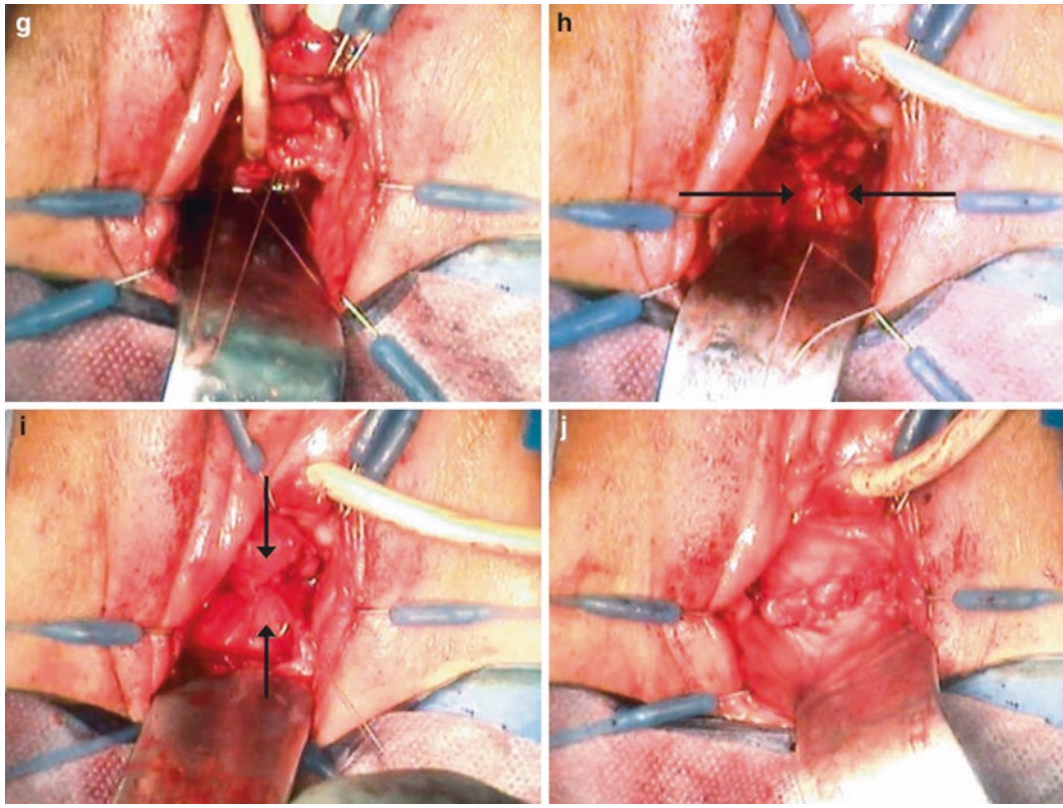

Fig. 31.3 (continued)

inverted U-shaped incision is made which circumscribes the fistula site. Anterior and posterior vaginal wall flaps are developed after hydro-dissection with sterile saline and retracted using the ring retractor. An alternative to the inverted U incision is the Latzko procedure. In this case an elliptical incision is made around the fistula tract including a small rim of vaginal epithelium, and the surrounding vaginal wall is mobilized for eventual closure [56]. In the case of either approach, the fistula is then closed in an interrupted fashion, typically using double-armed synthetic absorbable suture (SAS), The perivesical tissue is then closed over the initial suture line in an interrupted imbricated fashion, 90° with respect to the first layer. A peritoneal flap or a Martius flap can be positioned over the imbricated layer of perivesical tissue. The posterior vaginal wall flap is advanced over the suture line anteriorly to complete the closure.

Interpositional Tissue Flaps

As mentioned above, adjacent tissue flaps can be useful to reinforce repairs in the setting of radiotherapy, obstetric fistula, large fistula tracts or other complex fistula in which surrounding tissue quality may be compromised. Pshak et al. found that prior failed repair did not diminish success rates among patients undergoing VVF repair without interposition, leading them to conclude that recurrence alone is not an indication for interposition [57]. In common practice, however, flaps are still often used in cases of prior failure. Transvaginal and transabdominal approaches offer different options for these tissue flaps. For patients undergoing a transvaginal approach, a labial fat pad (Martius) or peritoneal flaps are most frequently utilized with success rates of greater than 90% [7, 39, 58–60]. The Martius graft is harvested from the fibrofatty tissue of the labia majora. It maintains blood supply from the

external pudendal artery superiorly or the inferior labial artery inferiorly, allowing rotation and mobilization from either pedicle. Once mobilized via a labial incision, this flap can be tunneled into the vaginal dissection for an additional layer of fistula closure. Overall martius flaps have very low complication rates and cause minimal anatomic distortion [58, 61]. In high VVF repairs from a transvaginal approach, the peritoneum is often encountered during the course of dissection. The peritoneum can be advanced over the fistula repair as an additional layer of closure, with success rates of 91–96% [7, 54, 62].

As noted previously, omental interposition flaps are useful adjunctive procedures when performing transabdominal VVF repairs. Interposition flaps or peritoneal flaps can be incorporated into transabdominal fistula repairs between bladder and vaginal wall suture lines. The omental vascular supply is based on the right and left gastroepiploic arteries. In order to provide sufficient length for the flap to reach the pelvis, the omentum can be mobilized along the greater curvature of the stomach, sacrificing the left gastroepiploic artery and allowing larger right gastroepiploic artery to maintain blood supply.

Urethrovaginal Fistula

Etiology and Presentation

As with VVF, the etiology of urethrovaginal fistulae are strongly linked to the part of the world in which they occur. In the industrialized world, these fistulae are relatively rare and typically occur in the context of prior vaginal surgery, such as anti-incontinence procedures, anterior prolapse repair and urethral diverticulectomy [63–66]. Though an uncommonly reported cause of urethrovaginal fistula, the widespread utilization of synthetic midurethral slings could potentially conceivably lead to this lesion occurring in greater numbers in the future. Pelvic radiation, trauma, including pelvic fracture, and vaginal and urethral neoplasms are less common causes of urethrovaginal fistula. In non-industrialized nations, obstructed labor is the most common cause, creating large complex fistulae often containing urethrovaginal and vesicovaginal components [67]. Congenital urethrovaginal fistulae due to cloacal or other anomalies are a distinct cause of urethrovaginal fistula, which often require complex repair, and will not be considered further here. In female patients with long-term indwelling urethral catheters and cognitive or sensory impairments, pressure necrosis of the urethrovaginal septum can result in hypospadiac urethrovaginal fistulae. Such individuals often require bladder neck closure and urinary diversion [68].

Symptoms of urethrovaginal fistula are dependent on the size of the fistula and its location relative to the urethral sphincter. Large fistulas are more likely to present with continuous large volume incontinence, whereas small fistulas may produce only a small amount of leakage. Fistulas proximal to the urethral sphincter mechanism, either in the proximal urethra or at the bladder neck, can present with continuous incontinence, similar to VVF. Fistulas distal to the sphincter can be asymptomatic or present with a splayed urinary stream. Occasionally, patients will present with vaginal voiding or "pseudo-incontinence," due to accumulation of urine within the vaginal vault following micturition. These patients will leak when rising from a seated position after voiding. Such a presentation can be due to an occult urethrovaginal fistula or, alternatively, vaginal voiding due to aberrant anatomy such as a receded urethral meatus.

Diagnosis and Management

The diagnosis of urethrovaginal fistula can be made based on history, physical exam, and cystourethroscopy, and radiologic imaging. A thorough pelvic exam is essential though sometimes limited. Speculum examination can occasionally identify the fistula tract on the anterior vaginal wall, however natural rugation of the vaginal wall can make visualization difficult. Vaginal tissues should be inspected for viability, infection, and atrophy, and treated with antibiotics or estrogen cream as needed. On exam one must be cognizant of the possibility of additional pathology, particularly given that an associated VVF is found in up

to 20% of patients [69]. Cystourethroscopy is an essential, yet challenging, process due to the short length of the female urethra. Distal compression at the meatus, and a short beak "female" cystoscope or flexible fiberoptic cystoscope can assist in visualization. The bladder neck and bladder should be examined for an additional fistula. Voiding cystourethrography can aid in assessment of the anatomic relationship of the fistula to the bladder neck and sphincter, and can at times identify secondary fistulae. This can be done in conjunction with urodynamics, particularly if a component of stress or urgency incontinence is suspected, or if the patient has suspected concomitant detrusor dysfunction.

Surgical repair of urethrovaginal fistulae is guided by the same principles as VVF repair. They can present added difficulty, however, as a result of extensive soft tissue defects and a dearth of viable tissue for a multilayered closure. These challenges make careful consideration and operative planning essential [10]. Distal fistulas can be managed conservatively with observation or extended meatotomy if there is no associated incontinence or voiding symptoms [70]. If formal repair is elected, timing of the operative intervention is controversial, similar to VVF.

The surgical approach is similar to that of a VVF, with both inverted U and Latzko incisions described [71, 72]. The fistula tract itself may or may not be excised, but it should be left in place if excision would significantly enlarge the defect and complicate closure. The placement of a urethral catheter into the bladder aides in further dissection and mobilization of the surrounding tissues. Depending on the size and location of the fistula, extensive mobilization of the vaginal wall may be necessary to expose adequate periurethral fascia. Multilayer closure begins with approximation of healthy urethral edges transversely in an interrupted fashion using dissolvable monofilament suture. This mucosal layer should be watertight. The mobilized periurethral fascia is then approximated in a perpendicular orientation as a second layer of closure. As with VVF, various forms of tissue interposition can serve as s useful adjuncts to decrease failure rates, particularly in larger fistulae or those with more attenuated periurethral fascia [10, 66, 73, 76, 77–81]. Some larger fistula may require more extensive surgery involving urethral reconstruction [67, 74, 75].

An additional level of complexity often exists in urethrovaginal fistulae associated with midurethral slings. This is a relatively rare entity, described in case reports and small series [82–87]. Urethral erosion occurs in 0.5% of midurethral slings [88], and only a subset of these cases will result in fistula formation. The cause of erosion may be related to technical factors such as urethral injury or overtensioning, or to sling migration or inflammatory "rejection" of the synthetic material. Removal of the eroded mesh involves extensive anterior vaginal wall dissection and identification of the sling arms lateral to the midline, where they are divided. The arms are carefully dissected medially, freeing them from the periurethral fascia approaching the urethra. If possible, one arm may be pulled through the urethral lumen out the contralateral defect. The intraurethral portion of the sling can then typically be dissected free with minimal disruption of the ventral urethral wall. The remaining urethral defects are then closed using interrupted dissolvable monofilament closure in a watertight fashion. A multilayer closure is then completed with or without tissue interposition in the manner described above.

In the small series of women undergoing urethrovaginal fistula repair in conjunction with removal of eroded urethral slings, postoperative incontinence rates of 28–71% are reported [86, 87]. In these patients, or in patients with pre-existing SUI undergoing urethrovaginal fistula repair, there should be a discussion regarding an anti-incontinence procedure. Excellent outcomes have been shown with both concomitant and staged sling placement in patients undergoing mesh removal due to transvaginal sling related complications [89]. The decision to combine or stage these procedures should be based on an assessment of the patients' level of incontinence or the risk for the development of incontinence. If the decision is made to undergo concomitant anti-incontinence surgery, the use of mesh must be

avoided and placement of an autologous fascial pubovaginal sling is preferred [90]. The decision to stage does provide does proved two advantages—the avoidance of morbidity in a subset of patients who ultimately will not need (or not want) an anti-incontinence procedure, and the freedom to use either autologous or synthetic materials in the second surgery.

Ureterovaginal Fistula

Etiology and Presentation

Fistulas from the ureter to the urogenital tract are uncommon, most frequently involving the proximal vagina and rarely the uterus or fallopian tubes [91]. Risk factors include endometriosis, obesity, pelvic inflammatory disease, radiation therapy, and pelvic malignancy [92]. Iatrogenic injuries during pelvic surgery, specifically gynecologic surgery, are the most common etiologies of ureterovaginal fistulae (UVF), with the incidence estimated at 0.5–2.5% [92, 93]. Most commonly, UVF result from surgeries for benign disease, during hysterectomy, caesarean section, or cystocele repair [94] rather than oncologic procedures. Risk of injury appears greatest from laparoscopic hysterectomy, followed by abdominal, then vaginal hysterectomy [95]. The ureter is injured in the distal one third or pelvic portion, due to its close proximity to the uterosacral ligaments, uterine artery, and cervix. Direct injury or devascularization with subsequent necrosis can cause urinary extravasation, urinoma formation, and eventual drainage into the vagina at the level of the vaginal cuff.

Patients typically present with clear or serous continuous vaginal discharge 1–4 weeks following the surgery in question [94]. Occasionally, this is associated with a prodrome of flank or abdominal pain, nausea and low-grade fevers. These symptoms can be a result of urinoma formation and/or ureteral obstruction [69]. In contrast to VVF, patients will continue to urinate at normal intervals, as the contralateral kidney maintains cyclic bladder filling.

Diagnosis and Management

Diagnosis of a ureterovaginal fistula can usually be accomplished with a complete history and physical examination, followed by radiologic evaluation with studies, including intravenous urogram (IVU)/CT urogram (CTU), cystoscopy, retrograde pyelography, and cystography (Fig. 31.4). It is imperative to distinguish UVF

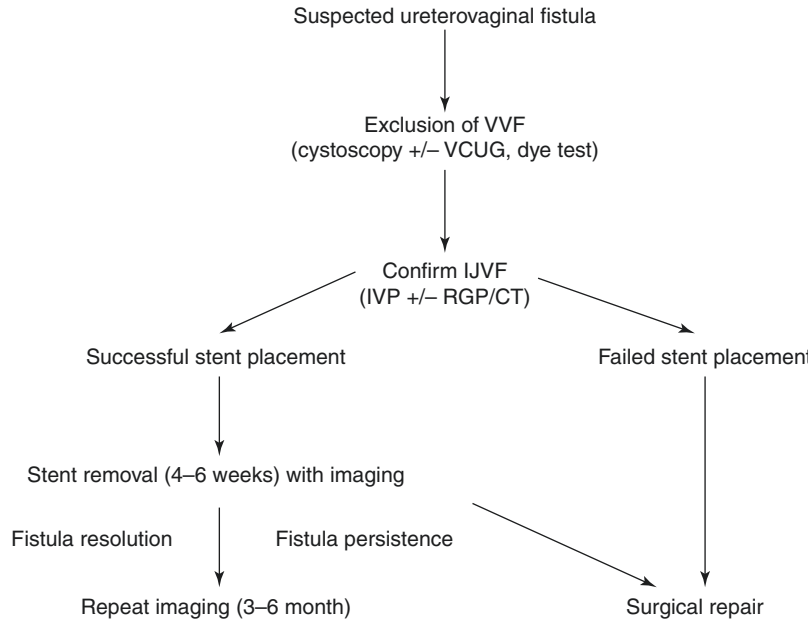

Fig. 31.4 Algorithm for the diagnosis and management of ureterovaginal fistula

from VVF and evaluate for concomitant VVF during the course of evaluation. A double dye test is an easy and cheap test to perform which may allow differentiation of UVF and VVF in cases of continuous leakage (Table 31.2). It involves oral administration of a medication such as phenazopyridine, which colors the urine orange, along with intravesical instillation of a dye such as methylene blue or indigo carmine, which is blue. A tampon, pad or gauze is inserted into the bladder. If it turns blue, VVF is suspected. If it turns orange, UVF is suspected. If both colors are present there may be concern for the presence of two lesions [23].

Once the physical exam, cystoscopy, and cystography have ruled out VVF, attention should be turned to upper tract evaluation (Fig. 31.5). An IVU or CT urogram (CTU) will often demonstrate some degree of ureteral dilation or pelviectasis as a result of varying degrees of distal obstruction [96]. Vaginal drainage can be identified on post-void images if the caliber of the fistula is large. CTU can assess ureteral anatomy as well as investigate for abscess, urinoma or additional intra-abdominal pathology. Retrograde pyelogram may be the best test to diagnose a ureteral injury and can usually identify the fistula site or level of ureteral pathology [93]. If ureteral continuity or patency is confirmed in the presence of a fistula, then an attempt at a period of drainage with indwelling ureteral stent is warranted. Seltzman et al. demonstrated complete resolution of ureterovaginal fistulae in 7 of 7 patients in whom ureteral stenting was performed [96]. Others found similarly encouraging results [97, 98].

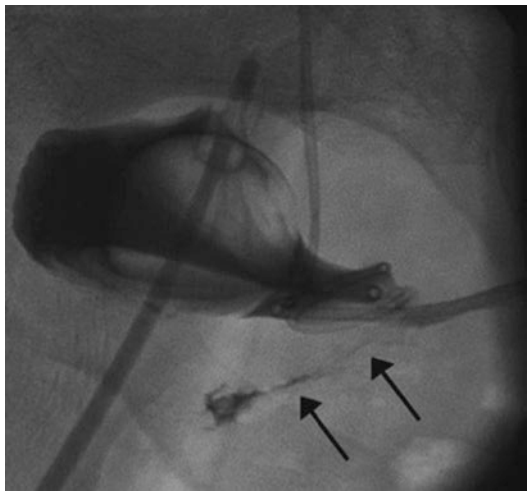

Fig. 31.5 Anterograde pyelogram in a patient with bilateral nephro-ureterostomy tubes and indwelling foley catheter. *Arrows* identify the ureterovaginal fistula

Once the diagnosis of ureterovaginal fistula is confirmed, prompt drainage of the upper tract is essential. Partial or complete obstruction is often present at the level of the fistula, which can lead to progressive renal damage, infection, or sepsis. If retrograde stent placement at the time of retrograde pyelogram is unsuccessful, antegrade stent placement at the time of percutaneous nephrostomy placement can be attempted. Conservative management with ureteral stenting will occasionally result in fistula closure. In a study by Dowling et al., 11 of 23 patients with ureteral injuries recognized postoperatively had fistula closure with stenting or percutaneous drainage alone [99]. If leakage persists, or complete ureteral occlusion is identified, then formal surgical repair is warranted.

The ureter is approached transabdominally. The site of primary injury at the distal ureter is generally surrounded by fibrosis and inflammation, precluding primary ureteroureterostomy. After dissection from surrounding tissues, division of the ureter just above the level of injury, and confirmation of the viability of the proximal margin, the ureteral length is usually adequate for ureteroneocystostomy. Psoas hitch or Boari flap can provide additional length for a tension free anastomosis. These procedures have been well described laparoscopically and robotically as well, utilizing straightforward adaptations of the open technique [100–102].

There have been a small number of reported cases of transvaginal repair of ureterovaginal fistulae. These have been performed utilizing techniques similar to transvaginal VVF repair. One description involved creation of a U-shaped vaginal flap, closure of the ureteral tissue without tract excision, interposition of the endopelvic fascia, and final flap closure. The patient is discharged without a foley and a ureteral stent is left in place

for 6 weeks [103]. Another reported case utilized the Latzko technique with partial vaginal obliteration [104]. All cases were reported to be successful at follow-up. The authors stress that follow-up imaging is essential due to the risk of obstruction due to ureteral narrowing. They ultimately conclude that transvaginal ureterovaginal fistula repair may be considered in the setting of ureteral patency, small fistula size, transvaginal accessibility and patient comorbidities that increase the risk of transabdominal intervention [103].

In patients with extensive ureteral damage, trans-ureteroureterostomy, ileal interposition, or renal autotransplant can be an option. If extensive renal injury has already occurred, nephrectomy may be the most expeditious form of management. Successful repair of ureterovaginal fistula occurs in greater than 90% of cases [12, 94].

Vesicouterine Fistula

Etiology and Presentation

Vesicouterine fistulae are rare, with little more than 100 cases reported in recent literature [105]. Caesarean section is the most common etiology of this type of fistula, with the majority occurring during repeat sections [106]. Numerous case reports of other etiologies include vaginal deliveries after caesarean section, radiation, iatrogenic catheter trauma, or placenta percreta [107–110]. Although congenital vesicouterine fistulae have been reported, they are a separate clinical entity requiring complex reconstruction, often in the setting of multiple anomalies with other clinical implications, and will not be considered further here.

Following uterine rupture during labor, the posterior bladder wall can be torn along the margin of the rupture leading to eventual vesicouterine fistula formation. Unrecognized injury to the bladder at the time of uterine surgery or incorporation of the bladder into a uterine suture line can also result in fistula. The most common location for vesicouterine fistula is from the posterior midline bladder wall to the uterus above the proximal cervical margin. Because the cervical os is generally closed, patients may not present with incontinence. Continuous incontinence can occur in cases of cervical incompetence, or immediately following vaginal delivery when the cervical os is incompetent [105]. Patients may also present with menouria and cyclic hematuria in the setting of urinary continence. "Youssef's syndrome" describes this symptom complex of menouria, cyclical hematuria, apparent amenorrhea, infertility, and continence of urine [105]. This must be differentiated from endometriosis of the bladder.

Diagnosis and Management

A history of prior uterine surgery in the setting of compatible symptoms as described above is strongly suggestive of a vesicouterine fistula. Cystoscopy, hysteroscopy, and radiologic imaging can assist in definitive diagnosis. Cystoscopy can visualize the fistula tract along the posterior bladder wall. Urine cytology may reveal endometrial cells during workup of hematuria. Cystogram or hysterosalpingogram can identify the abnormal flow of contrast via the fistula tract from urinary to genital tracts. In cases of continuous incontinence, VCUG and CTU can be utilized to rule out the presence of coincident VVF or ureterovaginal fistula.

Successful treatment of vesicovaginal fistula has been well documented using conservative as well as surgical management. Watchful waiting with spontaneous fistula resolution, urinary diversion with prolonged catheterization, and hormonally induced uterine involution have all been described with successful outcomes [111–113]. Surgical intervention can include hysterectomy with primary closure of the bladder. If the patient desires fertility, uterine sparing surgery can be performed in a technique similar to the O'Conor transabdominal VVF repair with or without omental interposition. Full-term deliveries have been reported following such repairs [114]. Laparoscopic and robotic assisted repairs have been described [115, 116].

Uroenteric Fistula

Vesicoenteric Fistula

Vesicoenteric fistula is most likely to occur in the setting of bowel diseases such as diverticuli-

tis, colorectal carcinoma, and Crohn's disease. Less commonly, radiation, infection, trauma, or iatrogenic surgical injury can result in fistula formation. Approximately 2% of patients with diverticulitis will develop vesicoenteric fistulas secondary to their disease, and these patients account for approximately 70% of all diagnosed colovesical fistulas [117–119]. Ileovesical fistulae are more common in Crohn's disease patients, who have a 2% incidence of vesicoenteric fistula formation [120]. Symptoms of vesicoenteric fistula can be gastrointestinal or urologic. Pneumaturia is the most common presenting symptom, occurring in 70% of cases [121]. Persistent or recurrent UTI or cystitis refractory to antibiotic management may suggest colovesical fistula [122].

Endoscopic and radiologic imaging can be helpful in diagnosis. Cystoscopic examination is sensitive for detecting mucosal abnormalities such as erythema or bullous edema in >90% of cases, but is not definitive for a fistula diagnosis [123]. A biopsy is indicated at the time of endoscopic evaluation to rule out malignancy. CT scan is the most sensitive and specific modality for the diagnosis of colovesical fistula [118]. Identification of the bladder adjacent to a thickened loop of colon, air within the bladder, and colonic diverticula are highly suggestive of a possible fistula [124]. If there is question of a subclinical fistula, the diagnosis can be confirmed by oral administration of activated charcoal, which will appear in the urine as black particles [125].

Conservative management of vesicoenteric fistula includes bowel rest with total parenteral nutrition and antibiotics in patients with minimal symptoms and no evidence of toxicity [126]. In accordance with the general principles of fistula repair, optimization of nutritional status is important. Surgical intervention can be complicated due to the inflammation and scarring associated with fistula formation. Both single stage and staged operations employing fecal and/or urinary diversion have been described depending on the circumstances of the individual case including stool contamination, nutritional status of the patient and other factors. Often resection of the involved bowel segment is necessary. With respect to the urinary tract, dissection should continue until viable tissue margins are obtained for bladder closure. An omental flap can be used to prevent overlapping suture lines and recurrence of the fistula [38]. If the patient is acutely ill, or abscess or obstruction complicates the procedure, bowel diversion with later reanastomosis (two-stage repair) should be considered [127].

Pyeloenteric Fistula

Pyeloenteric fistula can develop from inflammatory diseases of the kidney, such as xanthogranulomatous pyelonephritis, tuberculosis, chronic pyelonephritis, or inflammatory diseases of the bowel, such as Crohn's disease [128–130]. Iatrogenic trauma from percutaneous nephrolithotomy access and lithotripsy has been associated with an increasing number of fistulas involving the duodenum or the colon in left sided intervention [131]. Cryoablation or alternative minimally invasive renal tumor surgery can result in fistula formation [132]. The majority of patients have nonspecific symptoms of malaise, mild GI symptoms, urinary frequency, flank mass, or tenderness; however, many fistulas are diagnosed incidentally on radiographic imaging [128, 133]. If there is a suspected pyeloenteric fistula, urinary or GI contrast-based imaging with traditional or CT urography, retrograde pyelogram, nephrostogram, barium swallow, or contrast enema can confirm the diagnosis. Conservative management with large nephrostomy tubes, bowel rest, antibiotics, or internal stenting may result in fistula resolution [128]. Definitive treatment includes open primary repair if renal preservation is desired or nephrectomy with bowel closure for a poorly functioning renal unit.

Urethrorectal Fistula

Rectourethral fistulae (RUF) can be extraordinarily difficult to treat. Management strategies must take into account, among other things, the underlying cause, the size and location and complexity of the lesion, the health and viability of

the surrounding tissue, and the functionality of the fecal and urinary continence mechanisms. This abundance of variables has inspired a wide range of surgical approaches without any becoming a true standard.

Etiology and Presentation

Acquired RUF has been reported in association with a variety of clinical situations. They may arise as a result of local trauma, pelvic malignancy, or inflammatory or infections conditions effecting the GU or lower GI tract. Many causes of RUF are iatrogenic, most often in association with the treatment of prostate cancer [38]. The classic scenario of RUF development involves an unrecognized rectal injury at the level of the vesicourethral anastomosis during a radical prostatectomy [134]. Thomas et al. performed a retrospective review of 2447 patients who underwent an open radical prostatectomy and found that the rate of RUF formation was significantly higher after perineal prostatectomy (1.04%) than after retropubic prostatectomy (0.34%). Among the patients who developed RUF, 54% had an identified intraoperative rectal injury, which was closed in 2 layers [135]. In a large modern series of 6650 robotic-assisted laparoscopic prostatectomies, the rate of rectal injury was 0.17% and the overall rate of RUF was .06% [136]. Prior history of pelvic radiation, rectal surgery, or TURP increases the risk of RUF formation following prostate surgery [134].

In the modern era, however, with the proliferation of multimodal treatment for prostate cancer, energy based ablative therapies are playing an increasing role in fistula formation [137]. One systematic review found that prior to 1997 <4% of RUF occurred in patients with a history of pelvic radiation, while since 1997 50% had received external beam radiation, brachytherapy or combination therapy [138]. Primary treatment of prostate cancer via brachytherapy is accompanied by a 0.4% risk of RUF [139]. Contemporary series of patients undergoing primary whole gland cryoablation for prostate cancer report fistula rates of 0.5–1.2% [140–142]. When cryoablation is used as a salvage treatment after radiation the risk of RUF rises to 1–3.3% [143, 144]. High intensity focused ultrasound (HIFU) as a primary treatment carries a 1.2–2% risk of fistula formation, and as high as 4.5–6.5% risk when used in the salvage setting [145–147]. The risk of RUF associated with HIFU does appear to diminish as technology and protocols evolve [148].

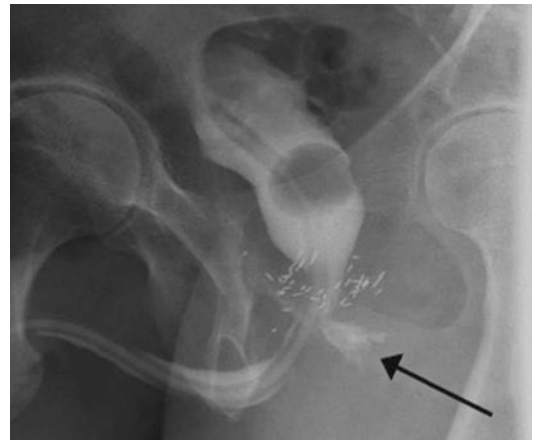

Fig. 31.6 Voiding cystourethrogram in a patient with history of brachytherapy for prostate cancer. *Arrow* identifies the rectourethral fistula

Patients may present with urologic complaints of UTI, fecaluria, pneumaturia, hematuria, or gastrointestinal problems such as watery stools, nausea, vomiting, or peritonitis. Visualization of the fistula via cystoscopy and proctoscopy/sigmoidoscopy is essential to determine the location of the fistula relative to the urinary and anal sphincters, respectively. It also provides an opportunity to assess the health of surrounding tissues, identify other pathology and obtain biopsies to rule out malignancy. Voiding cystourethrogram or retrograde urethrogram can allow definitive diagnosis and provide more details of anatomic location and fistula size (Fig. 31.6). In cases of high index of suspicion for RUF but negative studies, an oral activated charcoal test or a poppy seed test can be performed, where the eponymous substance is ingested and then tested for in the urine as an indication of direct transit from the GI tract.

Diagnosis and Management

As stated above, decision-making must take into account the function of the urethral and anal sphincters, the presence of concomitant lesions

such as urethral stricture or bladder neck contracture, the size and location of the fistula and the health of the surrounding tissue. Assessment and optimization of nutritional status is paramount to recovery and healing. In select patients with small minimally symptomatic fistulae, spontaneous closure can rarely be achieved with urinary catheter drainage alone, in conjunction with hyperalimentation and antibiotics. In patients who are suffering from fecaluria, recurrent UTIs or sepsis, severe incontinence or pain associated with an RUF, fecal diversion in the form of a colostomy should be performed as well. A small subset of these patients may experience spontaneous resolution with this intervention alone [135, 149].

In most cases, however, surgical closure of RUF is ultimately necessary [150]. Surgery is typically delayed anywhere from 2–3 months to achieve control of local inflammation, and as long as 6 months in cases involving radiation [135, 151, 152]. Decisions regarding fecal diversion, tissue interposition and surgical approach should be made on a case-by-case basis based on patient factors and surgeon experience.

Fecal diversion, as discussed previously, should be performed several months prior to definitive repair in patients who are highly symptomatic, have a history of radiation or have evidence of severe inflammation. In patients who proceed to repair without pre-op diversion, diversion at the time of surgery may be unnecessary in select cases. In situations where fistulas are larger in size, radiation or cryotherapy induced, associated with poor tissue quality or for any other reason the closure is at all tenuous, fecal diversion is strongly recommended if not mandatory [94, 153, 154]. Tissue interposition is also advised in complex cases where tissue integrity is in question. The most common form of this is the gracilis muscle flap. The gracilis is a long, thin muscle from the medial thigh. It functions in knee flexion and thigh adduction, however harvesting it causes no significant loss of function. Rotation of the gracilis into the site of repair provides reliable, robust and healthy tissue to reinforce a potentially tenuous closure. The use of buccal mucosa graft interposition has been described as well, with and without utilization of a gracilis flap [155, 156].

A variety of surgical approaches have been described for the repair of RUF, among them transperineal, transrectal, transsphincteric, transabdominal and abdominoperineal. Transperineal is by far the most common approach, typically performed in an anterior anal-sphincter sparing fashion [138]. This involves an inverted U incision anterior to the anal verge carried laterally to the ischial tuberosities. Dissection is carried along the medial aspect of the ventral rectal wall across the GU diaphragm until the plane between the rectum and the prostate can be developed. Once identified, the fistula can be transected, debrided and closed on both the rectal and urethral sides. Via this approach, a gracilis can be easily rotated and secured into a position separating the two suture lines. Success rates of anterior perineal repair have been reported as high as 95% [137].

Another notable approach is the transanosphincteric York-Mason repair. This involves placement of the patient in a prone jackknife position. An incision is carried from the tip of the coccyx to the anal verge, and down through the posterior rectal wall and anal sphincter. Great care is taken to stay in the midline and tag each individual muscular layer of the sphincter for subsequent reconstruction. This typically provides excellent exposure of the anterior rectal wall and the fistula. This fistula tract can then be excised, and the rectal and urethral walls separated and closed individually. This procedure is well suited for small post-surgical fistulas. It should not be performed in more complex fistulas as the ability to perform flap interposition or more involved urethral reconstruction is severely limited. Proper reconstruction of the external anal sphincter results in very limited post-operative fecal incontinence, nonetheless, this procedure should not be attempted in patients with preexisting bowel dysfunction [157].

Transabdominal repair can be performed, often in conjunction with omental flap interposition. The downsides to this approach are the increased morbidity associated with abdominal surgery and the difficulty exposing and reaching the fistula, which is typically deep within the pelvis. These issues may be alleviated somewhat via a robotic-assisted laparoscopic approach [158].

In patients with very complex strictures or those that have proved recalcitrant to repair, permanent urinary diversion should be considered, though the associated complication rates are high [159].

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Urothelial Cancer of the Upper Urinary Tract

32

Steffen Rausch and Arnulf Stenzl

Introduction

Although urothelial carcinoma of the bladder is the fourth most common cancer entity in men, upper urinary tract (UTT) cancer is rare, since these tumors represent only 5–10% of urothelial tumors [1, 2]. Men are affected 3× as often as women and tumors of the renal pelvis occur about twice as frequently as tumors of the ureter [3]. Moreover, a bladder tumor exists concurrently in about 17% of cases of a UUT tumor [4]. An intravesical recurrence after UUT tumors is observed in 22–47% of cases [2]. In general, recurrences in the contralateral UUT are rare with only 2–6% [2, 5, 6].

In stark contrast to urothelial bladder tumors, 60% of newly diagnosed UUT tumors are found at an invasive tumor stage (>T1) [7]. UUT tumors invading the muscle layer are associated with a poor prognosis. The 5-year survival rate is less than 50% for pT2/3 tumors and below 10% for pT4 tumors [8, 9].

Radical nephroureterectomy (RNU) is the gold standard for operative management of larger UUT tumors. However, kidney-preserving therapy strategies are being used with increased frequency for tumors affecting the ureters only [10]. RNU is regularly performed with the inclusion of a bladder cuff resection (BCR) and surgery may be performed via an open, laparoscopic or robot-assisted approach along with a lymph-node dissection [11]. Interestingly, retrospective SEER Database analysis including T1-T3 N0 M0 patients with UUT cancer found no significant 5-year overall survival or cancer specific survival benefit utilizing bladder cuff resection, despite the observation of a growing number of guideline conform performance of bladder cuff resection, in 68% of all patients [12]. A systematic review of available, merely retrospective data confirms that laparoscopic RNU is a safe method as compared to open surgery with similar minor and major complication rates and offers beneficial effects such as reduced blood loss, transfusion rates and shorter hospital stay [13]. No differences in 5-year recurrence rates or cancer specific survival could be observed [13]. Noteworthy, longer operation time has been reported for the both the conventional and robotic minimal invasive approach [11, 13]. The issue of how an oncologically safe and surgically standardized BCR may be accomplished during a minimal invasive procedure represents a relevant question still to be answered, given the variable techniques described in the literature. BCR may be performed through a transvesical, extravesical, or endoscopic approach and currently, these methods include open excision via a Gibson incision, transurethral resection (TUR) of

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ureteral orifice (pluck technique), ureteric intussusception, and pure laparoscopic or pure robotic-assisted laparoscopic resection techniques [14]. Irrespective of the surgical approach, a single postoperative dose of intravesical mitomycin C appears to reduce the risk of a bladder tumor within the first year following RNU for UUT cancer. An absolute risk reduction of 11% was reported in a prospective randomized trial, while the relative risk reduction was 40%, and the number needed to treat to prevent one bladder tumor was nine [15].

Recent study results, which describe prognostic disadvantages of reduced kidney function after RNU, highlight the principle of organ-preserving therapy, also in patients without imperative indications for organ preservation [16] and have led to a more frequent utilization of endoscopic approaches in urothelial cancer. By contrast, given the paucity of published data for non-urothelial cancer of the UUT, treatment for aberrant histology usually requires radical surgery [17, 18].

Diagnostics and Imaging of Tumors of the Upper Urinary Tract

With the establishment of modern computer tomography (CT) techniques, excretory urography has finally lost its relevance in the diagnostics of UUT tumors, and it is no longer discussed in the current guidelines [2]. Nonetheless, it still represents an established diagnostic tool in the clinical routine. Retrograde ureteropyelography is frequently used for the assessment of the upper urinary tract, because of the possibility of simultaneous cystoscopic evaluation. Moreover, a selective urine sample from the renal pelvis can be obtained for cytological analysis prior to application of contrast agents.

With a sensitivity of 67–100% and a specificity of 93–99%, CT imaging is the technique with the highest diagnostic precision for UUT tumors [19, 20]. Performing a urographic phase, 10–15 min after application of contrast agents, is necessary for meaningful diagnostics. The diagnostic advantage of CT in comparison to excretory urography is the option to also detect a contrast-enhanced thickening of the wall of the renal pelvis or the ureter in the arterial or portal-venous phase, without the existence of a urographically suspicious area.

Analogously to excretory urography, the glomerular filtration rate should not fall below 45 mL/min during the i.v. application of contrast agents containing iodine [21].

In cases of intolerance of contrast agents, magnetic resonance (MR) urography is, besides retrograde pyelography, the diagnostic alternative of choice. For UUT tumors <2 cm, the sensitivity of MR urography around 75% [22]. The kidney function of the patients should be given consideration also for MR urography, since gadolinium increases the risk of renal systemic sclerosis in patients with chronic renal insufficiency or at a glomerular filtration rate <30 mL/min [23].

Biomarker Analysis

In the diagnostic work up for UUT cancer in cases of positive urine cytology and after cystoscopic exclusion of a bladder tumor, it should be kept in mind that the sensitivity of urine cytology is lower for the upper urinary tract than for bladder tumors. This is true also for carcinoma in situ (CIS). This fact is discussed as the consequence of a smaller size of UUT lesions and a lower likelihood of shedding of UUT cells in comparison to bladder tumors [24]. Urine cytology of the upper urinary tract should always take place before application of large quantities of contrast agents during retrograde urography, in order to not negatively influence the quality of the cytology specimen [24]. Furthermore, Guidelines recommend performing the urine cytology in situ, thus for example directly in the renal pelvis [2]. Fluorescence in-situ Hybridization (FISH) reportedly has a sensitivity of 56% and a specificity of 80% for UUT tumors [25]. Similar to the case for urothelial cancer of the bladder, a decisive limitation is especially the low sensitivity for low-grade tumors, e.g. during follow-up after organ-preserving therapy of a UUT tumor [25]. However, conversely, in a

recent comparative analysis of lower vs. upper tract urine specimen, UUT-derived samples outperformed bladder-derived urine samples and reached sensitivities for cytology, FISH, NMP22, and uCyt+ were 74.6, 79.0, 100.0, and 100.0, while specificities were 66.6, 50.7, 5.9, and 66.7%, respectively. Concomitant existence of urothelial cancer in the bladder led to false-positive findings in UUT-urine analysis [26]. With regard to prognostic molecular biomarkers for treatment selection, to date, limited evidence is available and guideline recommendations are yet focusing on clinical and pathological parameters for risk stratification.

In preliminary studies, serum derived and surgery specimen derived microRNAs (miRNAs) were identified to be potentially useful as minimally invasive predictive biomarkers of tumor progression and survival in UTUC patients [27, 28]. Within a total of 800 candidate miRNAs, 38 differentially expressed miRNAs were identified to discriminate between progressing and non-progressing UTUC patients ($p < 0.05$). Validation of these 38 miRNAs in an independent set of UTUC patients confirmed the differential expression in 18 of them ($p < 0.05$). Cox Regression analysis showed miR-151b and pathological stage as significant prognostic factors for tumor progression and cancer specific survival [27].

Endoscopy

The method of choice for the evaluation of the UUT is diagnostic (flexible) ureterorenoscopy with the option of simultaneously taking a biopsy. Tumor detection by biopsy and prediction of the grade of differentiation is successful in 90% of the cases, with a low false-negative rate [29]. Nonetheless, undergrading and understaging is possible through the use of biopsies. A reliable differentiation of invasive and non-invasive lesions is made difficult both because of the anatomical features of the upper urinary tract and also because of the technique of taking the biopsy and the size of the resulting sample. The limited size of the biopsy needle and sample does not allow for exact prediction about the wall layers, i.e. the degree of infiltration. Furthermore, the biopsy usually contains only tissue from the papillary part of the tumor. Moreover, pathological upgrading was reported to occur in up to 51% of cases when preoperative and postoperative specimen after definitive surgery were compared, indicating the need for extensive endoscopic sampling in case of an organ-sparing approach [30]. Given the recent development in molecular analysis of tissue specimen, preliminary results exist that illustrate reproducibility of mutation analyses between biopsies and RNU specimen [31]. However, no clear determination of candidate aberrations or panels have so far been established as clinical routine.

Studies on filter-based endoscopic procedures show results that are quite promising, even though preliminary, especially for the endoscopic evaluation of flat urothelial lesions [32]. In narrow-band imaging, the wavelength of white light, for example, is specifically reduced (415–540 nm). In this way, fine structural changes of the mucosa can be made identifiable more effectively. The deeper tissue layers are not reached, and the light is absorbed by blood vessels, so that the contrast of epithelial, light-reflecting areas and heavily vascularized, non-reflecting areas is intensified. With the SPIES SPECTRA™ technology, specific regions of the color spectrum are intensified through color-tone shifting, so that blood vessels and capillaries are represented more clearly. The spectral separation takes place within the camera system without the need for a special light source. Clinical investigation for the application of this technology in the bladder and upper urinary tract is under way. The use of photodynamic diagnostics (PDD) in the upper urinary tract has been evaluated in a few studies. The instillation of 5-aminolevulinic acid (5-ALA) in the urinary tract via a percutaneous nephrostomy or a ureteral stent was described as technically feasible for the preoperative evaluation of a UUT tumor and the detection of a CIS [33]. Nonetheless, the small capacity of the cavities of the renal pelvis and the ureter and the shortened duration of local exposition should be considered as a detrimental factor. Somani and colleagues have also reported on the possibility of a PDD

endoscopy 3–4 h after oral administration of 5-ALA in four patients [33].

Prognostic Factors and Risk Stratification for Tumors of the Upper Urinary Tract

Besides radiological and endoscopic diagnostics, the identification of patient-associated and pathological prognostic factors in UUT cancer is highly relevant, with regard to a possible curative organ-preserving procedure. Analogous to the treatment of non-muscle invasive urothelial bladder cancer [34], preoperative risk stratification for UUT tumors is recommended, in particular addressing the question of an organ-preserving therapy. The European Association of Urology (EAU) Guidelines recommend that patients with normal contralateral kidneys are divided into the "low risk" and "high risk" categories as suggested in Table 32.1. Figure 32.1 illustrates a possible clinical algorithm for UUT tumors, based on this risk stratification [10].

Table 32.1 Risk stratification of UUT tumors with normal contralateral kidney according to EAU guidelines

High-risk	Parameter
Clinical factors	Hydronephrosis
	High-grade URS biopsy
	High-grade cytology
	Tumor size >1 cm
	Invasive aspect in cross-sectional imaging
	Multifocal lesions
	Endoscopic therapy failure for "low-risk UTUC"
Patient-related factors	Previous Urothelial carcinoma of the bladder and/or cystectomy
	Smoking
Low-risk UTUC	
Clinical factors	Low-grade URS biopsy
	Low-grade cytology
	Tumor size <1 cm
	No invasive aspect in cross-sectional imaging
	Unifocal lesion
Patient-related factors	Intensive follow-up possible and accepted by the patient

Pathological tumor stage and grade, as well as the proof of an extra-nodal extension in lymph-node positive UUT tumors are relevant for prognosis [8, 9, 35]. Patient sex has not been identified as an independent prognostic factor for overall survival. A high patient age at radical nephroureterectomy has been shown to be associated with a reduced tumor-specific survival [36, 37]. The primary localization of a UUT tumor in the renal pelvis or the ureter is also relevant for prognosis: ureteral and multifocal tumors have a poor oncological outcome as compared to tumors localized in the renal pelvis, after adjusting for tumor stage [38].

Furthermore, smoking at the time of diagnosis, as well as the duration and intensity of tobacco consumption are proven prognostic factors for UUT cancer [39, 40]. An additional, important pathological risk factor is the presence of lymphovascular invasion, so the pathology analysis should be performed with particular attention to this finding [41, 42]. Although diverse molecular markers have been investigated with regard to their prognostic importance for UUT tumors, there is currently no sensible parameter included into the preoperative risk stratification. Considering the difficult classification of tumors with high or low malignant behavior, the search for suitable prognostic factors at the molecular level remains however important for tumors of the upper urinary tract. Table 32.2 summarizes patient-associated and pathological prognostic factors for UUT tumors.

Organ-Preserving Therapy Strategies for Tumors of the Upper Urinary Tract

Endoscopic Therapy

For the purpose of an organ-preserving treatment of UUT cancer, a basic distinction must be made between situations where it is imperative to preserve the kidney (e.g. functional /anatomic single organ or advanced renal

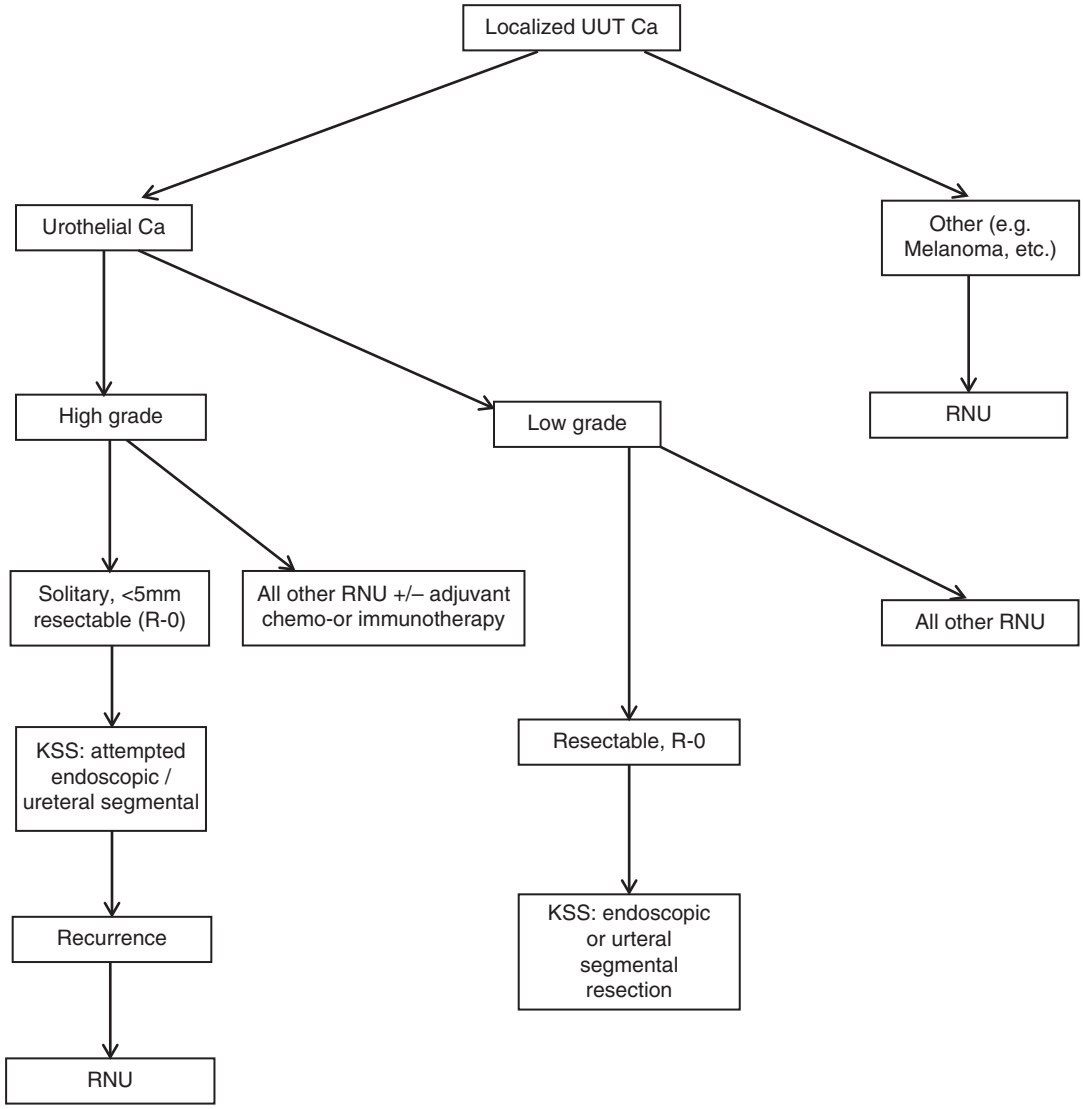

Fig. 32.1 Algorithm for treatment of UUT malignancies. *KSS* kidney sparing surgery, *UUT* Upper urinary tract, *RNN* radical neproureterectomy, *Ca* Cancer

insufficiency) versus elective situations with presence of low-risk UUT tumors. In the latter case, the benefit of an organ-sparing, endoscopic approach consists in is the favorable situation of a functional preservation along with a reduced morbidity in comparison to radical surgery. The endoscopic route is defined individually according to the anatomical localization of the lesion(s), technical prerequisites, and the experience of the surgeon. For all endoscopic ablative procedures, it is necessary to thoroughly inform the patient about the necessary stringent postoperative care and to obtain the patient's consent to that. Technical requirements are defined by the availability of a flexible ureteroscope and a suitable laser for tissue ablation [43]. The complete resection of the tumor is obligatory. As described before, there exists a risk for understaging the tumor in endoscopic procedures. A recent single-center analysis revealed that in comparison to the radical nephroureterctomy group, patients managed

Table 32.2 Prognostic factors in tumors of the upper urinary tract

Risk factor
Patient-related
Age > 80
Smoking (at the timepoint of diagnosis; duration/intensity of tobacco consumption)
Tumor localization: Ureter vs. renal pelvis
American Society of Anesthesiologists (ASA) score
BMI >30 kg/m^2
Histopathology
T-stage
Tumor grade
Lymphovascular invasion
Extranodal extension with pN+
Positive surgical margins
Extensive tumor necrosis (>10% of the tumor)
Tumor architecture (sessiles vs. papillary growth pattern)
Carcinoma in situ (concomitant, known CIS of the bladder)

with Thulium-Laser-ablation of UUT cancer had significantly less impairment of postoperative renal function and length of hospitalization, while the recurrence rate was higher in the endoscopy cohort [44]. Technically, ablation using 10–20 W laser power and 272 and 365mum fibres has been described as beneficial with regard to both, intraoperative hemostasis and tissue vaporization [45].

In a retrospective study of 74 patients receiving endoscopic therapy of UUT tumors, the 5-year survival rate was 89% and the 10-year survival rate was 77%. For G1 tumors ($n = 34$), the Kaplan-Meier survival estimate was 100% after 5 years and 80% after 10 years the documented high risk of a recurrence in this cohort was reported at 69%. Nonetheless, at a median observation time period of 54 months, 32% of the patients were recurrence-free, so a RNU was not necessary [46]. Given the need for appropriate selection factors for radical or endoscopic treatment, a National Cancer Database analysis comparing overall survival in low risk UUT cancer revealed that tumor size <2 cm vs. tumor size <1 cm was a significant discriminative variable for improved survival with RNU [47, 48]. In the absence of prospective evaluation, in general, the utilization of endoscopy remains left up to an individual clinical decision.

Percutaneous Access

Non-invasive low-grade tumors in the renal pelvis calyx system can be reached and treated nephroscopically via percutaneous access [49, 50]. A possible indication for this form of therapy is cancer in the lower calyx group that cannot be reached or completely removed by flexible URS. The basic disadvantage of percutaneous access consists in the increased perioperative morbidity. So for example, bleeding requiring transfusion was observed in a substantial portion (20%) of reported complications [51]. Obstructions of the renal pelvis, injuries of surrounding organs, or pleural injuries were observed in a minority of cases.

Referring to surgical outcome, Palou et al. reported a rate of recurrence in the upper urinary tract of 41% after a median follow-up time period of 51 months in an institutional retrospective study. In that study collective, 15% of the patients had a solitary kidney or bilateral tumors. The overall survival rate was 75%, and the cancer-specific survival was 94%. Organ-preservation was possible for 74% of the patients [49]. Roupret et al. observed a cancer-specific 5-year survival rate of 79.5% in a cohort of 24 patients who received percutaneous UUT therapy [50]. Five patients with high-grade or invasive tumors needed nephroureterectomy during follow-up.

Operative Segmental Removal of the Ureter

A segmental removal of the tumor-bearing section of the ureter with sufficient resection margins allows adequate tumor staging as well as preservation of the ipsilateral kidney. A segmental resection of the middle and proximal ureter is however associated with an elevated rate of treatment failure if compared with distal ureter resection [52]. Uretero-ureterostomy is indicated for high-grade tumors with an imperative indication for organ preservation and localization in the proximal and mid ureter. The same procedure can be performed for low-grade tumors, provided

that endoscopic resectability is not given. Distal ureterectomy and ureterocystoneostomy should be used for low-grade tumors localized in the distal ureter that cannot be controlled endoscopically. Such a procedure is also applicable for locally invasive high-grade tumors.

For ureteral lesions whose length or localization does not permit treatment by means of a psoas hitch procedure or utilization of a Boari flap, reconstruction should be performed using an isoperistaltic ileal segment. Bilateral ureters can be implanted into a common ileum segment and be anastomosed onto the bladder, for example in a "7" or "reverse 7" configuration [53].

Simhan and colleagues evaluated the data of 1227 patients in the SEER tumor registry and compared the cancer-specific and overall survival of RNU versus organ-preserving procedures. Nephroureterectomy was not associated with any improvement of cancer-specific survival. Patients with intermediate or high grade UUT tumors and low T stages who received kidney-preserving treatment were older and had a higher non-tumor-associated mortality [54].

In a French multicenter study on 416 patients with RNU and 52 patients with segmental ureter resection, there was no significant difference in the cancer-specific (86.3% vs. 87.9%) or recurrence-free survival (47.9% vs. 37%) at a median follow-up of 26 months. The type of surgery was also not a relevant prognostic factor for these outcomes in multivariate analysis [55].

Instillation Therapy for Tumors of the Upper Urinary Tract

An antegrade instillation therapy with Bacillus Calmette Guerin (BCG) or mitomycin is possible in the upper urinary tract and can be carried out, e.g., via a percutaneous nephrostomy. Here, the intrarenal pressure should not exceed 20 cm H_2O, in order to prevent a pyelovenous influx with the danger of systemic spreading of the chemoinstillation [56]. For retrograde instillation via a ureteric stent, the risk of a possible obstruction of the stent and thus consecutive pyelovenous influx is present. Application via a bladder instillation with double-J catheter has also been described in the literature, however it was shown that the agent often does not reach the renal pelvis [57].

Adjuvant BCG therapy appears to be more reliably performable, but the effectiveness is discussed controversially. BCG has been reported to be curative for 50% of CIS tumors of the renal pelvis, whereas, papillary and solid UUT tumor recurrences cannot be prevented by administration of BCG. About 25% of the patients can develop a granulomatosis of the urinary tract, while the clinical relevance of this condition remains unclear [58].

Follow-Up Care

For patients with UUT tumors and organ-preserving therapy, intensive follow-up care is mandatory. Follow up should not only involve screening for local tumor recurrences and distant metastases but consider the emergence of metachronous bladder tumors. Thus the follow-up of patients under conservative therapy of a UUT tumor should take place with regular endoscopic control of the urinary tract, since especially recurrences of the ipsilateral urinary tract are common [59]. As a suggestion for the follow-up scheme, CT urography is advised at 3 and 6 months post-operatively and then annually; cytoscopy, ureteroscopy, and cytology in situ should be performed at 3 and 6 months post-operatively, then every 6 months for the next 2 years, and then annually. Post RNU, different follow-up schemes exist albeit all of them integrate risk factor subgroup adapted individual examination schedules including physical examination, cystoscopy and cytology, chest radiography and abdominal imaging [2, 60].

Systemic Treatment in Advanced and Metastatic UUT Cancer

Overall, data on neoadjuvant systemic therapy in UUT cancer are limited and no results from prospective comparative trials are available. However, application of platinum based perioperative chemotherapy regimen may portend a

beneficial effect compared to surgery alone in patients with an UTUC having a high risk of relapse [61].

Liao and colleagues recently reviewed records of 240 patients at The Johns Hopkins Hospital from 2003 to 2017. Patients with biopsy proven high grade disease and a visible lesion on cross-sectional imaging ($n = 32$) were offered neoadjuvant chemotherapy prior to RNU. A control group, consisting of a time matched cohort of patients ($n = 208$) with biopsy proven high grade disease underwent extirpative surgery alone. Significantly lower pathological stage was noted in the study group than in the control group ($p < 0.001$) and there was a 46.5% reduction in the prevalence of pT3 disease or higher in study group patients. A 9.4% complete remission rate was observed in patients who underwent neoadjuvant chemotherapy [62].

Few data exist describing the potential benefit of systemic treatment with chemotherapy in the setting of primary metastatic UUT cancer. In a large multi-institutional retrospective series with non-surgically treated primary metastatic UUT cancer, a total of 539 patients (51.4%) received chemotherapy. The observed survival rate was impaired with a median of 9 months in the chemotherapy cohort and 2 months in the remaining control group ($p < 0.001$) [63]. Vinflunine is another chemotherapeutic agent, approved in Europe for the second-line treatment of urothelial cancer. In the phase III trial, 370 previously treated patients were randomly assigned to either vinflunine or best supportive care [64], where treatment with vinflunine resulted in a 9% objective response rate and an increase in survival (6.9 versus 4.6 months, hazard ratio 0.88, 95% CI 0.69–1.12).

In recent years, with an increased understanding of cancer immunology, systemic immunotherapies targeting immune checkpoint inhibition have been introduced for UC of the bladder. The programmed cell death 1 receptor (PD-1) and its ligand (PD-L1) represent relevant negative immune regulators, preventing the destruction of normal tissues and autoimmunity. In total, five immune checkpoint inhibitors blocking PD-1 (pembrolizumab, nivolumab) or PD-L1 (atezolizumab, durvalumab, and avelumab) have been approved for first- or second-line use in metastatic UC based on favorable therapeutic response and manageable safety profiles in prospective clinical trials [65]. Noteworthy, these trials primarily investigated advanced or metastatic urothelial cancer originating from the bladder. However, study protocols also allowed the inclusion of patients with UUT cancer.

In the phase II (KEYNOTE-052) study, 370 patients with advanced urothelial carcinoma who were not eligible for a cisplatin-based regimen were treated with pembrolizumab (200 mg every 3 weeks for up to 2 years) [66]. In the study population, 42% were ECOG performance status 2 and 50% of patients were included because of renal impairment. At a median follow-up of 9.5 months, the objective response rate was 29% for the entire cohort, including 7% complete responses and 22% partial responses. Objective response rates were higher in patients with PD-L1 expression >10%, but responses also were observed in those with PD-L1 expression <10% [66].

In analogy, Atezolizumab was investigated in platinum-ineligible patients. In a single-arm phase II study, Atezolizumab (total dose 1200 mg every 3 weeks) was used as first-line therapy in 119 patients with advanced or metastatic urothelial carcinoma of the bladder or upper urinary tract [67]. At a median follow-up of 17 months, objective responses were observed in 27 patients (23%), including 11 (9%) with a complete response. Median duration of response had not been reached, and 19 of 27 continued to respond at the time of analysis. The median OS for the entire cohort was 16 months [67].

In a second line scenario after progression during or after platinum-based chemotherapy, Pembrolizumab has also shown to prolong overall survival in patients with metastatic urothelial carcinoma. In the phase III (Keynote-045) trial, 542 patients who had recurred after or progressed on a platinum-containing regimen were randomly assigned to pembrolizumab (200 mg every 3 weeks for 24 months) or investigator's choice chemotherapy (paclitaxel, docetaxel, or vinflunine) [68]. Patients were enrolled regardless

of the level of PD-L1 expression. Overall survival was significantly increased with pembrolizumab compared with chemotherapy (median 10.3 versus 7.4 months). The 12-month overall survival rates were 44.4 versus 36.1%, and the 18-month overall survival rates were 36.1 and 20.5%, respectively. The response rate was higher with pembrolizumab than with chemotherapy (21.1% vs. 11.0%), and the estimated rate of response duration of 12 months or longer was also higher with pembrolizumab (68% vs. 35%).

Atezolizumab is a PD-L1 inhibitor that is indicated for the treatment of advanced urothelial carcinoma that has progressed during or after previous platinum-based chemotherapy, either for metastatic disease or for progressive disease less than 12 months after adjuvant or neoadjuvant chemotherapy. In the IMvigor 210 trial, patients with metastatic UCs who progressed during or after platinum-based chemotherapy treatment received atezolizumab and showed an objective response rate of 15% and a 12-month OS rate of 37%. On the basis of these favorable results, the US Food and Drug Administration approved atezolizumab for the treatment of patients with locally advanced or metastatic UCs who have progressed during or after platinum-based chemotherapy, or whose disease has worsened within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy. However, in a recent analysis of a Phase III randomized dataset (IMvigor211): atezolizumab failed to improve OS in the overall population (8.6 vs. 8.0 months for atezolizumab and chemotherapy, respectively; HR 0.85) and in patients with high PD-L1 expression (11.6 vs. 10.6 months, HR 0.87) [69].

In phase I and II studies, nivolumab, another PD-1 inhibitor that has been approved for the treatment of advanced melanoma, Hodgkin's lymphoma, non-small cell lung cancer, head and neck cancer and renal cell cancer has had significant activity in patients who have progressed after previous platinum-based therapy for metastatic urothelial carcinoma [70], while other PD-L1 inhibitors (avelumab, durvalumab), and CTLA-4 inhibitors (Ipilimumab) are under clinical investigation. Moreover, the combination of immune checkpoint inhibitors and other agents is another inspiring avenue to explore that could benefit even more patients, however prospective evaluation is under way and meticulous attention should be paid on the resulting toxicity profiles during treatment.

Summary

Endoscopic therapy and segmental ureter resection are available as function-preserving alternatives to radical nephroureterectomy for elective and imperative treatment situations for urothelial cancer of the upper urinary tract. Preoperative imaging and endoscopy, cytology and pathological analysis, the anatomic localization and extent of the lesion, and individual patient-related risk factors represent important parameters for risk stratification and choice for organ-preserving procedures. Figure 32.1 illustrates a clinical algorithm for elective situations. During endourological procedures, recent technical innovations and novel biomarkers from molecular analysis may help to overcome the current limitations of pathological staging with biopsies of the upper urinary tract, and thus to make the risk classification and treatment stratification more precise. To date, stringent endoscopic follow-up must be given the highest importance after organ-preserving therapy.

Conclusions

- Organ-preserving strategies for urothelial carcinoma of the upper urinary tract are technically feasible and functionally desirable, but carriy the risk of understaging the pathology in the endoscopic diagnostics.
- Careful preoperative risk stratification of patients is mandatory prior to organ-preserving therapy; elective endoscopic treatment should remain reserved for situations with "low-risk" tumors.
- Stringent endoscopic reevaluation is imperatively indicated for the follow-up after organ-preserving procedures.

- Along with the development of immune-checkpoint-inhibition in urothelial bladder cancer, novel treatment options for advanced or metastatic stages of UUT cancer have become available

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Renal Cancer Including Molecular Characterization

33

Egbert Oosterwijk and Peter F. A. Mulders

Introduction

Kidney cancer is the ninth most commonly occurring cancer in men and the 14th most commonly occurring cancer in women. There were over 400,000 new cases in 2018 worldwide [1]. In view of the multiple cell types present in the kidney, all with specialized function, it is not surprising that renal tumors represent a heterogeneous group. In the Vancouver consensus conference of the International Society of Urologic Pathology the foundation for the 2016 World Health Organization (WHO) renal tumor classification was laid [2]. This was a revision of the 2004 renal tumor classification that was deemed necessary because knowledge on pathology, genetics and epidemiology had greatly improved. Whereas renal tumor subtypes were formerly named and categorized based on cytoplasmic, morphologic and anatomic locations, a number of new entities have been added on the basis of distinctive molecular alterations. This shows that molecular characterization needs to be integrated in the diagnosis of renal cancer.

The WHO classification of tumors of the kidney distinguishes Renal Cell tumors (N = 16), metanephric tumors (N = 3), Nephroblastic and cystic tumors (N = 3), Mesenchymal tumors (N = 4 occurring mainly in children, N = 16 occurring mainly in adults), Mixed tumors (N = 2), Neuroendocrine tumors (N = 4) and Miscellaneous tumors (N = 2). Renal Cell Carcinoma (RCC) is the most prevalent adult Renal Cell tumor [2].

Worldwide, RCC represents the sixth most frequently diagnosed cancer in men and the tenth in women, accounting for 5% and 3% of all oncological diagnoses, respectively [3]. It affects nearly 300,000 individuals worldwide annually and is responsible for more than 100,000 deaths each year. The incidence of RCC varies worldwide, with higher incidence in developed countries. Several risk factors have been identified, most notably smoking, obesity, and hypertension [4]. Initially RCC was considered one entity, but it is now clear that RCC is also a very heterogeneous group of tumors, each with its own clinical and molecular manifestations. These differences are a reflection of the different cells of origin. As such, implementation of accurate biomarkers appears to be mandatory to guide clinical management.

Molecular Markers in the Diagnosis of Renal Cancer

In the 1970s clear cell RCC and granular RCC were distinguished based solely on morphological features. In 1997 the Heidelberg classification

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was published: the first attempt to include molecular features of RCC to subdivide RCC [5]. Clear cell RCC (ccRCC) remained as a single entity (common or conventional RCC), but the granular RCC cases were subclassified based on the then available genetic knowledge into papillary RCC, chromophobe RCC and RCC, unclassified. Papillary RCC was further divided into type 1 and type 2 pRCC based on morphological characteristics [6].

With the introduction of rapid and cheap sequencing methods molecular RCC subtypes within morphological homogeneous RCC subtypes are becoming visible. Within morphological homogeneous RCC subtypes the most frequent molecular aberrations and translocations in the most frequently occurring RCC have now been established (Table 33.1). Secondly, the vast amount of expression data has also allowed comparison of expression profiles of normal tissues and derived tumors, based on the assumption that many of the molecular differences that exist are a reflection of their respective cells of origin. Clear cell RCC is thought to arise from cells in the proximal convoluted tubule, while chromophobe RCC is thought to arise from intercalated cells in the distal convoluted tubule of the nephron [7]. Comparison of clear cell, chromophobe, and papillary RCC expression profiles with the expression profiles of normal tissue microdissected from various regions of the nephron [8] showed that indeed ccRCC expression profiles were most similar to the proximal nephron, whereas chRCC was most similar in expression to the distal nephron, while pRCC was most similar in expression to the proximal nephron [9].

Systematic analysis of The Cancer Genome Atlas (TCGA) cohort of 894 RCC cases of various histological types revealed nine major genomic subtypes [9]. Interestingly, this included three different subtypes of ccRCC, four different subtypes of pRCC, chRCC and mixed or unclassified RCC. Thus, even within histological homogeneous groups subclassification was possible based on molecular characteristics. Such further subclassification has major ramifications for the clinical management of patients who were formally treated homogeneously. Interestingly, analysis of this TCGA cohort has revealed correlation of specific somatic alterations and metabolic pathways with subtype-specific decreased survival, as well as common signatures correlating with decreased survival within all subtypes [10]. Indeed, personalize medicine, which is foreseen as the next step forward in cancer management, is likely to become possible for RCC by including such molecular information.

Table 33.1 Frequent molecular aberrations of most common renal cell tumors

Renal cell type	Copy number variations/ translocations	Somatic mutations or alterations	Hereditary kidney cancer syndrome and associated molecular alterations
Clear cell RCC	-3p Additional: +5q, −9p, −14q, −6q, −8p	VHL, PBRM1, SETD2, BAP1, KDM5C	Von Hippel Lindau syndrome VHL
Papillary RCC type 1	+7, +17, −Y	MET	MET
Papillary RCC type 2	+7, +17, +12, +16, +20, −Y	MET, SLC5A3, NF2, PNKD, CPQ, LRP2, CHD3, SLC9A3R1, SETD2,CRTC1, PBMR1, BAP1, activation of the NRF2-ARE pathway (NFE2L2, CUL3, KEAP1, SIRT1), CDKN2A, CIMP	Hereditary leiomyomatosis RCC Fumarate hydratase
Chromophobe RCC	−1, −2, −6, −10, v13, −17, −21	TP53, PTEN, mTOR pathway, TERT promoter, mitochondrial DNA mutations	Birt-Hogg-Dubé Folliculin Tuberous sclerosus complex TSC1, TSC2

Clear Cell RCC

Clear cell RCC (ccRCC) represents the most common type of RCC and comprises approximately 80% of RCCs that metastasize. Large molecular studies ultimately lead to the recognition that mutations in the Von Hippel Lindau (VHL) gene were drivers of ccRCC [11]. The investigators first studied families suffering from the autosomal dominant VHL syndrome. Affected family member frequently develop multiple, bilateral ccRCC, among others. Once it was evident that mutations in the VHL gene played a critical role in the development of ccRCC in these families, VHL mutations and VHL promoter silencing were shown to play a critical role in sporadic ccRCC [11, 12]. VHL mutations in combination with VHL promoter silencing has been reported in 60–90% of cases. This variation in detection reported between different studies is likely to be caused by sampling in combination with low coverage rate [13]. Thus, the most common alterations found in ccRCC are loss of 3p, the region where the VHL gene resides, combined with inactivation of the VHL gene in the other allele. Expression of an aberrant VHL protein or complete loss of VHL gene expression results in aberrant stabilization of hypoxia-inducible factor (HIF), a transcription factor which is responsible for transcription of numerous genes also involved in tumor formation under hypoxic conditions [14].

Other somatic mutations are now being recognized as important driver genes in ccRCC, owing to large scale sequencing efforts [15–18]. In a multi-center prospective study seven molecular subtypes were described that correlated with diverse clinical phenotypes in ccRCC [13], suggesting that a molecular subtype can serve as a potential biomarker to guide clinical management. Interestingly, one of the subtypes concerned a subtype of RCC with wild-type VHL gene, a previously unrecognized variant. Intratumor heterogeneity was one of the defining characteristics of different subtypes [13, 19] and this feature may be difficult to capture in regular clinical practice as it requires analysis of multiple tumor areas.

The most frequently involved genes in ccRCC are PBMR1, SETD2, BAP1 and KDM5C [13, 16, 17]. Remarkably, the genes encode for chromatin modifiers and loss can lead to dramatic changes. For instance, SETD2 loss leads to depletion of nucleosomes, loss of DNA methylation, aberrant splicing, and expression of abnormal intragenetic RNAs [18]. PBMR1, SETD2 and BAP1 are all located in close vicinity of VHL on 3p emphasizing the importance of 3p loss in ccRCC. The importance of loss of VHL and PBMR1 in driving renal transformation was also shown in the mouse kidney: kidney-specific deletion of Vhl and Pbrm1, but not either gene alone, resulted in bilateral, multifocal, transplantable clear cell kidney cancers [20, 21].

Interestingly, PBMR1, SETD2 and BAP1 levels have been associated with worse outcome in ccRCC [10, 22–24]: survival of patients with $BAP1^{mut}$ tumors is lower compared to patients with $PBMR1^{mut}$ tumors and survival of patients with $BAP1^{mut}$/$PBMR1^{mut}$ tumors is very poor, but this entity is also very rare [25]. It also appears that complete SETD2 loss may be a later event: SETD2 protein expression levels were lower in ccRCC metastases compared to primary ccRCC, suggesting that complete loss of SETD2 protein expression may not be required for the development of ccRCC, but that the decrease is related to tumor progression or adaptation [26]. Finally, the frequency of $SETD2^{mut}$/$PBMR1^{mut}$ is high, suggesting that these genes corporate in ccRCC tumorigenesis [27].

The large sequencing efforts have also revealed that a metabolic shift can occur in ccRCC cells. Gene expression in high-grade, high-stage ccRCC tumors reflects increased lactic acid fermentation and decreased oxidative phosphorylation. In ccRCC with a worse prognosis, the cellular metabolic activity involved increased dependence on the pentose phosphate shunt, decreased AMPK, decreased Krebs cycle activity, increased glutamine transport and fatty acid production [10]. Whether this information can lead to alternative treatment strategies remains to be established.

In several biomarker studies the potential prognostic value of epigenetic alterations has been examined (reviewed in [28]). These comprise different aberrations, such as changes in

histone modifications and DNA methylation, and in view of the importance of histone modifying genes in ccRCC epigenetic alterations are regarded as potential biomarkers for the early detection of disease and for prediction of prognosis and treatment response. TCGA studies showed that promoter DNA hypermethylation frequency increases with ccRCC stage and grade [16]. In other studies, integration of global transcription levels with massive parallel sequencing data revealed a gene signature of 4 genes that correlated with poor survival [29]. This signature was validated in 2 independent cohorts. The biological relevance of the 4 genes included in this signature in ccRCC is unclear and still needs be elucidated. Moreover, independent validation by other investigators is still warranted, and the effect of tumor heterogeneity on the prognostic value of this epigenetic biomarker needs to be established.

Papillary RCC

Papillary RCC (pRCC) accounts for about 10–20% of RCC tumors and is the second most common renal neoplasm. Disease progression and patient outcome can be highly variable, and two histological subtypes have been distinguished. pRCC type 1 is often multifocal, with a quite homogeneous histological appearance, whereas the histological defined type 2 pRCC exhibits a rather diverse morphologic spectrum, and several features are shared with other non-ccRCC tumors, often leading to inconsistent diagnosis. Hereditary pRCC is a rare disorder associated with an increased risk of type 1 pRCC, characterized by activating germline mutations in c-MET [30]. Comprehensive molecular analysis confirmed that type 1 and type 2 pRCC are indeed two different entities, and that type 2 could be further stratified into three different subgroups on the basis of patient survival [31]. Similar to the hereditary type 1 pRCC, sporadic pRCC was characterized by alterations in the c-MET pathway [31]. Detailed analysis revealed 10 significantly mutated genes (MET, SLC5A3, NF2, PNKD, CPQ, LRP2, CHD3, SLC9A3R1, SETD2 and CRTC1) with somatic c-MET mutations occurring most frequently (13–15%) [32]. Activation of the NRF2-ARE pathway was associated with pRCC type 2 as earlier described [33]. Remarkably, in pRCC type 2 tumors chromatin-modifying genes SETD2, PBMR1 and BAP1 are frequently mutated, similar to ccRCC [31]. Within pRCC type 2 loss of CDKN2A, a gene playing an important role in cell cycle regulation, and CIMP, a phenotype characterized by simultaneous hypermethylation of numerous promoters, correlated with poor prognosis. CDKN2A alterations may serve as an independent prognostic marker associated with type 2 tumors, but this requires validation.

Based on genome-wide profiling of transcription-binding events providing insight in gene expression programs, pRCC was also subdivided in 3 clusters. Overexpression of MECOM, a transcriptional regulator was significantly associated with poorer OS [34]. Importantly, MECOM overexpression could not readily be explained by previously identified subgroups of pRCC. This shows the value of various molecular approaches and the results suggest that pRCC with MECOM activation identifies a subgroup of pRCC patients with adverse outcomes. Collectively pRCC type 2 is a very heterogeneous from a molecular standpoint (Table 33.1): many different events can ultimately culminate in the occurrence of pRCC type 2.

Based on the observation that c-MET plays a prominent role in type 1 pRCC foretinib, an oral multikinase inhibitor targeting MET, VEGF, RON, AXL, and TIE-2 receptors was tested in a phase 2 clinical trial [35]. Disappointingly, responses were very limited: only one of five patients with somatic MET mutation had a PR, responses were absent in 2 patients with MET amplification and only one of 18 patients with a gain of chromosome 7 experienced a PR. Possibly, other molecular aberrations lead to a foretinib-resistant phenotype. In contrast, the presence of a germline c-MET mutation was highly predictive of a response: 5/10 patients experienced a PR, 4/10 had a SD as best response. Thus, in this cohort where c-MET was possibly the most relevant driver c-MET inhibition resulted in a sub-

stantial anti-tumor effect. However, as mentioned by the investigators, this is a rare entity: germline mutations in a pRCC population from the Mayo clinic approached 0% [36], and development of foretinib for pRCC treatment was discontinued.

Chromophobe RCC

Chromophobe RCC (chRCC) is a rare type of kidney cancer accounting for approximately 5% of kidney cancer cases. ChRCC can occur in patients suffering from the Birt-Hogg-Dubé (BHD) syndrome, a rare genetic disorder. In approximately one-third of BHD patients chRCC develops and this is associated with germline mutations of the FLCN gene, a gene that encodes for a protein involved in MAPK and mTOR pathways [37]. Molecular studies of sporadic chRCC have been hampered by its rare nature. The most extensive study was reported by Davis et al. who examined 66 cases of chRCC [38]. The study confirmed that chRCC could be distinguished from ccRCC at the molecular level. Importantly, TP53 and PTEN, both tumor suppressor genes that normally regulate cell growth and apoptosis, were frequently mutated. Moreover, structural rearrangements were discovered in the TERT gene promoter. Because telomerase plays a pivotal role in senescence, deregulation of telomerase provides cancer cells the opportunity to divide indefinitely.

Because nearly all genes encoding enzymes in the Krebs cycle showed increased expression over normal in chRCC mitochondrial DNA analysis has been performed. Interestingly, mutations were observed in many chRCC with up to 18% of cases with alterations in electron transport chain Complex I genes leading to a complex metabolic phenotype [38].

Molecular Markers in the Treatment of Metastatic ccRCC

Our increased understanding of molecular events underlying ccRCC has resulted in the discovery and implementation of new treatment for patients with metastatic ccRCC (mccRCC). The central role of the HIF/VHL dysregulation lead to the development of multiple vascular endothelial growth factor (VEGF)–targeted therapies (bevacizumab, sorafenib, sunitinib, pazopanib, axitinib, and cabozantinib) and mTOR inhibitors (temsirolimus and everolimus). However, only a minority of mccRCC patients respond to a given treatment and molecular biomarkers able to predict the likelihood to respond to a particular treatment is greatly needed to help clinicians select optimal treatment for individual patients.

Several studies have shown an association between PBRM1 mutation status and patient outcome. In the RECORD-3 study, a randomized trial comparing first-line sunitinib with everolimus in patients with mccRCC, PBRM1 mutations were shown to be associated with a longer progression-free survival (PFS), whereas in the sunitinib treated patients longer PFS correlated with KDM5C mutations [39]. Similarly, mccRCC patients with PBRM1 mutant tumors treated with either sunitinib or pazopanib had significantly improved OS and PFS compared with patients with PBRM1 wildtype ccRCC [40]. Finally, in the phase II IMmotion 150 trial PBRM1 mutations were associated with improved PFS in the sunitinib treated patients but not in the other treatment groups [41]. The possibility that PBRM1 status may serve as a predictive biomarker for VEGF-targeted therapy is intriguing. It is possible that ccRCC mutated in VHL as well as PBRM1 are extraordinary dependent on HIF signaling [21], resulting to a more anti-angiogenic sensitive phenotype.

Unsupervised transcriptome analysis has identified gene signatures related to different responses to sunitinib treatment [42]. Based on this analysis a 35-gene classifier was developed which correctly classified the samples. Sunitinib response differed significantly between the identified groups. Remarkably, subtype classification was the only significant covariate in multivariate analyses for PFS and OS [42]. Similarly, these molecular subtypes were associated with outcome on pazopanib as first-line therapy [43]. Using another approach, this group studied whether mRNA-expression of genes associated with angiogenesis was correlated with sunitinib

treatment outcome. On multivariate analysis, HIF2A-, PDGFRB-, VEGFC-, VEGFR1- and VEGFR2-expression were correlated with PFS and HIF1A-, HIF2A-, VEGFR1- and VEGFR2-expression with OS. VEGFR2-expression showed the strongest association with outcome, but prognostic impact was lacking [44]. Independent validation of these observations is still pending, and therefore it is unclear whether the described 35 gene signature can be clinically implemented.

Immunotherapy with immune checkpoint inhibitors has recently been developed in ccRCC. Treatment of a population of previously treated mccRCC patients with nivolumab, a PD-1 checkpoint inhibitor demonstrated OS and ORR benefits compared with everolimus in patients who had prior anti-angiogenic therapy [45]. To improve its efficacy nivolumab has been combined with other immunomodulatory agents [46, 47]. Combination of nivolumab with ipilimumab, a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) checkpoint inhibitor for treatment-naïve patients with advanced ccRCC showed a significant improvement in OS and ORR compared with sunitinib [46]. Biomarker analysis for immunotherapy with checkpoint inhibitors has focused on gene signatures related to angiogenesis, T-effector/Interferon-ɣ response, inflammatory gene signatures, neoantigen burden and associated with a high cytolytic CD8+ T cell expression signature [41, 48, 49].

Interestingly clinical benefit has been associated with loss-of-function PBRM1 gene mutations in mccRCC patients treated with PD-1 or PD-L1 blockade therapy alone or in combination with anti-CTLA-4 [50].

The Impact of Tumor Heterogeneity on Molecular Markers

Intratumor heterogeneity has been suggested as a major hurdle for molecular subtyping: study of a single tumor-biopsy can lead to underestimation of the tumor genomics landscape [51]. Indeed, using ultra-deep sequencing on multiple regions of ccRCC intratumor heterogeneity was identified in all cases. Importantly, in 75% of cases ccRCC driver aberrations were subclonal [52], emphasizing the importance of multiregional analysis to capture all relevant driver events. In a recent 3D tumor sampling study, it was calculated that on average, two biopsies were required to detect ≥50% of all variants and seven were required to detect ≥75% of all variants [13]. For large tumors, four to eight biopsies may be required to capture the majority of events (≥75% detection). Clearly, important driver events may still go unnoticed even when ccRCC samples quite extensively. Obviously, this presents a major challenge to personalized-medicine and biomarker development for ccRCC.

Another aspect that deserves attention is the fact that almost invariably studies have focused on analysis of primary RCC. However, understanding of the molecular landscape of RCC metastasis is needed to ultimately be able to discover and validate predictive biomarkers for response. Studies on paired primary ccRCC and metastases have revealed substantial differences at the protein level and transcriptome level [53–55]. In the largest study conducted thus far, 575 primary and 335 metastatic biopsies across 100 patients with metastatic ccRCC were included [55]. Importantly, the overall number of driver events in metastases was lower compared to primary tumors and metastases were significantly more homogeneous. Across all primary-metastasis pairs, the majority of driver events were shared between primary tumors and metastases (62.5%), followed by driver events private to primary tumors (31.7%), and driver events private to metastases were limited (5.4%). This shows that sufficient sampling of the primary tumor will most likely reveal the vast majority of relevant driver events [13].

The Impact of Molecular Profiling on Therapy Choice

Implementation of molecular markers to guide therapy choice has not occurred in RCC, despite the exquisite molecular knowledge that has been accrued. It has well been established that genome-

driven treatment can guide clinical management and lead to impressive responses. For instance, due to the implementation of imatinib for the treatment of chronic myelogenous leukemias (CML) harboring the BCR–ABL translocation patients with CML have life expectancies approaching that of the general population today [56]. Similarly, specific targeting agents have dramatically improved outcomes in solid tumors such as a monoclonal antibody against HER2 in epidermal growth factor receptor 2 (HER2)-expressing breast cancer [57], vemurafenib in BRAF V600-mutant melanoma [58], and gefitinib in EGFR-, ALK-, and ROS1-mutant lung cancer [59].

Our understanding of RCC's detailed molecular profile has already lead to the implementation of numerous small molecule drugs such as tyrosine kinase inhibitors (TKI) and mTOR inhibitors, but personalized medicine approaches are lacking. Various VEGFR inhibitors can be used as first line treatment modality for metastatic ccRCC [60] and it is important to realize that these inhibitors in essence do not target the tumor cells but are anti-angiogenic. In general almost all patients show progression of disease after a longer progression free survival period. This progression can either be caused by vascular co-option, a process where tumors use normal blood vessels to sustain their metabolic needs [61, 62], or to activation of alternative pathways. In most cases patients are therefore treated with another small molecule drug as second line therapy such as cabozantinib, a VEGFR2/MET/AXL/RET inhibitor that has recently been approved. However, ultimately almost invariably patients progress and die of metastatic RCC.

Because molecular profiling is not common, it is not unlikely that responses can be improved by molecular profiling before treatment initiation. However, oncogenic mutations in a gene are often not limited to a single codon, and this may lead to different drug sensitivity. The results in pRCC with a c-MET inhibitor are exemplary: whereas mutations in the target gene c-MET were molecularly defined, responses in sporadic pRCC were absent, whereas responses were observed in germline pRCC patients. This study underscores that the benefits of genomically targeted therapy are conditioned by a multitude of factors. Facilitating the matching of highly relevant molecular characteristics with treatment modalities is going to be of utmost importance in the near future.

In conclusion, the extensive sequencing efforts have led to the recognition of multiple molecular RCC subtypes within the three main RCC subtypes. The improved understanding of the molecular landscape of RCC has led to the development of more effective therapies for metastatic RCC. However, because only subsets of patients with metastatic RCC respond to a given treatment, predictive biomarkers are needed to guide treatment selection. It is envisioned that molecular markers can play a key role in personalizing treatment [19].

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Bladder Cancer

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Non-muscle Invasive Bladder Cancer (NMIBC)

Introduction

Approximately 75% of Bladder Cancer (BC) patients present with a non-muscle invasive disease (NMIBC) confined to the mucosa (Ta, CIS) or submucosa (T1). NMIBC represents a heterogeneous disease with different clinical outcomes. These tumors vary from low-grade to very aggressive high-grade disease showing a high risk of recurrence and progression. Thus, an early diagnosis and accurate stratification is necessary to achieve an adequate therapeutic management [1].

Epidemiology

Bladder cancer (BC) is the ninth most common cancer worldwide with a yearly incidence of approximately 430,000 cases in 2012 [2]. BC predominates in males, tobacco smoking and occupational exposure to carcinogens represent the main risk factors [3], however, nowadays the evidence regarding gene-environment interactions is increasing [4].

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Non-muscle Invasive Bladder Cancer Pathology

Urothelial tumor staging is crucial, the selection of the treatment, the prognosis and the follow-up scheme depends of an accurate staging. Therefore, staging of BC represent a challenge by the uro-pathologist. According 2016 WHO classification distinguishes pTa, pT1 and pTis are recognize as non-muscle-invasive bladder cancer [5]. pT1 tumors have shown different outcomes according to the depth of invasion, therefore, some studies have divided pT1 tumors into pT1a (invasion above the muscularis mucosae), pT1b (invasion into the muscularis mucosae), and pT1c (invasion under the muscularis mucosae), pT1b-c tumors have shown worse recurrence/progression and cancer-specific survival [6, 7]. Other authors measuring the depth or diameter of the invasive focus divided pT1 tumors as; micro-invasion (T1 m) as a single invasive focus <0.5 mm and T1 extensive-invasive (T1e) as ≥0.5 mm and some studies have suggested that the maximum depth of invasion is associated with tumor recurrence and progression [8]. With regards to the tumor grading, two grading systems coexist, the 1973 WHO and the 2004 WHO/ISUP grading system. While, the EAU guidelines recommends reporting of both the 1973 and 2004 WHO grading systems for NMIBC [1], the AUA guidelines mentions that only the WHO 2004 classification should be used [9]. The WHO 2004 classification

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system NMIBC was divided into low-grade and high-grade tumors. This modification remains part of the WHO 2016 system, which categorized NMIBC in three categories; papillary urothelial neoplasms of low malignant potential (PUNLMP), noninvasive papillary urothelial carcinoma low-grade (NILGC), and noninvasive papillary urothelial carcinoma high-grade (NIHGC) tumors [5]. The distinction between PUNLMP and NILGC has no major implications in outcomes [10], but the distinction between NILGC and NIHGC tumors show important differences in management and prognosis [11].

Risk Stratification

The clinical practice guidelines on NMIBC from different urological associations stratify BC patients into risk groups according to clinicopathological features associated to the risk of recurrence and progression allowing to stratify the patients in three categories (low-risk, intermediate-risk and high-risk). Thus, the EAU, AUA, NICE guidelines present a risk stratification models which allow an evidence-based and risk-adapted treatment and follow-up [1, 9, 12]. The EORTC risk tables are the most used and best validated tool for risk stratification in NMIBC patients. The EORTC risk tables are based on an analysis of 2596 BC patients included in seven different RCTs, most of them with tumors having favorable characteristics and treated with chemotherapy (only 7% were treated with BCG without maintenance). The number of tumors, their size and prior recurrence rates were the most important prognostic factors for recurrence. T-category, grade, and the presence of concomitant CIS were the factors associated with progression [13] (Table 34.1). On the other hand, The CUETO scoring model is based on the data obtained from 1062 BC patients with intermediate- and high-risk NMIBC enrolled in four RCTs comparing different intravesical BCG treatments. Female gender, history of recurrence, multiplicity, and presence of associated CIS were the factors associated with recurrence. Age, history of recurrence, high grade, T1 stage, and

Table 34.1 EORTC and CUETO group scoring models [13, 14]

	EORTC			CUETO		
Factor		Recurrence	Progression		Recurrence	Progression
N° tumors	Single	0	0	≤3	0	0
	2-7	3	3	>3	2	1
	>8	6	3	No	0	0
Prior recurrence	Primary	0	0	No	0	0
	≤1 per yr	2	2			
	>1 per yr	4	2	Yes	4	2
T category	Ta	0	0	Ta	0	0
	T1	1	4	T1	0	2
Concomitant CIS	No	0	0	No	0	0
	Yes	1	6	Yes	2	1
WHO 1973 grade	G1	0	0	G1	0	0
	G2	1	0	G2	1	2
	G3	2	5	G3	3	6
Tumor diameter	<3 cm	0	0			
	≥3 cm	3	3			
Gender				Male	0	0
				Female	3	0
Age (yr)				<60	0	0
				60-70	1	0
				>70	2	2
Total score		0-17	0-23		0-16	0-14

recurrence at first cystoscopy were the factors associated with progression [14] (Table 34.2). Comparative analyzes of both models have shown significant differences in the progression score. Moreover, a recent analysis of external validation of EORTC risk tables involved 1062 patients treated with BCG, show that EORTC risk tables are more accurate to stratify recurrence and progression in low- and intermediate-risk patients.

However, the ability of the EORTC risk tables to estimate the risks of recurrence and progression of patients treated with BCG intravesical instillations were overestimated [15]. The most important pitfalls of all available scoring models are the lead-time bias, secondary to multiple changes in the current standard of treatment, which, cause the scoring models to estimate erroneously the risk of recurrence and progression in patients treated according to current guidelines. Currently, the risk models updated to modern clinical practice are not available, in addition, in the era of precision medicine the optimization of predictive models with the incorporation of new molecular markers (signaling molecules, miRNA and genes expression) is necessary for optimal management.

Table 34.2 Ten items checklist reporting in high-quality TURBT

Prognostic factor for clinical staging	
Number of tumors	1, 2-5, >5
Size of largest tumor	Cutting loop is approximately 1 cm wide
Arquitecture of tumors	Solid or papillary/sessile, pediculate, or flat
Status of tumor	Primary/recurrent
Suspicion of CIS presence	Yes or no
Clinical tumor stage	cTis, cT1-cT4
Intraoperative variables	
Bimanual exam under anesthesia	Yes or no
Complete resection according to the surgeon	Yes or no
Detrusor layer presence according to the surgeon	Yes or no
Bladder wall perforation	Yes or no

Adapted from Anderson C, et al. [27] according to the EAU guidelines [1]

Diagnosis

Imaging techniques: Currently no imaging modality is sufficiently sensitive for the detection of urothelial carcinoma of the bladder and cystoscopic evaluation of the lower urinary tract is essential in the thorough evaluation of hematuria. The ultrasound (US) represents the first-line imaging investigation of BC in patients with hematuria. A recent study that enrolled 148 patients using US showed; sensitivity, specificity, positive and negative predictive values of 87.1%, 98.1%, 94.4% and 95.4% respectively for BC diagnosis [16], however, the diagnosis performance of US depends of operator experience and the body habitus of the patient. The main advantages of ultrasound are that it does not emit ionizing radiation, is not expensive and is easy to carry out. Contrast-enhanced computed tomography (CT) is the most accurate modality for diagnosis in patients with gross hematuria, commonly CT protocol includes three-phases (unenhanced, nephrographic and excretory phases). The diagnosis performance of CT scan protocol has been evaluated in a study that recruited 435 patients with gross hematuria, 55 patients were diagnosed to BC, the BC detection rate for CT was 87% (48 patients), the sensitivity, specificity, positive and negative values were; 87%, 99%, 91%, and 98%, respectively [17].

Cystoscopy: The white light cystoscopy (WLC) is the current standard of care for the diagnosis of BC. WLC should be performed in all patients with symptoms and/or a suspected BC, it consists in an invasive endoscopic evaluation of the urethra and urinary bladder. WLC can be performed using a rigid or flexible instrument and the urologist should evaluate the entire bladder mucosa surface and describe all the detected lesions (number, size, site and appearance). WLC cannot distinguish benign flat lesions and carcinoma in situ (CIS), and cannot distinguish benign lesions from malignant lesions [1].

Urinary cytology and other urinary markers: The cytological examination of voided urine or washed bladder specimens represents the standard urinary marker in the diagnosis and surveillance of BC. According an accuracy metanalysis

the sensitivity and specificity are 37% and 95%, respectively by patients with NMIBC at all stages [18]. However, the diagnostic accuracy in CIS patients shows a better sensitivity (sensitivity and specificity of 87.1% and 63%, respectively) [19]. The Paris System is the standardized terminology and criteria used for urine cytology reporting. The diagnostic categories are: (1) non-diagnostic/unsatisfactory, (2) negative for HGUC (NHGUC), (3) Atypical Urothelial Cells (AUC), (4) suspicious for HGUC (SHGUC), (5) HGUC, (6) Low-grade urothelial neoplasm (LGUN) and (7) secondary malignancies [20]. The United States Food and Drug Administration (FDA) has approved six urinary biomarkers (Bladder Tumor Antigen [BTA] stat, BTA TRAK, nuclear matrix protein [NMP22], and UroVysion, ImmunoCyt, and uCyt) for the diagnosis and surveillance of BC [21]. However, they have not been routinely incorporated in the EAU or AUA guidelines in daily clinical practice. All these markers present a high sensitivity and low specificity, which limit its value as a screening test, however, currently new proteomic, genomic, epigenomic, transcriptomic and metabolomic biomarkers are under investigation.

Optical technologies: Despite the optical quality of new cystoscopes allow a high detection of papillary tumors, the flat lesions and smaller or satellite tumors are important clinical concerns. Therefore, new optical technologies have emerged to improve the detection of BC. Narrow band imaging (NBI) uses the blue (415 nm) and green (540 nm) spectra from white light, these lights are absorbed by hemoglobin, thus highlighting the contrast between capillaries and mucosa. A recent meta-analysis that included 2806 patients show that NBI improve the detection rate of BC; the pooled additional detection rate was 9.9% at all stages, and 25.1% in CIS patients only [22]. Photodynamic diagnosis consists on the intravesical instillation of photosensitizing agents (Hexaminolevulinate or 5-aminolevulinic acid) which accumulated in tumor cells and emit red fluorescence with the exposure to blue light cystoscopy (380–480 nm). The results of a meta-analysis show that PPD improves the detection rate of BC between 9.7–40% in Ta tumors and 3.6–54.5% in T1 tumors, this improvement of the detection rate is higher in CIS patients showing and additional detection rate between 31.9 and 70.6% in this population [23].

Disease Management

Transurethral resection of bladder tumors (TURBT): TURBT is the standard procedure for the diagnosis, staging and treatment of NMIBC. The EAU, AUA and NCCN guidelines on NMIBC recommend complete resection of all visible tumors including sampling of the muscularis propria whenever possible [1, 5, 11]. The difficulty of carrying out a complete resection is reflected in the high rate of residual tumor evident in the literature, which ranges between 17 and 71% for all stages [24]. BC is the most expensive urological malignancy and a high-quality TURBT is critical to correct staging, risk cancer stratification and management [25]. Moreover, there is a growing body of evidence that a complete TURBT is associated with improved NMIBC outcomes [26]. The criteria of a high-quality TURBT do not present a standard definition, however; complete tumor excision with the presence of surrounding normal tissue and muscle layer, register of information for a correct clinical staging and cancer risk stratification and absence of complications have been suggested by some authors as plausible features of a high-quality TURBT [26, 27].Therefore, with the aim of standardized the reporting and TURBT quality improvement, a 10-item checklist (Table 34.2) has been evaluated in clinical practice showing a TURBT improved reporting of critical procedural elements, and enhanced surgeon attention to important aspects of the procedure [27]. In order to increase the quality of the TURBT, the use of new optical technologies has been evaluated. Thus, NBI-TURBT shows to reduce residual disease compared to WLC-TURBT (overall 6.3% vs. 17.5% and primary site 4.2% vs. 13.4%, respectively) [28]. Similarly, PPD has been shown to improve the quality of resection and decrease residual tumor disease [29]. On the other hand, TURBT could be performed using

two methods; Conventional TURBT (cTURBT) that consists of standard retrograde excision of the tumor using an electrical wire loop used via a resectoscope [1], this is still the gold standard, these techniques can be performed using monopolar energy, bipolar energy or bipolar plasmakinetics in large tumors [30, 31]. There is a lot of evidence that bipolar energy decreased bladder injury associated with obturator nerve reflex and improve the detrusor sampling without changes in outcomes [30]. However, there are several clinical concerns using cTURBT, such as; multiple tumor fragmentation, risk of tumor cell seeding, high rate of residual disease and missing of detrusor sampling. Therefore, in the last decade, en-bloc resection of bladder tumor (EBRT) has gained acceptance, it can be performed using monopolar and bipolar energy, lasers, or water jet. The main advantages described for the EBRT are; preservation of tumor architecture, improve detrusor sampling and lower risk of complications. To date, ERBT is still under investigation and information on outcomes is missing [32].

Biopsies of suspicious areas of the bladder mucosa, Random biopsies (RBs) and biopsy prostatic urethra: According to the EAU guidelines, all suspected areas should biopsied, Random biopsies should be performed for non-papillary tumors or when cytology is positive [1]. This recommendation is based on two trials with a very low incidences of positive biopsies (1.5–3.5%) [33]. In a recent meta-analysis that enrolled 10,975 NMIBC patients at all stages who underwent RBs shows a CIS incidence of 17.35%. The authors found a higher incidence of CIS in patients with positive cytology, multiple tumors, nonpapillary tumors, stage T1 tumors, and tumor grade G2/G3, and when the RBs had been performed in a standardized manner according to the EAU guidelines. Based on this data, the authors suggest that RBs should be perform in high-risk and intermediate-risk groups [19]. Prostatic urethral involvement has described as a silent process associated to high-risk tumors [34, 35]. The biopsy of the prostatic urethra is recommended in cases of bladder neck tumor when CIS is present or suspected, when cytology is positive without evidence of tumor, and when abnormalities of the prostatic urethra are visible [1]. Biopsies of the prostatic urethra in the paramontanal zone with a resection loop have been shown to have higher diagnostic performance than cold cup biopsy, allowing characterization of the prostatic urethral mucosa, paraurethral ducts, and stromal invasion [36].

Second-TURBT: According to guidelines, a second-TURBT of bladder tumors within 2–6 weeks after initial resection is indicated when; (1) incomplete first TURBT, (2) absence of detrusor muscle in the initial specimen, (3) clinical suspicion of worse disease than reported by the pathology (4) T1 stage tumors [1]. This recommendation is based on follow issues; (1) high rate of residual disease; (17–67% and 20–71%; for Ta and T1 initial tumors, respectively) and (2) high rate of upstaging; (0–23% and 0–32%; for Ta and T1 initial tumors, respectively) [24]. Second-TURBT reduces the uncertainty of the depth of tumor invasion, permits better control of the initial tumor, and provides additional pathologic information to select the treatment. Despite published data, the impact of second-TURBT on outcome is still controversial, however, recently, Gontero et al. in a cohort of 2451 patients with T1-HG/G3 treated with BCG (935 underwent second-TURBT) show that second-TURBT improved outcomes only when the muscle layer is not present in the initial specimen, these data suggest that second-TURBT could be unnecessary when the muscle layer is present in the initial specimen [37]. Moreover, Palou et al. using the same cohort of patients found that the recurrence rate, progression rate, and cancer-specific mortality is significantly higher in patients with T1 stage at second-TURBT compared to patients with Ta tumors, however, the authors indicated that the pathology at second-TURBT might not be enough to support early radical treatment, based on the fact that 79% of T1G3 patients do not progress during 10-years of follow-up [38].

Intravesical Chemotherapy

Single Immediate Instillation of Chemotherapy After Transurethral Resection: According to

EAU and AUA guidelines on NMIBC a single immediate instillation (SII) of chemotherapy after complete transurethral resection of the bladder (TURBT), is recommended in patients with low- or intermediate-risk NMIBC or with small-volume, low-grade Ta NMIBC, respectively [1, 9]. This recommendation is based on an individual patient data meta-analysis that shows a global reduction in recurrence risk by 35%, without changes in progression or mortality. However, SII appears to be not effective in patients with a prior recurrence rate of more than one recurrence per year or in patients with EORTC recurrence risk score >5 [39]. Despite these findings, in daily clinical practice it is difficult to identify patients in whom a SII could be useful at the time of TURBT. There are different chemotherapeutic agents that have shown their effectiveness in RCTs, such as; mitomycin C (MMC), Pirarubicin, Epirubicin, and Gemcitabine, however, there is no consensus regarding which agent presents the best oncological outcomes. Recently, a network meta-analysis of RCTs shows that Pirarubicin, MMC and Epirubicin are the most effective drugs and they decrease tumor recurrence in 69%, 60%, and 38%, respectively [40]. Moreover Messing et al., in a randomized double-blind clinical trial conducted at 23 centers concluded that among patients with suspected low-grade NIMBC, immediate post-resection intravesical instillation of gemcitabine, compared with instillation of saline significantly reduced the risk of recurrence over a median of 4.0 years [41]. Although the use of the SII seems to be rational, its role to improve BC outcome has been questioned. Thus, in a RCTs where 404 patients enrolled to 50 mg Epirubicin versus Placebo the recurrence rate was 51.0% in the Epirubicin group and 62.5% in the placebo group ($p = 0.04$), overall 63% of the recurrences were between 1 and 5 mm and half of the patients were treated with outpatient fulguration. The authors concluded that SII of chemotherapy only prevents small recurrences which could be treated by fulguration in an outpatient setting and therefore questioned the value of SII of chemotherapy after TURBT [42]. Another clinical concern is the ideal time to perform early instillation, this question still remains unanswered, however, it appears that to perform installations even a few days after TURBT could be acceptable. However, the results of RCTs and meta-analyses support that the use of SII reduces recurrence rate after TURBT in well-selected patients.

Adjuvant chemotherapy: The EAU guidelines recommend 6–12 months of intravesical chemotherapy (or a minimum of 1 year of BCG) following complete TURBT in intermediate risk patients [1]. Since the inclusion of chemotherapeutic instillations in the diary clinical practice, different clinical concerns have arisen, first of all the lack of a standard administration schedule (optimal dose, frequency or duration of such a course and the best chemotherapeutic agent) and secondly the lack of efficacy to prevent or delay the progression of the disease that has been described for treatment with BCG, which could suggest that the initial treatment with BCG could offer better outcomes [43]. Epirubicin, doxorubicin, and MMC are the most studied agents, however, to date there are no studies comparing efficacy between them. Regarding schedules, frequency and duration there are several heterogeneity in RCTs and conflicting evidence has been published. Despite of these issues, the rationale use of chemotherapy after TURBT is based on its ability to reduce the risk of recurrence. Thus, a systemic review on intravesical chemotherapy administered in an adjuvant setting after TURBT showed improvement in short-term (1–3 years) recurrence rate (approximately 20%) [44]. Likewise, Huncharek et al. in a meta-analysis of 11 RCTs that involved 3703 primary tumors patients comparing patients treated with intravesical chemotherapy after TURBT versus TURBT alone shows 44% reduction in 1-year recurrence among patients treated with intravesical chemotherapy versus those treated with TURBT alone [45]. Using the same methodology; Huncharek et al. in another meta-analysis including 1609 patients with recurrent tumors found a 38% reduction in the risk of disease recurrence at 1 year [46]. Although the evidence shows a superior efficacy of BCG compared with chemotherapy due to BCG ability to improve the progression rate, these findings have

not been corroborated recently. In that sense, a contemporary individual patient data meta-analysis that included 2820 patients found that BCG with maintenance schedules appears to be better to MMC in reducing the risk of recurrence, however, no statistically significant differences between MMC and BCG were found on progression and survival [47]. Another critical issue is the need for a maintenance schedule, however, published RCTs show contradictory results. The most evidence suggests that there is no significant advantage of maintenance schedule over induction therapy alone in recurrence, progression, or survival [48].

BCG immunotherapy: Intravesical instillation of BCG is the standard therapy for intermediate- and high-risk BC [1, 9, 12]. The absolute efficacy of BCG instillation has been shown in several clinical trials comparing the TURBT plus adjuvant BCG versus TURBT alone and reported an improvement in recurrence, progression and CSS [49], these findings have been corroborated in recent meta-analyses [50]. BCG instillation also has been compared with intravesical chemotherapy.

Thus, an individual patient data meta-analysis (over 2800 patients) of nine randomized studies comparing BCG maintenance showed a 32% reduction in risk of recurrence on BCG compared to MMC without differences in progression and survival [43]. There is a lack of evidence as to which schedule, strains, duration, the timing of administration, doses, frequency of administration, and sequencing of therapy are the most effective. In this sense, the role of the maintenance schedule of BCG therapy is classically supported by the Sylvester et al.'s meta-analysis which involved 24 trials (4863 patients at all stages) showing an overall risk reduction in progression of 27% and this findings has been recently confirmed in a contemporary metanalysis that involved ten RCTs [51]. Although, there is no consensus about most efficient maintenance and schemes vary from one instillation every 3 months during 1 year to 21 instillations given over 3 years has been described, the classical maintenance BCG protocol was established in the Lamm et al. study (induction and 3-week maintenance at 3, 6, 12, 18, 24, 30, and 36 months) based on 384 patients randomized to BCG maintenance therapy versus no BCG maintenance therapy, finding a significant improvement in recurrence-free and progression-free survival of 19% and 6%, respectively in favor to maintenance arm [52]. Regarding the strains, an RCT involving 142 high-risk NMIBC patients comparing two BCG strains (Connaught and Tice) showed that Connaught strains significantly improved 5-year recurrence-free survival compared with treatment with BCG Tice [53]. However, these findings have not been confirmed by a recent network meta-analysis that failed to show a significantly superiority to another BCG strain during direct and indirect comparisons. However, Tokyo 172 strain shows a trend to superiority and should be compared with other strains in a RCT [54]. Side effects are important disadvantages of intravesical BCG treatment. The most studied strategy in order to reduce side effects, is the instillation of low-dose BCG. In this regard, some RCT and metanalysis have been shown that low-dose BCG is not inferior to standard-dose BCG for tumor recurrence and progression, moreover, low-dose BCG appear to reduce overall side effects, especially systemic side effects but no local side effects [55].

Role of early cystectomy in high-grade T1 bladder Cancer: According to clinical practice guidelines, the treatment of choice in patients with high-risk bladder tumors is intravesical instillations of BCG [1, 9, 12], however, it is known that between 23 and 74% have recurrence and even 50% progress during follow-up [56]. It has been described that deferring radical cystectomy presents worse outcomes compared to early cystectomy (5 years CSS; RC before progression (≤pT1) vs. RC after progression during follow-up (≥pT2); 85.4% vs. 52.9%) [57].

However, the ideal timing and the selection of the suitable patient for early radical cystectomy is a challenge, moreover, based on the substantial morbidity of the surgery it could be considered overtreatment. The validation risk stratification tools proposed by EORTC and CUETO group appear to have limited predictive value in patients with high-grade T1 tumors, tending to overesti-

mate progression. A recent retrospective review of 2451 high grade T1 tumor patients was found that age, tumor size, and concomitant carcinoma in situ (CIS) are the most important prognostic factors for progression and propose dividing the patients into four risk groups according to the number of prognostic factors (progression rate of 17.3%, 25.3%, 32.2%, and 52% in patients with zero, one, two, and three progression predictive factors) [58].

Likewise, a meta-analysis that involved a total of 15,215 high-grade T1 tumor patients showed that the depth of invasion into lamina propria (T1b/c) is the most important risk factor for progression. Other factors that also impacted progression and mortality were lymphovascular invasion, concomitant CIS, lack of BCG treatment, tumor size more than 3 cm, and older age.

Despite the optimal management strategy for high-grade T1 tumor patients remain controversial and selection between bladder preservation and radical cystectomy is an important clinical concern in urology, published data can improve the selection criteria of patients undergoing early radical surgery and reducing the risk of over-treatment.

Conclusions and Recommendations

- The accurate staging of BC is essential for risk-adapted treatment and follow-up. Risk stratification and prognosis estimation should be performed in NMIBC patients using available scoring models EORTC tables and CUETO scoring model due to prognosis importance.
- The current standard for the diagnosis of BC is white light cystoscopy and cytology, however, it shows that new optical technologies (NBI and PDD) significantly increase the detection rate of BC, although, its use has not been standardized in daily clinical practice.
- TURBT is the standard procedure for the diagnosis, staging, and treatment of NMIBC. High-quality TURBT is a not well-defined concept but it has been suggested that complete tumor excision, correct clinical staging and absence of complications are plausible features.
- The use of an SII of a chemotherapy agent after TURBT has some beneficial effect on BC recurrence and it should be always considered in low-risk patients (EORTC recurrence risk score ≤ 5).
- Intravesical chemotherapy following complete TURBT is the evidence-based treatment for intermediate-risk BC patients. It has been shown to reduce recurrence risk in both primary and recurrent intermediate-risk tumors without changes in progression.
- Intravesical BCG immunotherapy is standard therapy for intermediate- and high-risk BC. BCG has shown to have superior efficacy compared with chemotherapy due to BCG ability to improve the progression rate in high-risk but not in intermediate-risk patients.
- Early radical cystectomy should be offered in a risk-adapted manner in high-grade T1 tumors with other factors of poor prognosis to improve survival and avoid the risk of overtreatment.

Muscle-Invasive Bladder Cancer (MIBC)

Introduction

Bladder cancer (BC) is the ninth most frequent cancer and responsible for the 3% cancer-related deaths. Muscle Invasive Bladder Cancer (MIBC) represents 25% of all new diagnosed BC. MIBC is an aggressive and life-threatening disease and requires timely management in highly specialized centers. A correct diagnosis and staging requires a combination of imaging, and a correct TURBT to assess good information about histology and molecular and clinical predictive factors. It has been recently published that patients untreated are at near term for cancer-specific mortality (CSM) with a 5 years overall survival (OS) rate of 5% [59]. The current standard of treatment is neoadjuvant chemotherapy followed by radical cystectomy. Nevertheless, both treatments result in a high probability of complications

and toxicities. Bladder preservation protocols in well-selected patients can lead to acceptable oncological outcomes with a good quality of life. The implementation of novel molecular markers for a better risk adaptation of the patients who better respond to chemotherapy, the new imaging technologies and advances in minimally invasive and robotic surgery will improve in the next future the quality of life and survival of patients with MIBC.

The most common clinical presentation is asymptomatic hematuria, which should prompt evaluation with cystoscopy, renal function testing, and upper urinary tract imaging in adults 35 years and older and in those with irritative voiding symptoms, risk factors for bladder cancer, or gross hematuria at any age [60].

Risk Factors

Several risk factors that have been linked to BC and are involved in the pathogenesis and response to treatment in MIBC. Cigarette smoking has been associated with adverse pathological response to neoadjuvant chemotherapy (NAC) in patients with MIBC [61]. Synthetic nitrogen fertilizers, organophosphate-based pesticides, aromatic amines, pelvic irradiation, A cyclophosphamide, chronic cystitis, schistosomiasis, human papillomavirus, genetic predisposition, and some occupations are also risk factors linked to the pathogenesis of BC [62].

While global incidence BC is less common among women, female gender has worse oncological outcomes. Female gender is associated with higher clinical stage at diagnosis, more frequent non-urothelial carcinoma and worse oncological outcomes [63].

Clinical Staging

Transurethral Resection of Bladder Tumor (TURBT)

The diagnosis and local staging of MIBC is based on the endoscopic examination. A correct TURBT must obtain the information necessary for accurate clinical classification of clinical stage and cancer risk. It is highly important to achieve a complete resection of all visible tumors and suspicious areas when safe, feasible and bladder preservation is planned [27]. TURBT should be as complete as possible to facilitate good local symptoms control and improve the effectiveness of bladder sparing protocols [64].Random biopsies of the normal-looking mucosa would assess the presence of concomitant carcinoma in situ (CIS). Despite CIS status at TURBT don't affect pathological response to neoadjuvant or induction chemotherapy [65], it is important to know the status of the prostatic urethra to adapt the type of diversion at cystectomy.

Exam under anesthesia (EUA) should be performed before and after TURBT with the bladder empty. In a model including age, Body Mass Index (BMI), ethnicity, year of operation, and NAC among other factors, the only factors predictive of pT3 disease were EUA and imaging ($p = 0.002$). The combination of EUA and imaging improved the accuracy of clinical staging compared to either modality alone [66].

Imaging

Multiphasic CT urography with and without intravenous contrast and excretory phase should be part of the workup in MIBC. It has the highest sensitivity (95%) and specificity (92%) of all upper urinary tract imaging modalities. Magnetic resonance urography and ultrasonography are alternative imaging options for patients with contraindications to CT urography, such as pregnancy, contrast allergy, or renal insufficiency. If metastatic disease is suspected, chest radiography and imaging of the abdomen and pelvis with CT or magnetic resonance imaging (MRI) should be obtained [60]. Evidence suggests that 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT might have potential effectiveness for staging in MIBC. The diagnostic accuracy of F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) for preoperative lymph node (LN) staging in newly BC patients has been analyzed in a recent systematic review. Results from

14 studies revealed a sensitivity of 0.57 and a specificity of 0.92 [67].

Predictive Factors

Age: Advance chronological age (>65 y.o) is associated with more advanced pathological stage, nodes involvement and worse oncological outcomes [68].

Lymphovascular invasion (LVI): In patients with MIBC with no involvement of the nodes, the presence of LVI is an independent predictive factor of aggressive disease, recurrence and survival [69]. Together with well established prognostic factors, models that include the presence of LVI at TURBT might aid patient selection for early radical cystectomy or perioperative chemotherapy [70].

Prior non- muscle invasive disease: Patients with prior non-muscle invasive bladder cancer that progress to MIBC have worse outcomes than those primary MIBC. Two retrospective large studies have confirmed a higher rate of hydronephrosis, pathological stage, and positive nodes [71, 72].

Timing to cystectomy: Delays in care from the time longer than 12 weeks of either the initial diagnosis or the completion of NAC to RC are associated with worse overall survival among patients with MIBC [73].

Histological subtype: Urothelial carcinoma (transitional cell carcinoma, TCC) is the most common histological subtype of primary BC, which accounts for >90% of all BC. Other histological subtypes include squamous cell carcinoma (SQCC), adenocarcinoma (AD), small cell carcinoma (SCC) and some other rare non-epithelial subtypes. Among these, SQCC, AD, and SCC account for less than 5%, 2% and 1% of all primary bladder tumors, respectively. AD has been significantly associated with longer and SQCC with shorter survival time as compared to TCC [74].

Biomarkers

Biomarkers have the potential to aid treatment decisions; prognostic biomarkers might help to inform the need for treatment intensification whereas predictive biomarkers might have a role in specific treatment selection [64]. Up to date none of the biomarkers analyzed have been included in clinical practice. Advanced technology uses patients' blood or urine as samples instead of primary BC tissue to analyze BC prognosis and to explore novel prognostic or predictive biomarkers. A liquid biopsy involves the analyses of circulating tumor cells (CTCs), exosomes, and circulating miRNAs in patients' blood or urine. Preoperative CTCs in peripheral blood are detected in 23% of non-metastatic advanced bladder cancer. There was concordance between HER2 expression on CTC and the HER2 gene amplification status of the primary tumor and lymph node metastases in CTC-positive cases [75]. TP53, a transcription factor, has many functions, such as induction of apoptosis, inhibition of cell proliferation, and arrest of the cell cycle. Nuclear accumulation of TP53 is a predicting factor of poor prognosis in advanced BC. In multivariable analyses of 692 patients with invasive cancer treated with radical cystectomy and lymphadenectomy, TP53 expression was independently associated with disease recurrence and cancer-specific mortality [76]. Loss of RB1 expression is also an adverse prognostic biomarker in MIBC [77]. MicroRNAs (miRNAs) are 18–24-nucleotide-long noncoding RNA that inhibit gene function by endogenous blocking. Several miRNAs are involved in carcinogenesis as the tumor suppressor or oncogenic molecules. miR-145 is one of the most recurrently down-regulated miRNAs in bladder cancer. miR-141 and miR-205 are poor prognostic biomarkers of overall survival in bladder cancer [78].

Recent studies have identified molecular subtypes of MIBC using gene expression profiling. Choi et al. performed whole-genome mRNA expression profiling and unsupervised hierarchical cluster analyses on a cohort of 73 primary fresh frozen MIBC obtained by TURBT. The authors discovered three molecular subtypes of MIBC. Basal MIBC was characterized by p63 activation, squamous differentiation, and more aggressive disease at presentation. Luminal MIBCs contained features of active PPARγ and estrogen receptor (ER) transcription and were enriched with activating *FGFR3* mutations and potentially FGFR inhibi-

tor sensitivity. p53-like MIBCs were consistently resistant to neoadjuvant MVAC chemotherapy, and all chemoresistant tumors adopted a p53-like phenotype after therapy [79]. Seiler et al. suggested that patients with basal tumors should be prioritized to receive NAC [80].

Treatment

The treatment of MIBC is multidisciplinary and requires the participation of the Urologist, Radiation and Medical Oncologist. The current standard of treatment is NAC plus radical cystectomy and lymphadenectomy. Nevertheless, some patients with a very low tumoral volume or on the other hand patients unfit for surgery or ineligible for cisplatin-based regimes are candidates for bladder sparing protocols. Apart from chemotherapy, the promising results of recent clinical trials make that immunotherapy is gaining space in locally advanced and metastatic disease.

Radical Cystectomy

Radical cystectomy (RC) represents the surgical gold standard for MIBC. Moreover, RC represents also an indication in very high risk NMIBC [81]. It is important to consider that the quality of the surgery has an important impact on the oncologic results and quality of life. Cancer-specific survival (CSS) depends on age, clinical stage, node status, and surgical margins. Herr et al. reported a mortality Hazard Ratio (HR) of 2.7 for patients with positive margins and 2.0 for those with less than 10 nodes removed [82]. In a retrospective series of 1100 patients with MIBC treated with RC and without perioperative chemotherapy CSS was 88.9–59.7% for pT1 and pT3a respectively and 31.4–14.3% for those pt3b-pN+. Retrospective long term oncological results following robotic-assisted radical cystectomy (RARC) have reported similar oncologic results compared to open radical cystectomy (ORC) [83].

Predictive factors for recurrence-free survival (RFS), CSS and overall survival (OS) were age, gender, node status, margin status, adjuvant chemotherapy and histology [83]. The 5 year RFS, CSS and OS were 67%, 75% and 50% respectively [83]. Conclusions of a recent systematic review revealed than when ORC is compared to RARC oncologic and functional results are similar but more long-term prospective studies are needed [84]. Regarding perioperative complications, cumulative analysis demonstrates shorter operative time with ORC whereas RARC may provide some advantages in terms of blood loss and transfusion rates and, more limitedly, for postoperative complication rates over ORC and laparoscopic radical cystectomy (LRC) [85]. An analysis comparing intracorporeal (ICUD) versus extracorporeal urinary diversion (ECUD) revealed similar hospital stay, 30 days readmission rate higher in ECUD, and lower complication risk in ICUD [86]. A recent prospective randomized non-inferiority trial concluded that RARC is not inferior compared to ORC in terms of progression-free survival (PFS) at 2 years. Moreover, RARC has better results in terms of perioperative complications without differences in terms of complications and quality of life (QoL) [87].

Systemic Therapy for MIBC

Although RC remains to be the headstone treatment in MIBC, perioperative chemotherapy has improved outcomes, specifically NAC. The bladder preservation strategies have also emerged as treatment options. A systematic review and meta-analysis reported a 5% improvement in 5 year OS and 9% in CSS with the use of platinum-based NAC before RC [88]. Moreover, NAC with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has demonstrated in a phase III trial a significant higher rate of patients with complete clinical response (pT0); 23%, compared to patients treated only with RC [89]. NAC with cisplatin, methotrexate, and vinblastine (CMV) presents also an advantage in oncological outcomes (6% advantage in OS) compared to RC alone [90]. The combination of Gemcitabine and cisplatin (GC) had similar pathological and oncological outcomes compared to MVAC y NAC before RC [91] with less toxicity [92]. A recent study has suggested that GC presents a higher risk for death than patients who received dose-dense (dd MVAC); (HR 2.07, 95% CI 1.25-3.42,

p = 0.003) [93]. Presently, no approved biomarkers have been released to support in individualized treatment decisions of whether to indicate NAC for a particular patient or to choose among the different NAC regimens. This may change the following completion of the currently ongoing SWOG 1314 study, which randomizes MIBC patients to receive either ddMVAC or GC as NAC before cystectomy. The primary endpoint of this study is to prospectively validate the co-expression extrapolation (COXEN) score, which assesses tumor sensitivity to chemotherapy based on gene expression.

This is a novel trial design in which the COXEN score generated based on gene expression in the transurethral resection of bladder tumor (TURBT) specimen will be assessed in its ability to predict the patient's pathologic response at the time of cystectomy to either ddMVAC or GC NAC regimen. The role of adjuvant therapy is more difficult to establish in MIBC. The main reasons are the small patient numbers, early closure of trials and poor compliance with trial protocols. A meta-analysis from six trials with 491 patients found a 9% improvement in 3-year OS [94]. A 2014 update with 945 patients; For CSS, the pooled HR across seven trials reporting this outcome was 0.66 (95% CI, 0.45-0.91; p = 0.014). The CSS benefit was more apparent among those patients with positive nodes [95].

Neoadjuvant Immunotherapy

Immune checkpoint inhibitors have become a treatment option in metastatic MIBC. Results of a phase II trial with Atezolizumab (anti-PD-L1 antibody) in patients with locally advanced and metastatic MIBC who have progressed following platinum-based chemotherapy With a median follow-up of 11·7 months (95% CI 11·4–12·2), ongoing responses were recorded in 38 (84%) of 45 responders [96]. In the neoadjuvant settings, the phase-II PURE-01 study investigated the role of Pembrolizumab. Initial results have reported a 42% pT0 rate [97].

Bladder Preservation Strategies

RC is associated with a high rate of complications that could have a negative effect on the quality of life (QoL) of the patients [98]. Evidence from retrospective studies suggests that in highly selected patients with MIBC Trimodality Bladder-Sparing treatment (TM) and RC have comparable outcomes. A meta-analysis of 29 TM studies and 30 radical cystectomy studies found that the 5-year OS was 63% for TM and 61% for RC for patients with T2 disease (P = 0.30) and was 45% and 40%, respectively, for patients with >T2 disease (P = 0.36) [99]. TM treatment requires a maximal TURBT followed by radiotherapy and a concurrent radiosensitizing agent that function in a synergistic manner with radiotherapy. The most common radiosensitizer is chemotherapy. Predictive biomarkers might help to identify patients who will respond to TM treatments. Specifically biomarkers to hypoxia modification such as double-strand break repair protein MRE11, carbonic anhydrase IX (CAIX), necrosis and a 24-gene hypoxia signature [64]. There is a lack of prospective studies that compare RC and TM treatment.

The early closure of the Selective bladder Preservation Against Radical Excision (SPARE) trial has been attributed to several factors, including the complexity of the patient referral and management pathways (which had multiple specialist teams and centers involved) and the importance of patient preference in a trial that randomizes patients to two distinctly different treatment options [64]. Up to now, it is recommended to offer TM treatment as an alternative to selected, well-informed and compliant patients, especially for whom cystectomy is not an option [81].

Metastatic Bladder Cancer

Five percent of patients with BC present metastatic disease at diagnosis. Chemotherapy is the first-line treatment for these patients. Gemcitabine and cisplatin (GC) been compared with MVAC in a phase-III randomized controlled trial, which showed that GC had significantly less toxicity with significantly lower rates of neutropenic sepsis and grade 3 or 4 mucositis and a reduction in drug-related mortality, though the latter was not statistically significant. Response rates for GC versus MVAC were

49.4% and 45.7%, respectively, the median survival of 13.8 and 14.8 months, and the time to progressive disease was identical in both groups at 7.4 months [100]. Potential second-line options in metastatic bladder cancer include single-agent vinflunine, taxanes, and combination regimes. Patients with metastatic BC who are not fit for cisplatin-based regimens, treatment should be planned according to performance status and ability to tolerate systemic therapy. Options include treatments with chemotherapy and immunotherapy. Patients with ECOG<2 who are fit for a combination regimen, options include carboplatin-based regimens or a non-platinum-based combination like paclitaxel plus gemcitabine [88]. Single-agent chemotherapy is an alternative or treatment with best supportive care is a reasonable option. Checkpoint inhibition immunotherapy with an agent targeting the programmed cell death-1 protein (PD-1) or its ligand (PD-L1) is an option for patients with access to one of these agents. Enrollment in a formal clinical trial assessing the role of immunotherapy is recommended whenever possible. For patients who relapse following treatment with a platinum-based regimen, checkpoint inhibition with an agent targeting the programmed cell death-1 protein (PD-1) or PD-L1 is an option that should be considered. Whenever possible, patients should be enrolled in formal clinical trials. The best candidate for surgery in metastatic BC are those with resectable disease (pelvic or retroperitoneal nodes, and pulmonary metastases in selected cases) who demonstrate a measurable response to chemotherapy with good performance status [101].

Conclusions and Recommendations

- MIBC is an aggressive and life-threatening disease and requires timely management in highly specialized centers.
- Tobacco smoking is an important risk factor even for a worse response to NAC.
- Accurate staging of MIBC should be based on a combination of an extensive TURBT combined with an exam under anesthesia and Multiphasic CT urography. 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT might have potential effectiveness for staging in MIBC.
- Important Clinico-pathological predictive factors for worse outcomes in MIBC are advanced age, prior NMI disease, Delays in care from the time longer than 12 weeks, lymphovascular invasion in the TURBT specimen and histological variants as squamous cell carcinoma.
- Currently, there is no evidence enough to consider biomarkers for decision making in clinical practice. Nevertheless, the new molecular subtypes based on gene expression profiling will be promising to select the best candidates for NAC.
- Radical cystectomy with NAC is the most offered treatment in MIBC. The current evidence shows non-inferior oncological outcomes at 2 years for RARC compared to ORC.
- Evidence from retrospective studies suggest that in highly selected patients with MIBC, Trimodality Bladder-Sparing treatment (TM) and RC have comparable outcomes
- Patients with good performance status, adequate renal function, and metastatic or inoperable locally advanced urothelial cancer should be treated with cisplatin-based combination chemotherapy.
- Patients with advanced urothelial cancer who are not fit for cisplatin, treatment should be considered according to the patient's performance status and ability to tolerate systemic therapy. Options include both chemotherapy and immunotherapy.

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35 Management of Localized and Locally Advanced Prostate Cancer

Derya Tilki and Christopher P. Evans

Introduction

Prostate cancer (PCa) is the most commonly diagnosed non-cutaneous cancer type, and the second and third leading cause of cancer death, among men in the United States and in Europe, respectively [1]. Based on risk group, preference and patient factors such as age and comorbidities, different treatment options are available for newly diagnosed PCa, which include active surveillance, radical prostatectomy, radiation treatment and focal therapy. The current chapter provides an overview of current management strategies for localized and locally advanced PCa.

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Management of Localized Prostate Cancer

Active Surveillance

Despite misgivings and concerns at the time of its initial introduction [2], active surveillance (AS) for very low-risk (VLR) and low-risk (LR) prostate cancer (PCa) has become a guideline accepted standard of care. In contrast to watchful waiting, AS is defined as conservative management with periodic monitoring and selective delayed intervention with curative intent. With regular monitoring, AS enables appropriate reclassification and better patient selection for definitive treatment, such as radical prostatectomy and radiation therapy.

Active surveillance protocols may vary by institution, but most share the following features: confirmatory biopsy following initial prostate biopsy, serum PSA every 6–12 months, digital rectal exam at the time of clinic visits, serial repeat prostate biopsies every 1–3 years. Following an initial biopsy, a confirmatory biopsy within 6–12 months is recommended prior to enrollment onto AS as 20–30% of men are upgraded on repeat biopsy [3, 4]. Multiparametric magnetic resonance imaging (mpMRI) has been increasingly incorporated into the diagnostic pathways for prostate cancer and is now recommended prior to confirmatory biopsy and subsequent serial prostate

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biopsies in men on AS, having demonstrated the ability to identify clinically significant prostate cancer missed by standard prostate biopsy sampling [5, 6].

There have been five large prospective series evaluating AS [7–11]. While the inclusion criteria for these were variable, the majority of men met the following criteria: Gleason Grade Group 1 disease, clinical stage T1–2, PSA ≤10 ng/mL, and minimal core involvement (<1/3 cores and <50% each positive core). These resulted in 60–85% 5-year treatment-free survival and <1–5% prostate cancer specific mortality [12]. While there are no prospective studies specifically assessing AS, data from three randomized clinical trials comparing immediate definitive therapy to conservative management (active monitoring and watchful waiting) suggest that conservative management is a safe option for men with low-risk PCa [13–15]. In addition, large retrospective surgical series identified rates of metastasis approaching zero in men with confirmed Gleason 6 prostate cancer, demonstrating the indolent natural history of this disease [16, 17].

Based on the strength of this evidence, current international guidelines designate AS as the "preferred" management and standard of care for VLR and LR prostate cancer [18]. Despite this, uptake of AS remains moderate, hovering around 40% in patients with LR disease [19, 20]. Ultimately, the decision to proceed with AS is a shared decision with the patient, and options of definitive therapy should be offered. In some men, anxiety associated with living with untreated cancer may inform their decision to undergo treatment early, but they should be counseled regarding the significant complications and quality of life implications of definitive therapy.

As final caveats, it should be noted that while current research into the use of biomarkers may help safely expand AS to a selective population of men with intermediate risk prostate cancer, AS is not recommended for men with IR prostate cancer at this time. Furthermore, the integration of mpMRI with AS remains in evolution. It is not known or established how often mpMRI should be performed or whether patients with a negative mpMRI can safely avoid surveillance biopsies, recognizing a small false negative rate exists.

Radical Prostatectomy

Radical prostatectomy (RP) remains a standard of care for management of localized prostate cancer. The surgery includes removal of the entire prostate with its capsule and seminal vesicles. In contrast to other treatment options, RP offers pathologic evaluation of the true tumor grade and enables staging by pelvic lymph node dissection.

Outcomes of Radical Prostatectomy in Localized Prostate Cancer

In the Scandinavian Prostatic Cancer Group Study Number-4 (SPCG-4) 695 patients with clinically detected PCa were randomized to watchful waiting (WW) versus RP between 1989 and 1999 prior to the PSA era [21]. Long-term data (29 year follow-up) have just been reported and showed that at 23 years, a mean of 2.9 extra years of life were gained with RP compared with WW.

In the Prostate Cancer Intervention versus Observation Trial (PIVOT) 731 patients have been randomized to RP versus WW between 1994 and 2002 [15]. In contrast to the SPCG-4 trial, surgery was not associated with significantly lower all-cause or prostate-cancer mortality than observation within a median follow-up of 12.7 years. A significant overall survival benefit for RP was only seen in patients with serum PSA > 10 ng/mL or high risk PCa (reduction in mortality of 33% and 31%, respectively). Main limitation of this study is the high overall mortality in the WW group (almost 50% at a median of 10 years).

To date, one randomized study, the Prostate Testing for Cancer and Treatment (ProtecT) trial, exists, which compared oncological outcomes of active monitoring, RP and radiation treatment after a median follow-up of 10 years [14]. Prostate cancer specific survival was at least 98.8% in all groups, and there were no significant differences in the three randomized groups ($p = 0.48$). Men in the group of active monitoring

(approximately 40% with intermediate-risk PCa) had an increased risk of developing metastases. However, it has to be noted that active monitoring in the study was different from active surveillance. Active monitoring was based mainly on PSA alone without use of multiparametric MRI or regularly scheduled repeat biopsies.

The study included several further limitations. The study population consisted predominantly of low-risk patients (60% of patients had low-risk disease; 77% of patients had Gleason 6 PCa), which were eligible for Active Surveillance because of their low risk for progression. Furthermore, after a median follow-up of 10 years, prostate cancer mortality was very low at 1%. There were a total of 17 prostate cancer deaths. Thus, a mortality analysis at present is too early and conclusions should be made with caution. At the time of study initiation the assumption was for a mortality of 10% after a median follow-up of 10 years. In addition, definitive treatment of the included patients has not been performed according to current standards (radiotherapy: no intensity-modulated radiation therapy (IMRT), RP: 24% positive margins), which may have influenced the results.

While RP provides excellent oncological outcomes, it can cause severe side effects such as urinary incontinence and erectile dysfunction, which negatively affect Quality of life [14, 22–25]. Numerous population-based studies or randomized controlled trials reported worse urinary continence and erectile function rates for patients that underwent RP compared to patients who received primary radiation treatment or active surveillance [26–28]. Rate of urinary incontinence (use of any pad) was 26% for RP patients within the ProtecT study, and only 15% of the patients had erections firm enough for intercourse 1 year after RP [26]. Similarly, urinary incontinence rates were up to 43% and erectile dysfunction (defined as erections not hard enough for intercourse) rates were 80% in the SPCG-4 trial 12 months after RP [29]. However, functional outcomes in high-volume centers have been reported to be better [30]. Pompe et al. reported 12-, 24- and 36-months erectile function rates of 45%, 51% and 53%, which reached up to 66% in preoperatively potent patients with bilateral nerve sparing. Urinary continence rates were 89% and 91% at 12 and 24 months postoperatively [30].

Open Versus Robotic-Assisted Radical Prostatectomy

With the introduction of robotic-assisted techniques, the surgical management of prostate cancer has evolved. The uptake has varied by country, depending on cost, patient preference, insurance coverage, and healthcare system [31]. Numerous reports have been published assessing the safety of robotic-assisted RP (RARP) and its perioperative, functional and oncologic outcomes, as compared to open RP. RARP has generally been accepted to have lower estimated blood loss and shorter hospital stay [32, 33]. Lower incidence of bladder neck contractures or anastamotic strictures [34] and lower intraoperative complication rates [32] have been reported for RARP in some series. There is conflicting evidence regarding the effect of the robotic-assisted approach on functional outcomes and no reliable data on differences in oncologic outcomes.

Gershman et al. retrospectively evaluated patient-reported functional outcomes in men undergoing RARP or ORP by high-volume surgeons at two high-volume centers in the USA and did not find any differences in urinary or sexual function outcomes depending on surgical technique [35].

Ficarra and colleagues analyzed 51 articles reporting urinary continence outcomes, of which 9 compared RARP to open RP [36]. The authors showed a mean urinary continence rate (no pad or one safety pad) of 91% at 12 months, with continence rates superior in men undergoing RARP compared to open RP (OR 1.53; $p = 0.03$) [36]. In a separate systematic review and meta-analysis assessing potency, 15 case series were analyzed, in 6 comparing RARP to open RP, Ficarra et al. identified 12 and 24-month potency rates of 54–90% and 63–94%, respectively. Potency rates were significantly higher in men undergoing RALP at 12-months (OR 2.84; $p = 0.002$), and trended towards significance at the 24-month (OR 1.89; $p = 0.21$) [37]. However, with variable definitions of potency and differ-

ences in the quality of the included studies, the results of the meta-analyses must be interpreted with caution.

Sooriakumaran et al. recently presented results of the LAParoscopic Prostatectomy Robot Open Trial LAPPRO (LAParoscopic Prostatectomy Robot Open) trial, a prospective non-randomized study, which included 2545 Swedish men PCa who underwent either RARP or open RP at 14 different Swedish institutions by 50 experienced surgeons over a 3-year period [38]. While the authors have previously reported on perioperative [39] and urinary continence outcomes [40], they focused on erectile function (EF) recovery and oncologic outcomes in this study [38]. Erectile function recovery was significantly better in the RARP patients through 24 months than in the open RP patients (51% for RARP and 39% for ORP at 24 months). The authors report 10% vs. 17% PSM rates in pT2 tumors for open and robot-assisted surgery, respectively [38]. Corresponding rates for pT3 tumours were 48% and 33% [38]. The reported differences were associated with biochemical recurrence in pT3 but not pT2 disease.

In their systematic review and meta-analysis of 79 papers, Novara et al. reported a positive surgical margin (PSM) rate of 15% for all RARPs, while the rate was 9% in patients with localized disease. Similar overall PSM rates (RARP vs. RP: OR 1.21; $p = 0.19$), PSM rates in localized ≤ pT2 disease (OR 1.25; $p = 0.31$) and similar BCR-free survival (HR 0.9; $p = 0.526$) have been demonstrated when comparing RARP to ORP [41]. However, all of the data included was from high-volume centers with experienced surgeons, thus limiting the generalizability of the analysis.

To date, only one randomized controlled trial (RCT) assessing RARP and ORP has been conducted and reported [32, 42]. In the initial publication of early 12-week results in 308 randomized patients, no significant difference in the 6-week and 12-week urinary continence and erectile function recovery rates between the two groups has been seen [32]. Moreover, there was no significant difference in the surgical margin rates between the two treatment arms. Coughlin et al. recently presented the 24-months outcomes of this study, which again showed similar functional outcomes for RARP compared to open RP after 12 and 24 months [42].

However, this randomized study has a relatively low sample size ($n = 308$) compared to the available retrospective studies and was performed at a single institution by two surgeons, making the generalizability of results difficult.

Role of Lymphadenectomy at the Time of Radical Prostatectomy

Extended lymphadenectomy includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery [43].

Fossati et al. recently published a systematic review on pelvic lymphadenectomy (PLND) during RP and found that PLND was not associated with improved oncological outcomes [44]. Nevertheless, extended lymph node dissection is recommended by the EAU (European Association of Urology) guidelines in all patients with high risk PCa and patients with intermediate risk PCa, who have a risk of metastasis of more than 5% (e.g. estimated by the Briganti nomogram [45, 46]), because of information for staging and prognosis [43]. If RP is performed in low-risk PCa, pelvic LN dissection is not necessary (risk of positive lymph nodes ≤5%). This risk stratified application of which patients should undergo PLND with RP eliminates PLND in up to 70% of patients undergoing RP, depending on the risk distribution in one's practice.

Radiation Treatment

External Beam Radiation Therapy (EBRT)

Radiation therapy uses high-energy particles to damage cellular DNA and induce apoptosis in cancer cells. Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy, is the gold standard for external beam radia-

tion therapy (EBRT) [43]. IMRT uses dynamic multileaf collimators to provide a high dose to the target while minimizing toxicity to surrounding tissue. A dose of 76–78 Gy is recommended for EBRT plus androgen deprivation (ADT) in intermediate and high-risk PCa patients [43]. In intermediate-risk patients not willing to undergo ADT, an escalated dose of EBRT (76–80 Gy) or a combination with brachytherapy is recommended [43].

Brachytherapy

For low-dose rate brachytherapy (LDR brachytherapy) radioactive seeds are permanently implanted into the prostate. Inclusion criteria for this treatment option according to the EAU guidelines are as follows [47]: Stage cT1b-T2a N0, M0; ISUP grade 1 with ≤50% of biopsy cores involved with cancer or ISUP grade 2 with ≤33% of biopsy cores involved with cancer; An initial PSA level of ≤10 ng/mL; a prostate volume of <50 cm^3; and an International Prostatic Symptom Score (IPSS) ≤12 and maximal flow rate >15 mL/min on urinary flow tests. For ISUP grade 1 patients 10-year BCR-free survival was reported to range from 65 to 85% [48–55].

For high-dose rate brachytherapy (HDR brachytherapy) the radioactive source is only temporarily introduced into the prostate. HDR brachytherapy is often combined with EBRT of at least 45 Gy [47]. Only limited data exists regarding the superiority of EBRT with brachytherapy compared to EBRT alone in the treatment of intermediate- and high-risk PCa (also see Section "Management of Locally Advanced Prostate Cancer").

Focal Treatment

Focal treatment of prostate cancer represents the targeted destruction of cancer within a specific part of the prostate gland, while sparing the rest of the prostate and nearby tissue. It is intended to potentially reduce side effects when compared with established standard treatments. Success of focal therapy depends on the ability to identify and target the lesion. Several energy sources, such as high-intensity focused ultrasound (HIFU), cryotherapy, photodynamic therapy (PDT) or irreversible electroporation (IRE), have been employed for focal therapy [56]. None of these ablative technologies has been demonstrated to be successful all of the time and rates of positive control biopsy range from 20 to 30% for all of them [56].

Because of lack of validated data, focal treatment remains experimental and should only be performed in a clinical trial setting [43].

Management of Locally Advanced Prostate Cancer

An inverse stage migration towards more aggressive and locally advanced tumors has been demonstrated during the last decade [57, 58]. This can be attributed to both the increasing acceptance of local therapy in locally advanced PCa as well as the increasing use of active surveillance in low-risk PCa patients. Moreover, the USPSTF (U.S. Preventive Services Task Force) issued a draft guideline in October 2011 discouraging prostate specific antigen (PSA) based screening for PCa (grade D recommendation), which has led to a decrease in incident diagnoses of prostate cancer, while the incidence of men presenting with metastatic disease seems to be rising recently [59, 60].

Locally advanced PCa is a clinical diagnosis and is defined as a tumor which extends through the prostate capsule, the seminal vesicles or has spread into tissue around the prostate, e.g. rectum, bladder, urinary sphincter or the pelvic wall. Patients with evidence of lymph node metastases are not regarded as locally advanced.

According to the current EAU Guidelines on PCa no standard for treatment of locally advanced PCa can be currently defined [43]. Treatment options include surgery as part of a multimodal therapy or upfront external beam radiation treatment (EBRT) combined with androgen deprivation (ADT), while HIFU, cryotherapy or focal therapies are not recommended in the management of locally advanced PCa.

Natural History of Patients with Locally Advanced Prostate Cancer

Akre and colleagues analyzed data from the register-based nationwide cohort study within the Prostate Cancer DataBase Sweden including 12,184 men with locally advanced PCa (defined as local clinical stage T3 or T4 or with T2 with serum levels of prostate-specific antigen (PSA) between 50 and 99 ng/mL and without signs of metastases) managed with noncurative intent [61]. PCa-specific mortality at 8 year of follow-up was 28% for Gleason score (GS) 2–6, 41% for GS 7, 52% for GS 8, and 64% for GS 9–10 [61]. Even for men in the oldest age group (>85 years at diagnosis), PCa was a major cause of death. Gleason score was the most important predictor of tumor progression in this study.

Albertsen et al. utilized data from a retrospective population-based cohort study from the Connecticut Tumor Registry of 767 men aged 55 to 74 years with clinically localized prostate cancer diagnosed between 1971 and 1984 [62]. Patients were treated with either observation or immediate or delayed ADT therapy, with a median observation of 24 years. The authors showed that men with well differentiated tumors rarely died from their disease, while men with poorly differentiated tumors frequently died within 5–10 years of diagnosis despite aggressive interventions.

Outcomes of Radical Prostatectomy in Locally Advanced PCa

Currently, there has been an increase in radical prostatectomy number for locally advanced PCa [63]. To assess the benefits of RP in this setting, oncological, functional and perioperative results have to be taken into account.

The presence of locally advanced PCa in comparison with clinically localized PCa represents a significant risk factor for worse oncological outcome. The risk of dying from PCa within 10 years after RP is two- to fivefold higher in these patients [64–67]. Nevertheless, absolute death rates after RP remain low in patients with high-risk and locally advanced PCa [68, 69]. Published studies describing oncological outcomes after RP in patients with locally advanced PCa are summarized in Table 35.1 [65–67, 70–81]. Patients with locally advanced PCa who underwent RP show 10-year biochemical recurrence-free survival rates of 45–50%. The probability of 10 years without local recurrence or metastases after RP is 70–85% and without cancer death is 90%. Analogous to localized PCa, further oncological outcome in locally advanced PCa is largely dependant on PSA, Gleason score, pT stage, surgical margins, and lymph node status [66, 80, 82]. Probability of downstaging of a cT3/4 PCa to a pathological stage <pT3 after RP is approximately 20% and depends on PSA, biopsy Gleason score [80, 82, 83].

Studies examining functional outcomes in patients with locally advanced PCa are rare and show inferior functional results compared to patients with localized PCa [66, 76, 84, 85]. Nerve-sparing is often omitted in these patients [66, 76, 84, 86]. Rates of nerve-sparing surgery can be increased in these men by the use of intraoperative frozen section analysis, which may lead to better postoperative continence and potency [87–91]. Moreover, the increased likelihood of adjuvant or salvage therapies (ADT and/or radiation) as part of a multimodal regimen can result in a significant reduction of continence and potency rates after RP [92, 93].

In most studies investigating perioperative morbidity in RP among patients with $cT \geq 3$ and $cT \leq 2$, no significant increase in perioperative morbidity within patients with locally advanced PCa was found [66, 76, 94–96]. Nevertheless, some studies have shown an increase of intraoperative complications such as rectal injury and subsequent development of a recto-vesical fistula in patients with more advanced PCa [97].

Comparative Effectiveness of Surgery vs. Radiation in Locally Advanced PCa

While a large randomized trial has compared RP with external beam radiotherapy (EBRT) for the

Table 35.1 Oncolocial results after radical prostatectomy (RP) in patients with locally advanced prostate cancer (PCa)[a]

Author	Year	Definition of locally advanced	N	Median/mean follow-up	Biochemical recurrence-free survival (%)			Metastasis-free survival (%)			Cancer-specific survival (%)		
					5	10	15	5	10	15	5	10	15
Ward et al.	2005	cT3	842	10.3 years	58	43	38	85	73	67	95	90	79
Carver et al.	2006	cT3	176	6.4 years	48	44		86	76		94	85	76
Freedland et al.	2007	cT3a	62	10.3 years	62	49	49	90	80	73	98	91	84
Hsu et al.	2007	cT3a (unilateral)	235	70.6 months	60	51		96	85		99	92	
Loeb et al.	2007	cT3	34	88 months		15					84		
Yossepowitch et al.	2008	cT3	243	5.5 years				85	72		96	89	
Xylinas et al.	2008	cT3a	100	69 months	45						90		
Stephenson et al.	2009	cT3	254	48 months				85	62				
Walz et al.	2010	cT3	293	2.4 years	52	44							
Joniau et al.	2012	cT3b-cT4	72	108 months	53	46		78	73		92	92	
Mitchell et al.	2012	cT3	843	14.3 years						75			83
Yamamoto et al.	2014	cT3	112	93 months					74			94	
Gandaglia et al.	2014	cT3a-cT4	474	Not reported								88	
Moltzahn et al.	2015	cT3b-cT4	266	111 months								87	
Bandini et al.	2018	cT3	2507	Not reported								92	

[a]Adapted from Mandel, Tilki et al. 2015 [68]

treatment of men with favorable-risk PCa, results from prospective, randomized trials are currently lacking to answer the question, whether initial surgery or initial radiation is superior with regards to oncological effectiveness in patients with locally advanced PCa [14].

In a recent multi-institutional retrospective study, Kishan et al. reported that among patients with Gleason score 9–10 PCa, treatment with EBRT+brachytherapy with ADT was associated with significantly better PCa–specific mortality and longer time to distant metastasis compared with EBRT with ADT therapy or with RP [98]. However, the authors did not compare EBRT+brachytherapy with ADT to RP in a multimodal setting including adjuvant EBRT, ADT or both.

In contrast, Tilki et al. analyzed 639 men with Gleason score 9–10 PCa and found no significant difference after RP, adjuvant EBRT, ADT (termed MaxRP) or EBRT, brachytherapy, and ADT (termed MaxRT) [99].

Ennis et al. studied patients with high-risk PCa in the National Cancer Database (NCDB) and did not find an overall survival difference between RP, EBRT (+ADT), and EBRT + brachytherapy (with or without ADT) [100]. However, limitation of the study included the short follow-up and inclusion of elderly patients and patients with comorbidities.

When limiting the analysis of patients from the NCDB to younger and healthier men and patients with longer follow-up, Berg and colleagues found a survival benefit for patients with RP as compared to EBRT + brachytherapy [101].

A prospective phase 3 randomized study (SPCG-15) comparing RP (with or without adjuvant or salvage EBRT) against primary EBRT and ADT among patients with locally advanced (T3) disease is currently recruiting [102].

Summary

Depending on disease stage and risk group, patient characteristics such as age and comorbidities and patient preference, many options are available for PCa treatment. These include active surveillance, radical prostatectomy, radiation treatment and focal therapy as well as multimodal strategies for locally advanced PCa, and are associated with differing effects on Quality-of-life. Advantages and disadvantages of each treatment option should be well-known by the clinician and should be discussed with the patient.

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Management of Local, Regional, and Metastatic Penile Cancer

36

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Introduction

Penile cancer (PeCa) constitutes malignant lesions of the penis originating from the squamous epithelium of the prepuce, glans, and/or penile shaft. About 95% of such cancers are of squamous cell histology [1]. Most primary lesions are localized to the glans, followed by the prepuce, and then the penile shaft [2]. In 2018, the estimation for new cases of penile and other genital cancers among men in the United States was 2320 [3].

Risk Factors

Risk factors for penile cancer include [1] presence of an uncircumcised penis or phimosis, [2] human papillomavirus (HPV) infection, [3] lower socioeconomic status, [4] chronic inflammatory conditions, [5] smoking, and [6] poor genital hygiene [4]. A growing interest has been the impact of HPV and it thought to be causing nearly 4.5% of all cancer cases worldwide and 13,000 penile cancer cases/year [5]. HPV is found in the majority of basaloid and warty penile carcinomas, and found in about one-third of keratinizing and verrucous penile carcinomas [6].

Staging

The most important prognostic factor for penile cancer is the stage of disease. Staging is based on primary tumor depth as well as metastasis [7]. Table 36.1 details the stages (AJCC, 8th edition) of penile cancer according to the status of the primary tumor, regional lymph nodes, and distant metastasis.

It is important to note several changes in the most recent AJCC update for cancer staging with cT2 defined as invasion of corpus spongiosum and now invasion of the corpus cavernosum regarded as cT3 regardless of urethral involvement. Minor changes were made to three other primary tumor stages and two regional lymph node pathologic stages. Stage Ta is now non-invasive localized squamous cell carcinoma. T1a penile cancer is considered low risk, with an absence of lymphovascular or perineural invasion and no high grade

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Table 36.1 AJCC TNM staging system for penile cancer, 8th edition

Stage	Characteristics
Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive localized squamous cell carcinoma
Tis	Carcinoma in situ (CIS)
T1	Invades lamina propria
T1a	No lymphovascular or perineural invasion, or grade 3 tumor
T1b	With lymphovascular and/or perineural invasion, and/or grade 3 tumor
T2	Invades corpus spongiosum with/without urethra invasion
T3	Invades corpus cavernosum (including tunica albuginea) with/without urethra invasion
T4	Invades into adjacent structures (scrotum, prostate, bone)
Regional lymph nodes (N)	
Clinical stage definition	
cNX	Regional lymph nodes cannot be assessed
cN0	No lymph node metastasis
cN1	Palpable mobile unilateral inguinal lymph node
cN2	Palpable mobile multiple or bilateral inguinal lymph nodes
cN3	Palpable fixed inguinal nodal mass or pelvic lymphadenectomy unilateral or bilateral
Pathologic stage definition	
pNX	Regional lymph nodes
pN0	No regional lymph node metastasis
pN1	≤2 unilateral inguinal metastases, no extra-nodal extension
pN2	≥3 unilateral metastases or bilateral metastases
pN3	Extranodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

pathology. The number and type of metastases in pN1 and pN2 have been modified with pN1 being ≤2 unilateral inguinal metastases without extra-nodal extension and pN2 including bilateral or ≥3 unilateral metastases.

Management of the Primary Penile Tumor

After appropriate clinical examination with use of suitable and judicious imaging such as ultrasound (U/S) or magnetic resonance imaging (MRI), complete resection of the primary penile tumor is necessary for accurate clinical staging and delineating the suitable initial primary treatment. Although complete tumor removal should be the aim in all cases with negative surgical margins to reduce local recurrence rates, local recurrence has little influence on long-term overall survival (OS) [8–10] but should be adhered to in maintaining our robust oncological principles. Organ-preservation strategies with penile-sparing treatments, often times, are justified to achieve local oncological control without compromising functional and/or cosmetic outcomes that would occur with more radical surgery (i.e. partial or total penectomy).

Options for local treatment of the primary penile tumor include topical chemotherapy, excisional surgery, glans resurfacing, Mohs micrographic surgery, laser ablation, brachytherapy, and external beam radiotherapy (EBRT) [11, 12]. Patients should be counselled regarding the risks and benefits of each treatment option including long-term recurrence rates, functional outcomes, and likely cosmetic appearance.

Topical Chemotherapy

Topical chemotherapy with imiquimod or 5-fluorouracil (5-FU) is an effective first-line treatment for penile carcinoma in situ (CIS), with complete responses (CR) reported in up to 57% of cases [13]. Due to high persistence/recurrence rates with superficial non-invasive disease, treatment must be assessed by biopsy if suspicious lesions appear or persist and long-term surveillance is warranted with frequent physical examination. Topical chemotherapy can also be used in concurrence with laser abla-

tion and/or circumcision to minimize recurrence rates with CR achieved in as high as 73.7% of patients [14, 15].

Laser Ablation

Laser treatment with a neodymium:yttrium-aluminium-garnet (Nd:YAG) or carbon dioxide (CO_2) laser is an effective treatment option for superficial non-invasive disease or CIS [8, 16–18]. Tang et al. reported 5-year local recurrence-free survival rates of 50% for pTa/Tis disease, 41% for pT1a disease, and 38% for pT1b disease in 161 patients treated with only laser ablation for squamous cell carcinoma (SCC) of the penis [8]. The 5-year inguinal/pelvic nodal recurrence rate was 2% for pTa/Tis disease, 5% for pT1a disease, and 18% for pT1b disease. Meijer et al. reported a pooled local recurrence rate of 48% in 44 consecutive patients treated with laser therapy for penile cancer although 17 patients had pT2 disease compared to 31 with pT1 and 6 with pTis [17]. For penile CIS, Chipollini et al. observed that the majority of recurrences occurred after laser ablation (58.3%) compared to circumcision, glansectomy, wide local excision, or total glans resurfacing [9]. Follow-up rebiopsy to ensure treatment control, therefore, is recommended after laser ablation for primary penile SCC [10].

Moh's Micrographic Surgery

Moh's micrographic surgery is a technique by which histological margins are taken in a geometrical fashion around a conus of excision with tissue is examined for cancer cells until negative surgical margins are obtained with maximum preservation of normal tissue. Shindel et al. reported on 33 patients who underwent a total of 41 Mohs procedures for penile SCC [19]. Of the tumors, 26 were stage pTis, 4 were pT1, 7 were pT2, and 4 were pT3 with five procedures terminated with positive surgical margins. Follow-up data on 25 patients at mean follow-up of 58 months revealed an overall recurrence rate of 32% ($n = 8$) of which repeat Mohs micrographic surgery was performed in 7. Machan et al., however, reported a cure rate as high at 94.7% in 42 patients with 44 penile SCCs treated with Mohs micrographic surgery as an alternative to partial or total penectomy [20] but one must remember this was within a highly selected patient population with the majority of these tumors being of low-grade and superficial.

Wide Local Excision

Penile-conserving surgery with wide local resection with negative surgical margins is an alternative approach to preserve functional and anatomic outcomes for primary penile SCC. Feldman et al. showed an overall recurrence rate of 21.4% in 60 patients with penile CIS or pT1 disease treated with wide local excision at mean follow-up of 5 years [21]. T1 tumors on the glans carried the highest risk of recurrence although no patient with pTis disease showed evidence of metastasis during follow-up. Philippou et al. also demonstrated an overall 5-year local recurrence-free rate of 86.3% in 179 patients with penile SCC treated with penile-sparing surgery with a surgical excision margin of less than 5 mm [22]. Tumor grade, stage, and lymphovascular invasion were identified as predictors of local recurrence on multivariate analysis.

Glans Resurfacing

Partial or total glans resurfacing involves excision of the glans epithelium and subepithelium of either the entire glans or the locally affected area with a macroscopic clear margin with reconstruction of the penis using a split-thickness skin graft. Shabbir et al. initially reported on 25 patients with biopsy-proven pTis of the glans penis treated with partial or total glans resurfacing [23]. At mean follow-up of 29 months, the overall local recurrence rate was 4% although 12 patients (48%) had positive surgical margins with 7 (28%) requiring further surgery. In a prospective study from 2013 to 2015, O'Kelly et al. followed 19 patients with penile cancer who underwent total

glans resurfacing [24]. There was 1 local and no regional nodal recurrence at a mean follow-up of 23 months. One-year progression-free and OS rates were both 100%, and the 1-year recurrence-free survival rate was 95%. Of the patients, 81% reported an improved sex life postoperatively.

External Beam Radiation

External beam radiotherapy for localized penile cancer can provide local control and a reasonable chance of organ preservation. For pT1–T2 tumors, the 5-year local control rate has been reported at 62% with preservation of the penis approaching 40% [25]. For more advanced pT3–T4 penile tumors, local control has been observed to decrease to 40% with a 10-year probability of penile preservation of 38% [26]. Treatment of the primary tumor may be combined with concomitant treatment of the inguinal and/or pelvic nodal packets in regionally advanced cases but radio-sensitization with concurrent chemotherapy should be considered.

Partial or Radical Penectomy

Partial or radical penectomy remains the standard of care for high-risk (i.e. high-grade, pT2-T4) tumors of the penile shaft to minimize risk of local recurrence or metastatic spread. The decision for partial or radical penectomy depends on the proximal extent of tumor extension. The sensitivity and specificity of penile MRI in predicting corporal or urethral invasion was reported as 82.1% and 73.6%, and 62.5% and 82.1%, respectively [27]. Penile Doppler U/S, however, has been reported to have a higher staging accuracy than MRI in detecting corporal infiltration [28]. Patients do need to be counseled about the risk of possible placement of a perineal urethrostomy for urination with either surgical approach [10].

Management of Lymph Nodes in Low Risk Setting

A complete and thorough assessment of the inguinal region is critical given that the most important predictor of survival is involvement of the lymph nodes (LNs) [10, 29, 30]. Even for patients with clinically negative groins (cN0), the risk of micrometastases approaches 25% [10]. Hence, inguinal lymph node dissection (ILND) is an essential consideration in the management of PeCa patients.

Clinical Evaluation

A clinical exam for LN involvement should assess for palpability, size and number of inguinal masses, laterality, mobility or any degree of fixation. Imaging with Computer Tomography (CT) or Magnetic Resonance Imaging is also an option for those with a challenging physical examination.

Consideration of the primary tumor is the main determinant for lymphatic staging. There are well established clinical predictors for harboring LNM, including: primary tumor stage, degree of differentiation, perineural invasion, and the presence of lymphovascular invasion [31, 32]. Given the low incidence of PeCa, which limits patient enrollment in prospective studies, controversies on the optimal management of the LNs continue to this day.

Prophylactic vs. Delayed ILND

For cN0 patients, early lymphadenectomy has been shown to have superior oncologic outcomes versus waiting for nodal disease to occur [33, 34]. Even a delay of up to 3 months can negatively impact recurrence in both LN negative and positive cases [35]. Thus both European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guide-

lines recommend invasive LN staging for any cN0 patient with high risk primary tumor features at risk of micrometastases, i.e.: pT1 with presence of lymphovascular invasion, perineural invasion and/or poor differentiation (pT1b) or any tumor pT2 and above [10] [36].

For patients with clinically positive groins (cN+), an ILND can still be beneficial while curing a subset of patients with nodal metastatic disease [37, 38]. For that reason, it is no longer recommended to await the traditional 4–6 weeks of antibiotic treatment for patients presenting with palpable disease. For atypical presentation or when in need for systemic therapy, a fine needle aspiration with cytology (FNAC) can be performed when in need of histologic confirmation of disease [39]. In select patients with symptomatic inguinal LNM, upfront ILND may be considered if deemed to be resectable with consideration for adjuvant therapy. Current guidelines recommend a multimodal approach for those with bulky disease consisting of neoadjuvant chemotherapy followed by surgical resection, although the timing of systemic therapies continues to be controversial.

To help answer some of these controversies, the International Penile Advanced Cancer Trial (InPACT) (NCT02305654) has recently opened. This is a large, multinational collaboration with plans to accrue 400 cN+ patients over a 5-year period to be randomized into three arms: upfront ILND, neoadjuvant chemotherapy, or neoadjuvant chemoradiotherapy; the latter two followed by surgery. The trial will undoubtedly provide valuable prospective data and answer some important questions in the optimal timing of surgery and its integration with systemic therapy.

Dynamic Sentinel Node Biopsy

An alternative approach to cN0 disease is to perform a dynamic sentinel node biopsy (DSNB). The method includes preoperative usage of lymphoscintigraphy to identify the sentinel nodes (SN), patent blue dye injection, and intraoperative guidance with a γ-probe to visualize lymphatic drainage, with a negative DSNB considered adequate staging of cN0 groins, and if positive proceeding with traditional ILND [40]. There are still however complications associated with this procedure including infection, seroma and wound edge necrosis as described in a large study with complication rate of 4.7% [41]. DSNB has acceptable sensitivity when performed at high volume centers using a standardized protocol [42]. Therefore, its utility and applicability should be limited to centers with experienced surgeons and nuclear medicine specialists.

Modified vs. Radical ILND

ILND has traditionally been known as a technically demanding procedure with high complication rates. In 1988, Catalona introduced the modified LND by reducing dissection lateral to the femoral vessels and caudal to the fossa ovalis while preserving the saphenous veins [43]. Over time, other modifications have added a shorter incision and avoidance of Sartorius muscle transposition [44]. Although this dissection is appealing for cN0 patients in whom the risks of surgery may outweigh the benefits, a radical ILND is still recommended in the presence of inguinal disease. Figure 36.1 displays the differences in extent of dissection between the two procedures.

Minimally-Invasive ILND

Another area of interest to minimize morbidity and complications is to utilize minimally invasive and robotic techniques. Several advantages are achieved with the robotic approach when compared to the standard laparoscopic approach including increased magnification, ergonomic platform, and three-dimensional vision that allows for greater precision and dexterity [45]. However, prospective studies comparing these techniques head-to-head are currently lacking and still require further validation with larger sample sizes and longer follow up.

Open Surgical Techniques

The most common types of incisions reported in the literature have been the horizontal versus "S" or "T"-type incisions, although the former has been the most commonly used by centers of excellence due to its lower risk of skin necrosis [37, 44]. There is little reported on the ideal number of LNs removed at the time of ILND although a registry study reported a LN yield >15 to be an independent predictor of survival [46].

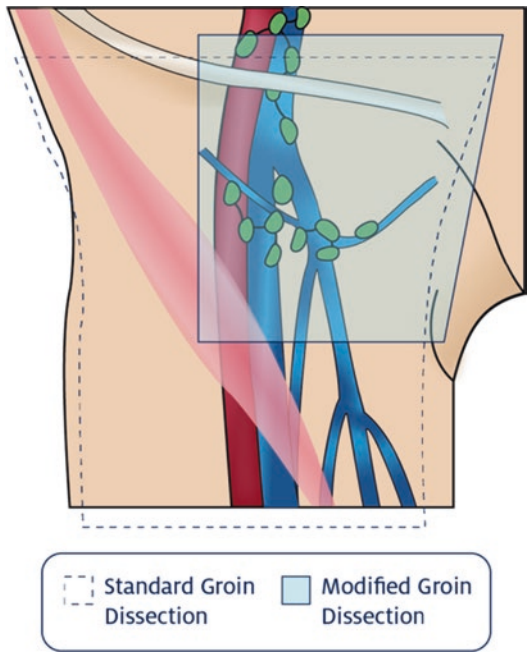

Fig. 36.1 Limits of dissection of standard versus modified ILND

Patients are placed in the frog-leg position and 10-cm parallel incision below the inguinal ligament is usually enough to gain exposure to the superficial inguinal nodes. The skin flaps should not be too thin and should keep a good amount of subcutaneous tissues above Camper's fascia to keep vascularization of the flaps and minimize risks of wound ischemia and dehiscence; skin hooks can be used to minimize disturbance of subcutaneous tissues [47, 48].

Careful and meticulous ligation of lymphatic channels is necessary to decrease risk of leaks and seroma. All nodes above the fascia lata are considered the superficial inguinal LNs and are typically divided into five zones in relation to the femoral vessels (Fig. 36.2) [44, 49].

ILND should be carried to the level of the external oblique fascia and external ring, and proceed superiorly to the edge of the skin flaps as well as distally to the edge of the template. Intraoperative frozen section has been shown to have diagnostic value in determining the need to proceed to a radical dissection [50]. To harvest the deep nodes, the fascia lata is entered at the level of the fossa ovalis. The deep nodes are typically no more than 3–5 LNs contained within the femoral sheath. The node of Cloquet is the most

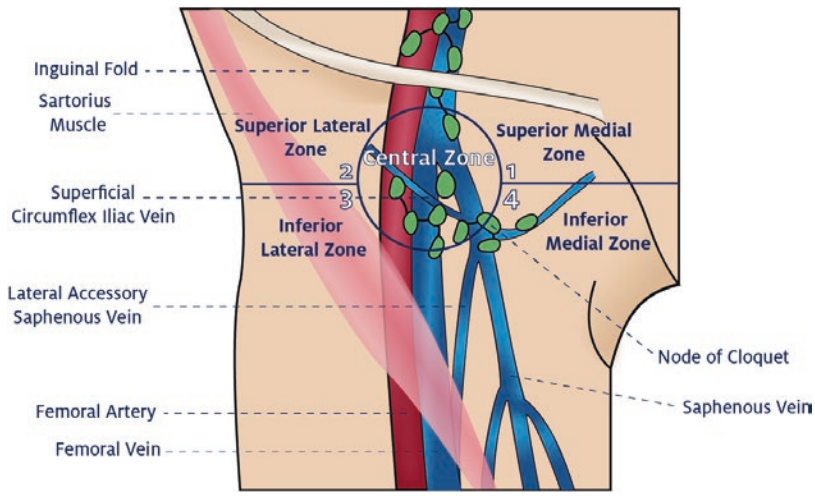

Fig. 36.2 Anatomical zones in inguinal node dissection

proximal and considered the margin between the inguinal and pelvic LNs.

If a deep dissection is required, a Sartorius transposition maybe required for coverage of the femoral vessels. Postoperative closed suction drainage within the inguinal wound is also recommended and removed once outputs are less than 30–50 mL per 24 h period [48]. For larger defects, tissue flaps using gracilis, anterolateral thigh, internal oblique, tensor fascia lata and rectus abdominis have been described in small retrospective series although not without their own complications and should be done in centers with adequate experience with these reconstructive techniques [44, 51].

Prevention and Management of Complications

Currently, the majority of the ILND-related complications are secondary to infections, wound healing, and lymphedema, with the latter two shown to be decreasing over time [48, 52]. With hopes of decreasing complications, trends in operative management have resulted in more limited dissection techniques especially for those with cN0 disease at the time of surgery. Surgical morbidity remains a significant concern for those requiring more extensive dissections and some of these complications can result in long-term disability. Table 36.2 contains a list of common complications from contemporary series of patients after prophylactic or therapeutic ILND.

Management of Locally Advanced Penile Cancer

Current recommendations for locally advanced disease (≥4 cm inguinal lymph node, bilateral lymph nodes, or positive pelvic lymph nodes) are to proceed with neoadjuvant chemotherapy followed by post chemotherapy surgical resection (in patients with a favorable response) entailing an inguinal and possible pelvic lymph node dissection based on clinicopathologic features [53]. In this section, we will discuss management of advanced disease, particularly patients with pelvic nodal involvement.

Penile cancer has characteristic lymphatic spread, with initial metastases proceeding in a stepwise manner from inguinal to pelvic lymph nodes [54]. It is estimated that up to 20–30% of patients with inguinal nodal disease will also have metastatic spread to the pelvic lymph nodes [55]. Patients with positive nodes in pelvic lymph nodes have demonstrably poor survival, with an average 5 year overall survival of 10% [56].

Identification of Micrometastatic Disease

Accurate identification of disease in pelvic lymph nodes is therefore important in determining candidates for PLND. For micro-metastatic disease, Leijte et al. evaluated the use of 18F-fluorodeoxyglucose positron emission tomography (PET-CT) to detect disease in patients with unilateral or bilateral LN positive disease and found

Table 36.2 Contemporary reports of post-operative morbidity after ILND

First author	Year	Country	Number of patients	Complication rate	Most common complications
Gopman et al. [109]	2015	United States, Netherlands, China, Germany	327	55.4%	Infection, seroma, dehiscence, lymphocele, necrosis, scrotal edema
Koifman et al. [52]	2013	Brazil	170	10.3%	Lymphedema, seroma
Stuvier et al. [110]	2013	Netherlands	163	58%	Infection, seroma, necrosis
Yao et al. [111]	2010	China	75	24.7%	Infection, necrosis, lymphedema, seroma, lymphocele
Spiess et al. [48]	2008	United States	43	49%	Lymphedema, wound dehiscence, infection

specificity of 92% [57]. In another study of 18 patients with proven inguinal metastases, PET CT showed a sensitivity of 91%, specificity of 100%, with a negative predictive value 94% and positive predictive value of 100% [58]. More studies are needed, but NCCN guidelines currently incorporate PET-CT when pelvic lymph nodes are enlarged and a biopsy is not feasible or in selected cases, such as an equivocal CT or MRI [58].

Others have investigated risk factors for the presence of pelvic lymph node disease. Lughezzani et al. looked at 142 high-risk penile patients with inguinal lymph node involvement. They found patients with ≥3 inguinal lymph node metastases, and inguinal nodal diameter ≥3 cm were at increased risk of having pelvic nodal metastatic spread ($p < 0.05$) [59].

Technique

Pelvic lymph node dissection can be performed typically through a midline, suprapubic, infraumbilical, or extraperitoneal incision [60]. Boundaries of dissection are the bifurcation of the common iliac arteries superiorly, the ilionguinal nerve laterally, and the obturator nerve medially. PLND can be performed at the same time as ILND or in a delayed fashion. Per NCCN guidelines, a PLND is indicated in the following settings. A) in patients with unilateral lymph nodes ≥4 cm which are mobile and found to have ≥2 positive lymph nodes or with extranodal extension at time of inguinal lymph node dissection. B) unilateral lymph nodes which are fixed or bilateral lymph nodes c) Clinically enlarged pelvic lymph nodes [61].

Unilateral vs. Bilateral PLND

There is a lack of clarity and robust clinical data as to whether a PLND needs to be performed unilateral vs. bilateral in the setting of unilateral positive inguinal lymph node disease as crossover disease in pelvic nodes has not been demonstrated. One study by Zargar-Shostari et al. evaluated risk factors for bilateral pelvic metastatic disease and positive unilateral LN and found that detecting four or more positive inguinal LN had 95% sensitivity in predicting bilateral pelvic nodal metastasis on final pathology. Furthermore, variables associated on multivariable analysis for OS included ≥4 positive inguinal LN, use of adjuvant chemotherapy, inguinal ENE, and bilateral LND and authors recommend that bilateral PLND should be considered for patients with four or more positive inguinal LN [62].

Follow-Up

After primary treatment, surveillance is of the upmost importance for penile cancer. Patent's risk of recurrence depends on both histopathologic features as well as initial treatment of disease. In a retrospective study of 700 patients, Leijte et al. noted that 29.3% of patients had recurrence with 92.2% occurring within 5 years. Local recurrence rate was 27.7% after penile sparing therapy and 5.3% after amputation [60]. Therefore, current NCCN guidelines recommend a differing follow-up schedule depending on initial treatment of the primary tumor and inguinal lymph nodes. If undergoing penile sparing treatment, clinical exam is indicated every 3 months within the first 2 years, every 6 months in years 3–5, and annually in years 5–10. After amputation, clinical exam should be performed every 6 months in the first 2 years, and annually till year 5 [61].

For surveillance of lymph nodes, patients on active surveillance of cN0 nodes with low risk of metastasis, clinical exam should be performed every 3 months for the first 2 years, and every 6 months for years 3–5. If pN0 or pN1, clinical examination every 6 months for years 1–2, and annually for years 3–5. With pN2, N3 disease, clinical examination is indicated every 3–6 months for years 1–2, and 6–12 months for years 3–5. As these patients are higher risk for regional and systemic recurrence, cross sectional imaging of abdomen and pelvis with CT or MRI is needed every 3 months in year 1 and every

6 months in year 2. Likewise, chest imaging with CT or x-ray should be performed every 6 months for years 1–2 [61].

Management of Recurrent and Metastatic Disease

Management of recurrent and metastatic penile cancer remains a challenge for physicians with a scarcity of high-quality evidence. Despite recent improvements in diagnostics and therapeutics, overall survival in penile cancer remains unchanged [63, 64]. Five-year survival rate is below 10% in patients with pelvic lymph node metastasis [65, 66]. Patients with distant metastasis have a very poor prognosis with median survival rates less than 18 months [38].

Achieving local oncological control and sparing organ for better functional and cosmetic outcomes, if feasible, should be aimed during management of local recurrence. Management of recurrence in regional lymph nodes mainly depends on the extent of recurrence and previous treatment. During treatment decision-making process patients should be made aware of long-term metastasis risk and functional outcomes. For management of recurrence in pelvic lymph nodes and metastatic disease, the main aim should be to maximize potential for cure while minimizing adverse effects and preserving quality of life.

Local Recurrence

Penile sparing treatments (PST) have emerged as an attractive alternative to radical surgery with improved outcomes in terms of orgasm, cosmetic appearance, urinary function and quality of life [67], at the expense of increased local recurrence (27% vs. 5%) [60]. Nevertheless, local recurrences did not appear to have an impact on cancer-specific survival; and local control can be achieved in 90–100% of recurrent cases [68].

Recent studies indicate that repeat penile-sparing treatment of local recurrent tumors can be a safe and acceptable option in patients who are motivated to comply with surveillance [68, 69]. In a multi-institutional retrospective cohort of 1188 patients with ≤pT2 tumors, 58% of the local recurrences could be managed with repeat organ sparing procedures such as wide local excision, laser therapy with or without local excision, glans resurfacing and glansectomy [70]. Of note, secondary penectomy (partial or total) rate for this cohort was only 19% and positive resection margin was only significant risk factor for local recurrence. Nevertheless, in a retrospective analysis, recurrent squamous cell carcinoma of penis was associated with high-risk features, and 52% of recurrent tumors had invasion of the corpus cavernosum and penile skin [71]. Compared to non-recurrent tumors, vertical growth pattern (52% vs. 34%) and aggressive histologic subtypes such as sarcomatoid and basaloid types (36% vs. 14%) were more common in these recurrent tumors. Radical surgery (partial or total penectomy) is currently recommended by NCCN and EAU guidelines for treatment of local recurrences invading corpora cavernosa and/or large high-stage recurrent tumors [10, 36].

Regional Recurrence

Optimal management of nodal recurrence in penile cancer remains elusive. The majority of lymph node occurs within 2 years following primary treatment [60, 72]. Nodal recurrence rate following treatment for primary tumor was 9% in a large retrospective cohort of 700 patients, and overall 5-year disease-specific survival was 32.7% in these patients. In a retrospective cohort of 161 patients with pathological node positive PeCa, 26 patients (16%) had inguinal recurrence after therapeutic lymphadenectomy [72]. As salvage treatment, 1 patient was treated with surgery, 5 with external radiotherapy, 13 with chemotherapy, 2 with chemoradiation and 5 with no treatment. Twenty-four patients (94%) died of disease within 14 months after inguinal recurrence. In a multi-institutional retrospective cohort of 20 patients with inguinal recurrence treated with salvage inguinal lymph node dissection, 11

patients were alive and 9 patients had no evidence of disease after a median follow-up of 12 months [73]. However the rate of pre-operative wound infection was around 30% and salvage ILDN was associated with high perioperative complication rate due to decreased vascularity, impaired lymphatic drainage and redo surgery.

Neoadjuvant chemotherapy and subsequent radical surgery is another alternative to salvage ILND alone in patients who responds to chemotherapy. In a retrospective cohort of 19 patients with unresectable locally advanced disease, eight out of nine neoadjuvant chemotherapy responders subsequently treated with consolidation surgery remained long-term survivors without evidence of disease [74]. Moreover, in patients without previous history of radiotherapy, inguinal radiotherapy can be another option for management of nodal recurrence. In a retrospective cohort of patients presenting with metastatic nodes larger than 4.0 cm, perioperative radiotherapy and subsequent ILND was associated with fewer perinodal infiltration and less post-operative inguinal recurrence [75]. The NCCN currently recommends ILND, chemotherapy followed by subsequent ILND and chemoradiotherapy for management of patients who has nodal recurrence after primary treatment of N+ disease [36].

Systemic Disease

About 4% of all penile cancer cases presents with metastatic disease [76], however, 5-year cancer-specific survival rate at the metastatic stage disappointingly approaches close to 0% [77]. Currently the mainstay treatment for metastatic penile cancer is platinum-based multiagent systemic chemotherapy, but with limited efficacy and high toxicity. Several clinical trials of immunotherapy for management of metastatic penile cancer are currently being tested. Moreover personalized cancer treatment and targeted therapy might cause a paradigm shift in management of metastatic disease in the near future.

Systemic Chemotherapy

Although systemic chemotherapy has been the most commonly utilized treatment for metastatic penile cancer, there exists no curative first- or second-line systemic chemotherapy regimen. Visceral metastasis, along with poor performance status, is significant unfavorable prognostic factor for men treated with systemic chemotherapy [78]. There are no randomized clinical trials for PeCa and metastatic disease, and NCCN guidelines currently recommends cisplatin based combination chemotherapy for management of metastatic cancer [36].

In some historical cohorts, methotrexate, bleomycin and cisplatin as single chemotherapeutic agents were shown to have activity against advanced penile cancer [79]. However, unfavorable toxicity profile and limited efficacy of single agent chemotherapy agents led to exploration of combined chemotherapy regimens.

The Southwest Oncology Group evaluated combination chemotherapy in a large scale multiinstitutional phase II trial that included 40 evaluable patients with locally advanced and metastatic penile cancer (Table 36.3) [80]. Chemotherapy regimen consisted of 75 mg/m^2 cisplatin on day 1 IV, 25 mg/m^2 methotrexate on days 1 & 8 IV and 10 Units/m^2 bleomycin on days 1 & 8 IV. Complete response and partial response was noted in five and eight patients, respectively. Objective response rate of 32% was obtained at the expense of high toxicity: Four treatment-related deaths occurred due to pulmonary complications and one death due to infection. Its high toxicity necessitated elimination of bleomycin from combination chemotherapy regimens.

The safety profiles of other combination regimens were remarkably higher than the combination regimens including bleomycin. The efficacy was similar: Combined chemotherapy with irinotecan and cisplatin for treatment of metastatic penile cancer provided overall response rate of 31% at first-line setting [81]. Likewise, a combination of cisplatin and 5-fluorouracil as first-line treatment provided objective response rate of 32% in patients with stage IV penile cancer [82].

Table 36.3 Outcomes of chemotherapy for metastatic penile squamous carcinoma

Authors	N	Setting	Regimen & dose	Cycle	Response
Haas et al. [80]	40	First-line	Cisplatin 75 mg/m^2 d 1 Methotrexate 25 mg/m^2 d 1,8 Bleomycin 10 U/m^2 d 1,8	Up to 6 × q. 21 d	CR 5 pts, PR 8 pts
Theodero et al. [81]	19	First-line	Irinotecan 60 mg/m^2 d 1,8,15 Cisplatin 80 mg/m^2 d 1	Up to 8 × q. 28 d	CR 1 pts, PR 5 pts
Pagliaro et al. [83]	30	Neoadjuvant	Paclitaxel 175 mg/m^2 d 1 Ifosfamide 1200 mg/m^2 d 1,2,3 Cisplatin 25 mg/m^2 d 1,2,3	4 × q. 21 d	CR 3 pts, PR 12 pts
Di Lorenzo et al. [88]	25	Second-line	Paclitaxel 175 mg/m^2 d 1	Up to 10 × q. 21 d	PR 5 pts
Di Lorenzo et al. [82]	25	First-line	Cisplatin 75 mg/m^2 d 1 5-Fluorouracil 900mg/m^2 d 1,2,3,4	6 × q. 21 d	PR 8 pts, SD 10 pts
Nicholson et al. [84]	26	First-line	Docetaxel 75 mg/m^2 d 1 Cisplatin 60 mg/m^2 d 1 5-flurouracil 750 mg/m^2 d 1,5	3 × q. 21 d	CR 2 pts, PR 8 pts
Houédé et al. [85]	25	First-line	Gemcitabine 1250 mg/m^2 d 1 Cisplatin 50 mg/m^2 d 1	5 × q. 14 d	CR/PR 2 pts, SD 13 pts
Pickering et al. [89]	22	First-line	Vinflunine 320 mg/m^2 d 1	4 × q. 21 d	CR/PR 6 pts, SD 10 pts

Abbreviations: *CR* complete response, *PR* partial response, *SD* stable disease, *d* day, *q*. every, *N* number of patients, *pts* patients

In a retrospective cohort of 30 patients with nodal metastatic disease, 50% of them showed objective response to combined chemotherapy with cisplatin, ifosfamide and paclitaxel [83]. Seventy three percent of the responding patients underwent surgery, and nine patients (30%) remained free of recurrence after a median follow-up of 34 months. Grade 3 febrile neutropenia or infection occurred in six patients, whereas grade 4 neutropenia occurred in one patient. This regimen was well tolerated and provided a clinically meaningful response in patients with bulky lymph node metastasis from penile cancer. It is currently the recommended standard treatment for penile cancer for NAC, first-line and second-line settings by NCCN guidelines.

Combined chemotherapy with docetaxel, cisplatin and 5-flurouracil failed to meet its treatment benefit end-point and use of this combination was not recommended [84]. An intermediate analysis of a phase II trial evaluating gemcitabine and cisplatin in locoregional or metastatic penile squamous cell carcinoma enrolled 25 patients from France [85]. Objective response was seen in only 2 (8%) patients while progression in 8 (32%) patients, and this combination was proven ineffective as well.

Use of radiotherapy in combination with chemotherapy was proposed for management of advanced and metastatic penile cancer; however it seemed to provide no additional survival benefit. A chemoradiotherapy regimen consisting of external beam radiotherapy (median dose: 49 Gee) and cisplatin-based chemotherapy demonstrated poor outcomes with a median overall survival of approximately 7 months [86].

No standard salvage systemic therapy exists for progressive/recurrent metastatic penile cancer. In a retrospective multi-institutional cohort of 65 patients with metastatic penile cancer who failed first-line systemic treatment, salvage treatment with various chemotherapy regimens demonstrated a median progression-free and overall survival of 3 and 6 months, respectively [87]. Di Lorenzo and colleagues reported five partial responses (20%) after treatment with paclitaxel in 25 patients with pretreated metastatic penile cancer [88]. As a salvage therapy, paclitaxel was moderately active and considerably safe. A trend for improved response-rates compared to other agents was noted in patients treated with

cetuximab-including salvage regimens, which underscores the potential benefits of combined treatments targeting different axis of the progressive cancer.

Vinflunine, a third-generation synthetic vinca alkaloid chemotherapeutic, was recently evaluated as first-line chemotherapy in 22 patients with locally-advanced and metastatic carcinoma of the penis [89]. This phase II trial (VinCaP) was performed in patients with good performance status and treatment consisted of 4 cycles of vinflunine 320 mg/m2 given every 21 days. Clinical benefit was noted in 45% of all patients and objective response rate was 27%. Fifteen patients (68%) experienced grade 3/4 adverse events, and there were two treatment-related deaths (one sepsis and one neutropenia). Initial results of vinflunine are promising and the primary endpoint was met with an acceptable toxicity profile. However larger multi-institutional studies with longer follow-up are needed to assess its efficacy and safety in metastatic penile cancer.

Targeted Therapy

Targeted therapy emerged as one of treatment alternatives to systemic chemotherapy owing to recent demonstration of various novel molecular biomarkers. Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor that stimulates intracellular PI3K/Akt and Ras-Raf-MEK-ERK pathways via ligand-receptor binding [90]. EFGR expression is common in penile cancer and associated with poor prognosis [91, 92].

First studies of anti-EGFR antibodies in metastatic penile cancer focused at second-line management. Panitumumab, a selective monoclonal antibody targeting EGFR, provided complete response in two (18%) patients who failed first-line chemotherapy [93]. In a retrospective single institutional study of advanced penile cancer, a total of 24 patients received EGFR-targeting agent alone (cetuximab, erlotinib or gefitinib), in combination with a single chemotherapeutic agent or in combination with triple-agent chemotherapy [94]. There was no response to erlotinib or gefitinib. Among 17 patients treated with combined therapy with cetuximab and a chemotherapeutic agent, however, four (23%) patients had partial response.

In a recent phase II trial that enrolled 28 patients with locally advanced and metastatic penile cancer, objective response rate to first-line treatment with dacomitinib, an orally available second-generation irreversible inhibitor of EGFR, was 32% [95]. One (3%) and 8 (29%) patients showed complete and partial response, respectively and 13 patients (46%) had stable disease. In eight patients with visceral metastasis, 6-month progression-free survival was %16 and 12-month overall survival was 35%. Overall grade 3 treatment-related AEs were noted in only 10% of the Dacomitinib-treated penile cancer patients. So far, the most promising results in field of targeted therapy came from dacomitinib, and reported survival outcomes were comparable to first-line chemotherapy regimens [78, 80]. This justifies that, at the very least, targeted therapy can provide benefit to the patients ineligible for systemic chemotherapy.

Vascular endothelial growth factor (VEGF), another targetable receptor by current agents, was found to be an independent prognostic factor for metastatic progression in penile cancer and shown to be overexpressed about half of the cases [96, 97]. In a small retrospective study that enrolled six advanced penile patients who were refractory to at least two chemotherapy regimen, one patient demonstrated partial response to sorafenib and sunitinib and three patients showed pain response [98]. Moreover, afatinib, an orally administered EGFR tyrosine kinase inhibitor, is currently being tested in a non-randomized phase 2 trial (NCT02541903) for management of progressive metastatic disease (Table 36.4).

Immunotherapy

Approximately half of all penile cancer cases are known to harbor HPV infection [99]. The rationale for testing and vaccination for HPV is already justified for cervical cancer. In a phase II study (NCT01585428) of tumor infiltrating

Table 36.4 Ongoing clinical trials of systemic therapy for metastatic penile squamous carcinoma

Trial identifier	Status	P	N	Treatment type	Agent	Treatment population
NCT02541903	Recruiting	II	29	Targeted therapy/EGFR TKI	Afatinib	Progressive after prior chemotherapy (only PSCC)
NCT02858310	Recruiting	I/II	180	T cell receptor immunotherapy	HPV-16 E7 targeting TCR cells Aldesleukin Fludarabine Cyclophosphamide	Progressive HPV-positive after chemotherapy OR declined standard therapy (HPV-related tumors)
NCT02379520 (HESTIA)	Recruiting	I	32	Adoptive cell transfer	HPV specific T lymphocytes Cytoxan Fludarabine Nivolumab	Progressive HPV-positive after standard therapy/ unable to receive standard therapy (HPV-related tumors)
NCT02526316 (VICORYX-2)	Completed	I	11	HPV-vaccination	P16 peptide vaccine Cisplatin	First-line concurrent with cisplatin-based chemotherapy (HPV-related tumors)
NCT03418480 (HARE-40)	Recruiting	I/II	44	RNA-vaccination	HPV Anti-CD40 vaccine	Palliation for progressive HPV-16-positive disease (HPV-related tumors)
NCT02837042	Recruiting	II	35	Checkpoint blockade	Pembrolizumab	Progressive after prior chemotherapy (Only PSCC)
NCT03391479	Recruiting	II	24	Checkpoint blockade	Avelumab	Progressive after prior chemotherapy (Only PSCC)
NCT02721732	Recruiting	II	275	Checkpoint blockade	Pembrolizumab	Progressive after standard systemic therapy (Rare tumors)
NCT03357757 (LATENT)	Recruiting	II	39	Checkpoint blockade	Avelumab Valproic acid	Any patient with minimum life expectancy (HPV and EBV-related tumors)
NCT03333616	Recruiting	II	57	Checkpoint blockade	Nivolumab Ipilimumab	New or progressive metastatic disease (Genitourinary solid tumors)
NCT02834013	Recruiting	II	707	Checkpoint blockade	Nivolumab Ipilimumab	Progressive after prior standard therapy (Rare tumors)
NCT02496208	Recruiting	I	152	Checkpoint blockade	Nivolumab Cabozantinib ± Ipilimumab	New or progressive metastatic disease (Genitourinary solid tumors)
NCT03439085	Recruiting	II	77	DNA-vaccination + Checkpoint blockade	Durvalumab DNA Plasmid-encoding vaccine	Progressive HPV-positive after standard therapy (HPV-related tumors)

Abbreviations: *EGFR* epidermal growth factor receptor, *N* number of estimated enrollment, *P* phase of clinical trial, *NCT* national clinical trial (clinicaltrials.gov), *TCR* T cell receptor, *TKI* tyrosine kinase inhibitor

lymphocyte (TIL) therapy, objective tumor response to HPV-oncoprotein reactive TIL therapy occurred in one quarter of the patients with cervical, anal and oropharyngeal cancer [100].

Moreover, a phase I/II trial of T cell receptor gene therapy targeting HPV-16 E7 is underway for HPV-associated cancers including metastatic and refractory penile cancer (NCT02858310) (Table 36.2). A phase I study is recruiting patients with relapsed HPV-associated cancers and will evaluate dose-limiting toxicity and overall response rate to adoptive cell transfer of HPV-16/18 E6/E7-specific T lymphocytes (NCT02379520). Another phase I trial aims to evaluate immune response to P16 peptide vaccination in combination with cisplatin-based chemotherapy (NCT02526316). A phase I/II clinical trial (NCT03418480) is investigating safe, tolerable and recommended dose of HPV RNA vaccine in patients with advanced HPV16-positive cancers.

Immunotherapy with immune checkpoint blockade showed excellent efficacy in particular solid cancer types and it rapidly evolved the systemic treatment landscape for many cancer such as melanoma and non-small cell lung carcinoma [101]. For other epithelial cancer types including penile squamous cell carcinoma, however, the efficacy of PD-1/PD-L1 axis blockade is still unknown. High tumor mutation load was related to increased objective response to checkpoint blockade [102] and penile cancer cases were shown to have low tumor mutation load [103]. The percentage of penile squamous cell carcinoma specimens showing high tumor mutation load was reported 6.5%, and notably less than melanoma and bladder carcinoma (40% and 14%, respectively). Nevertheless, in a retrospective cohort of 200 patients with penis cancer, PD-L1 expression was noted in 48% of the all cases and diffuse expression was associated poor survival especially in high-risk HPV negative subgroups [104]. Currently there are many ongoing clinical trials exploring immune checkpoint blockade for management of metastatic penile cancer (Table 36.4). A phase II trial of pembrolizumab and avelumab are underway and they aim to evaluate efficacy of anti-PD-1 and anti-PD-L1 inhibitors in patients with advanced penile squamous cell carcinoma (NCT02837042 and NCT03391479). Moreover, activity of some other novel therapies or combinations is being tested in basket trials that enrolling patients with rare or viral-related tumors. Pembrolizumab alone is being tested in patients with rare tumors including metastatic and stage IV penile cancers (NCT02721732). Combined immunotherapy with nivolumab and ipilimumab (anti-PD-1 and anti-cytotoxic T lymphocyte protein 4 (CTLA1) antibody) is currently being tested in rare tumors (NCT03333616 and NCT02834013). A phase I trial that evaluating combined therapy of an anti-VEGF antibody, cabozantinib, with nivolumab and ipilimumab is enrolling patients with rare genitourinary tumors (NCT02496208). Valproic acid was demonstrated to enhance efficacy of chemotherapy by increasing lytic viral gene expression [105]. It is currently being tested in a phase II trial in combination with avelumab in patients with viral-related cancers (NCT03357757). Another phase II trial study is currently exploring how gene-modified virus vaccine helps to build immune response against tumor cells, and a combination of DNA-plasmid therapeutic vaccine with durvalumab is being tested in HPV-associated cancers (NCT03439085).

Foundation Testing

Recent advancements in molecular genetics contributed to the understanding of genomic and epigenomic alterations driving penile carcinogenesis. It was recently revealed that 95% of advanced penile carcinoma cases harbored at least one clinically relevant genomic alteration: *CDKN2A* point mutations and homozygous deletion (40%), *NOTCH1* point mutations and rearrangements (25%), *PIK3CA* point mutations and amplification (25%), *EGFR* amplification (20%), *CCND1* amplification (20%), *BRCA2* insertions/deletions (10%), *RICTOR* amplifications (10%), and *FBXW7* point mutations (10%) [106]. Moreover *EGFR* gene alterations (25%) and *PIK3CA* and/or *FBXW7* alterations (30%) were demonstrated to occur in a mutually exclusive

manner, both of which are currently targetable by available therapies. In a comprehensive next generation sequencing study of penile cancer, 28% of all HPV-positive penile cancer cases showed p16 overexpression which was associated with longer event-free survival [107]. *EGFR* overexpression and *EGFR* amplification were highly discordant, which suggest that *EFGR* amplification rather than *EGFR* overexpression might be a better predictor of treatment response in EGFR-targeting therapy. Moreover, PeCa was shown to have less tumor mutation load compared to cutaneous squamous cell carcinoma, thus targeted therapy and precision medicine was suggested to provide more benefit than immunotherapy in PeCa [108]. Likewise alterations in MTOR, DNA repair and tyrosine kinase pathways were detected in more than one quarter of this metastatic penile cancer patient cohort.

Given the low success rates of available systemic treatment options, novel therapies are desperately needed for this physically and psychologically devastating disease. The outcomes of ongoing clinical trials evaluating efficacy and safety of novel therapies in metastatic penile cancer are eagerly awaited.

Conclusion

Though penile cancer is a rare entity, its diagnosis and management remains a therapeutic challenge. Advances have led to increased options for treatment of primary disease, including penile sparing approaches in selected patients, but many patients still undergo radical amputation. The most important factor for survival continues to be the presence and treatment of disease in both inguinal and pelvic lymph nodes and recent developments have led to a paradigm shift of upfront neoadjuvant chemotherapy in advanced disease followed by surgical consolidation. With limited prospected data in this area, the ongoing InPACT trial will aid in management of advanced and regional disease. And the landscape of systemic therapy is evolving, and targeted therapy and immunotherapy show promise. However, much work remains to be done to address this uncommon, but impactful disease process.

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37 Chemotherapeutic Agents for Urologic Oncology: Basic Principles

Simon Y. F. Fu, Martin Gleave, and Kim N. Chi

Introduction

The term chemotherapy denotes the use of chemicals to treat disease, and was coined by German chemist Paul Ehrlich in the early 1900s. The revelation of cisplatin's antitumour activity by Rosenberg in 1965, followed by the demonstration of efficacy in metastatic testicular germ cell patients receiving cisplatin-based combination chemotherapy in 1977 cemented the vital role of cytotoxics in the treatment of genitourinary cancer [1, 2]. Chemotherapy not only provides palliative relief, but long-term survival can be achieved despite widely disseminated malignancies as in the case of germ cell cancers. The following decades saw the introduction of various classes of chemotherapeutics targeting different stages of the cell cycle, and the identification of the most active agent or combination of agents in different malignancies. Tables 37.1 and 37.2 summarise common cytotoxic agents and combination chemotherapy regimens used in genitourinary cancers.

The intent of chemotherapeutics can be curative or palliative. Curative intent treatment aims to eradicate all tumour cells to achieve long term survival. It is usually given in the peri-operative setting to eliminate micrometastatic disease either in the adjuvant setting after local therapy (i.e. surgery or radiotherapy), or in the neoadjuvant setting which can also serve to decrease primary tumour bulk to facilitate local therapy. Chemotherapy is also used concurrently as a radiosensitizer to improve efficacy of radiotherapy. Testicular germ cell tumour is the rare example where chemotherapy is given with curative intent even when distant metastases are clinically apparent. Palliative chemotherapy aims to prolong survival as well as improving quality of life by reducing malignancy-related complications.

This chapter outlines major chemotherapeutic agents and regimens used in urological cancers. Although the term "chemotherapy" can be applied to any drug treatment, a traditional classification of non-specific anti-cancer agents is being applied here. Targeted cancer therapies (agents that directed against molecular targets involved in the growth, progression, and spread

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Table 37.1 Key features of commonly use chemotherapeutics in genitourinary cancer

	Classification	Mechanism of action	Common Scheduling	Adverse effects of interest
Cisplatin	Platinum	DNA damage	50–100 mg, q3 weeks	Nephrotoxicity Neurotoxicity Otoxicity Nausea and vomiting Electrolyte disturbances Hypersensitivity reaction
Carboplatin	Platinum	DNA damage	AUC 5–7 (Calvert formula), q3 weeks	Myelosuppression Nephrotoxicity, neurotoxicity, and nausea and vomiting is less frequent or severe than cisplatin
Docetaxel	Taxane	Anti-microtubule	75 mg/m^2, q3 weeks	Myelosuppression Neuropathy Pneumonitis/pulmonary fibrosis Hypersensitivity reactions Reversible alopecia Nail/skin changes Myalgia, arthralgia Fluid retention
Gemcitabine	Cytidine analog	Inhibition of DNA synthesis	1000 mg/m^2, q3 weeks	Myelosuppression Fever and flu-like symptoms Deranged liver function tests Pulmonary toxicities Hemolytic uremic syndrome Peripheral edema
Bleomycin	Antitumor antibiotic	DNA damage	30 units Day 1, 8, 15, q3 weeks	Pneumonitis/pulmonary fibrosis (oxygen enhances pulmonary toxicity) Desquamation, rash Raynaud's phenomenon ∗Non-myelosuppressive
Etoposide	Topoisomerase II inhibitor	Inhibit DNA synthesis and DNA repair	100 mg/m^2, D1–3 or 1–5, q3 weeks	Myelosuppression Secondary malignancies Reversible alopecia
Mitoxantrone	Anthracenedione/ Topoisomerase II inhibitor	Inhibit DNA synthesis and DNA repair	12 mg/m^2, q3 weeks	Cardiotoxicity: congestive heart failure, cardiomyopathy Myelosuppression Blue discolouration to the sclera
Ifosfamide	Alkylating agent	Inhibit DNA and protein synthesis	1200 mg/m^2, D1–5, q3 weeks	Hemorrhagic cystitis Neurotoxicity Myelosuppression

AUC area under the curve, *D* day

of cancer) and immunotherapy will be discussed elsewhere in this issue.

Bladder Cancer

The majority of bladder cancer is non-muscle invasive and is treated with local therapy. About 25% of bladder cancer is muscle-invasive, and 4% has metastatic disease on initial presentation [3]. Prognosis for patients with muscle invasive bladder cancer (MIBC) varies with TNM staging. Five-year recurrence-free survival decreases from 80–90% in organ-confined node-negative disease, to 50–60% in patients with extravesical involvement (pT3–4N0), and 35% with nodal metastasis [4]. Urothelial bladder cancer is considered chemosensitive with a response rate of up to 70% in metastatic disease, but duration of response in this setting can be limited. The

Table 37.2 Common combination chemotherapy regimens in genitourinary cancer. *D* day

	Dose	Scheduling	Main indications	Adverse events of interest
BEP	Bleomycin (B) 30 units, D1, 8, 15; Etoposide (E) 100 mg/m^2, D1–5; Cisplatin (P) 20 mg/m^2, D1–5	q3 week for 3 (favourable risk) or 4 (intermediate/poor risk) cycles	Advanced germ cell tumor	Myelosuppression Pulmonary toxicity Neuropathy Nephrotoxicity Ototoxicity Nausea and vomiting Secondary malignancy Reversible alopecia
VIP	Etoposide (V) 75 mg/m^2, D1–5; Ifosfamide (I) 1500 mg/m^2, D1–4; Cisplatin (P) 20 mg/m^2 D1–5; Mesna 300 mg/m^2, D1–5	q3 weeks for 4 cycles	Advanced germ cell tumor with contraindication to bleomycin or expected lung surgery	Myelosuppression Neuropathy Nephrotoxicity Ototoxicity Nausea and vomiting Secondary malignancy Reversible alopecia Haemorrhagic cystitis
TIP	Paclitaxel (T) 175 mg/m^2, D1; Ifosfamide (I) 1200 mg/m^2, D1–5 in germ cell tumour, or D1–3 in penile cancer; Cisplatin (P) 20 mg/m^2, D1–5 in germ cell tumour, or 25 mg/m^2, D1–3 in penile cancer; Mesna 300 mg/m^2, D1–5	q3 weeks for 4 cycles	Relapsed germ cell tumor, penile cancer	Myelosuppression Neuropathy Nephrotoxicity Ototoxicity Nausea and vomiting Secondary malignancy Reversible alopecia Haemorrhagic cystitis
MVAC	Classical MVAC: Methotrexate (M) 30 mg/m^2 D1, 15, 22; Vinblastine (V) 3 mg/m^2 D2, 15, 22; Doxorubicin (A) 30 mg/m^2 D2; Cisplatin (C) 70 mg/m^2 D2 Dose-dense MVAC: M 30 mg/m^2 D1; V 3 mg/m^2 D2, A 30 mg/m^2 D2; C 70 mg/m^2 D2	Classical MVAC: q3–4 weeks for 3–6 cycles Dose-dense MVAC: q2 weeks for 4 cycles	Urothelial cancer	Myelosuppression Nausea and vomiting Diarrhoea Oral mucositis

(continued)

Table 37.2 (continued)

	Dose	Scheduling	Main indications	Adverse events of interest
GC	Gemcitabine (G) 1000–1250 mg/m^2, D1, 8 Cisplatin (C) 70 mg/m^2, D1	q3 weeks for 4–6 cycles	Urothelial cancer	Myelosuppression Nephrotoxicity Neurotoxicity Otoxicity Nausea and vomiting Electrolyte disturbances Fluid retention
CaG	Carboplatin AUC 5 (Calvert formula), D1 Gemcitabinej 1000–1250 mg/m^2, D1, 8	q3 weeks for 6 cycles	Urothelial cancer	Myelosuppression Fluid retention
Cisplatin Etoposide	Cisplatin 75 mg/m^2, D1 Etoposide 100 mg/m^2, D1–3	q3 weeks for 4–6 cycles	Small cell carcinoma	Myelosuppression Nephrotoxicity Neurotoxicity Ototoxicity Nausea and vomiting Electrolyte disturbances Secondary malignancies
Carboplatin Etoposide	Carboplatin AUC 5 (Calvert formula), D1 Etoposide 100 mg/m^2, D1–3	q3 weeks for 4–6 cycles	Small cell carcinoma As part of TI-CE protocol for relapsed germ cell tumor	Myelosuppression Secondary malignancies Reversible alopecia

treatment landscape of MIBC is rapidly changing with the introduction of immunotherapy, but chemotherapy is still the current systemic therapy of choice in both perioperative and first-line palliative settings.

Advanced Bladder Cancer

First-Line Chemotherapy

Platinum-based chemotherapy is the standard first-line treatment for patients with advanced unresectable or metastatic bladder cancer. As patients with metastatic urothelial cancer often are elderly and have multiple comorbidities, 'cisplatin-fit' patients must have a good performance status (e.g. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤1), with adequate renal function (CrCl ≥60 mL/min), cardiac function (New York Heart Association, NYHA class II or less), without significant hearing impairment (≤grade 1 audiometric hearing loss of ≤25 dB averaged at 2 contiguous test frequencies) or peripheral neuropathy (≤grade 1 neuropathy i.e. able to carry out instrumental activities of daily living) (Table 37.3) [5]. Acute kidney injury due to urinary tract obstruction should be reversed before considering patients unfit for cisplatin.

Options for first-line treatment depend on patient's performance status. For medically fit patients, MVAC (methotrexate, vinblastine, adriamycin, cisplatin) [6], dose-dense MVAC (ddMVAC) [7], or GC (gemcitabine, cisplatin) [8] are commonly used regimens (Table 37.2). MVAC has been a standard first-line regimen for metastatic urothelial cancer since 1990 [6]. The substantial toxicity and poor long-term survival with median survival just over 1 year led to the EORTC 30924 trial testing for dose dense 2-weekly MVAC. Concomitant granulocyte colony-stimulating factor (G-CSF) support was given to

Table 37.3 Consensus definition of fitness for cisplatin-based chemotherapy in patients with metastatic urothelial carcinoma

– WHO or ECOG of ≥1, or Karnofsky performance status >70%
– Creatinine clearance ≥60 mL/min
– Audiometric hearing loss of ≤25 dB averaged at 2 contiguous test frequencies
– Peripheral neuropathy not affecting instrumental activities of daily living
– NYHA class II or less heart failure

WHO World health organization, *ECOG* Eastern cooperative oncology group, *NYHA* New York Heart Association

mitigate neutropenia and mucositis associated with ddMVAC. Dose-dense MVAC resulted in a higher overall response rate (72% vs. 58%, $p = 0.02$), complete response (25% vs. 11%, $p = 0.006$), improved progression-free survival (median 9.5 vs. 8.1 months; HR 0.73, 95% confidence interval (CI) 0.56–0.95, $p = 0.017$), and 5-year survival (21.8% vs. 13.5%, $p = 0.042$) compared with the classic four weekly MVAC [7, 9]. However, the difference in primary endpoint of overall survival was not clinically meaningful (median 15.1 vs. 14.9 months; HR 0.76, 95% CI 0.58–0.99, $p = 0.04$). Dose-dense MVAC was better tolerated than classic MVAC with less febrile neutropenia (10% vs. 26%, $p < 0.001$) and mucositis (grade ≥ 3, 10 vs. 17%, $p = 0.03$). Toxic death rate was similar between both groups (3% vs. 4%).

To further improve tolerability of palliative chemotherapy, GC was compared with MVAC in a phase III trial by von der Maase and colleagues. Although overall survival was not different between GC and MVAC (median 14 and 15.2 months respectively; HR 1.09, 95% CI 0.88–1.34, $p = 0.66$), GC was more tolerable [8, 10]. Compared to MVAC, GC had a lower rate of grade ≥3 neutropenia (82% for MVAC vs. 71% for GC), neutropenic fever (14% vs. 2%), neutropenic sepsis (12% vs. 1%), grade ≥3 mucositis (22% vs. 1%), and treatment-related death (3% vs. 1%) [10].

Two weekly dose dense GC (ddGC) was also evaluated against ddMVAC and resulted in comparable overall survival (median 18 vs. 19 months, respectively) and objective response rates (65.3% vs. 60%), but a safety profile that favoured ddGC (≥G3 neutropenia 13% vs. 19%; febrile neutreopenia 0 vs. 5%; treatment related death from non-neutropenic sepsis 0 vs. 3%) [11].

The addition of paclitaxel to GC (PGC) vs. GC improved response rate (55.5% vs. 43.6%, respectively) but the 3.1 month survival advantage did not reach statistical significance (15.8 vs. 12.7 months, HR 0.85, 95% CI 0.72–1.02, $p = 0.075$) [12]. PGC was also associated with more toxicity with higher rates of febrile neutropenia (13.2 vs. 4.3%), and toxicity-related death ($n = 6$ vs. 3). There was no statistically significant difference in all efficacy outcomes between GC and carboplatin gemcitabine (CaG), although 1-year survival rate was 63.6% vs. 37.3% for GC and CaG respectively [13]. Overall toxicity was similar between GC and CaG (grade 3 toxicities 60% vs. 69.1%, respectively), and CaG was associated with less grade ≤ 2 nephrotoxicity (16% vs. 26%) and grade 3–4 nausea and vomiting (3.6% vs. 9.1%). Cisplatin in combination with docetaxel was inferior to MVAC in terms of response rate, time to progression, and median survival [14].

For cisplatin unfit patients with metastatic urothelial carcinoma, EORTC 30986 showed a trend towards higher confirmed response rate (36.1% vs. 21%) and overall survival (median 9.3 vs. 8.1 months) with carboplatin gemcitabine (CaG) versus MCAVI (methotrexate, carboplatin, vinblastine), respectively, but neither reached statistical significance [15]. Severe acute toxicity (9.3% vs. 21.2%) and febrile neutropenia (4.2% vs. 14.4%) were less common with CaG compared to MCAVI, respectively, but CaG caused more grade ≥3 thrombocytopenia (48.3% vs. 19.4%). Two toxic deaths were seen in CaG arm, and four in MCAVI. Other non-cisplatin containing regimens with anti-tumour activity demonstrated in single-arm phase II trials included gemcitabine and paclitaxel [16], gemcitabine docetaxel [17], gemcitabine pemetrexed [18], gemcitabine epirubicin [19], gemcitabine vinorelbine [20], paclitaxel + carboplatin + gemcitabine [21], sequential carboplatin gemcitabine then paclitaxel [22], and dose-dense doxorubicin then carboplatin paclitaxel [23].

Second-Line Chemotherapy

Second-line chemotherapy in patients with advanced urothelial cancer progressed after MVAC or GC has largely been superseded by immunotherapy, but can be considered in patients who are intolerant of immunotherapy or progressed during or after prior immunotherapy.

The optimal second-line chemotherapy is not yet defined. A number of chemotherapeutics including vinflunine [24], docetaxel [25], paclitaxel [26], nab-paclitaxel [27], gemcitabine [28], pemetrexed [29], and ifosfamide [30] showed anti-tumour activity in the second-line setting. However there is no phase III trial data to demonstrate significant survival advantage with second-line chemotherapy. These patients have a poor prognosis with life expectancy between 5 and 10 months [24–26, 28, 29]. A retrospective pooled analysis of eight phase II trials of salvage taxane-based chemotherapy showed combination chemotherapy significantly improved overall survival compared to taxane monotherapy (HR 0.6, 95% CI 0.45–0.82, $p = 0.001$) [31]. Prospective randomised controlled trials are needed to validate this finding. Combination chemotherapy is often more toxic, and treatment must be tailored to individual patient, and participation in clinical trials should be encouraged.

Muscle Invasive Bladder Cancer

Neoadjuvant Chemotherapy

The tendency for MIBC to metastasize early makes neoadjuvant chemotherapy an ideal treatment option. Neoadjuvant chemotherapy aims to eliminate micrometastatic disease early, offers an opportunity to assess tumour response to therapy, increases rate of pathologic complete response (pT0) and reduces the rate of positive surgical margins [32]. The ABC meta-analysis showed cisplatin-based neoadjuvant chemotherapy is associated with an absolute improvement of 5% in 5-year overall survival (from 45 to 50%; hazard ratio (HR) 0.86, 95% CI 0.77–0.95, $p = 0.003$) [33]. As in the metastatic setting, commonly employed neoadjuvant regimens include MVAC, ddMVAC, and GC. However, there are no trials directly comparing different neoadjuvant combinations, and the optimal regimen is undefined. Retrospective studies showed similar pathologic complete response rates (pT0pN0) between neoadjuvant MVAC vs. GC [34–36], and MVAC vs. ddMVAC (38% vs. 35%, $p = 0.72$) [37]. These results are in contrast with two recent multicentre retrospective studies with propensity score analysis of clinical outcomes. Higher complete response rates of 28%–41% vs. 15%–25% between neoadjuvant ddMVAC vs. GC were observed [38, 39]. The study from Zargar and colleagues reported mean Kaplan-Meier estimates of overall survival were significantly higher in ddMVAC compared to GC groups (7 vs. 4.2 years, $p = 0.001$) [38], while Peyton and colleagues showed survival benefit favoured ddMVAC over GC but did not reach statistical significance in propensity weight modelling (HR 0.44, 95% CI 0.14–1.38, $p = 0.16$) [39]. These findings must be interpreted with caution due to the limitations inherent in retrospective trial design, including potential selection bias for less well patients to receive GC due to its tolerability, and uncaptured data for patients who did not receive surgery due to intolerance, treatment complications, and disease progression.

Adjuvant Chemotherapy for MIBC

Adjuvant chemotherapy is an option for patients who did not receive neoadjuvant chemotherapy. Accurate pathological staging post cystectomy allows selection for patients with high risk features for relapse (pT3–4 or node positive disease) who may derive greater benefit with adjuvant treatment. Clinical trials data supporting adjuvant chemotherapy for MIBC is less robust. An individual-patient data meta-analysis by Medical Research Council (MRC) in 2005 reported a hazard ratio for survival of 0.75 (95% CI 0.6–0.96, $p = 0.019$) in favour of adjuvant chemotherapy over observation post surgery [40]. This translates to an absolute 3-year survival benefit of 9%. The authors however cautioned interpretation of their findings owing to issues in clinical trial design and conduct with four of six trials stopping early, patients not receiving allocated treatments or salvage therapy at relapse. An updated

meta-analysis by Leow and colleagues in 2013 found a pooled hazard ratio for survival of 0.77 (95% CI 0.59–0.99, $p = 0.049$) favouring adjuvant chemotherapy over surgery alone [41]. Limitations of this analysis included that only trial-level data was used, results from unpublished trials were included, trials include had variable inclusion criteria, as well as the limitations associated with the MRC meta-analysis. The most recent EORTC 30994 trial failed to detect a significant improvement in overall survival with adjuvant chemotherapy vs. observation in patients with pT3–4 or node positive MIBC after radical cystectomy (HR 0.78, 95% CI 0.56–1.08, $p = 0.13$) [42]. Only 284 patients out of the planned 660 patients were enrolled and trial was stopped due to poor accrual, limiting sufficient power for survival analysis. As with neoadjuvant chemotherapy, the choice of adjuvant chemotherapy is a cisplatin-based regimen derived from experience in the metastatic setting. Options for adjuvant therapy may include MVAC, ddMVAC, and GC.

Chemotherapy in Bladder-Sparing Strategies: Trimodality Therapy

Patients with MIBC are often elderly with multiple co-morbidities. For patients who are not surgical candidate or wish to retain their bladder, a bladder-preservation approach with trimodality therapy (TMT) is a potential definitive treatment option. TMT involves maximal transurethral resection of the bladder (TURBT) followed by concurrent chemoradiation. Radiation alone is seldom pursued because of inferior outcomes, although long term survival can be observed in 35% [43]. Five year disease-specific survival is comparable between surgery and TMT in carefully selected patients [44].

Single centre experience has shown favourable oncological outcomes with TMT, with improvement in 5-year disease specific survival from 60 to 84%, and reduction in the rate of salvage cystectomy from 42 to 16%, across the periods 1986–1995 and 2005–2013 [45] This is likely related to improvement in treatment techniques and more stringent patient selection criteria [46]. The landmark trial BC2001 showed a significant decrease in 2-year locoregional disease-free survival from 67 to 54% (HR 0.68, 95% CI 0.48–0.96, $p = 0.03$) in MIBC patients receiving chemoradiation compared to radiation alone [43]. This locoregional control benefit with chemoradiation persists in an updated analysis with a median follow up of 118 months [47]. There was no difference in overall survival.

Cisplatin alone or in combination with 5FU or paclitaxel [48–50], 5FU plus mitomycin [43], and gemcitabine [51] have been used concurrently with radiation for bladder preservation approach. Direct comparison between different regimens is not available and the optimal radiosensitizer has not been defined.

The role of neoadjuvant chemotherapy prior to definitive bladder chemoradiation is not clear. BC2001 trial allowed but did not require neoadjuvant chemotherapy, and about 33% of the patients received neoadjuvant chemotherapy [43]. The effect of chemoradiotherapy vs. radiotherapy on disease-free survival was similar irrespective of neoadjuvant chemotherapy in subgroup analysis. However BC2001 trial was not designed to address the benefit of neoadjuvant chemotherapy. In the RTOG 89–03 trial, cT2 to cT4aNxM0 bladder cancer patients received two cycles of neoadjuvant cisplatin, methotrexate, and vinblastine prior to concurrent cisplatin radiotherapy were compared to chemoradiotherapy alone [52]. Five-year overall survival rate was 48% and 49% respectively. There is no level 1 data evaluating the benefit of adjuvant chemotherapy following chemoradiotherapy. A systematic review by Ploussard et al. concluded the absence of definitive data to support the benefit of neoadjuvant or adjuvant chemotherapy in bladder cancer patients treated with trimodality therapy [53].

Prostate Cancer

Hormonal manipulation with either surgical or chemical castration has been the cornerstone of treatment for advanced adenocarcinoma of the prostate since 1941 [54]. Hormonal therapy is effective in reducing tumour burden and PSA

levels, but treatment resistance is inevitable. Chemotherapy was traditionally considered a palliative treatment of 'last resort' in patients with symptomatic prostate cancer. This changed with the demonstration of improved overall survival for patients with metastatic castration resistant prostate cancer (mCRPC) treated with docetaxel chemotherapy [55]. More recently, significant survival benefit has been observed when chemotherapy was added to ADT earlier in the disease for patients with castration sensitive disease.

Metastatic Castration-Resistant Prostate Cancer

The development of rising PSA, progressive symptoms or radiological progression despite castrated levels of testosterone ≤0.5 ng/mL (1.73 nmol/L) heralds the disease state termed castration-resistant prostate cancer. There are two life-prolonging chemotherapeutic agents with docetaxel and cabazitaxel for patients with mCRPC [55, 56]. The prognosis of mCRPC is guarded, with the median overall survival for patients with treatment naïve-mCRPC ranging from 25 to 35 months in contemporary randomised control trials [57–59].

Docetaxel

Docetaxel is an anti-microtubule taxane chemotherapy (Table 37.1). Two parallel phase 3 trials, TAX 327 and SWOG 99–16 independently showed docetaxel extended survival in patients with mCRPC in 2004 [55, 60]. In TAX 327, median overall survival was significantly increased by 2.4 months with docetaxel 75 mg/m^2 given once every 3 weeks and prednisone 5 mg twice daily, compared to mitoxantrone and prednisone (median 18.9 and 16.5 months respectively, HR 0.76, 95% CI 0.62–0.94; p = 0.009) [55]. Secondary endpoints including pain response, quality of life score as assessed by the functional assessment of cancer therapy – prostate (FACT-P) questionnaire, and PSA decline ≥50% from baseline (PSA50, 45% vs. 32%) were significantly improved with docetaxel. Bone marrow suppression, gastrointestinal (GI) toxicities, peripheral neuropathy, fatigue, nail changes, and reversible alopecia were adverse effects of interest with docetaxel. The SWOG 99–16 also showed a significant survival benefit of 1.9 months with three weekly docetaxel 60 mg/m^2 in combination with estramustine and prednisone against mitoxantrone and prednisone (HR 0.8, 95% CI 0.67–0.97, p = 0.02) [60]. Subsequent study comparing docetaxel with or without estramustine failed to demonstrate survival advantage with the addition of estramustine [61], and docetaxel and prednisone is the established regimen for mCRPC.

Alternative scheduling with weekly docetaxel was also explored in TAX 327 trial, but overall survival was not significantly different compared to mitoxantrone [55]. In another phase 3 trial comparing two and three-weekly docetaxel schedules, the primary endpoint of time to treatment failure (TTTF) was significantly longer in the two weekly group (5.6 months vs. 4.9 months, respectively, HR 1.3, 95% CI 1.1–1.6, p = 0.014), although the absolute difference was only 0.7 months [62]. Two-weekly schedule was well tolerated with less myelosuppression (grade ≥ 3 neutropenia (36% vs. 53%) and febrile neutropenia (4% vs. 14%) in the two and three-weekly groups, respectively), and two-weekly schedule can be considered in patients where there are concerns about myelosuppression with the every 3 week regimen.

Cabazitaxel

Cabazitaxel is another taxane chemotherapy (Table 37.1). It has less affinity for drug efflux pump P-glycoprotein than docetaxel, and has shown anti-tumour activity in docetaxel-refractory pre-clinical models [63]. In mCRPC patients who had progressed during or after docetaxel-based therapy, the TROPIC trial showed an overall survival benefit of 2.4 months comparing three weekly cabazitaxel 25 mg/m^2 and prednisone to mitoxantrone and prednisone (median 15.1 vs. 12.7 months, respectively, HR 0.7, 95% CI 0.59–0.83, p < 0.0001) [56]. Objective response rate (14.4% vs. 4.4%, p = 0.0005) and PSA50 (39.2% vs. 17.8%,

p = 0.0002) were all significantly in favour of cabazitaxel. Cabazitaxel also has anti-tumour activity in the first line setting. FIRSTANA showed comparable overall survival with a median of 25.2, 24.5, and 24.3 months, in patients with chemotherapy-naïve mCRPC randomised 1:1:1 to receive cabazitaxel 25 mg/m^2, 20 mg/m^2, and docetaxel 75 mg/m^2, respectively [59].

Compared to three weekly schedule, weekly cabazitaxel (weekly for 5 out of 6 weeks) resulted in comparable median doses, PSA50, and median PFS (6 vs. 6.4 months, respectively; HR 0.73, 95% CI 0.47–1.13, p = 0.156) [64] in a small phase II Scandinavian trial. Febrile neutropenia was more common with the three-weekly schedule (10 vs. 1 events), while weekly scheduling had more haematuria (20 vs. 6 events, p = 0.001). Three cases of painful ureteric inflammation were described with weekly cabazitaxel.

Cabazitaxel has a different toxicity profile from docetaxel, with adverse effects of interest including myelosuppression (8% febrile neutropenia), diarrhoea and haematuria. Alopecia and peripheral neuropathy are uncommon with cabazitaxel. Cabazitaxel-related toxicities including myelosuppression can be partially mitigated by prophylactic G-CSF or reducing cabazitaxel dose to 20 mg/m^2, which has been shown to be non-inferior to the 25 mg/m^2 dosing in terms of overall survival in the PROSELICA trial [65].

Mitoxantrone

Mitoxantrone is an anthracenedione (Table 37.1). It inhibits type II topoisomerase and is structurally similar to doxorubicin and daunorubicin. Mitoxantrone and prednisone were shown to be superior to prednisone alone using palliative response as the primary endpoint in patients with metastatic CRPC in 1996 [66]. Palliative response, as defined by a 2 point decrease in pain in a 6-point pain scale completed by patients, was 29% in the mitoxantrone group and 12% in the prednisone alone arm (p = 0.01). The duration of symptom control was 43 and 18 weeks, respectively (p < 0.001). There was no difference in overall survival between the two groups. The absence of survival advantage with mitoxantrone and corticosteroid combination was confirmed by Kantoff and colleagues comparing mitoxantrone plus hydrocortisone against hydrocortisone [67].

Platinum-Based Chemotherapy

Platinum-based chemotherapy (including cisplatin, carboplatin, oxaliplatin, satraplatin) exerts its cytotoxic effects by covalently binding to purine DNA bases, forming DNA intrastrand and interstand cross-links. This disrupts the normal functions of cellular DNA, causing DNA double-strand breaks and cell death. Platinum has shown anti-tumour activity in mCRPC either as monotherapy or in combination, but this enthusiasm has dampened since the phase III SPARC trial failed to demonstrate an overall survival benefit with oral satraplatin in unselected mCRPC patients [68].

The phase II RECARDO trial evaluated the benefit of adding carboplatin AUC4 to docetaxel 60 mg/m^2 compared to docetaxel 75 mg/m^2 in previously docetaxel-treated mCRPC patients with a progression-free interval of ≥3 months [69]. The primary endpoint of progression-free survival was 11.7 and 12.7 months in the combination and docetaxel arm, respectively (p = 0.98).

There is renewed interest in platinum-based chemotherapy with the increased understanding of the genomic landscape of mCRPC, particularly the high prevalence of germline and somatic alterations in homologous recombination repair genes especially BRCA1 and BRCA2 [70–73]. Although predictive of response to PARP inhibitors [74], tumour with a homologous recombination deficiency (HRD) have exhibited a high response rate to platinum-based therapy in retrospective studies [75–77].

Small Cell Carcinoma of the Prostate

Platinum-etoposide is the treatment of choice for patients with small cell carcinoma of the prostate, as extrapolated from the management of small cell lung cancer and supported by the NCCN clinical practice guidelines [78]. Although de novo small cell carcinoma of the prostate is rare [79], incidence of treatment-emergent neuroendocrine prostatic cancer (t-NEPC), or small cell carcinoma,

increases with treatment and advanced disease, and was observed in 17% (27 of 160) of mCRPC patients [80].

As with small cell lung cancer, treatment response of t-NEPC to platinum chemotherapy is high but often short-lived, and new treatment strategies are needed. In an attempt to improve oncological outcomes, Aparicio and colleagues select 120 patients based on seven aggressive clinical features suggestive of small-cell carcinoma in a single arm phase II trial [81]. The seven inclusion criteria include small cell histology (pure or mixed), visceral metastases, predominant lytic bone metastases, bulky (≥5 cm) lymphadenopathy or bulky (≥5 cm) Gleason ≥8 prostate/pelvic mass, low PSA (≤10 ng/mL) plus high volume (≥20) bone metastases, presence of neuroendocrine markers on histology or in serum plus either one of elevated LDH (≥2 x institutional upper limit of normal, IULN), malignant hypercalcaemia, or elevated serum CEA (≥2 x IULN), and short interval (≤6 months) to androgen-independent progression. Histologic confirmation of small cell carcinoma was not required. Patients were treated with docetaxel 75 mg/m^2 and carboplatin AUC 5, then cisplatin and etoposide upon progression, and achieved an overall survival of 16 months.

A retrospective study identified 29% (5/17) of patients with small cell prostatic carcinoma also harboured biallelic loss of DNA repair genes [79]. The median overall survival of these subsets of patients with or without DNA repair defects was 40.7 months and 20.1 months ($p = 0.088$), respectively. One patient with homozygous BRCA2 deletion had an exceptional durable response first to platinum-based chemotherapy and CNS radiation, and subsequently to olaparib which continued for at least 16 months was reported. This suggested novel therapeutic opportunities in a population traditionally with very poor outcomes.

Metastatic Castration-Sensitive Prostate Cancer (mCSPC)

Surgical or chemical castration with androgen deprivation therapy (ADT) alone has been the standard of care for patients with mCSPC for over 70 years when first described by Hugginsand Hodges [54]. The treatment landscape for mCSPC was transformed by the publications of CHAARTED and STAMPEDE trials in 2015 and 2016, respectively, to incorporate docetaxel with ADT in patients with mCSPC.

CHAARTED randomised 790 patients with metastatic castration-sensitive prostate cancer to ADT and six cycles of docetaxel 75 mg/m^2 or ADT alone [82]. Concomitant prednisone was not a requirement. The addition of docetaxel significantly improved median overall survival by 13.6 months (57.6 vs. 44 months for chemohormonal combination vs. ADT alone, respectively; HR 0.61, 95% CI 0.47–0.8, $p < 0.001$). Time to CRPC was delayed by 8.5 months (median 20.2 vs. 11.7 months, respectively; HR 0.61, 95% CI 0.51–0.72, $p < 0.001$). With a longer median follow-up of 53.7 months, an a priori subgroup analysis revealed a median overall survival benefit of 17 months in patients with high-volume disease (defined as the presence of visceral metastases or ≥ 4 bone lesions with ≥1 beyond the vertebral bodies and pelvis) treated with chemohormonal therapy vs. ADT (median 51.2 vs. 34.4 months, respectively; HR 0.63, 95% CI 0.5–0.79, $p < 0.001$) [83]. No overall survival advantage was observed in patients with low-volume disease (HR 1.04, 95% CI 0.7–1.55, $p = 0.86$). There were no new safety concerns with docetaxel use in the castration-sensitive setting.

The survival benefit with chemo-hormonal treatment vs. ADT alone in mCSPC was confirmed in the multi-arm, multi-stage STAMPEDE trial. In the standard of care (SOC) + docetaxel arm, median overall survival was 81 months compared to 71 months in the SOC arm (HR 0.78, 0.66–0.93, $p = 0.006$) [84]. Failure free survival was also significantly improved with combination therapy over ADT alone (median 37 vs. 20 months, respectively; HR 0.61, 95% CI 0.53–0.7, $p = 0.413 \times 10^{-13}$). Unlike the CHAARTED trial, outcomes analysis according to tumour burden was not possible as this was not prospectively predefined in STAMPEDE. About 40% of patients had high-risk localised prostate cancer. Although failure-free survival was improved by

the addition of docetaxel to ADT (HR 0.6, 95% CI 0.45–0.8; $p = 0.28 \times 10^{-3}$), overall survival data was immature in the subset of non-metastatic patients. The febrile neutropenia rate was high at 15% compared to 6.1% [82] in CHAARTED, otherwise the toxicity profile of docetaxel was in accordance with previous experience.

The above findings were in contrast with GETUG-AFU 15 [85]. Overall survival was not significantly different between mCSPC patients receiving docetaxel plus ADT vs. ADT alone (median 58.9 vs. 54.2 months; HR 1.01; 95% CI 0.75–1.36, $p = 0.955$). A post hoc retrospective analysis of the survival data according to volume of disease showed a nonsignificant trend towards improved overall survival in high-volume disease (39.8 vs. 35.1 months; HR 0.78, 95% CI 0.56–1.09, $p = 0.14$), and no overall survival difference in low volume disease [86].

The results of these three trials (CHAARTED, GETUG-15, STAMPEDE) were analysed by the Systemic Treatment Options for Prostate Cancer (STOpCaP) meta-analysis. It confirmed a significant survival benefit with the addition of docetaxel to standard of care in patients with mCSPC (HR 0.77, 95% CI 0.68–0.87, $p < 0.0001$), which translated to an absolute improvement in 4-year survival of 9% (95% CI 5–14) [87].

Taken together, these data confirm the benefit of docetaxel + ADT in *metastatic* CSPC patients. Subgroup analysis from CHAARTED indicated that the benefit is restricted to high volume disease, and the benefits and risks of adding docetaxel to SOC to patients with non-high volume disease must be carefully considered. Recently, abiraterone + ADT has been shown to improve overall survival (LATITUDE and STAMPEDE) and a further option for patients with mCSPC [88, 89]. An opportunistic analysis of the STAMPEDE trial comparing ADT + docetaxel vs. ADT + abiraterone suggested similar overall survival outcomes, although there are obvious difference in schedule and toxicity associated with each regimen [90]. ADT plus docetaxel plus next generation androgen receptor inhibitor will be evaluated directly and indirectly in several trials including PEACE1 (NCT01957436), TITAN (NCT02489318), ENZAMET (NCT02446405), and ARASENS (NCT02799602).

Localised Prostate Cancer

The practise-changing data from CHAARTED and STAMPEDE suggested earlier use of chemotherapy provided the greatest benefits for patients with metastatic disease. However, results from perioperative chemotherapy in localised prostate cancer have not been as promising, with no evidence of overall survival benefit identified as yet.

GETUG-12 compared four cycles of three-weekly docetaxel 70 mg/m^2 + estramustine + 3 year of ADT vs. ADT alone in patients with high risk localised prostate cancer [91]. Local therapy was given after 3 months of systemic therapy, and could have been either radiotherapy (87%) or prostatectomy. The updated survival outcomes were recently presented in ESMO 2018. With a median follow-up of 12 years, clinical relapse-free survival was improved in the combination arm compared to ADT alone (adjusted HR 0.75, 95% CI 0.56–1, $p = 0.049$). Median metastases free survival (MFS) rates at 12 year were 62.2% vs. 55.8% (adjusted HR 0.81, 95% CI 0.6–1.09) [92].

RTOG 0521 randomised high-risk localised prostate cancer patients to docetaxel + ADT vs. ADT alone after definitive radiotherapy [93]. Preliminary results after a median follow-up of 5.5 years showed an improvement in 4-year overall survival (93% vs. 89%, docetaxel + ADT vs. ADT, respectively; HR 0.68, 95% CI 0.44–1.03, 1-sided $p = 0.03$). However, one must interpret these results with caution as non-prostate cancer death due to other primary tumour was disproportionately higher in the ADT arm than the combination arm.

The STOpCaP meta-analysis showed an absolute reduction of 8% in 4-year failure-free survival rates from 30 to 22% with docetaxel (HR 0.7, 95% CI 0.61–0.81, $p < 0.0001$) [87]. There was no statistically significant difference in 4-year overall survival between docetaxel and ADT (HR 0.87, 95% CI 0.69–1.09,

p = 0.218). Since the report of the STOpCaP meta-analysis, SPCG12 trial reported no difference in the primary endpoint of PSA progression between adjuvant docetaxel without ADT or corticosteroids vs. surveillance in patients after prostatectomy. Note that 20% had detectable PSA at trial entry, one third of patients had no pelvic lymph node dissection, and this trial included patients without high-risk features e.g. pT2, Gleason 7.

SWOG S9921 trial with adjuvant mitoxantrone + prednisone + ADT (MP) vs. ADT post prostatectomy was a negative trial with comparable 10-year overall survival (86% vs. 87% respectively) [94]. More patients in the MP than ADT arm died of other cancers (36% vs. 18%, respectively).

At present, there was no evidence of either metastases-free survival, a potential surrogate for overall survival [95], or overall survival advantage of neoadjuvant or adjuvant docetaxel in localised prostate cancer. Results from two ongoing trials CALGB 90203 (NCT00430183) and PEACE-2 (NCT01952223) evaluating perioperative chemotherapy in localised prostate cancer will be reported in 2019.

Germ Cell Tumours

Testicular germ cell tumours (GCT), even in patients with widely disseminated disease, are highly curable neoplasms with chemotherapy. Treatment strategy varies with staging. Management of early stage disease focuses on minimising exposure to treatment-related toxicity, while high dose myeloablative chemotherapy followed by autologous peripheral blood stem cell transplant (PBSCT) is used to overcome treatment resistance in relapsed disease.

Stage I Seminoma

Orchiectomy alone cures over 80% of patients with stage I seminoma [96–98]. The risk of relapse can be reduced to <5% with adjuvant radiotherapy or one cycle of carboplatin. However, active surveillance is often adopted to avoid late toxicities associated with adjuvant therapy, and effective salvage therapy exists such that long term overall survival and cause-specific survival are comparable and approach 100% regardless of the strategy used [98–100].

Traditionally, adjuvant radiotherapy has been the standard of care prior to the availability of effective chemotherapy for testicular GCT. The emerging knowledge of late toxicities including secondary malignancies and increased cardiovascular risks associated with radiotherapy has resulted in decline of adjuvant radiotherapy use in stage I seminoma [101, 102]. The finding of similar 5-year relapse-free rate of 94.7% for carboplatin and 96% for radiotherapy, the reduction in the rate of contralateral GCT with carboplatin versus radiotherapy (HR 0.22, 95% CI 0.05–0.95, p = 0.03), and the potential cumulative toxicities of salvage chemotherapy after adjuvant radiotherapy has made carboplatin the ideal choice should adjuvant therapy be considered [99]. It is important to dose carboplatin to AUC 7 as a lower dose is associated with a trend toward an inferior 5-year relapse-free rate [99].

A single course of carboplatin is usually well-tolerated. A prospective UK study evaluated 199 patients with a median follow-up of 9 years failed to show an excess mortality from secondary malignancies for adjuvant carboplatin [103]. A high standardized mortality ratio of 4.59 (95% CI 0.56–16.6) was observed for cerebrovascular disease but this was not statistically significant. Longer follow up measuring in decades is needed to establish the presence (or absence) of late toxicity for adjuvant carboplatin as testicular GCT patients are usually young men.

In practice, most men undergo active surveillance after orchiectomy unless compliance to regular follow-up is a concern. Giving adjuvant therapy to patients with high risk of relapse in a risk-adapted strategy has been proposed. Primary tumour size >4 cm and rete testis invasion were identified as independent predictors for relapse [96, 97]. Five-year relapse-free rates were 87.8%, 84.1%, and 68.5% for 0, 1, and 2 risk factors, respectively [97]. However effort to validate these risk factors in a prognostic model for risk of

relapse in patients with stage I seminoma undergoing active surveillance has not been successful [104, 105]. Furthermore, in patients with equivocal retroperitoneal nodes, active surveillance would be the preferred option as carboplatin may be an insufficient treatment if stage II disease emerges with time.

Stage I Nonseminoma

Patients with clinical stage I nonseminomatous germ cell tumour (NSGCT) whose tumours exhibited lymphovascular invasion (LVI) and/or embryonal carcinoma predominant histology are at higher risk for relapse [106–108]. The risk of relapse was 10–15% in patients without LVI, compared with 40–50% in patients with LVI positive tumour [109, 110]. The majority (90%) of relapsed patients developed International Germ Cell Cancer Consensus Group (IGCCCG) good-risk disease [109]. Most relapses (>90%) occurred within 2 years, and all late recurrences were cured with standard of care. Importantly five-year disease specific survival was 99.7%.

Management options for stage I NSGCT post orchiectomy include active surveillance, nerve-sparing retroperitoneal lymph node dissection (RPLND), or adjuvant chemotherapy. Adjuvant RPLND was the standard of care prior to the advent of effective chemotherapy. The relapse rate after RPLND varies between 5 and 15%, and higher at 32% in patients with pathological stage II disease [111–113]. By excluding patients with persistently elevated serum tumour markers post RPLND or stage IIB disease, the 4-year progression-free probability improved from 83 to 96% [112]. Adjuvant chemotherapy with one cycle of bleomycin, etoposide and cisplatin (BEP, Table 37.2) reduced the relapse rate of LVI-positive and LVI-negative stage 1 nonseminoma to 3.2% and 1.3%, respectively, in the SWENOTECA trial [110]. An excellent long term outcome was achieved with 100% 5-year relapse free survival [114]. In a phase 3 trial comparing one cycle of adjuvant BEP versus RPLND, the 2-year recurrence-free survival rates were 99.5% and 91.9%, respectively, with a hazard ratio for recurrence of 7.9 for surgery versus chemotherapy (95% CI 1.8 to 34.5) [113].

Most oncologists recommend active surveillance for stage I nonseminoma patients with no risk factors for relapse and can adhere to regular follow up. There is still much debate over the optimal management of high risk stage I nonseminoma patients [115, 116]. NCCN guidelines recommended either active surveillance, RPLND, or adjuvant chemotherapy, and many large specialised centres advocate active surveillance regardless of risks [117–119]. RPLND is still an option for patients who would like to minimise their risks of relapse and avoid adjuvant chemotherapy, but it should be performed in high volume centres by an experienced surgeon to optimise clinical outcomes [113]. BEP-related toxicities is expected to be lower with only one cycle, as the risks of acute leukaemia, cardiovascular disease, pulmonary toxicity, nephrotoxicity, peripheral neuropathy, and ototoxicity increase with higher cumulative dose of BEP [120–124]. The extent of risk in particular late-toxicity remains unknown but is unlikely to be negligible. Ideally, adjuvant therapy should be given only to patients who will relapse to avoid unnecessary intervention for 85% of the low risk and 50% of high risk stage I nonseminoma patients who otherwise would have been cured with orchiectomy alone.

Stage II Seminoma

For patients with stage IIA disease, radiotherapy to the paraaortic and ipsilateral iliac lymph nodes, or chemotherapy with either three cycles of BEP or four cycles of etoposide cisplatin (EP) is indicated. Carboplatin AUC 7 alone is not recommended for clinical stage IIA seminoma as viable residual disease is unacceptably high and found in 19% of cases, including one patient (0.9%) with progressive disease [125].

The SWENOTECA study found 10.9% (3/29) of clinical stage IIA patients relapsed after radiotherapy, compared with no relapses (0/73) in clinical stage IIA/B patients who received chemotherapy [105]. The lower total radiotherapy dose of 27 Gy used in the SWENOTECA study

compared to the conventional dose of 30–36 Gy may contribute to a higher reported relapse rate [126]. The efficacy of BEP x3 or EP x4 was again demonstrated in a study by the Spanish Germ Cell Cancer Group, which showed no relapses (0/18) in stage IIA patients treated with chemotherapy [127].

Chemotherapy with three cycles of BEP or four cycles of EP is the standard of care for patients with bulky (>3 cm) stage II disease. Five year cancer-specific and overall survival rates were 97.6% and 95.1%, respectively, in patients with stage IIC seminoma treated with chemotherapy [105].

Stage II Nonseminoma

Patients with clinical stage II nonseminoma with elevated serum tumour markers are treated as advanced disease according to IGCCCG risk groups with chemotherapy (see 'Advanced Testicular Germ Cell Tumours below). RPLND may be an option for stage II nonseminoma with normal serum tumour markers and slowly growing tumours suspicious of teratoma or undifferentiated malignancy.

Advanced Germ Cell Tumours

The discovery of cisplatin's efficacy in germ cell tumours has revolutionised the management of germ cell tumour [1]. The addition of vinblastine and bleomycin to cisplatin (PVB) in 1977 [2], and the substitution of vinblastine to etoposide in 1987 [128] improved the long term outcomes and tolerability of chemotherapeutics, and formed the basis of contemporary treatment for patients with advanced germ cell tumours.

Prognosis of advanced germ cell tumour is stratified into three risk groups by IGCCCG based on serum tumour marker levels, location of the primary tumour and metastases [129]. Five-year survival rates were 94%, 83%, and 71% for low, intermediate, poor risk groups, respectively [130]. Seminoma is only classified as low and intermediate risk as it is a more chemosensitive tumour and thus has a more favourable prognosis than nonseminoma.

Good-Risk Advanced Germ Cell Tumours

Three cycles of BEP or four cycles of EP is the standard of care for patients with good-risk advanced GCT. Substituting cisplatin with carboplatin is associated with inferior outcomes and is not recommended [131, 132].

To minimise chemotherapy-related toxicities in this patient group with generally favourable prognosis, three cycles of BEP was compared to four cycles of BEP and showed no significant difference in survival [133, 134]. EORTC compared four cycles of EP vs. four cycles of BEP, although in this study the etoposide dose utilized was lower at 360 mg/m^2/cycle than the conventional dosing of 500 mg/m^2/cycle [135]. The inclusion of bleomycin was associated with higher complete response (95% vs. 87%), fewer deaths (3% vs. 6%), at the expense of greater rates of pulmonary toxicity, neurotoxicity, and Raynaud-like phenomenon. Using the conventional etoposide dosing of 500 mg/m^2/cycle, GETUG designed an equivalence trial which aimed to detect no more than 10% difference in favourable responses (clinical, biochemical and pathological complete responses or partial responses with normal serum tumour markers and subcentimeter residual masses) between three cycles of BEP and four cycles of EP [136]. No significant differences in 4-year event-free survival (91% vs. 86%, respectively; HR 0.58, 95% CI 0.29–1.19, $p = 0.135$) or 4-year overall survival (5 vs. 12 deaths, respectively, $p = 0.096$) were observed, but BEP x3 had significantly more all grade neurotoxicity (16% vs. 5%), dermatological toxicity including Raynaud phenomenon (29% vs. 8%), without significant difference in pulmonary toxicity (9% vs. 6%).

The importance of maintaining treatment dose-intensity was shown in the Australian and New Zealand Germ Cell Trial Group. The standard BEP was compared with an alternative regimen consisted of four cycles of three weekly 100 mg/m^2 cisplatin on day 1, 120 mg/m^2 etoposide and days 1–3, and 30 kU bleomycin on day

1 [137]. The trial was stopped at the second planned interim analysis due to a substantially better overall survival with the standard BEP (HR 0.22, 95% CI 0.06–0.77, $p = 0.008$), with 1 and 9 disease-related death seen in the standard and alternate BEP respectively.

Intermediate/Poor Risk

Four cycles of BEP is the standard of care for intermediate and poor-risk patients. Other strategies including doubling cisplatin dose, alternating or sequential chemotherapy regimens, and high dose chemotherapy with stem cell rescue all failed to improve clinical outcomes over the standard BEP and are often associated with more toxicity [138–141].

Treatment intensification with the addition of paclitaxel to BEP in intermediate-risk patients was not associated with a significant difference in 3-year progression-free survival, although this EORTC 30983 trial was underpowered and included non-eligible patients with good and poor prognosis patients [142]. Serum tumour marker directed treatment intensification was explored in poor risk patients. After one cycle of BEP, patients with favourable tumour marker decline had ongoing BEP, while the rest were randomised to BEP or an intensified regimen with the addition of paclitaxel, oxaliplatin, and ifosfamide to BEP. This GETUG 13 trial showed patients with an unfavourable tumour marker decline treated with an intensified regimen had a superior 5-year progression-free survival compared to standard BEP (60% vs. 47%, respectively; HR 0.69, 95% CI 0.43–0.97, $p = 0.04$), but the difference in 5-year overall survival was not significantly different [143, 144]. The intensified regimen is also more toxic.

Although ifosfamide in combination with etoposide and cisplatin (VIP) was not superior to BEP and was more toxic [145, 146], it is an option for patients with underlying lung disease, high volume of pulmonary metastases or mediastinal NSGCTs in anticipation of upcoming thoracic surgery who would like to avoid bleomycin-related pulmonary toxicity.

A modified treatment in the first cycle with cisplatin 20 mg/m^2 and etoposide 100 mg/m^2 on days 1–3, followed by bleomycin 30 IU and 2 days of cisplatin etoposide between day 10 and 15, is recommended in patients with choriocarcinoma syndrome at risk of acute respiratory distress syndrome (ARDS) from induction chemotherapy [147].

Relapsed Disease

Patients with relapsed germ cell tumour after cisplatin-based therapy can be managed with either conventional-dose chemotherapy (CDCT) or high-dose chemotherapy (HDCT) followed by peripheral blood stem cell transplant (PBSCT).

Common CDCT salvage regimens include VeIP (vinblastine, ifosfamide, ciplastin), TIP (paclitaxel, ifosfamide, cisplatin), and VIP (Table 37.2) [148–150]. As chemotherapy is often selected on the basis of absence of prior exposure in salvage therapy, TIP is commonly used as second-line therapy after standard first-line BEP. However, there is no direct comparison between different CDCT salvage regimens. For HDCT, two cycles of tandem carboplatin 2100 mg/m^2 + etoposide 2250 mg/m^2 over 3 days followed by PBSCT, and the TI-CE protocol (two cycles of paclitaxel + ifosfamide, followed by three cycles of high-dose carboplatin etoposide and PBSCT) is advocated by Indiana University and Memorial Sloan Kettering Cancer Center, respectively [151, 152]. More than one cycle of HDCT is preferred. A phase III trial showed 5-year overall survival was superior in the group receiving one cycle of VIP followed by three cycles of HDCT with carboplatin and etoposide, than three cycles of VIP followed by one cycle of HDC (49% vs. 39%, respectively, HR 1.42; 95% CI 0.99–2.05; $p = 0.57$) [153].

It is unclear whether patient with relapsed germ cell tumour should be treated with CDCT or HDCT as initial salvage therapy, and the optimal regimen for HDCT is undefined. Multicentre retrospective study showed 5-year overall survival was improved with HDCT compared with CDCT (53.2% vs. 40.8%, respectively; HR 0.65, 95% CI 0.56–0.75, $p < 0.001$) [154]. Apart from low risk group, this survival benefit was seen

across all prognostic groups, and 27% of very high-risk patients who had HDCT were alive at 5 years compared to 3% for those with CDCT. Multivariable analysis of 364 patients from Indiana University identified HDCT as third-line or later therapy, platinum-refractory disease, mediastinal primary, nonseminoma histology, intermediate- or poor-risk disease at diagnosis, hCG ≥1000 U/L at initiation of HDCT as factors associated with disease progression [155]. Toxic death was reported in 2.5% (n = 9) of patients, and secondary leukaemia in 5 patients. The results of the TIGER study (NCT02375204) comparing CDCT using four cycles of TIP with HDCT using the TI-CE protocol as initial salvage treatment in patients with relapsed or refractory germ cell tumours are awaited.

Penile Cancer

Patients with locally advanced squamous cell carcinoma of the penis require multi-modality treatment including chemotherapy to improve long term outcomes. Palliative chemotherapy is the mainstay of treatment for patients with unresectable or metastatic disease. Due to the rarity of penile cancer it is difficult to validate standard of care in large prospective phase III trials, and only retrospective studies and small phase II trials are available to guide management.

Locally Advanced Penile Cancer

Patients with multiple, fixed, or bulky inguinal lymph node >4 cm, or evidence of pelvic lymphadenopathy i.e. ≥N2 disease can be considered for neoadjuvant chemotherapy followed by complete inguinal and pelvic lymph node dissection. Bleomycin-based and cisplatin-based regimens are both active in penile cancer, but bleomycin containing chemotherapy is poorly tolerated and associated with significant pulmonary toxicity [156, 157]. Taxane was later integrated into neoadjuvant chemotherapy to mirror its adoption in head and neck squamous cell carcinoma. A prospective, phase II, single arm trial evaluated the safety and efficacy of paclitaxel, ifosfamide and cisplatin (TIP) in patients with stage TxN2-3 M0 penile cancer (Table 37.2) [158]. Thirty men were recruited by MD Anderson Cancer Centre, of which 23 (77%) completed the scheduled four cycles of chemotherapy. Objective response rate (ORR) was 50%, including 3 (10%) complete response. Twenty-two (73.3%) patients proceeded to subsequent surgery. With a median follow up of 34 months, median time to progression (TTP) and overall survival were 8.1 months (95% CI 5.4–50+) and 17.1 months (95% CI 10.3–60+), respectively. Objective response to chemotherapy resulted in statistically significant improvement in TTP and overall survival. Univariate analysis showed absence of bilateral residual tumour, extranodal extension, or skin involvement were also associated with longer TTP and overall survival. A follow-up study increased the cohort size to 53 patients who had received neoadjuvant TIP. The updated ORR and CR were 65% and 19% respectively [159].

A similar regimen containing docetaxel, cisplatin, and 5-fluorouracil (TPF) was evaluated in two phase II studies [160, 161]. ORR ranged from 38.5 to 60%, with complete response seen in 4–8% (15/25). Median PFS and OS were 7 months and 10 to 14 months, respectively. About one quarter of patients failed to complete the planned cycles, and the regimen was poorly tolerated with 66% patients reported to have grade ≥3 toxicity. Due to substantial toxicity TIP is favoured over TFP. Other active neoadjuvant regimens include cisplatin + irinotecan and cisplatin +5-fluorouracil [156, 162] .

Standard adjuvant chemotherapy following surgery for locally advanced penile cancer has yet to be defined due to paucity of data. A retrospective multicentre study showed adjuvant chemotherapy (n = 36) was associated with improved overall survival (HR 0.4, 95% CI 0.19–0.87, p = 0.021) compared to expectant management (n = 48) in patients with positive pelvic lymph nodes following lymph node dissection from 1978 to 2013 [163]. A median OS of 22.7 months was achieved in another retrospective study in 21 patients who received adjuvant TPF [164].

NCCN guidelines recommend neoadjuvant TIP, and by extrapolation from the neoadjuvant data, adjuvant TIP in patients with penile cancer and ≥ N2 disease [165] . EAU guidelines also recommend neoadjuvant cisplatin and taxane based triplet in patients with fixed, unresectable lymphadnoeapthy [166]. Despite the curative intent of perioperative chemotherapy, prognosis is poor in patients with locally advanced penile cancer. In a multicentre analysis of individual patient-level data involving 201 patients who underwent perioperative chemotherapy and surgery from 1990 onward, 2-year survival in the neoadjuvant and adjuvant arms were only 36% and 57% respectively [167]. There was no statistically significant difference in overall survival between the two groups. The inherent limitations associated with small retrospective studies preclude accurate comparison of benefit derived from neoadjuvant versus adjuvant therapy. Objective response to neoadjuvant chemotherapy is an important prognostic factor. Patients who had an objective response following neoadjuvant chemotherapy achieved a 5-year survival rate of 50% in a series involving 61 patients [159].

Unresectable or Recurrent, or Metastatic Penile Cancer

Chemotherapy is the mainstay of treatment for patients with unresectable, recurrent, or metastatic penile cancer. First-line chemotherapy varies, and depends on prior treatment, patient's co-morbidities and performance status. Similar to neoadjuvant chemotherapy, cisplatin-based therapy is preferred over bleomycin-containing regimen as it has a more favourable toxicity profile.

First-line cisplatin monotherapy resulted in a response rate of 15.4% [168]. To improve clinical outcomes, cisplatin was combined with 5-fluorouracil [169] or irinotecan [162]. These combinations were well-tolerated and improved response rate to >30%. Triplet combination with cisplatin, 5-fluorouracil, and docetaxel yielded a response rate of 38% and was tolerable in a Chinese study [170]. Bleomycin-based regimen with cisplatin and methotrexate provided similar response rate of 32.5%, but the treatment was toxic with five (11%) treatment related deaths out of 45 patients [171]. Other active regimens include cisplatin + gemcitabine [172], and carboplatin + paclitaxel [173]. MD Anderson study described above reported recurrence in 19 (63.3%) of 30 TxN2-3 M0 patients who had received neoadjuvant TIP for penile cancer [174]. Two of five evaluable patients responded with second-line bleomycin, methotrexate, and cisplatin, but one developed fatal pneumonitis. Prognosis is poor in patients with disseminated disease, with median PFS reported as 20 weeks in patients treated with first-line cisplatin and 5-fluorouracil [169].

The role of second-line chemotherapy remains undetermined. A phase 2 multicentre study evaluated paclitaxel in patients with disseminated penile cancer who had prior cisplatin-based chemotherapy in the neoadjuvant, adjuvant, or advanced setting found a response rate of 20% [175]. Median PFS was only 11 weeks, and median survival in responders was 32 weeks.

In patients with metastatic or recurrent penile cancer, NCCN guidelines recommend cisplatin-based chemotherapy [165], and EAU guidelines suggest chemotherapy with a grade C recommendation [166]. Epidermal growth factor receptor (EGFR) targeted therapies e.g. cetuximab, erlotinib, gefitinib, and panitumumab have shown promising activity and tolerability in patients with unresectable or metastatic penile cancer [176, 177]. The efficacy of checkpoint inhibitor (NCT02837042, NCT02721732, NCT03333616) and its combination with tyrosine kinase inhibitor cabozantinib (NCT02496208) are being evaluated in clinical trials. Integrating these therapies into current clinical practice, either alone or in combination with chemotherapy, may improve clinical outcomes. Identification of a predictive biomarker is critical to enrich patients who will benefit from treatment, and to avoid futile treatment in this cohort of patients with otherwise very poor prognosis.

Kidney Cancer

Clear cell renal cell carcinoma originates from the renal cortex and represents up to 85% of primary kidney neoplasms [178]. Targeted therapy

such as anti-vascular endothelial growth factor (anti-VEGF) and immunotherapy with checkpoint inhibitor are the mainstay of treatment for advanced clear cell renal cell carcinoma. Chemotherapeutics have limited role in the management of renal cell carcinoma. The exceptions are collecting duct carcinoma and renal medullary carcinoma. Objective response rate to platinum-based regimens was 26% and 29%, respectively, in retrospective studies [179–181]. Prognosis was poor for these patients. The median overall survival was 10.5 months for patients with metastatic collecting duct carcinoma [179], and 2 year survival was only 13% in patients with renal medullary cancer [181].

Conclusion

Systemic therapy with chemotherapy plays an increasing role in the management of urological malignancies over the last 50 years. It contributes to incremental gain in survival in bladder, prostate, and penile cancer, and revolutionised treatment of testicular cancer offering cure to those even with advanced disease.

The optimal strategy to integrate chemotherapy with local therapies, as well as with other modalities of systemic therapies in the era of targeted therapy and immunotherapy requires multidisciplinary approach and will be the focus of future research. This is particularly relevant for urothelial and kidney cancer where the potential of immunotherapy is being realised. The absence of significant recent advances in the management of testicular and penile cancer, especially for patients with relapsed germ cell tumour and advanced penile cancer where prognosis remains dismal warrant novel therapeutic approaches. Understanding the tumour genomic profile can refine patient selection to optimise treatment response and reduce exposure to futile therapy, as observed in exceptional responders to platinum in mCRPC patients with HRD tumours. This is critical as chemotherapy is often toxic and patients with urological cancer are often elderly and multi-comorbid. Even with quality data from well-designed RCTs, the treatment strategy must be tailored to individual patients based on their unique clinical attributes. The goal of care will always aim to maximise clinical benefit while minimising therapy-related toxicity.

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38 Diagnosis, Staging and Management of Testis Cancer

Noel W. Clarke

Overview

Testicular tumours may be benign or malignant. The latter present either with signs and symptoms of the primary tumour or with problems relating to metastatic spread. The eighth edition of the Union for International Cancer Control (UICC) TNM classification of testicular cancer is shown [1]. Testis cancer is relatively rare, representing approximately 1% of all male cancers and 5% of all urological tumours. There are 3–10 new cases per 100,000 males per year in Western countries. However, the incidence is projected to rise in some of these to 10 cases/100,000 males by 2035 [2]. Higher incidence rates are seen in developed countries compared to developing countries. Risk factors for testicular cancer include a previous or family history, with a higher risk if the affected male family member is a brother. Additional, clinical risk features include the presence of germ cell neoplasia *in situ* (GCNIS) and/or testicular dysgenesis syndrome (cryptorchidism, hypospadias and impaired spermatogenesis).

Germ-cell tumours are responsible for 90–95% of testis tumours. Pure seminoma has a peak incidence in the fourth decade, whilst non-seminomatous germ cell tumour (NSGCT) has a peak incidence in the third decade [3]. Approximately 90% are localised to the testis at first presentation and 2–5% are extragonadal [3]. Most are unilateral although 1–2% occur bilaterally, usually as a metachronous event. The different types of testicular tumour are set out below (Box 38.1). NSGCT's have a tendency to spread more commonly via haematogeneous as well as lymph node routes and stage III metastasis occurs more common in these. By contrast, approximately 80% of seminoma

Box 38.1 Testicular Tumour Types

2016 WHO Classification of tumours of the testis.

Germ cell tumours derived from germ cell neoplasia in situ

- Germ cell neoplasia in situ
- Seminoma
- Embryonal carcinoma
- Yolk sac tumour
- Choriocarcinoma
- Teratoma (postpubertal-type, teratoma with somatic-type malignancy)
- Mixed germ cell tumours

Germ cell tumours unrelated to germ cell neoplasia in situ

- Spermatocytic tumour
- Teratoma, prepubertal type

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Sex cord stromal tumours

- Leydig cell tumours
- Sertoli tumours
- Granulosa cell tumours
- Fibroma/Thecome
- Mixed sex cord stromal tumour

Miscellaneous tumours/haematolymphoid tumours/tumours of the collecting duct & rete testis

- Ovarian epithelial type tumours
- Lymphoma
- Sarcoma
- Adenoma/Adenocarcinoma

patients have stage I disease at diagnosis, with only 15% having stage II disease and <5% presenting with advanced disease.

Most testicular germ cell tumours are confined to the scrotum at first presentation: these are usually cured by local surgery using inguinal orchidectomy. When patients present with metastases or develop distal spread after primary orchidectomy, the disease is usually chemo-sensitive, particularly to regimens involving cisplatin. This renders the condition curable in the majority, but not all cases. High risk NSCGT is still lethal in approximately 50% of patients. In light of this, preservation of reproductive function, quality of life and avoidance of delayed treatment effects are important concerns for testis cancer patients who survive long-term.

Presentation and Diagnosis

The commonest presentation is with a painless unilateral testicular mass. However a significant number of men may present with pain and are misdiagnosed with epididymitis or orchitis, leading to a delay in essential treatment. GCT's can also present with a secondary hydrocele or more rarely, a para-neoplastic syndrome. One rare example of this is hCG induced hyperthyroidism, seen in GCTs containing high levels of hCG. This can activate the TSH receptor as both TSH and hCG have similar alpha subunits.

An uncommon but well-recognised acute presentation is with symptoms and signs arising from disseminated disease. When patients present in this way it is ***an oncological emergency*** and urgent referral to a specialist oncology team is required. Such cases need immediate chemotherapy *without orchidectomy*. Patients with disease of this type *must* be referred within 24 h of presentation.

Examination of the patient should include inspection for and documentation of the condition of both testicles, noting the size of both the affected and contra-lateral testicle. The abdomen and thorax should be examined for nodal or visceral disease and gynaecomastia (present in 7% of men and associated with elevated hCG levels). In men with an unexplained retroperitoneal, pulmonary/mediastinal or mass, testis cancer should always be considered as a primary cause.

US scanning of the testis is the standard imaging modality, with a sensitivity of almost 100%. Difficulty can arise differentiating between orchitis and tumour. In addition, small intra-testicular lesions may produce considerable diagnostic uncertainty. Further imaging with contrast enhanced US or MRI can help clarify the diagnosis. MRI has a higher sensitively and specificity than US but in the main it is not necessary. PET scanning is not recommended for the initial staging of testicular cancer but it can be used for assessment of residual metastatic masses post chemotherapy [4].

Staging investigations include computed tomography (CT) of the thorax, abdomen and pelvis with IV and oral contrast. Cranial imaging should also be performed if there are neurological symptoms or if there is widespread metastatic disease with high marker levels at first presentation [4].

Where precise clinical diagnosis is impossible and a lesion is suspicious, biopsy or orchidectomy may be needed for definitive verification. In these circumstances, surgical exploration should *always* be through the groin: testis conservation should be attempted in the first instance where

possible. Percutaneous needle biopsy or testicular biopsy via the scrotum is only indicated in exceptional circumstances.

It is inevitable that following orchidectomy some lesions will ultimately prove to be benign: this should be explained to the patient pre-operatively.

Serum Tumour Markers

These include beta human chorionic gonadotrophin, (β-hCG), alpha- fetoprotein (AFP) and lactate dehydrogenase (LDH). AFP is raised in the presence of embryonal and/or yolk sac elements and has a half-life of 5–7 days after treatment. β-hCG is raised in the presence of syncytiotrophoblastic elements and has a half-life of 24–36 h. It is raised in all choriocarcinomas. Elevations of AFP are seen in 50–70% of NSGCTs. AFP is not elevated in pure seminomas. Seminoma with elevated AFP is treated as a NSGCT.

β-hCG is raised in 40–60% of men with NSGCTs and <30% of men with seminomas. LDH is a non-specific marker of tumour bulk but it is raised in 80% of patients with advanced disease [3]. Tumour markers are essential in the diagnosis and disease stratification for treatment in all patients with testicular cancer. New molecular markers are in development; there is evidence that micro-RNAs may be more accurate in detecting recurrent or residual disease. Further validation studies of these are required [3].

Primary Surgery

The standard treatment is radical inguinal orchidectomy. Prior to surgery each patient should be counselled regarding cryopreservation of semen and prosthesis insertion. Up to 50% of men will have evidence of impaired spermatogenesis and baseline sperm count and sperm banking is recommended. Unilateral surgery may not necessarily have an impact on fertility but with bilateral tumours, or where subsequent adjuvant chemotherapy ± surgery is required, fertility may be affected. Radical orchidectomy involves a groin approach, opening the inguinal canal surgically and detaching the spermatic cord at the level of the internal inguinal ring before delivering the testis from the scrotum and removing the testis and cord en-bloc (Fig. 38.1). If the patient wishes, a testicular prosthesis can be inserted at this time, although this should be avoided if the tumour is invading the scrotal wall or there is active infection. Debate about the suitability of testicular prosthesis insertion at the time of primary surgery has been resolved following a large UK study of testicular prosthetic implant at orchidectomy revealed an infection rate of only 0.4%. Synchronous prosthesis insertion can therefore be undertaken safely and should be offered at primary surgery [5].

Testis Preserving Surgery

This may be considered in specific circumstances, namely, when there is a high degree of confidence that a lesion is benign, when there are synchronous bilateral tumours, following development of a metachronous contralateral tumour, or in patients with a single testis and normal pre-operative testosterone levels. Organ sparing surgery can be performed when tumour volume is <30% of total testicular volume [3] although it may be possible to undertake local excision of larger tumours in the polar areas. Germ cell neoplasia *in situ* (GCNIS) is present in up to 80% of patients undergoing testis preservation. Sperm storage issues should be discussed prior to surgery and the patient should be counselled about the long-term risks of tumour recurrence, long term endocrine failure and the requirement for subsequent radiotherapy or completion orchidectomy if GCNIS is detected.

Contra-Lateral Testicular Biopsy & GCNIS

GCNIS is present in 4–8% of men presenting with testicular cancer: the risk of a contralateral metachronous tumour is approximately 2.5% [6]. When present there is a higher chance of progression to invasive disease as it is a malignant precursor

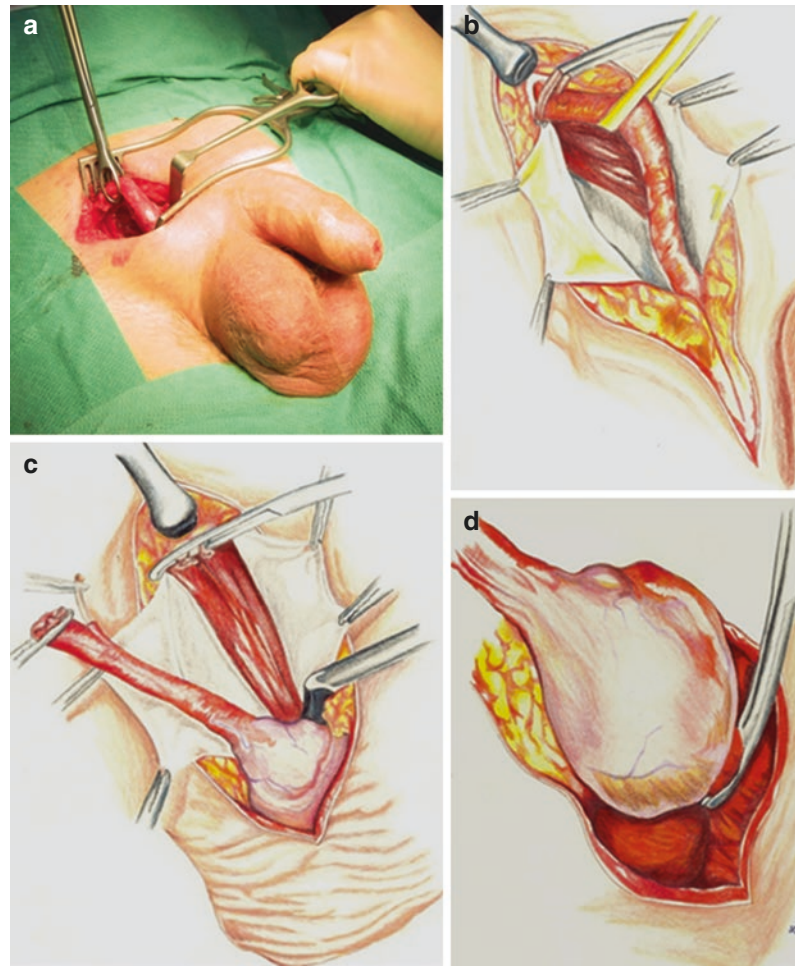


Fig. 38.1 Radical orchidectomy. Suspicious masses should be approached through the groin (**a**). The Inguinal canal is opened and the cord mobilised (**b**) before transection at the level of the internal ring (**c**). The testis is then delivered from the scrotum, dividing the gubernacular attachments (**d**)

lesion. GCNIS is now the WHO recommended term for all precursor lesions of invasive germ cell tumour [7]. This condition has previously been known either as carcinoma in situ or intratubular germ cell neoplasia unclassified (IGCNU). Treatment by low dose irradiation of the affected testis after preliminary storage of semen has been used previously but more recently, surveillance strategies using self-examination and interval US scanning have now been adopted almost universally. If low-dose radiotherapy has to be used, treatment comprises scrotal radiotherapy (16–20 Gy in fractions of 2 Gy [3]). If this treatment is used, the patient needs counselling that it will lead to irreversible infertility and that future Leydig cell insufficiency requiring testosterone substitution will occur in about 30% of patients.

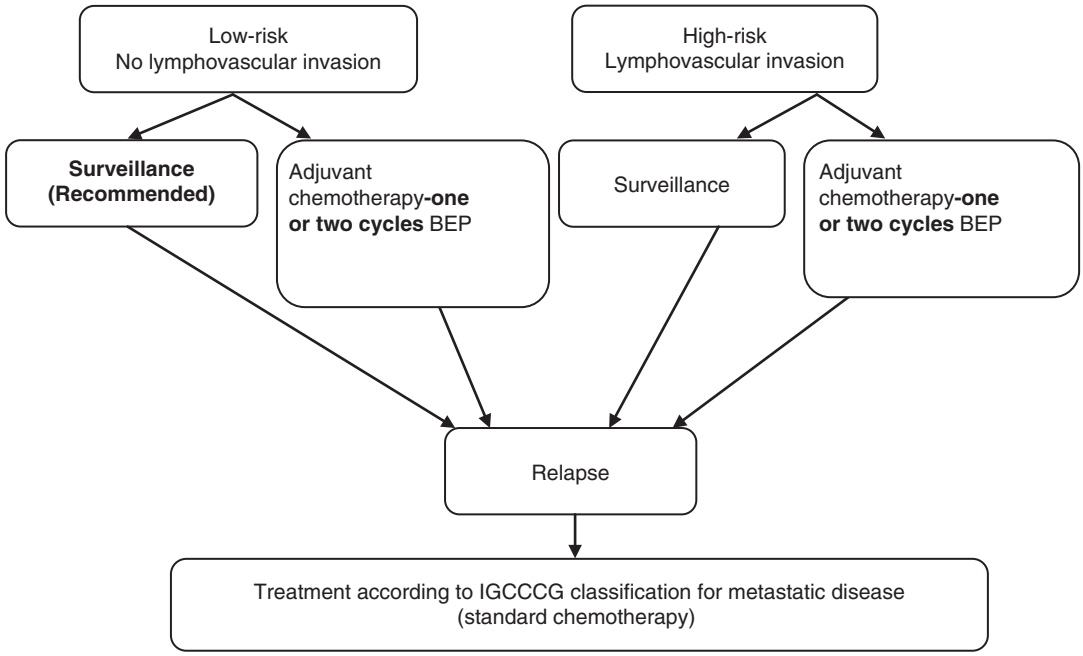
In the case of primary orchidectomy, there is uncertainty about routine synchronous contra-lateral testicular biopsy to identify GCNIS. Because of this, the policy of contra-lateral biopsy at the time of primary surgery varies. High-risk cases can be identified, limiting the need for contra-lateral sampling to those whose risk is greatest. Risk factors include cryptorchidism, younger age (<40 years), testicular microlithiasis, infertility and testicular atrophy (≤12 mL) [3, 4]. If biopsy is done, a two-site biopsy technique will improve detection by 18% compared to single-site biopsy methods [4].

Post Orchidectomy Management

This is predicated on the histological classification and clinical staging after primary orchidectomy. The disease stage is classified into two basic groups: clinical stage I (low and high risk)

or stage IIA/IIB/III. (Sub-categorised for the 3 International Germ Cell Collaborative Consensus Group (IGCCCG) types: see below [8]). These sub-types are based on the findings of cross-sectional imaging and post-orchidectomy tumour marker levels.

Defined treatment schedules are followed according to specific protocols (Figs. 38.2 and 38.3). Patients with clinical stage I (CS1) seminoma or NSGCT have traditionally been managed very differently. However in recent years there have been changes aligning the follow up of these two histological types. Surveillance is now the dominant option for both CS1 seminoma and NSGCT in the absence of high risk histological features. When intervention is chosen in CS1



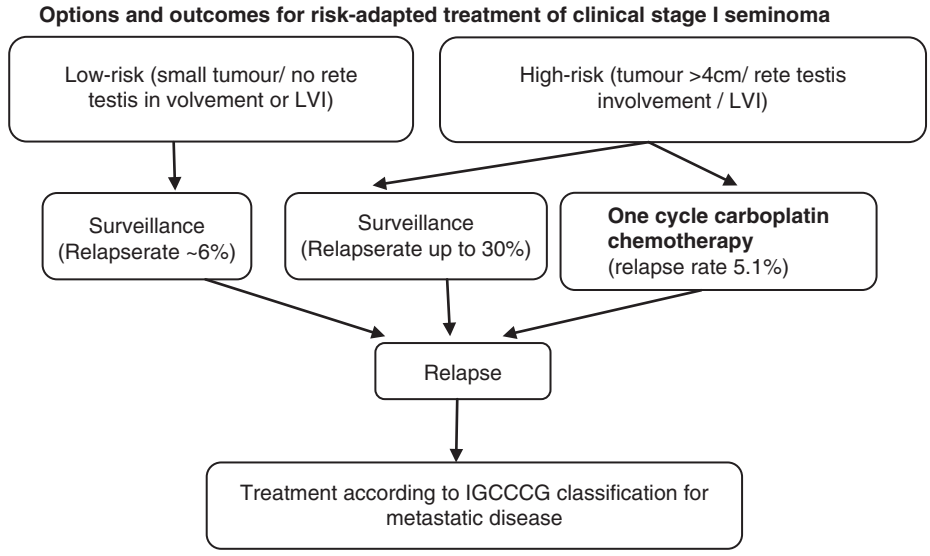


Fig. 38.2 Options and outcomes for risk-adapted treatment of clinical stage I NSGCT

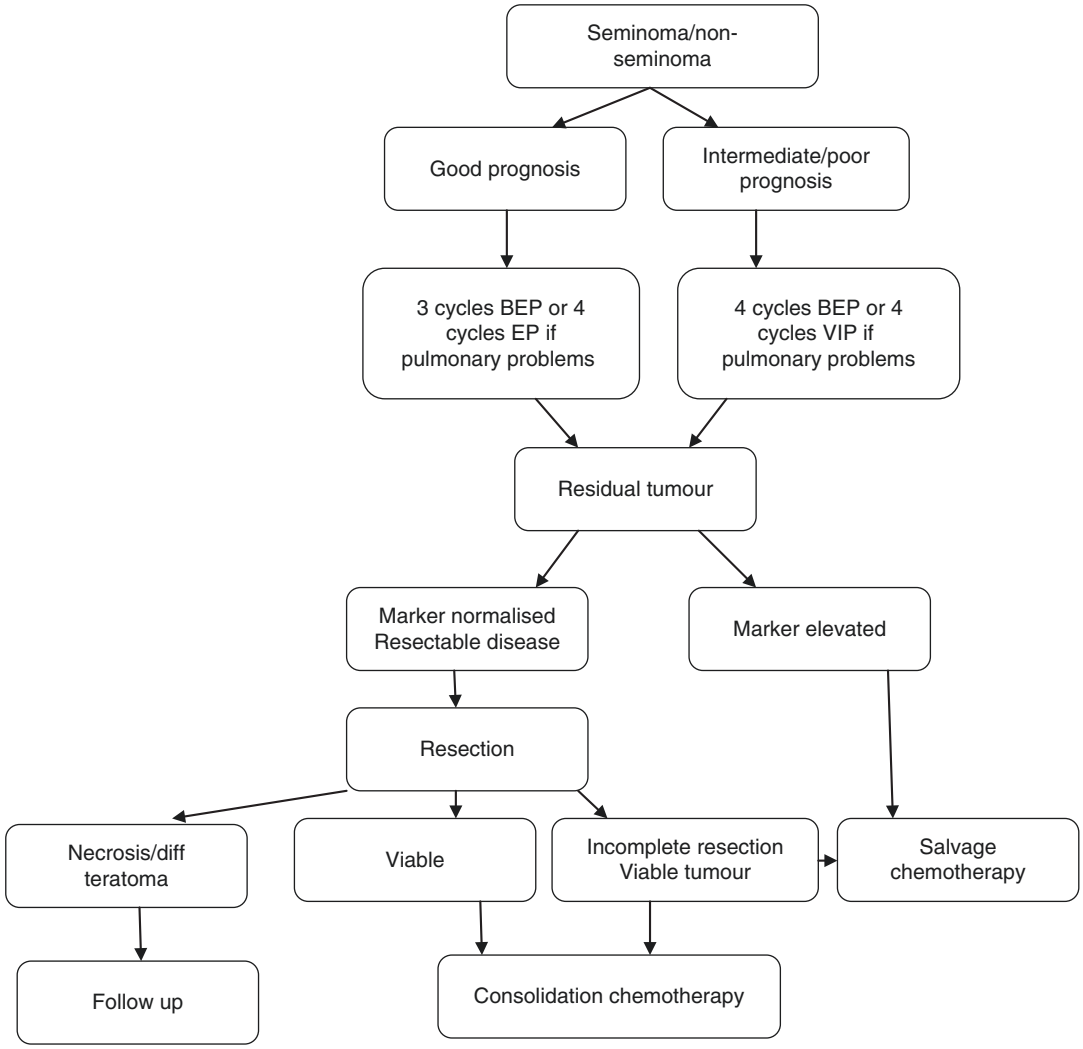


Fig. 38.3 Treatment options for advanced testis cancer

seminoma, single dose carboplatin is used according to a dose schedule known as area under the curve 7 (AUC7). Para-aortic radiotherapy is now only used in exceptional circumstances.

If the disease is Stage II or more, the standard treatment for most tumours utilises combination platinum based chemotherapy with bleomycin, etoposide and cisplatin (BEP) followed by surgical removal of post-chemotherapy residual masses when they are present and resectable. The combination of chemotherapy with post-chemo resection of surgical masses is undertaken for most NSGCT whilst chemotherapy is used alone for most seminomas, surgery being indicated only for highly selected cases.

Staging is by CT of the chest, abdomen and pelvis and assay of tumour markers (Box 38.2). The first order lymph nodes in the retroperitoneum are usually the initial site of metastatic spread although primary distal haematogenous dissemination can occur in up to 15% of men. CT scanning has its limitations: up to 30% of patients with negative CT scans will have microscopically positive lymph nodes detected subsequently at surgical staging. By contrast, up to 25% of patients may be radiologically over-staged, having abnormal nodes on CT staging which are subsequently shown to be negative following surgical exploration. MR imaging has been used in this scenario although it has not proved to be more

Box 38.2 Staging System

The two most commonly used staging systems worldwide are the Union for International Cancer Control (UICC) Eighth Edition (Europe) and the American Joint Committee on Cancer (AJCC) Eighth TNM Version.

The AJCC staging system subdivides seminomas into pT1a and 1b based on tumour size <3 cm or >3 cm. Rete testis invasion remains under T1 classification while hilar soft tissue and epididymal invasion have been reclassified as T2.This is considered to provide a better classification system.

Stage I encompassed all cases with no radiological evidence of disease outside the scrotum. Any patient with clinically evident macroscopic disease is classified as Stage II or greater. Clinical stage II is subclassified as follows:

Stage IA:	Primary tumour limited to the testis: No vascular/lymphatic invasion (pT1)
Stage IB:	Locally invasive tumour: No evidence of metastases (pT2, 3 or 4: N0M0S0)
Stage IC:	Marker elevation post orchidectomy (any pT: N0M0S+). This is seen in approximately 5% of patients after orchidectomy.

effective or reliable than CT scanning. PET scanning has significant problems with false negativity and therefore has no role in primary tumour staging. In the case of seminoma, PET does have role in assessing the post-chemotherapy residual retroperitoneal mass; a negative scan in this circumstance has a very strong association with post-chemotherapy fibrosis in residual masses. However, a positive scan does not indicate active disease: most post-chemotherapy PET positive seminoma masses contain only fibrous tissue and great care should be taken to avoid over-interpretation of the scan in this circumstance.

Management of Clinical Stage 1 Disease (CS1)

CSI Non-Seminomatous Germ Cell Tumour (NSGCT)

Risk Stratification

Approximately 30% of patients with CS1 NSGCT will have occult micrometastatic disease. A number of histopathological risk factors in the primary tumour predict for this in CS1, including lymphovascular invasion (LVI), the presence of embryonal carcinoma (undifferentiated cells) and the absence of yolk sac elements. The presence of lymphovascular invasion (LVI) is associated with a 44% relapse rate compared to 14% without LVI [9]. LVI is an important validated risk factor and if present with embryonal carcinoma and rete testis invasion is associated with a relapse risk of 50% compared to a relapse rate of 12% when these features are absent [10].

Active treatment schedules for CS1 NSGCT involve the use of low dose adjuvant chemotherapy with one or two cycles of BEP. However, surveillance with serial imaging and tumour marker assay is used more commonly. Retroperitoneal Lymph Node Dissection (RPLND) has largely been discontinued in this setting, although some centres in the USA still use this approach. It is rarely used elsewhere, apart from in patients with a contraindication to adjuvant chemotherapy or where there are patient compliance issues.

Surveillance in Clinical Stage 1 NSGCT

Using stratification profiles based on histology and markers, it is possible to predict with accuracy of approximately 80% that low risk cases will not relapse and furthermore, if they do, they can then undergo systemic treatment with chemotherapy with excellent long-term survival. Patients relapsing on surveillance are successfully treated with standard chemotherapy and have long-term cure rates of 98%, which is the

same as that for primary surgery. In addition, >95% of patients who relapse will do so within the first 2 years of diagnosis of their original cancer [9]. Prolonged and intensive follow up beyond 5 years is therefore not required in most cases.

Adjuvant Treatment for High Risk

Surveillance is the standard of care in most high volume centres for low and high-risk CS1 disease. More recently some groups have advocated adjuvant chemotherapy using one or 2 cycles of BEP when high risk features are present. Concerns about this approach are that 50% of cases who would not have relapsed are exposed to the significant long-term effects of platinum based chemotherapy. Long term studies have also shown that the survival of the 50% of high-risk patients who do relapse and require full dose systemic treatment have an excellent long-term survival [10]. However, there is debate and variation in practice amongst clinicians in this area.

In the presence of risk factors, 50% of patients with CS1 NSGCTs managed by surveillance will relapse. One cycle of adjuvant BEP chemotherapy will reduce this risk of relapse by over 90% whilst a two course regimen is even more effective. In 2015 the SWENOTECA group demonstrated that adjuvant treatment can safely be reduced to one cycle of BEP. A reduction in the relapse rate of >90% was seen with the benefit of reduced toxicity and decreased need for salvage therapy thus ensuring relapsing patients avoid the potential toxicity associated with salvage chemotherapy involving 3–4 cycles of BEP [11] However, this adjuvant intervention with chemotherapy is associated with measurable short-term toxicity and in the long term, BEP is known to have long-term adverse consequences. Whilst there seems to be benefit for those who will definitely relapse, there is clear and potentially avoidable toxicity for those who would not.

CS1 Seminoma

Risk Stratification

Compared to NSCGTs, seminomas have a more favourable prognosis: they remain localised for longer and approximately 75–80% have CS1 disease at initial diagnosis. Seminoma tends to metastasise to the retroperitoneal lymph nodes initially with a lower rate of haematogenous metastasis than NSGCTs. They are sensitive to radiotherapy and platinum-based chemotherapy. Adjuvant radiotherapy to the retroperitoneum is no longer used in CS1 due to the long-term risks associated with treatment. Single cycle AUC7 carboplatin chemotherapy is now the main intervention if surveillance is not adopted. This has less neurotoxicity, ototoxicity and nephrotoxicity compared to cisplatin. Overall only about 15% of patients with stage I will relapse without adjuvant therapy, although the relapse rate is higher in men with high risk features. Most recurrences occur in the retroperitoneal lymph nodes and are treated effectively with BEP.

Rationale for Surveillance in Clinical Stage 1 Seminoma

Since 2007, strategies have emerged using a similar approach to those adopted as standard practice in CS1 NSGCT. Approximately 16% of CS1 seminoma patients are at risk for recurrent disease: the median time to relapse is 12–15 months with 96% of these occurring in the retroperitoneal or inguinal regions.

Multivariate analyses of several retrospective observational studies have evaluated and concluded that risk factors related to increased rates of disease recurrence include:

- Tumour size >4 cm.
- Stromal invasion of the rete testis.
- Lymphovascular Invasion (LVI).

Patients with these adverse factors have a higher risk of disease relapse. If both risk factors are present, patients undergoing surveillance have a 32% risk of relapse, decreasing to 16% if one risk factor is present and 12% if there are no risk factors [12].Prospective studies using risk factors have now been performed: examples include the data from the Spanish Testicular Cancer Group. One-third of the patients in this group's study had neither of the

above risk factors: they were followed by surveillance after orchiectomy. Only 6% of these patients relapsed after a median follow-up of 3 years. The remaining patients with one or both risk factors were treated with adjuvant carboplatin, with a relapse rate of 3.3% [13]. Studies of this type represent a significant way forward in targeting post-orchidectomy treatment for patients with CS1 seminoma who have a high risk of occult metastatic disease at presentation.

Strategies to reduce immediate adjuvant treatment in as many patients as possible will confine treatment and treatment related risk to those who need intervention most. This approach has been used to show that if the risk of relapse in patients managed with surveillance is under 10%, the number of follow-up investigations can be reduced**.** It is, however notable that in the early surveillance series, patients needed up to 20 CT scans as part of their surveillance protocol as relapses occurred after more than 5 years of follow-up. MR based surveillance schedules are now replacing CT to reduce the high level of radiation associated with this approach.

Adjuvant Low Dose Chemotherapy: Studies using single agent chemotherapy with carboplatin as an alternative to radiotherapy in CS1 Seminoma have now shown that this therapeutic strategy is very effective. Pilot studies reported the relapse rate for patients treated with single dose carboplatin using an AUC7 regimen was 4% (median follow-up of 51 months) and that 99% of patients remained disease free. These results were consolidated in the MRC TE19 study of carboplatin monotherapy vs. adjuvant radiotherapy in CS1 seminoma. Results showed no statistical difference in recurrence rates with either approach. After a mean follow-up of >4 years the relapse rate with a single cycle of carboplatin at 3 years was 5.2% [14]. For this reason, single cycle carboplatin is the first line intervention treatment for CS1 seminoma with high risk characteristics. It is however notable that a number of relapses occurred after more than 2 years follow up and further long term analysis of data is required to assess the true long-term outcome. Furthermore, AUC7 carboplatin treatment has not been available for sufficiently long to determine its true long-term toxicity and its other potential effect, the acquisition of drug resistance following recurrences after AUC7 therapy. Longer term data relating to the use of this regimen is now becoming available and will help guide policy in this area. Data suggests that there is a higher relapse rate in those patients with higher risk categories. The optimal treatment strategy for this patient group does need further study.

Management of Metastatic Testis Cancer: Clinical Stage II and III

Following initial orchidectomy, tumour markers should be monitored. These should normalise at a rate reflecting the half-life of AFP, hCG and LDH as discussed previously.

Elevated or rising tumour markers indicate metastatic disease and this must be investigated with cross-sectional imaging to establish the location and extent of disease. The presence of a contralateral testicular tumour must also be considered as a cause.

Primary Combination Chemotherapy: As with CS1 tumours, the management of advanced disease is conducted according to risk stratified protocols. These are based on the collective outcome of >5000 patients with advanced disease, analysed by the International Germ Cell Consensus Collaborators Group and published in 1997 [8]. These outcomes have been made possible since the introduction of cisplatin based chemotherapy regimens. Good prognosis patients have the potential for excellent outcome, with a cure rate of >90% and even intermediate risk patients have a long term survival >75%. However, patients with high risk characteristics have a much worse prognosis, with <50% surviving 5 years.

Standard treatment for metastatic seminoma and NSGCT is with combination chemotherapy (Fig. 38.3) although there is still a role for radiotherapy in selected seminoma cases up to clinical stage IIA (see below). For these patients treatment involves radiation to the para-aortic

region and ipsilateral iliac nodes, usually at a dose of 30Gy in 2Gy fractions [3]. However ongoing concern remains regarding the long-term morbidity associated with this treatment including secondary malignancies, late cardiovascular events and retroperitoneal fibrosis. Combination chemotherapy is also an option for this cohort with three cycles of BEP or four cycles of EP in older patients or other with pulmonary risk factors. Patients with stage IIb disease should be treated with either 3 cycles of BEP or four cycles of EP as shown by a meta-analysis looking at the efficacy and toxicity of both treatments. Radiotherapy was associated with a slightly improved outcome for stage IIA patients with no difference observed for stage IIb patients [4]. Good prognosis seminoma is treated with three cycles or BEP or four cycles of EP. Four cycles of Vinblastine, Ifosfamide and Platinum (VIP) can be used for intermediate risk patients if there is a contraindication to bleomycin.

For GCT patients with low volume stage IIA disease it is important that metastasis is confirmed by repeat CT imaging 8–12 weeks following orchidectomy if the tumour markers are low. Reactive para-aortic lymphadenopathy after orchidectomy is relatively common and can lead to an incorrect attribution of "metastatic disease" in some circumstances. Patients with CSIIa NSGCT are treated with combination chemotherapy with cure rates of approximately 98%. Primary BEP/EP therapy is recommended for patients with CSIIb disease and normal tumour markers.

Good prognosis	BEP × 3 cycles or EP × 4 cycles (if contraindications to Bleomycin—advanced age, impaired renal function, significant lung disease or smoking history)
Intermediate prognosis	BEP × 4 cycles or VIP (if at risk of pulmonary toxicity)
Poor prognosis	BEP × 4 cycles or VIP (if at risk of pulmonary toxicity)

Assessment and treatment of all GCT's following primary orchidectomy should be in high volume cancer centres with multi-disciplinary medical, surgical, diagnostic and nursing oncological teams specialising in the management of testis cancer. There is clear evidence that such centres have better outcomes than those dealing with low numbers of patients. It is also important to emphasise that patients with high volume disease should be referred to a specialist centre immediately for evaluation and treatment without necessarily having an orchidectomy first.

There is variation in the chemotherapy dosage scheduling but most patients are treated with drugs given by centrally placed parenteral IV lines with added hydration, osmotic diuretics, anti-emetics and antibiotics (usually for the first cycle). Growth factor support is not usually necessary although it is used in some circumstances. Different combinations have been tried for good prognosis disease (e.g. the GETUG trial of 3 vs. 4 cycles of BEP) but to date, none of these, including studies of Taxanes, have shown superiority in outcome without adding significantly to the toxicity profile. In patients where there is concern about pulmonary function, bleomycin is used with caution or is omitted because of its known toxicity in inducing pulmonary fibrosis.

In intermediate and high risk tumours attempts have been made to improve outcome in the primary setting by using different schedules and drug combinations and by increasing the dose of the drugs in "High Dose" combinations. The augmented benefit of such toxic treatment regimens remains to be proven in adequately powered studies.

Late Toxicity: Combination chemotherapy has resulted in dramatic improvements in cure in testis cancer but there are long term toxicities related to treatment. Whilst these are relatively low in frequency they can be significant and the long-term cardiovascular effects of platinum based chemotherapy are only now beginning to emerge. They include a doubling of the rate of long term risks of treatment related malignancy, a doubling of the long term cardiovascular risk and additional effects on long term testicular endocrine, reproductive and psychological function. These must be borne in mind when counselling patients and when planning their long term survivorship.

Post Chemotherapy Resection of Residual Masses: The rationale for surgical removal of

post-chemotherapy residual masses is well established and a critical component of patient treatment. Most resections are required to remove retroperitoneal lymph nodes in a process known as retro-peritoneal lymph node dissection (PC-RPLND). Lymph nodes which are persistently enlarged (>1 cm) following primary chemotherapy are removed routinely. This is undertaken because of the risk of persistent active disease, presence of mature teratoma (associated with development of the "Growing Teratoma Syndrome") and the potential for teratomatous or somatic de-differentiation, which can occur in >1 in 5 of residual masses if left unresected.

PC-RPLND is not routinely indicated in seminoma except where there is a growing RP mass. This is because the incidence of fibrosis is very high, the technical challenges are greater and the risk of complications arising during and after surgery are much higher. Clearly, if there is strong evidence for active disease then resection is definitely indicated. However, where there is doubt, an expectant policy should be followed. PET scanning is only really helpful in this scenario when it is negative, in which case there is a very high chance that any detectable residual mass contains only fibrous tissue.

Resection is usually indicated in NSGCT for residual masses of 1 cm or more. Pathological analysis shows that the residual masses contain mature teratoma in 50%, necrotic fibrotic tissue in 40% and vital cancer in about 10% [3]. Resections in this setting are usually curative if all the residual disease is removed and the overall outcome is better if resection is undertaken early rather than when residual lesions show signs of progression. Imaging is usually undertaken 6–8 weeks after the last chemotherapy cycle and surgery is not usually undertaken if the tumour markers have not normalised. In this circumstance, further chemotherapy is given before assessment of response and surgery is then considered thereafter.

The surgery is technically challenging and should not be undertaken outside specialist centres. It involves full mobilisation of the great vessels using the "split and roll" technique (Fig. 38.3) and en-bloc resection of concomitant, structures (kidney/bowel/vena caval resection/aortic replacement) is required in some circumstances. There is debate as to whether bilateral or template based PC-RPLND should be used. Bilateral procedures induce ejaculatory failure but there is a small risk of leaving vital disease using template methods in all cases. Large scale data has now shown that template techniques are quite safe when used in selected cases (masses confined to the ipsilateral landing sites of up to 5cms in diameter). Following resection the long term outcome is good if all disease can be removed but if there is residual vital disease left after surgery, the long term outcome is poor. The natural history relating to retained/residual low volume mature teratoma is less clear (Fig. 38.4).

Salvage Strategies: Salvage treatment is used for early (<2 years) or late (>2 years) relapse. Early relapse is usually due to platinum resistance, which may be complete at the outset or apparent after an initial response to primary treatment. In establishing a diagnosis of "relapse" it is vital to be aware of the pitfalls which can mimic disease persistence or recurrence. These include the growing teratoma syndrome, whereby residual masses increase in size after chemotherapy because of cystic change and transformation from vital cancer to mature teratoma, false positive marker relapse, new pulmonary nodules arising secondary to bleomycin and elevations in tumour markers from a metachronous new primary testicular cancer. Approaches to treatment involve re-challenge with cisplatin based chemotherapy, acceleration of cisplatin dose, use of newer drugs including combinations of Ifosfamide, Paclitaxel, Gemcitabine and Oxaliplatin, high dose chemotherapy and "Desperation" surgery. There is evidence that high dose regimens may confer benefit of around 10% and that sequential high dose chemotherapy (HDC) may be advantageous. However, these are toxic regimens which carry a significant mortality of themselves. Salvage "desperation" surgery is indicated but only in the very limited circumstances where there is a feasible chance of resecting all residual tumour tissue. Patients do not benefit from this type of extensive surgery if all disease cannot be removed [15].

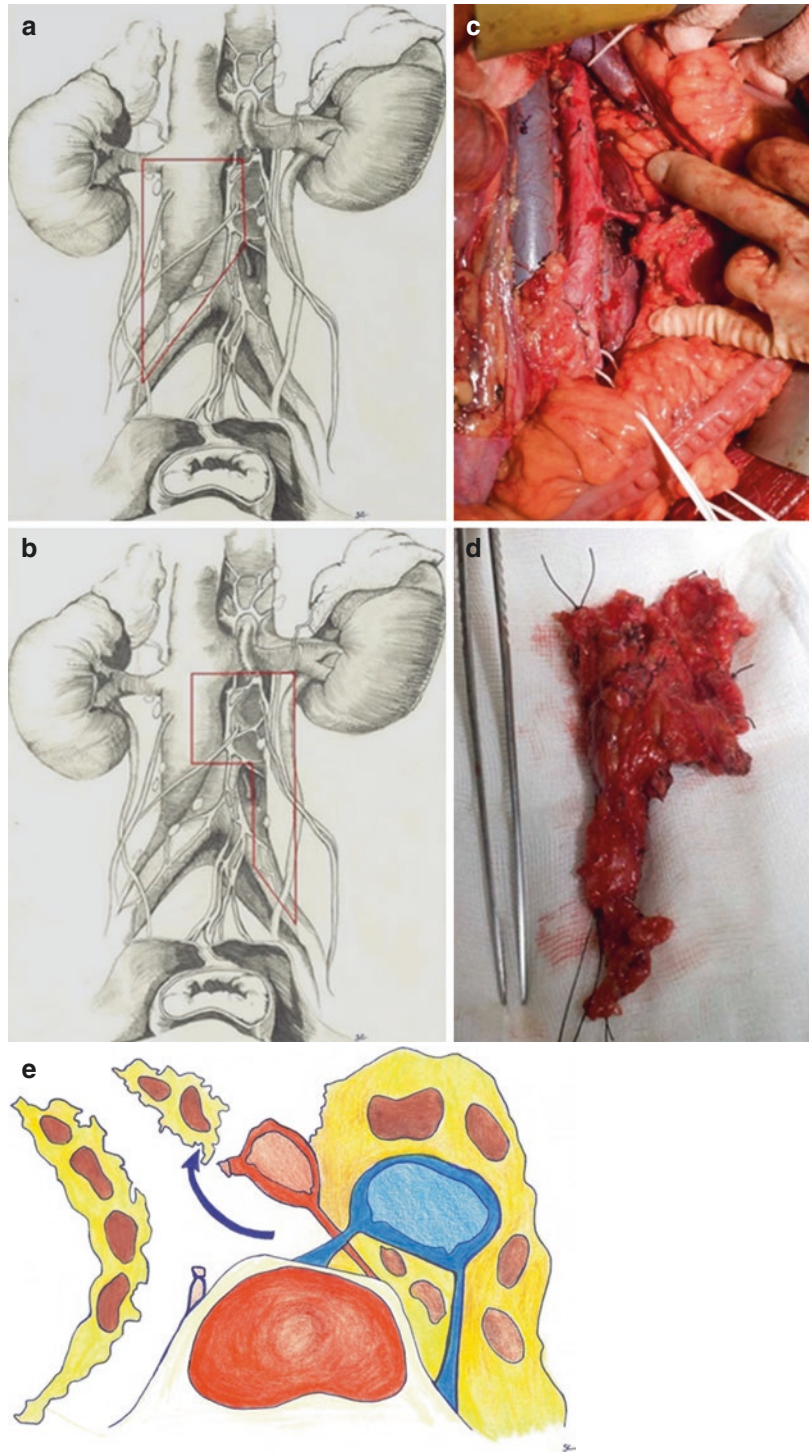


Fig. 38.4 Template techniques for post chemotherapy RPLND: The "Split and Roll" Method. (**a**, **b**) Right and Left Templates for RPLND: these remove tissue from the primary nodal landing sites including the retroperitoneum, with "dog-leg" extensions to the ipsilateral common iliac region, sparing the contralateral area. This preserves ejaculatory nerve function @85% of cases. (**c**) shows the dissection field and (**d**) the tissue removed (**d**) following completion of a left template dissection. (**e**) The "Split and Roll" Technique: lumbar branches of the aorta and vena cava are ligated and divided, enabling rolling and lifting of the great vessels off the anterior spinous ligament. This enables removal of the lymphatic tissue around and behind the aorta and IVC. In many circumstances it is possible to clear this area without dividing all the lumbar branches of the aorta, thereby preserving the integrity of the lumbar blood supply

Late relapse (defined as relapse following complete remission with chemotherapy occurring 2 years or more after treatment) occurs in approximately 3% of all cases. This is often associated with "somatic transformation". This is the de-differentiation of the cancer cell type to

a specific sub-type, most commonly adenocarcinoma (Fig. 38.5) and sarcoma, less commonly, neuro-endocrine differentiation (Fig. 38.6). Treatment of this tumour type is with surgery to remove the mass en-bloc with affected structures if this is possible. If it is, cure is possible in up to 50% but neuroendocrine type cases carry a much poorer prognosis. Treatment with chemo or radiotherapy is not effective in this type of relapse: tissue sampling with CT guided biopsy may be very helpful in establishing the definitive diagnosis and planning treatment.

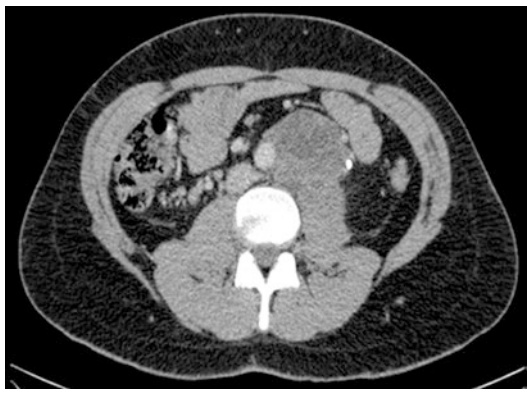


Fig. 38.5 Late relapse following remission after chemotherapy. 48 Year Old Male 14 Years on from successful remission following BEP Chemotherapy for metastatic NSGCT. Acute presentation with abdominal pain: CT revealed a large left sides RP mass confirmed as adenocarcinoma by CT guided biopsy. Surgical resection en bloc with left kidney and aorta with aortic replacement. Patient disease free 6 years post-resection

Conclusion

Testis cancer is a rare in general but it is the most common cancer in young men. With early diagnosis and appropriate treatment in expert centres the long term results are excellent in good prognosis cases. In intermediate prognosis disease the majority of patients are cured long term but in poor prognosis testis cancer, mortality is still significant and new approaches are required. By comparison with the outcomes from recent history in this disease, the advances in the last 40 years of testis cancer treatment are a testimony to the benefits of collaborative translational science, clinical trial planning and risk adapted therapeutic approaches.

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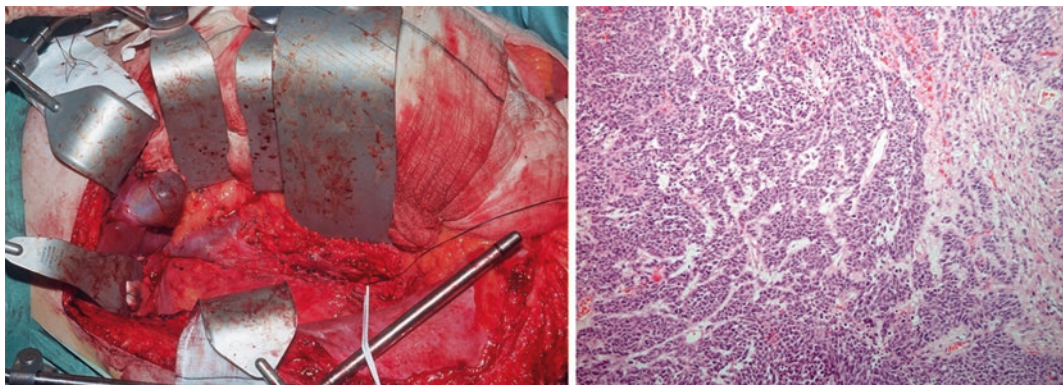

Fig. 38.6 Late relapse with neuroendocrine de-differentiation. Late retroperitoneal relapse following BEP therapy for NSGCT. Resection en-bloc with the infra-hilar IVC. Histology confirmed neuro-endocrine de-differentiation

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