Principles of Bladder Cancer Surgery

2

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Introduction

Despite contemporary refinements in the diagnosis and management of invasive bladder cancer, it remains a potentially lethal disease that will account for nearly 15,000 deaths in the USA in 2012 alone [1]. Radical cystectomy is the gold-standard treatment for most patients with muscle invasive bladder cancer and is also appropriate for those with high-risk noninvasive disease that have failed conservative treatments. When it was first introduced for treatment of bladder cancer, cystectomy was associated with significant morbidity and mortality [2]. However, with advances over the past 60 years in patient selection, perioperative management and surgical technique, it currently has relatively low perioperative mortality rate and an acceptable rate of complications [3].

A successful outcome with radical cystectomy is not only related to surgical technique and safe extirpation of the bladder but also to factors such as patient selection, coordinated perioperative care, and use of adjunctive treatments. In this chapter, we will outline the essential principles of radical cystectomy for bladder cancer, which are equally as important for robot-assisted radical cystectomy (RARC) as for open radical cystectomy (ORC).

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Surgical Indications

Radical cystectomy for bladder cancer is indicated in any fit patient with clinically organ-confined muscle-invasive disease and no evidence of metastasis. Patients with advanced disease may also be offered radical cystectomy, however, the goal of surgery is typically local disease control and symptom palliation, as the prospect of cure is much less likely [4]. Furthermore, patients with high-risk noninvasive disease that have failed intravesical therapy or have adverse pathologic features, such as variant histology or lymphovascular invasion, may be offered radical cystectomy. In fact, up to one-third of patients with clinical stage ≤ T1 are found to have muscle-invasive tumors at cystectomy and 15 % may have nodal involvement, prompting some to argue for "timely" cystectomy in select high-risk patients [5–7].

Patient Selection

Deciding which patients are candidates for radical cystectomy is of paramount importance given the potential morbidity and mortality of surgery. The first aspect of patient selection is proper disease *staging*. This includes physical exam, a thorough transurethral resection (TUR), pathologic analysis of the tumor biopsies, and cross-sectional imaging. Despite this evaluation, there is still a significant risk of clinical under-staging. A repeat TUR is generally recommended for any high-grade

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T1 tumor given the substantial risk of residual disease and tumor upstaging, particularly in patients without muscle in the original TUR specimen [5, 8–10]. In men, biopsies of the prostatic urethra should be obtained, especially if there is consideration for orthotopic neobladder (ONB). Although computed tomography (CT) imaging has limited sensitivity to detect locally advanced disease, it is important to identify features of aggressive disease, such as hydronephrosis [11]. While there is some evidence that magnetic resonance imaging (MRI) is useful for clinical staging [12], we do not routinely order MRI or positron emission tomography (PET) in this setting.

Once patients are properly staged and deemed surgical candidates, they must undergo a *risk assessment* to identify and manage comorbidities and determine if the risks of surgery are less than that of untreated bladder cancer. Many patients presenting for surgery are elderly and have significant medical comorbidities, including pulmonary and cardiovascular disease, which increase their operative risk. Cardiologists consider radical cystectomy an intermediate risk procedure, as it is associated with a 1–5 % risk of perioperative cardiac events [13]. According to the current cardiac risk assessment guidelines, patients with preexisting cardiac disease, cardiac risk factors, or a poor functional capacity generally require preoperative cardiac risk evaluation in order to optimize cardiac function and assess the need for revascularization [14]. For patients with cardiac stents, the risk of intraoperative bleeding is generally considered higher than the risk of stent thrombosis, and discontinuation of antiplatelet therapy is preferred. Surgery is delayed a minimum of 30 days and 6 months for patients who have bare metal stents and drug eluding stents, respectively [15, 16]. If the risk of discontinuing antiplatelet therapy is acceptably low, aspirin and thienopyridine agents are discontinued 7 days preoperatively, although some argue for perioperative continuation of low-dose aspirin in certain high-risk patients [15]. Patients on anticoagulant therapy with a history of vascular thrombosis or atrial fibrillation also require preoperative evaluation to determine their risk of recurrent thrombosis with the discontinuation of anticoagulation. For patients in whom anticoagulation may be safely discontinued, it is usually held 5–7 days preoperatively, however, certain patients may require heparin or low-molecular weight heparin bridging [15, 17]. The final preoperative dose of intravenous heparin and subcutaneous low-molecular weight heparin is approximately 4–6 h and 24 h preoperatively, respectively.

Poor nutritional status, a prevalent condition among bladder cancer patients, is associated with increased perioperative morbidity and mortality [18, 19]. Gregg et al. determined that nutritional deficiency in cystectomy patients was strongly associated with 90-day mortality [20]. Malnutrition may be related to a variety of factors including paraneoplastic tumor effects or poor oral intake due to disease symptomatology or patient anxiety. In the perioperative setting, poor nutrition can impair immune status and decrease the capability for tissue repair. Therefore, preoperative enteral nutritional supplementation and the selective use of perioperative total parenteral nutrition are strategies to improve nutritional status in malnourished patients. However, the benefit from such measures has yet to be demonstrated [21].

Obesity is another nutritional factor that can increase perioperative complications. In addition to poor wound healing and increased risks of wound infections and hernias [22–24], obesity is known to be associated with higher intraoperative blood loss and postoperative complications after cystectomy [25, 26]. Obesity can also produce challenges for anesthesiologists, such as difficulty intubating, ventilating, and positioning. While it is often impractical to recommend preoperative weight loss, knowledge of these risks is important for patient counseling.

Patient age may also factor into the decision to undergo cystectomy, yet it is clear that advanced age alone should not be an independent exclusion criteria. Although certain characteristics of elderly patients are associated with increased 90-day mortality [27], certain elderly patients, even some with significant medical comorbidities [28–30], do benefit from radical cystectomy. Elderly patients can tolerate the procedure and have complication rates similar to younger patients [31].

Although indications for RARC are similar to ORC, the choice of approach should be based on a combination of patient characteristics, shared patient and physician preference and physician experience. A robotic approach should only be considered if it can safely provide optimal oncologic control. Our preference has been to selectively offer RARC to healthier and thinner patients that have had less pelvic and/or intra-abdominal surgery and less bulky disease, especially early in our experience. Understandably, this has also been the trend at other institutions [32–34]. However, with continued experience and increased surgeon comfort, the types of patients eligible for RARC will continue to expand.

One of the final, and arguably most important, aspects of patient selection is establishing *realistic expectations*. While the majority of patients do not have the luxury to forego cystectomy, it is important that they understand the ways in which it will alter their functionality, impact their quality of life, and the complications they are at risk for. Many patients will be significantly debilitated, weakened, and experience substantial weight loss postoperatively. An extensive body of literature exists regarding the measurement of health-related quality of life in cystectomy patients, which, in large part, measures the impact of the urinary diversion. If a patient has multiple options for urinary diversion, a conversation should occur regarding the relative benefits and drawbacks for each type of diversion. Although each diversion is associated with a unique spectrum of risks and benefits, the relative impact of diversion type on overall health-related quality of life may be modest [35]. Using disease-specific instruments, such as the FACT-VCI [36], health-related quality of life in cystectomy patients can be assessed and used during patient counseling.

Preoperative Planning

Given the aggressive nature of high-risk bladder cancer, it is important to recommend a *timely cystectomy* to all surgical candidates. A delay of greater than 90 days from diagnosis of muscle-invasive disease to cystectomy is associated with higher pathologic tumor stage and worse overall and disease-specific survival [37, 38]. Thus, all preoperative planning and coordination of care should begin promptly upon diagnosis so as not to unnecessarily delay cystectomy.

In preparation for surgery, all patients visit the enterostomal nurse for *ostomy site evaluation* [39]. The nurse examines the patient in the supine, seated and standing positions, and identifies the preferred site in the right lower quadrant for an ileal conduit. Patients who have chosen an ONB also have an ostomy site marked, given the small risk of being unable to safely form a neobladder, and a colostomy site can be marked for patients that require a total pelvic exenteration. We also recommend all smokers *cease smoking*, as this has been shown to decrease several perioperative complications including respiratory complications and wound infections [40–42].

The day prior to surgery we start patients on a clear liquid diet and administer a *mechanical bowel preparation* with an oral laxative, such as magnesium citrate or GoLYTELY™. This is intended to reduce fecal load and enhance intraoperative bowel retraction. There is no single mechanical bowel preparation that has demonstrated superiority over another, however, oral antibiotics are no longer administered. Because a bowel preparation can cause dehydration, especially in the elderly, patients must undergo aggressive perioperative hydration. While the utility of a mechanical bowel preparation has been disputed and there is insufficient evidence to support its routine use [43], it is still practiced at our institution, especially in patients with planned colon reconstructive procedures.

It is important to *communicate with the anesthesia team* preoperatively and for the anesthesiologists to assess perioperative anesthesia risk [44]. All cystectomy patients must have their blood typed and screened and the anesthesia team must be made aware of the risks of blood loss. They also must be made aware of the inability to monitor the patient's vital status using urine output for the majority of the case, as the ureters will be clipped. As such, all patients will require two large-bore intravenous lines and, in some cases, an arterial or central line depending on anesthesia preference.

Patients must be positioned with all pressure points well padded and the surgical and anesthesia teams must understand the risks of nerve and limb injury due to improper patient positioning.

To *prevent surgical site infections* all patients are shaved with electrical clippers, receive intravenous antibiotic prophylaxis, and are cleansed with a chlorhexidine-based skin preparation [45, 46]. Because many patients have risk factors for deep vein thrombosis (older age, cigarette smoking, obesity, malignancy, pelvic surgery), and thromboembolic events are a significant source of morbidity and mortality among cystectomy patients, deep vein thrombosis *(DVT) prophylaxis* is critical and may significantly reduce the likelihood of a DVT and fatal pulmonary embolus [47–49]. We use sequential compression devices on all patients, although some higher risk patients may require chemothromboprophylaxis with subcutaneous heparin or low-molecular weight heparin [49]. In fact, continuing DVT prophylaxis after hospital discharge may help protect against the substantial rate of out-of-hospital thromboembolic events [50, 51].

Oncologic Principles

The improved outcomes of radical cystectomy over the past half-decade are largely thought to be secondary to improvements in surgical and anesthetic care. Meticulous surgical technique not only limits potential morbidity but also contributes to improved oncologic outcomes. While RARC may further temper the morbidity of cystectomy, it can only be feasible if it preserves the same oncologic efficacy as ORC. In order to achieve both, surgeons must adhere to strict surgical principles.

Basic principles of intra-abdominal cancer surgery include exploration of the peritoneal cavity for unrecognized metastasis, early vasculature ligation, minimization of tumor spillage, and a complete tumor resection with en bloc specimen removal. Given the risk of peritoneal seeding of bladder cancer, *minimization of tumor spillage* is very important. Occlusion of the ureteral stump with a clip is performed, due to the small risk of vesicoureteral reflux, and careful control of the transected urethra is strongly recommended. In RARC, the specimen is contained in an Endocatch™ bag (Covidien Surgical, Mansfield, MA) to avoid intraperitoneal spillage and port site metastasis [52]. In addition, one must carefully handle any grossly enlarged lymph nodes to avoid damage and resultant spillage of metastatic tumor cells.

To achieve a *complete tumor resection* and negative surgical margins, one must pay careful attention to tissue planes and extend the dissection widely if there is any concern for extravesical extension. Intraoperative frozen section analysis of the distal urethral margin is standard practice at our institution, regardless of diversion type. In patients who desire an ONB, it is essential to rule out disease in the proximal urethra, as this is generally a contraindication to ONB. Alternatively, involvement of the urethra may prompt a concurrent urethrectomy for those receiving a non-orthotopic diversion.

More controversy exists regarding the utility of intraoperative *ureteral frozen section analysis*. Advocates argue that by obtaining a negative distal frozen section there may be decreased anastomotic and upper tract recurrences and that patients with positive margins can be followed more closely [53, 54]. Those against contend that the result does little to change the risk of local recurrence and distant disease failure [54–56]. Furthermore, a negative ureteral frozen section is not associated with a clear survival benefit, does not exclude proximal carcinoma in situ (CIS) and conversion from a positive to a negative margin can be difficult, and does not eliminate the risk of local recurrence [56–59]. Upper tract recurrence after radical cystectomy is a rare event and, excluding obvious ureteral involvement, is more common with aggressive tumors and the presence of CIS [56, 59, 60]. Patients with these findings should be counseled preoperatively that they are at higher risk for upper tract recurrence and will require close postoperative surveillance, however, we do not routinely obtain a ureteral frozen section analysis.

Pelvic Lymphadenectomy

Pelvic lymphadenectomy is a critical element of a radical cystectomy. Approximately 20–25 % of patients undergoing cystectomy are found to have lymph node invasion at the time of pathologic analysis [61]. While patients with extravesical disease have a higher likelihood of positive lymph nodes (42–75 %), a significant percentage of patients with organ-confined tumors also have node positive disease (6–22 %), suggesting lymphadenectomy is indicated regardless of clinical tumor stage [62–66]. Lymphadenectomy is important for accurate disease staging, improves local control, and identifies those patients that might benefit from adjuvant therapy. Furthermore, approximately 30 % of patients with pathologically positive lymph nodes demonstrate long-term, durable responses after cystectomy, suggesting lymphadenectomy may be therapeutic for some patients [63, 67, 68].

The boundaries of a standard pelvic lymphadenectomy are the genitofemoral nerve laterally, wall of the detrusor medially, node of Cloquet distally, bifurcation of the common iliac artery proximally, and the internal iliac vessels posteriorly (Fig. 2.1). Some surgeons prefer to extend the lymphadenectomy cranially to the aortic bifurcation or even further to the inferior mesenteric artery. Several reports have demonstrated improved survival in patients with more lymph nodes removed, and some have suggested using lymph node yield as a proxy for surgical quality [67, 69–72]. Interestingly, this association has been demonstrated in both pathologically node positive and node negative patients [67]. Removal of more lymph nodes likely eliminates any micrometastatic disease, allows for wider surgical margins, and provides more tissue for pathologic staging [73, 74].

Still, using nodal yield as a quality indicator is controversial and is an imperfect measure of dissection adequacy. Similarly experienced surgeons using identical templates can produce a highly variable number of lymph nodes, indicating nodal yield may, in part, be associated with nonsurgical factors [62]. For example, nodal yield is highly dependent on methods of pathological analysis, such as the technique of lymph node identification and whether nodal tissue is submitted en bloc or in packets [75, 76]. Furthermore, there can be

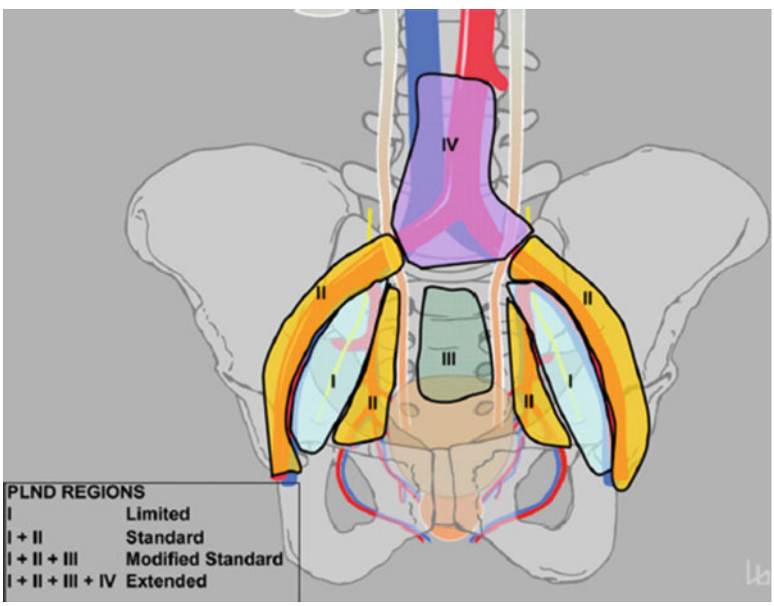

Fig. 2.1 Pelvic lymphadenectomy boundaries. Reprinted, with permission, from Elsevier Limited, Hurle, R., Naspro, R.: Pelvic lymphadenectomy during radical cystectomy: a review of the literature. Surg Oncol, 19: 208, 2010

significant intraobserver variability among pathologists in identifying what constitutes nodal tissue [77] and there is no standardized process of pathologic analysis consistently used across different institutions [78]. Finally, although recommendations have been put forth, there is no accepted minimum number of lymph nodes that defines an "adequate" lymphadenectomy [79].

Because nodal yield is an imperfect measure of surgical quality, an adequate pelvic lymphadenectomy must be defined as the removal of all nodal tissue within the bounds of the chosen template [62]. Still, the template boundaries and extent of dissection have been debated. An extended dissection has a higher nodal yield relative to a standard dissection, which may translate to improvements in recurrence and mortality with little added morbidity [80–82]. However, with the rarity of skip metastasis, a standard lymph node dissection may provide adequate staging for most patients [81, 83]. There is unlikely a survival benefit of a super extended lymphadenectomy over an extended dissection [84]. Regardless of the template chosen, a lymphadenectomy should include meticulous removal of all tissue in regions known to harbor lymph nodes that drain the bladder. Such a dissection is possible with RARC and is mandatory to ensure oncologic efficacy [85, 86].

Hemostasis

Hemostasis is essential during radical cystectomy, and there are several ways to control the vascular pedicles including clips and sutures, staplers, and bipolar electrocautery devices such as the Ligasure™ (Covidien, Boulder, CO). The use of a stapler is associated with lower blood loss than with the traditional suture and clips technique [87] and the Ligasure appears to be equally effective as a stapler, but more cost efficient [88]. One purported benefit to RARC is decreased intraoperative blood loss [33, 89], and we recently determined that RARC is associated with a lower estimated blood loss and transfusion requirement than ORC (*authors data, unpublished*). Regardless of the technique used to secure the vascular pedicles, every effort should be taken to avoid excess blood loss given the risks of a blood transfusion and its association with increased mortality after cystectomy [90].

Special Considerations in Men

Recently, new techniques have been introduced to manage the prostate and urethra during cystectomy in efforts to improve postoperative functionality and quality of life in men. Historically, *urethrectomy* was universally recommended at the time of cystectomy, however, given the low risk of urethral recurrence, the popularization of the ONB, and the possible protective effect of ONB on urethral recurrence, patients are now risk stratified to determine if urethrectomy is required [91, 92]. The primary risk factor for anterior urethral recurrence is cancer involvement of the prostate, a finding in upwards of 40 % of cystectomy specimens [91, 93]. Furthermore, CIS, multifocal tumors, and tumors involving the trigone or bladder neck are known to increase the risk of prostatic involvement [93, 94]. Thus, we generally do not perform a urethrectomy in men in the absence of risk factors for urethral recurrence. For those patients not receiving an orthotopic diversion that have a high risk of urethral recurrence, we recommend a urethrectomy at the time of cystectomy.

More recently, a *nerve sparing* approach to radical cystectomy has been proposed in an attempt to preserve potency and possibly continence with a neobladder. Initially described by Walsh [95], the technique for a nerve sparing radical cystectomy is similar to that of a nerve sparing radical prostatectomy. Some believe that sparing either one or both sets of nerves should be offered to all patients that do not have an oncologic contraindication, whether or not they receive an ONB [96]. Advocates of this approach believe that sparing the neurovascular bundle does not sacrifice the oncologic efficacy of radical cystectomy, as bladder cancer rarely extends through the prostatic capsule [97–99]. Schoenberg et al. presented 10-year data on 101 men who underwent this procedure and demonstrated no positive margins at the site of nerve sparing, survival outcomes similar to that of historic cohorts, and a significant proportion of patients who were able to engage in sexual activity postoperatively [98]. Other series have similarly shown that approximately 80 % of men who were potent prior to cystectomy had good postoperative sexual function with a nerve-sparing procedure [99, 100]. Kessler et al. demonstrated that attempted nerve sparing was associated with improved postoperative erectile function as well as continence with an ONB [101]. Thus, for properly selected sexually active men, nerve-sparing radical cystectomy appears to provide good oncologic control while increasing the likelihood of preserving erectile function and continence. There are no randomized studies of nerve sparing versus non-nerve-sparing cystectomy, thus no firm conclusions regarding these purported functional benefits can be made.

By maximally protecting the neurovascular bundle and rhabdosphincter, a *prostate capsule-sparing* radical cystectomy is an even more aggressive measure to preserve functionality in patients with an ONB. During this operation, the prostatic urethra, prostatic adenoma, and bladder are removed, a distal urethral frozen section margin is sent, and the prostatic capsule is left in place. Indications for capsule-sparing cystectomy include good preoperative sexual function with tumors that appear to be resectable without requiring a wide periprostatic margin. Contraindications include extravesical tumor extension, bladder cancer involvement of the prostate or bladder neck, CIS, hydronephrosis and biopsy-proven prostate cancer [102, 103]. Clinical staging with transrectal and transurethral evaluation of the prostate and bladder will identify most men that have contraindications to the procedure [104–106].

Although most studies are relatively small and nonrandomized, the functional outcomes with capsule-sparing cystectomy and ONB appear encouraging. Vallancien et al. reported that of 100 capsule-sparing cystectomy patients, over 80 % of previously sexually active men were able to have intercourse postoperatively [105]. In another series, Nieuwenhuijzen et al. reported 78 % of their 44 patients had satisfactory postoperative sexual function [107]. Postoperative daytime and nighttime continence in patients with ONBs also appear to be quite high with this procedure [102]. Still, capsule-sparing cystectomy is controversial given the oncologic concerns of leaving prostatic tissue behind and any conclusions regarding functional and oncological outcomes relative to traditional radical cystectomy are inferences, as no comparative studies exist.

Although urethral and prostatic fossa recurrences in capsule-sparing cystectomy series are low, the risk is cause for concern [105]. Urothelial carcinoma involvement of the prostate may be as high as 40 %, with an increased likelihood in patients with CIS or trigonal tumors [93, 94, 103, 108]. While most of these tumors can be identified preoperatively [106], urothelial carcinoma involving the prostatic capsule and periprostatic tissue (areas not well sampled during clinical staging) has been identified in cystectomy specimens [109]. Thus, advocats of this technique advise urethral and prostatic surveillance as would normally be done with an ONB, and to treat any such recurrences either endoscopically or with undiversion, if necessary [110].

Incidental prostatic adenocarcinoma can be identified in approximately 30 % of cystectomy specimens, up to one quarter of which are clinically significant, and some are located in areas that would be left behind with a capsule-sparing procedure [109, 111–115]. While there is a report of prostate cancer metastasis after radical cystectomy [116], the risk of prostate cancer-specific mortality and biochemical recurrence is low [117–120]. There are no reports of prostate cancer deaths in capsule-sparing cystectomy patients found to harbor occult prostate cancer, and most could be effectively treated, if required [121, 122].

Most importantly, oncologic outcomes with capsule-sparing cystectomy appear comparable to that of traditional radical cystectomy. In one of the largest series of capsule-sparing cystectomy patients, Rozet et al. reported a 4.7 % and 34 % rate of local and distant recurrence, respectively [122]. Despite these encouraging results, some argue that leaving the prostatic capsule is inappropriate, distant failure with capsule-sparing cystectomy is higher than would be expected, and the supporting data are limited by selection bias [123, 124]. Therefore, for properly motivated patients, capsule-sparing cystectomy with ONB may help preserve continence and sexual function, but the risk of residual or recurrent cancer must be understood and, until large randomized studies with extended follow-up exist, it cannot be considered oncologically equal to traditional radical cystectomy [124].

Special Considerations in Women

With the increasing use of ONBs in women [125], the preferred *management of the urethra* at the time of cystectomy has been called into question. While there is a relatively low risk of female urethral involvement (<10 %) by bladder cancer, patients with bladder neck and trigonal tumors are at higher risk [126–128]. In women at low risk for urethral involvement that have a negative intraoperative urethral frozen section analysis, the risk of urethral recurrence can be considered minimal and an ONB may be safely fashioned [129]. Otherwise, urethrectomy is generally performed along with radical cystectomy.

In an effort to improve functionality after cystectomy, some have recommended sparing the *gynecologic organs*. As vaginal shortening can lead to significant sexual dysfunction, young, sexually active women who desire ONBs and have minimal risk for vaginal wall involvement may be candidates of vaginal wall-sparing cystectomy [130]. Sparing the anterior vaginal wall and maximally preserving paravaginal and periurethral supporting tissues may decrease the risk of pelvic organ prolapse, maintain vaginal length, and reduce the risk of neobladder–vaginal fistula. Chang et al. demonstrated that preservation of the anterior vaginal wall in women with ONBs was associated with a low rate of complications and resulted in satisfactory functional voiding outcomes [131]. Furthermore, sparing the uterus is associated with improved incontinence in women with ONBs, further supporting the utility of preserving uninvolved gynecologic organs [132]. Importantly, sparing these organs does not appear to sacrifice the oncologic efficacy of radical cystectomy. Pathologic analysis of gynecologic organs taken during radical cystectomy demonstrated that, in the absence of gross tumor extension, they are unlikely to be involved by bladder cancer [133]. Ali-El-Dein et al. noted a 2.6 % prevalence of gynecologic organ involvement in cystectomy specimens, with a higher risk in women that had aggressive tumor characteristics [134]. Thus, it does not appear necessary to routinely remove all female gynecologic organs during radical cystectomy.

The *neurovascular bundles* that provide autonomic innervation to the vagina, clitoris, and proximal urethra run lateral to the vaginal walls and damage can result in sexual and urinary dysfunction [96, 135–137]. With an interest in improving postoperative quality of life in women, some have suggested preservation of these bundles [138, 139]. Several small case–series suggest that, in properly selected patients, sparing one or both of these nerve bundles may help preserve postoperative sexual function and urinary continence in women with ONBs [125, 140, 141]. Vaginal wall and gynecologic organ-sparing procedures may help avoid damage to these nerves.

Postoperative Care

Postoperative care is an essential element to any operation, no more so than with radical cystectomy. At our institution, we pioneered a *collaborative care pathway* for cystectomy patients, which incorporates evidence-based guidelines and standardizes patients' hospital course (Appendix). As a result, the cost and length of hospital stay after cystectomy decreased significantly with no impairment in quality of care [142, 143]. Part of this pathway was exclusion of routine postoperative surgical intensive care unit placement. While it is important to have the resources available to admit a cystectomy patient to an intensive care unit, it is not routine practice. In fact, with the use of a collaborative care pathway, only 6.5 % of radical cystectomy patients required postoperative intensive care unit admission [144].

Another component to postoperative patient care is *patient disposition* at the time of hospital discharge. With shorter lengths of inpatient stay, there is an increasing use of postoperative home healthcare services and rehabilitation facilities [145]. Aghazadeh et al. recently reported that approximately a third of cystectomy patients are discharged home with services and 9 % to an inpatient facility [146]. In fact, older age, lower preoperative albumin, being unmarried, and a higher Charlson comorbidity index (CCI) were independently associated with discharge to home with services, while older age, poor preoperative exercise tolerance, and a longer hospital stay were associated with discharge to a rehabilitation facility. It is important to educate patients preoperatively that only half are discharged home without services and patients at higher risk of requiring postdischarge care should be appropriately counseled.

Complications

Due to the substantial perioperative morbidity of radical cystectomy (Table 2.1), surgeons must be familiar with all possible complications and be prepared to recognize and manage them expediently. Importantly, patients should be counseled about the prevalence and spectrum of these risks preoperatively.

Historically, perioperative complications were reported within 30 days of cystectomy. One large series reported 30-day morbidity, readmission, and mortality rates of 45 %, 18 %, and 1.7 %, respectively [3]. However, given the considerable risk of additional complications in the months following surgery, there has been a trend to report up to 90 days postoperatively. Stimson et al. identified increases in readmission and mortality rates to 27 % and 7 %, respectfully, when following patients to 90 days [147]. Given the nonstandardized methods for reporting complications, it is difficult to compare different series and accurately define the morbidity of radical cystectomy [148]. Thus, using stringent criteria [149] to report 90-day complications, there was a 64 % prevalence of any complication, 26 % risk of readmission, and 2.7 % mortality rate (Table 2.2) [150]. Gastrointestinal, infectious, and wound complications were the most common diagnoses and 11 % required an interventional radiology procedure.

While studies reporting perioperative morbidity after RARC are limited by patient numbers and procedural selection bias, there appears to be

Table 2.1 Perioperative morbidity and mortality in contemporary radical cystectomy series

Series	Procedure	Time of assessment (days)	Number of patients	Mortality	Morbidity
Lee [1]	ORC	30	498	1.6	45
Hollenbeck [2]	ORC	30	2,538	–	30.5
Novotny [3]	ORC	30	516	0.8	27.3
Lowrance [4]	ORC	30	553	1.7	41
Stimson [5]	ORC	90	753	6.9	–
Stein [6]	ORC	90	1,054	2.5	28
Novarra [7]	ORC	90	358	3	49
Hautmann [8]	ORC	90	923	2.3	58
Svatek [9]	ORC	90	283	0	54
Shabsigh [10]	ORC	90	1,142	2	64
Smith [11]	RARC	30	227	0	30
Jonsson [12]	RARC	30	45	0	40
Ng [13]	RARC	90	79	0	49
Khan [14]	RARC	90	50	0	34
Hayn [15]	RARC	90	156	5.8	52

Table 2.2 Perioperative complications after open and robot-assisted radical cystectomy

Category	ORC [10]	RARC [15]
Number of patients	1,142	156
Number of complications	1,637	186
Number of patients with a complication	735	102
Gastrointestinal	29 %	31 %
Infectious	25 %	25 %
Wound/skin	15 %	7 %
Genitourinary	11 %	13 %
Cardiac	11 %	3 %
Pulmonary	9 %	4 %
Bleeding	9 %	
Hematologic/vascular		5 %
Thromboembolic	8 %	
Metabolic		3 %
Nervous	5 %	0.5 %
General		7 %
Miscellaneous	3 %	
Surgical	1 %	
Head and neck		1 %
Endocrine		0.5 %

a similar rate of complications. Hayn et al. reported perioperative complications on 156 RARC patients and found that 52 % of patients experienced at least one complication within 90 days of surgery [151]. Gastrointestinal, infectious, and genitourinary were the most common types of complications and 21 %, 8.3 %, and 5.8 % of patients were readmitted, required an interventional radiology procedure, and died, respectively. Thus, despite the purported benefits of RARC, it is clearly associated with a similar frequency and spectrum of complications as ORC (Table 2.2).

Quality Indicators for Radical Cystectomy

Although there have been vast improvements in the management of patients with bladder cancer, differences still exist in the quality of surgery delivered. Quality surgical care can be analyzed within the Donabedian framework of structure, process, and outcome [152]. While the components of this framework are interrelated, structural aspects (physical facilities, hospital/surgeon volume) help drive clinical processes (adequacy of lymphadenectomy, use of ONB), which, in turn, are related to outcomes (perioperative morbidity and mortality) [153]. Though certain outcomes may be impacted by patient factors, such as comorbidity and disease severity, some potentially modifiable surgical factors may also impact outcomes. Currently, there are no accepted quality of care indicators for radical cystectomy, thus proxies must be used to estimate surgical quality.

Surgeon and Hospital Volume

Hospital and/or surgeon case volume appear to be associated with several surgical outcomes and have been proposed as indicators for surgical quality [154–156]. In a seminal article by Birkmeyer, higher hospital volume was associated with lower perioperative mortality for several operations, including a greater than 50 % decrease in mortality for radical cystectomy [157]. In a subsequent study specifically examining the relationship between hospital volume and radical cystectomy outcomes, Hollenbeck et al. determined that patients treated at low volume hospitals were 46 % more likely to suffer a perioperative death than patients treated at high volume hospitals [158]. Potential explanations for improved outcomes at higher volume hospitals include employment of more specialized surgeons, more consistent postoperative processes of care, better intensive care unit staffing, greater resources for managing complications, and the practice of a more complete Donabedian framework [159, 160].

Higher surgeon volume may also be related to cystectomy outcomes, although this association does not appear to be as consistent. In another Birkmeyer article, higher surgeon volume was associated with lower perioperative mortality for several operations, including radical cystectomy, even when controlling for hospital volume [161]. However, a recent analysis of post-cystectomy survival suggested that the impact of surgeon volume is attenuated when accounting for hospital

Table 2.3 Standards for radical cystectomy and PLND stratified by patient age and stage [16]

Age at presentation	pT stage	Number of patients	Margins Positive *N* (%)	Margins Negative	Lymph nodes Mean	Lymph nodes SD	Lymph nodes Median
<65							
No	<T2	203	3 (1.5)	200	15.3	10.5	14
	≥T3	143	23 (16)	120	13.9	9.6	12
Yes	<T2	30	0 (0)	30	10.7	9.9	8
	≥T3	20	5 (25)	15	5.8	6.7	4
65–75							
No	<T2	202	4 (2)	198	13.5	10.8	12
	≥T3	161	17 (11)	144	14.7	9.4	13
Yes	<T2	32	1 (2)	31	7.6	6.3	9.5
	≥T3	22	4 (18)	18	6.4	6.2	6
>75							
No	<T2	105	2 (1)	103	10.5	7.8	9
	≥T3	108	10 (9)	98	10.2	7.9	10
Yes	<T2	25	0 (0)	25	7.6	6.4	7
	≥T3	40	2 (5)	38	5.3	5.6	4
Totals	All	1,091	71 (6.5)		12.5	9.7	11
	≥T3	494	61 (12)				

volume [155]. Still, there does appear to be a learning curve with RARC such that more surgeon experience is associated with improved outcomes [33, 162]. Together, these data imply differences in surgical quality based on hospital and/or surgeon volume, although the root causes remain to be explained and no definition of what "high" volume should be currently exists. Therefore, while it may be related to cystectomy outcomes in some way, the use of volume as a proxy for surgical quality is imperfect and remains a topic of debate.

Surgical Factors

In an effort to establish surgical parameters to define quality for radical cystectomy, Herr et al. led a collaborative effort to benchmark "reasonable standards" of care [163]. They proposed that a 75–80 % utilization of pelvic lymphadenectomy, 10–14 lymph nodes removed, a positive margin rate ≤10 % (preferably <5 %) and a minimum annual surgeon volume of ten cases could be considered as standards of care (Table 2.3). In a subsequent study, Herr et al. attempted to determine which surgical factors were most important for survival and local recurrence after cystectomy [67]. Negative surgical margins and ≥10 lymph nodes removed were independently associated with survival, while positive margins and <10 lymph nodes removed were independently associated with local recurrence. Interestingly, the type of surgeon (urologic oncologist) and type of institution (academic) were each inversely associated with positive margin status and removal of <10 lymph nodes. In all, surgical quality appeared to be related to survival and recurrence, and nontechnical factors, namely surgeon training and hospital setting, influenced surgical quality.

Adjunctive Therapies

Urothelial carcinoma is a chemosensitive malignancy and data over the past decade has solidified the use of chemotherapy in its management. Given the high rate of distant recurrences, there is no question that systemic therapy plays a role in the management of bladder cancer [164]. Chemotherapy can either be administered preoperatively or postoperatively, and there are advocates for each approach [165]. While neoadjuvant chemotherapy can allow for tumor downstaging, provide early treatment for systemic micrometastasis, is delivered to the tumor with an intact vasculature and may be tolerated better, it also may lead to overtreatment and unintentionally delay cystectomy. Adjuvant chemotherapy can be used selectively for high-risk patients and allows for immediate cystectomy but may be poorly tolerated and delays administration of systemic therapy to patients who may fail surgery due to distant recurrences [166].

Current level 1 data clearly demonstrates a survival benefit of neoadjuvant chemotherapy [167]. Based on a meta-analysis of over 3,000 patients from 11 randomized control trials, the use of multiagent cisplatin neoadjuvant therapy resulted in a 14 % relative risk reduction in mortality and a 22 % reduction in disease specific mortality at 5 years [168]. Patients with a good performance status and clinical factors concerning for high-risk and locally advanced disease are the best candidates for neoadjuvant chemotherapy [169]. However, despite supporting data, neoadjuvant chemotherapy remains relatively underutilized, providing a target for improvement in the quality of care delivered to cystectomy patients [170, 171]. While adjuvant chemotherapy may be beneficial, its use is not strongly supported based on a recent meta-analysis [172, 173]. Because there are no trials directly comparing adjuvant and neoadjuvant chemotherapy, the relative benefit of one over another is speculative.

Survivorship

The last element to a successful cystectomy is survivorship care. One such element of survivorship is cancer surveillance. At 5 years approximately 30–40 % of patients experience a recurrence, but most occur within 2 years of surgery [68, 174, 175]. Depending on pathologic risk factors, there is a small risk of urethral recurrence [91, 176] and an even smaller risk of upper tract recurrence [177]. Boorjian et al. demonstrated that post-cystectomy patients experienced improved survival if their recurrence was detected asymptomatically through routine surveillance imaging, and patients who presented symptomatically fared poorer, supporting the value in routine postoperative surveillance imaging [178]. Unfortunately, there are no set guidelines about the recommended frequency and method for postoperative surveillance and there remains tremendous variation in how patients are monitored [179]. At our institution we image the abdomen and pelvis, typically using CT with intravenous contrast, every 6 months for the first 2 years and then annually thereafter. We do not routinely screen for urethral recurrences in patients with incontinent diversions and retained urethras [180, 181].

Other elements of survivorship include management of late treatment effects, quality of life issues, and physical and psychosocial rehabilitation [169]. As these issues are unquestionably important to cystectomy patients and their families, instituting multidisciplinary survivorship programs continues to be a growing effort among urologists.

Conclusion

Radical cystectomy is the gold-standard treatment for high-risk bladder cancer and a successful result is dependent on multiple patient, surgeon, and institutional factors. The outcome of radical cystectomy can be optimized through proper patient selection, adherence to surgical principles, the use of adjunctive treatments, and regular postoperative follow-up. Regardless of the surgical approach chosen, these principles must be followed as they undoubtedly translate to improved surgical quality.

Editors' Commentary

Erik P. Castle and Raj S. Pruthi

Most who care for patients with bladder cancer understand that the ultimate goal of radical cystectomy is oncologic success and patient safety—irrespective of operative technique. As the authors state, a successful outcome with radical cystectomy is not only related to surgical technique and safe extirpation of the bladder but also to factors such as patient selection, coordinated perioperative care, and use of adjunctive treatments. Such principles are nicely outlined in this chapter by experts in the field of bladder cancer. Such principles are simply mandatory for all who perform this operation and care for the patient with bladder cancer.

Robotic techniques in bladder cancer surgery must continue to duplicate the surgical principles of open radical cystectomy with regard to the extirpative portion of the procedure and to the ability to perform adequate lymphadenectomy. Fortunately, the robotic approach to cystectomy appears to provide acceptable operative, pathological, and short-term clinical outcomes—seemingly duplicating the principles and practices of the time-tested open surgical technique.

Appendix

A. Radical cystectomy with ileal conduit pathway orders
  a. Admission
    i. Diagnosis: malignant neoplasm of bladder (188); s/p radical cystectomy with ileal conduit
    ii. Diagnosis: possible, probable, or r/o cancer/malignancy
    iii. Admit to: urology
    iv. Condition:
    v. Allergies:
  b. Nursing
    i. Vital signs q4h × 2 days
      1. Convert to vital signs q8h on POD 2
    ii. Strict I&O q4h
    iii. Drain: Jackson-Pratt to self-suction. Empty and record q4h. Change dressing around drain PRN daily starting POD 1
      1. Discontinue JP drain 4 h after stent removal prior to discharge
    iv. Ureteral stents to gravity drainage
    v. Volurex incentive spirometer q1h while awake
    vi. Sequential compression devices bilaterally
    vii. Notify house officer for Temp >101, SBP > 160, DBP > 100, HR > 120, UOP < 60 mL/2 h
    viii. Activity: out of bed to chair day of surgery with assistance
      1. Ambulate in halls TID POD 1 and POD 2
      2. Ambulate q2h while awake starting POD 3
  c. Diet
    i. NPO POD 0 × 24 h
    ii. POD 1: may chew gum while awake PRN, otherwise NPO
    iii. Begin restricted clear liquid diet POD 2: 8 oz q8h
    iv. Clear liquid diet POD 3
  d. Ostomy orders
    i. Wound ostomy nurse consult
  e. Medications
    i. D5LR at 150 mL/h × 1 bag
      1. Then, D5 1/2NS + 20 mEq/L KCl at 150 mL/h
    ii. Cefoxitin 2,000 mg IV q8h × 3 doses
      1. If allergic to PCN or cephalosporins and serum Cr < 1.3
        a. Gentamicin 3 mg/kg IV
        b. Clindamycin 900 mg IV
      2. If allergic to PCN or cephalosporins and serum Cr > 1.3
        a. Aztreonam 2,000 mg IV
        b. Clindamycin 900 mg IV
    iii. Bisacodyl 10 mg PR BID, start POD 3
    iv. Milk of Magnesia 30 mL PO BID, start POD 4
    v. Levofloxacin 500 mg PO ×1 with stent removal
    vi. *Pain medications*
      1. Ketorolac 30 mg IV in recovery room
        a. Then, 15 mg IV q6h × 24 h
      2. Hydromorphone 1 mg/mL PCA: 0.1 mg q8h × 3 days
      3. Oxycodone 5 mg/acetaminophen 325 mg POD q4h PRN × 3 days PRN pain score 2–5

4. Oxycodone 10 mg/acetaminophen 325 mg POD q4h PRN × 3 days PRN pain score 6–10

vii. *Prophylaxis*
1. Enoxaparin 40 mg subcut qday10
   a. Or for renal insufficiency: heparin 5,000 U subcut q8h
2. Famotidine 20 mg IV q12h × 5 days
3. Esomeprazole 20 mg PO daily when famotidine is discontinued

viii. *As needed medications*
1. Ondensetron 4 mg IV q6h PRN nausea
2. Acetaminophen 650 mg PO/PR q4h PRN temp > 101
3. Chloroseptic spray at bedside for PRN use

f. Labs
i. Hematocrit POD 1, 2, 4
ii. Basic metabolic panel POD 1, 4

g. Patient/family education
i. Instruction on changing pouch and wafer

B. Radical cystectomy with continent diversion pathway orders

a. Admission
i. Diagnosis: malignant neoplasm of bladder (188); s/p radical cystectomy with continent diversion
ii. Diagnosis: possible, probable, or r/o cancer/malignancy
iii. Admit to: urology
iv. Condition:
v. Allergies:

b. Nursing
i. Vital signs q4h × 2 days
   1. Convert to vital signs q8h on POD 2
ii. Strict I&O q4h
iii. Drain: Jackson-Pratt to self-suction. Empty and record q4h. Change dressing around drain PRN daily starting POD 1.
iv. Ureteral stents to gravity drainage
v. Foley catheter to bedside bag drainage
   1. Irrigate Foley catheter with 60 mL normal saline TID starting POD 1
vi. Volurex incentive spirometer q1h while awake
vii. Sequential compression devices bilaterally
viii. Notify house officer for Temp > 101, SBP > 160, DBP > 100, HR > 120, UOP < 60 mL/2 h
ix. Activity: out of bed to chair day of surgery if possible, with assistance
   1. Ambulate in halls TID POD 1 and POD 2
   2. Ambulated q2h while awake starting POD 3

c. Diet
i. Strict NPO until POD 5, no ice chips

d. Medications
i. D5LR at150 mL/h × 1 bag
   1. Then, D5 1/2NS + 20 mEq/L KCl at150 mL/h
ii. Cefoxitin 2,000 mg IV q8h × 3 doses
   1. If allergic to PCN or cephalosporins and serum Cr < 1.3
      a. Gentamicin 3 mg/kg IV
      b. Clindamycin 900 mg IV
   2. If allergic to PCN or cephalosporins and serum Cr > 1.3
      a. Aztreonam 2,000 mg IV
      b. Clindamycin 900 mg IV
iii. Bisacodyl 10 mg PR BID, start POD 4
iv. Milk of Magnesia 30 mL PO BID, start POD 5
v. Levofloxacin 500 mg PO ×1 with stent removal
vi. *Pain medications*
   1. Ketorolac 30 mg IV in recovery room
      a. Then, 15 mg IV q6h × 24 h
   2. Hydromorphone 1 mg/mL PCA: 0.1 mg q8h × 3 days
   3. Oxycodone 5 mg/acetaminophen 325 mg POD q4h PRN × 3 days PRN pain score 2–5
   4. Oxycodone 10 mg/acetaminophen 325 mg POD q4h PRN × 3 days PRN pain score 6–10
vii. *Prophylaxis*
   1. Enoxaparin 40 mg subcut qday10

a. Or for renal insufficiency: heparin 5,000 U subcut q8h
2. Famotidine 20 mg IV q12h × 5 days
3. Esomeprazole 20 mg PO daily when famotidine is discontinued

viii. *As needed medications*
1. Ondensetron 4 mg IV q6h PRN nausea
2. Acetaminophen 650 mg PO/PR q4h PRN temp > 101
3. Chloroseptic spray at bedside for PRN use

ix. *When taking PO, start one of the following*
1. Nitrofurantoin monohydrate 100 mg PO q12h × 14 days
2. Trimethoprim–sulfamethoxazole DS PO qHS × 14 days

e. Labs
i. Hematocrit POD 1, 2, 4
ii. Potassium POD 1
iii. Basic metabolic panel POD 4

f. Patient/family education
i. Begin teaching patient/family catheter care and instructions for irrigations of catheter with normal saline starting POD 1.

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