Anal Cancer

A Comprehensive Guide

Jeffrey Meyer
Lisa Kachnic
Editors

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I dedicate this book to the many patients that I have had the privilege to care for during my career. They have all shaped me into the physician and person I am today, and I hope that I have positively touched their lives in return.

Lisa Kachnic

Preface

A multidisciplinary team approach is paramount to the management of anal cancer; however, due to its low incidence as compared to other solid cancers, there are limited comprehensive published treatment guidelines. This need has become increasingly important over the past several years when we have seen advances in the prevention, detection, radiation delivery, and systemic approaches including immunotherapy.

As a result, it is currently very difficult for a clinician (either in training or in practice) to gain experience and expertise in the multidisciplinary management of this rare cancer. *Anal Cancer: A Comprehensive Guide* was created for the purpose of centralizing the knowledge and experience of experts across a variety of disciplines. The authors provide an overview of the principles of disease pathogenesis, anatomy, epidemiology, and staging, in addition to detailed established and cutting-edge clinical approaches for the treatment of anal cancer. Foundations, current evidence-based practices, and pathways for the future are the focus. Our vision is that this book may be used to serve as a definitive and comprehensive resource for the team-based management of all stages and histologies of anal cancer.

We thank our gracious contributors for lending their expertise toward the improved care of our patients.

Baltimore, MD, USA — Jeffrey Meyer
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Chapter 1
Anatomy and Histology of the Anus

Margaret H. Sundel, Lysandra Voltaggio, Ira L. Leeds, and Sandy Hwang Fang

Abbreviations

RAIR	Rectoanal inhibitory reflex
S2–S4	Sacral nerves S2–S4

Definitions of the Anal Canal

The anal canal is the final portion of the large intestine, connecting the rectum to the external opening of the anus. There are many ways to define the anal canal, each of which relies on different anatomic landmarks (Table 1.1). The pelvic floor is the muscular layer that separates the pelvic cavity from the perineal region and provides support to the pelvic viscera. The dentate line (or pectinate line) is a visibly scalloped border overlying the anal columns of Morgagni, located at the embryological transition from hindgut to proctodeum, i.e., the squamocolumnar junction. The 1–1.5 cm portion of the anal canal proximal to the dentate line is called the anal pecten or transitional zone. The transitional zone contains a conglomeration of both squamous epithelial cells and columnar cells. The anal sphincter complex is composed of the internal and external anal sphincters. The anal verge is the terminal portion of the anal canal, where the squamous epithelium of the canal (anoderm) meets the perianal skin.

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Table 1.1 Anatomical landmarks that define the anal canal

Pelvic floor	The muscular layer that separates the pelvic cavity from the perineal region and supports the pelvic viscera
Dentate line (also known as the pectinate line)	The visibly scalloped border overlying the anal columns and sinuses, located at the approximate embryological transition from hindgut (endoderm – mucosa) to proctodeum (ectoderm – epidermis)
Anal sphincter complex	The overlapping muscles responsible for the closure of the anal canal, composed of the internal and external anal sphincters
Anal verge	The terminal portion of the anal canal, where the squamous epithelium of the canal (anoderm) meets the perianal skin

Three of the most commonly used definitions of the anal canal include the anatomical, pathological, and surgical definitions (Fig. 1.1). The anatomical anal canal extends from the dentate line to the anal verge. Pathologists define the anal canal as the area lying between the upper and lower borders of the anal sphincter complex. The surgical anal canal is characterized as lying between the pelvic floor and the anal verge.

In adults, the canal lies in an anterior-superior axis, directed toward the umbilicus and creating an approximately 90-degree angle with the rectum. Using the surgical definition, the canal typically measures between 3 and 5 cm, with an average length of around 4 cm [1]. The anal canal is longer in men than in women. The perianal space surrounds the anal canal superficially and contains the external hemorrhoidal plexus. Posterior to the canal lies the anococcygeal ligament, which is a fibrous raphe connecting the posterior wall of the anal canal to the anterior coccyx. The superficial and deep postanal spaces are separated by the anococcygeal ligament inferiorly and superiorly, respectively. The ischioanal fossa (space), a fat-containing space into which the canal can distend during defecation, is found on both sides lateral to the anal canal. The superficial postanal space connects to the bilateral ischioanal spaces, forming the horseshoe configuration of a perianal horseshoe abscess. Superior to the anococcygeal ligament, the horseshoe configuration consists of the deep postanal space connecting to the bilateral ischiorectal fossae (spaces). Anterior to the canal is the perineal body, a mass of fibromuscular tissue between the anal canal and the vagina in women or membranous urethra and bulb of the penis in men.

The appearance of the pectinate (dentate) line is explained by the structures it overlies, namely, the anal columns and anal sinuses. The anal columns, or columns of Morgagni, are ridges of anal mucosa that extend proximally into the upper anal canal and terminate distally at the anal valves. The largest of these columns, located at the left lateral, right posterolateral, and right anterolateral positions, are called the anal cushions. The anal cushions contain terminal branches of the superior rectal (hemorrhoidal) artery and play an important role in maintaining continence. When the muscle of Treitz loses its architecture, then the anal cushions become engorged

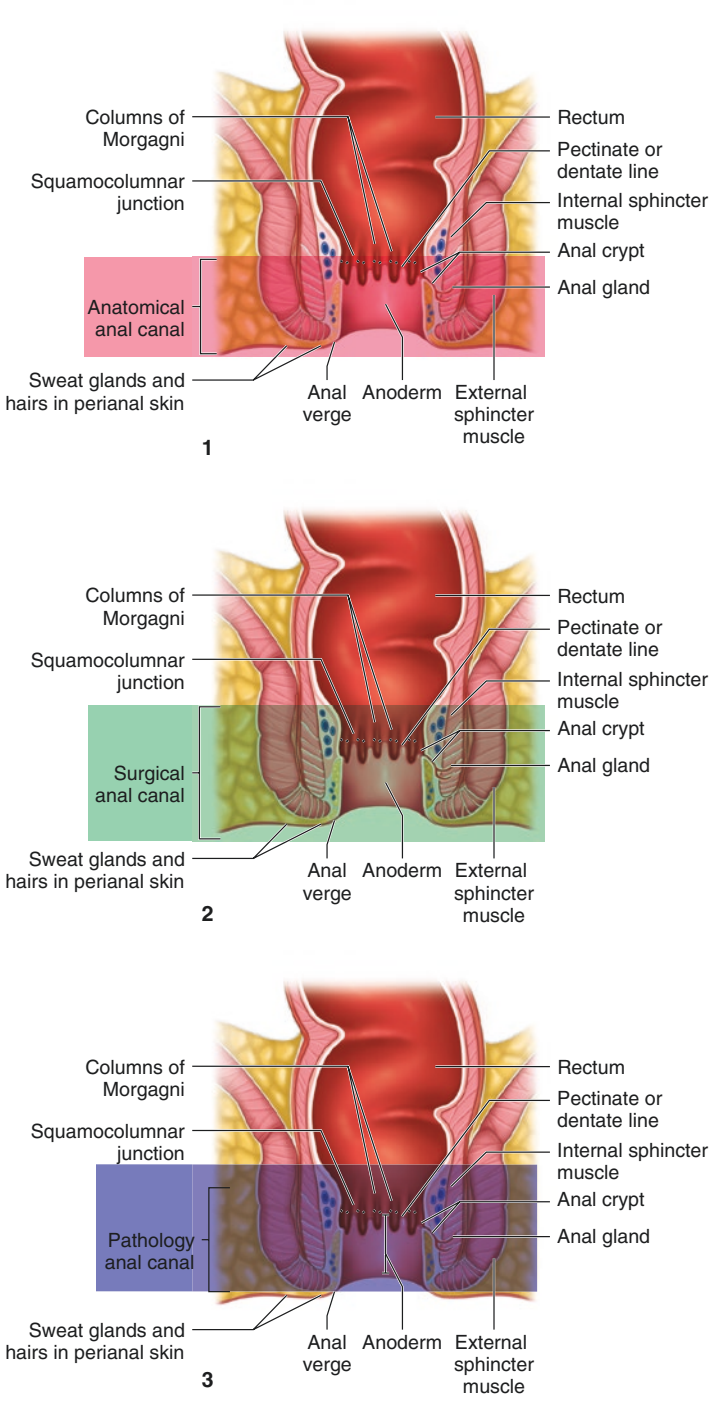

Fig. 1.1 Anatomy of the anus

and prolapse – causing symptomatic "hemorrhoids." Separating the anal columns are the anal sinuses; at their inferior ends these sinuses form the anal crypts, which collect mucus released from the anal glands.

Pelvic Floor and Anal Sphincter Musculature

The proximal portion of the anal canal is situated at the pelvic floor musculature. The pelvic floor is a funnel-shaped layer of muscle formed by the coccygeus and levator ani muscles. The coccygeus, also known as the ischiococcygeus, muscle is located posteriorly, originating at the ischial spine and inserting into the lateral sacrum and coccyx. The levator ani is further subdivided into the iliococcygeus, pubococcygeus, and puborectalis muscles, from lateral to medial. Covering both the superior and inferior surfaces of the pelvic floor musculature is the pelvic fascia, which thickens between the pubic symphysis and ischial spine to form the arcus tendineus, or tendinous arch. The iliococcygeus extends in a horizontal direction from the arcus tendineus laterally to the final two segments of the coccyx [2]. The pubococcygeus arises from the body of the pubis and inserts on the anococcygeal ligament. Medially, the puborectalis muscle forms a U-shaped sling arising from the pubis and traveling posteriorly around the rectum, lying superficial to the conjoined longitudinal muscle [3]. The puborectalis muscle sling supports the posterior portion of the anorectal junction, causing a narrowing of the distal rectum and forming the palpable anorectal ring. This muscular landmark demarcates the proximal end of the surgical anal canal.

Proximally, the anal canal arises from the outer longitudinal and inner circular layers of the rectum. The outer longitudinal layer of the anal canal is called the conjoined longitudinal muscle. This muscle is formed from an extension of the longitudinal smooth muscle of the rectum that combines with nearby skeletal muscle fibers. Specifically, the longitudinal smooth muscle of the rectum extends distally and fuses with fibers from the skeletal levator ani muscle, specifically the pubococcygeus and puborectalis muscles, as well as the supraanal fascia to become a combined longitudinal layer. The conjoined longitudinal muscle travels inferiorly along the canal, lying between the internal and external anal sphincters. It ultimately splits into muscular fibers that contribute to multiple nearby structures. Some of these fibromuscular bundles pierce the internal anal sphincter and submucosa to connect with the muscularis mucosa of the canal and support the surrounding vascular plexuses. These anchoring fibers both contribute to stability of the vasculature and aid in the prevention of rectal prolapse (the telescoping of the rectum through the anal orifice when it loses its surrounding attachments). Distally, the conjoined longitudinal muscle splits into septa that extend through the subcutaneous portion of the external sphincter to the perianal skin. This is referred to as the corrugator cutis ani muscle, which produces the ridged appearance of the perianal skin. Additional fibers pass through the external sphincter to become the transverse

septum of the ischioanal fossa [4]. Anteriorly, the longitudinal muscle fibers form the rectoperineal muscle, while posteriorly they contribute to the anococcygeal ligament.

The inner circular muscular layer of the anal canal is made up of the internal anal sphincter. The internal anal sphincter consists of concentric rings of smooth muscle formed from the thickened distal extension of the inner circular smooth muscle layer of the rectum [5]. The internal sphincter ends at the intersphincteric groove, also called the white line of Hilton. The intersphincteric groove is the palpable border between the internal anal sphincter and the subcutaneous part of the external anal sphincter where the part of the conjoined longitudinal muscle attaches to the epithelial lining of the canal.

The external anal sphincter consists of three layers of skeletal muscle that form the muscular exterior of the anal canal. It is classically considered to be made up of three portions – the subcutaneous, superficial, and deep parts [6] – though some recent work describes it as having only two distinct parts [7]. At the proximal end of the surgical anal canal is the deep part of the external anal sphincter. This segment is continuous with the puborectalis muscle. Distal to the deep portion is the largest of the three parts, which is called the superficial part of the external anal sphincter. Posteriorly, the superficial portion is attached to the coccyx, while anteriorly it attaches to the perineal body and bulbospongiosus muscle. Some fibers of the superficial portion contribute to the anococcygeal ligament. The subcutaneous portion is the most distal part of the external anal sphincter, lying medial to the other components of the external sphincter. It begins just distal to the internal anal sphincter at the intersphincteric groove and encircles the anal orifice.

Innervation of Sphincter Musculature

Autonomic and somatic nerves supply the anal canal, providing both involuntary and voluntary control of fecal continence. The internal anal sphincter receives autonomic innervation, both sympathetic and parasympathetic. Sympathetic input causes tonic contraction of the internal sphincter, promoting continence. Parasympathetic input in response to rectal distention leads to relaxation of the internal anal sphincter (rectoanal inhibitory reflex, RAIR), allowing receptors in the anal canal to sample its contents as stool versus gas while the anal cushions and external anal sphincter maintains continence. These sympathetic and parasympathetic inputs arise from the inferior hypogastric plexus, as well as the myenteric plexus [8]. The inferior hypogastric plexus, or pelvic plexus, is formed by contributions from the superior hypogastric plexus, a bilateral retroperitoneal structure that originates from the aortic plexus and travels medially to the internal iliac artery as the right and left hypogastric nerves before reaching the inferior hypogastric plexus on the pelvic sidewall. The lumbar and pelvic splanchnic nerves also provide contributions to this plexus [9].

In contrast, the external anal sphincter is under somatic control, with contraction contributing to continence and voluntary relaxation allowing for defecation to occur. Neural innervation comes from the inferior rectal and perineal branches of the pudendal nerve. The pudendal nerve arises from spinal levels S2–S4 of the sacral plexus, courses between the piriformis and coccygeus muscles, and exits the pelvis through the greater sciatic foramen. It then passes through the lesser sciatic foramen to reenter the pelvis, where it travels along with the internal pudendal artery and vein through the pudendal canal. It first gives off the inferior rectal branch and then the perineal branch, which course through the ischioanal fossa to reach the external anal sphincter [10, 11].

Histology of the Anal Canal and Perianal Skin

The anal canal forms during the fourth and seventh weeks of gestation; the upper two-thirds are endoderm-derived, and the lower one-third is ectodermally derived. The dentate, or pectinate line, is where these zones meet. A biopsy from the anatomic anus can display glandular, transitional, or squamous mucosa, and a biopsy labeled "anus," showing colonic-type mucosa, is not necessarily labeled incorrectly or obtained incompetently (Fig. 1.2).

Where the skin meets the canal, apocrine glands may be prominent and, like in skin, melanocytes can be encountered. Most of the anal canal is lined with squamous epithelium, which is present between the anal verge and the dentate (or pectinate) line. The dentate line is a visually identifiable border between the more distal squamous mucosa and a transitional area of squamous and non-squamous mucosa. The adjacent non-squamous lining can consist of either transitional (urothelium-like) (Figs. 1.2 and 1.3) or rectal glandular mucosa (Figs. 1.2 and 1.4) [12, 13]. Anal ducts and glands (Fig. 1.5) are found at the transition zone and lymphatic spaces are often prominent in these areas. The anal canal possesses a variable number of anal

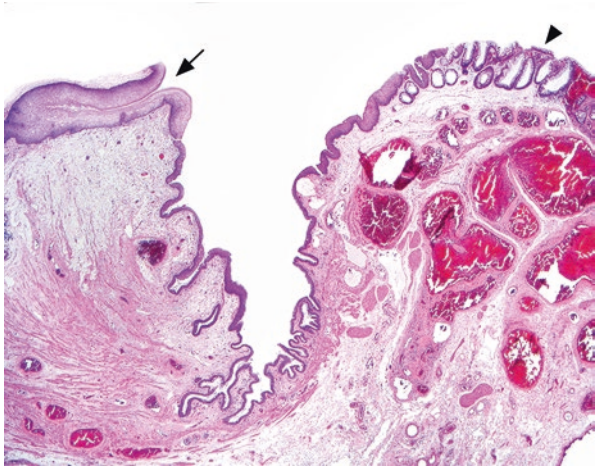

Fig. 1.2 This specimen shows squamous (arrow), glandular (arrow head), and transitional (center) mucosa. Hemorrhoidal varices are seen on the right

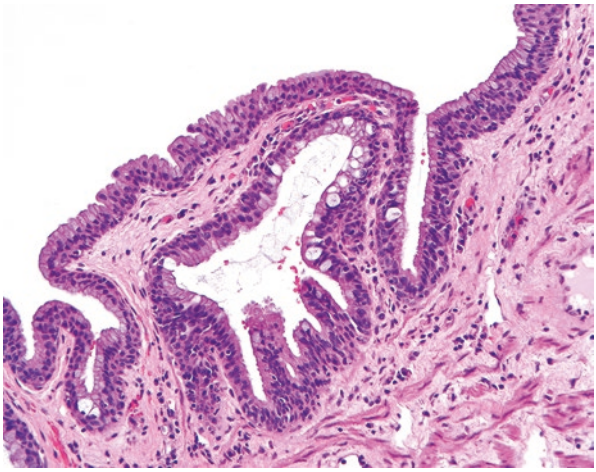

Fig. 1.3 Transitional anal mucosa shows squamous and glandular differentiation, as seen in this example

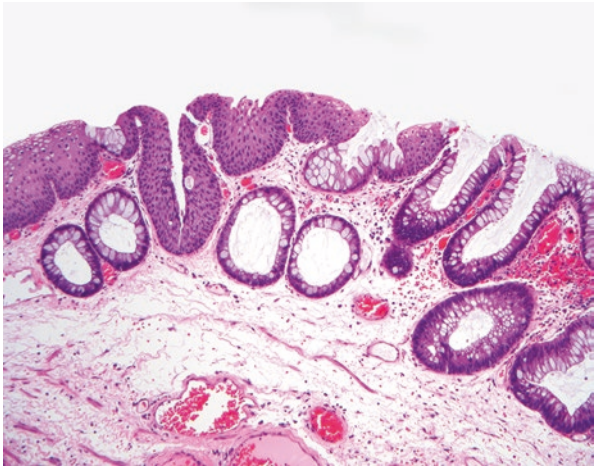

Fig. 1.4 In some cases, there is an abrupt change from rectal glandular to squamous mucosa

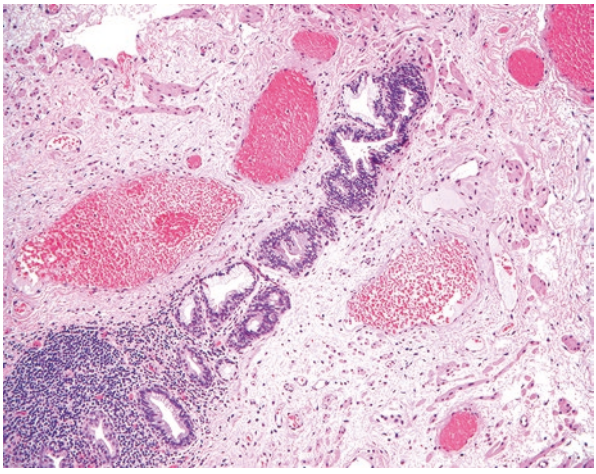

Fig. 1.5 Anal glands are mucus secreting, lined by stratified columnar epithelium, sometimes goblet cells, and are typically associated with a lymphocytic infiltrate

glands (Fig. 1.5), ranging from 3 to 10 with a median number of 6. Most are located within the submucosa but some may be found within the anal sphincters. These mucus-secreting glands are lined by stratified columnar epithelium, sometimes with goblet cells; are typically associated with a lymphocytic infiltrate; and are surrounded by one or two layers of myoepithelial cells (Fig. 1.5) [14]. Their secretions empty within the anal sinuses.

Vascular Supply

The difference in embryologic origin of structures above and below the pectinate line is reflected in their vascular supply. Proximal to the pectinate line, branches of the inferior mesenteric artery, namely, the superior rectal (hemorrhoidal) artery, are responsible for supplying the canal. The middle rectal (from the internal iliac) and inferior rectal (from the internal pudendal artery) arteries supply the anal canal distal to the pectinate line.

Venous drainage also differs with respect to the pectinate line. The internal hemorrhoidal plexus lies above the pectinate line and drains via the superior rectal vein to the inferior mesenteric vein and into the portal system. The external hemorrhoidal plexus is located below the pectinate line and drains via the inferior and middle rectal veins to the internal iliac veins.

Lymphatic Drainage

Lymphatic drainage of the upper and lower portions of the anal canal follows the locoregional vascular supply. Above the dentate line, local lymphatic drainage leads to mesorectal nodes contained within the mesorectal fascia before ascending further to the nodes along the superior rectal artery. The lymphatics subsequently drain to the inferior mesenteric nodes and ultimately to the preaortic lymph nodes. The internal anal sphincter and conjoined longitudinal muscle similarly follow this path of lymph drainage. Below the dentate line, lymph drains to the superficial inguinal lymph nodes [15]. These nodes lie immediately inferior to the inguinal ligament and ultimately drain to the external iliac and lateral aortic lymph nodes via the deep inguinal nodes. The external anal sphincter also drains along this lymphatic pathway.

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Chapter 2
Epidemiology and Pathogenesis of Anal Cancer

John David Roveda Jr and Clayton A. Smith

Abbreviations

5FU	5-Fluorouracil
AIDS	Acquired immunodeficiency syndrome
AIN	Anal intraepithelial neoplasia
APC	Antigen-presenting cells
ASC-US	Atypical cells of undetermined significance
DARE	Digital anorectal exam
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HRA	High-resolution anoscopy
HSIL	High-grade squamous intraepithelial lesion
LSIL	Low-grade squamous intraepithelial lesion
MSM	Men who have sex with men
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
Pap	Papanicolaou
qHPV	Quadrivalent HPV vaccine
SCC	Squamous cell carcinoma
SEER	Surveillance, Epidemiology, and End Results
SIR	Standardized incidence ration
TCA	Trichloroacetic acid
UK	United Kingdom
US	United States

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Introduction

The majority of cases of anal squamous cell carcinoma (SCC) are caused by chronic human papillomavirus (HPV) infection. Patients with additional risk factors including coinfection with human immunodeficiency virus, chronic immunosuppression, and cigarette smoking are at an increased risk of developing anal SCC. This chapter will review the data demonstrating the contribution of risk factors to anal dysplasia and invasive cancer incidence and how the incidence has changed over time with the introduction of highly active antiretroviral therapy to reduce HIV infection and HPV vaccines to reduce HPV infection. The pathogenesis of HPV infection and progression to anal dysplasia and invasive SCC will be reviewed as well as the limited data for the less common HPV-negative anal SCC. The closing sections will present evidence regarding screening programs for anal dysplasia in high-risk populations and treatment approaches for patients diagnosed with high-grade dysplasia.

A note on terminology: When discussing invasive anal cancer, this chapter refers to squamous cell carcinoma, unless otherwise stated. When referring to anal dysplasia, the consensus recommendations of the Lower Anogenital Squamous Terminology standard for HPV-associated lesions are used [1]. Dysplasia broadly refers to anal intraepithelial neoplasia (AIN). Low-grade squamous intraepithelial lesions (LSIL) correspond to AIN 1, while high-grade squamous intraepithelial lesions (HSIL) correspond to AIN 2 and 3.

Incidence of Anal Cancer

In the United States (US), there was an estimated incidence of 8580 new cases of anal cancer diagnosed in 2018, making it 0.5% of all new cancer cases [2]. Between 2011 and 2015, the overall incidence in the US population was 1.8 per 100,000 people, with a slightly higher rate in females (1.4:1). The median age at diagnosis is 62 years. Over the period from 2006 to 2015, the annual incidence in the US increased by 2.2% per year [2]. Notably, a Surveillance, Epidemiology, and End Results (SEER) data review from 1992 to 2011 found that this increase was specific to squamous cell carcinoma (2.9%/year) and carcinoma in situ (14.2%/year), while the less common adenocarcinoma of the anal canal/margin remained stable or slightly declined [3]. This increase in the incidence of SCC over time is likely related to the changes in risk factors that place certain populations at particularly increased susceptibility for this cancer.

Risk Factors for Anal Squamous Cell Carcinoma

There have been many population-based and case-control studies investigating risk factors for the development of invasive anal SCC. Several factors are closely associated, such as the number of lifetime sexual partners and acquisition of sexually

transmitted infections, namely, human papillomavirus and human immunodeficiency virus. Identification of patient risk factors is important for interventions aimed at primary prevention, secondary prevention, and management of invasive disease.

HPV Infection

An estimated >85% of anal cancers are associated with HPV infection, making it the strongest risk factor for the development of the disease [4, 5]. Underlying risk factors that increase the risk of HPV acquisition include an increased number of sexual partners, receptive anal intercourse, and prior HIV infection or immunosuppression [6, 7]. Additionally, prior HPV-related malignancy also increases the risk of developing anal HPV infection and anal cancer [8]. The remaining risk factors for anal cancer are considered to be permissive or facilitative of chronic HPV infection. The pathogenesis of HPV infection and of progression to malignancy is discussed in section "Pathogenesis."

There are currently three FDA-approved vaccines for the primary prevention of HPV: a bivalent vaccine against HPV types 16 and 18 approved for females aged 9–25 (Cervarix; GlaxoSmithKline Biologicals, Rixensart, Belgium); a quadrivalent vaccine against HPV types 6, 11, 16, and 18 (qHPV) approved for males and females aged 9–26 (Gardasil; Merck and Co., Kenilworth, NJ); and a nonavalent vaccine against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 approved for males and females aged 9–45 (Gardasil 9; Merck and Co., Kenilworth, NJ). Expansion to individuals aged 27–45 was approved in October 2018 [9]. The Gardasil vaccines specifically include prevention of anal cancer and dysplasia as indications for use. These vaccines contain virus-like particles with recombinant L1 capsid protein from the various targeted HPV types but do not contain virus DNA. They have shown great promise in decreasing the risk of cervical dysplasia and cancer in females, but the data on effects in preventing anal dysplasia and anal cancer are limited.

Palefsky and colleagues examined a subset of 602 men who have sex with men (MSM) from a larger double-blind, randomized placebo-controlled trial investigating the effect of qHPV vaccine on preventing genital warts in males [10]. The overall population was MSM aged 16–26, HIV-uninfected at study entry and without a prior history of anogenital lesions. The per-protocol population included patients who received all three doses of the vaccine and were HPV-negative at study entry. The intention-to-treat population received at least one dose of the vaccine and could be any HPV status. In the per-protocol population, qHPV demonstrated efficacy in preventing AIN by 78%, in preventing HSIL by 75%, and in reducing persistent anal HPV infection by 95% relative to placebo. Persistent anal HPV infection was defined as detection of the same HPV type on at least two consecutive anal swab tests performed at least 6 months apart through the 36-month follow-up period. In the intention-to-treat population, the vaccine demonstrated efficacy in preventing AIN by 50%, in preventing HSIL by 54%, and in reducing persistent anal HPV

infection by 59%. There were no incidents of invasive anal cancer during the study follow-up. These findings suggest that HPV vaccination, particularly for the high-risk population of MSM, can reduce the risk of HPV-related dysplasia, which in turn may prevent future invasive disease.

Since persistent HPV infection increases the risk of developing HSIL and invasive cancer, some have questioned whether HPV vaccination may benefit patients with a prior history of anal dysplasia in preventing a recurrence. An early nonconcurrent cohort study of 202 MSM (88 qHPV vaccinated, 114 non-vaccinated) with previously treated HSIL assessed recurrence rates and factors influencing recurrence [11]. Patients receiving qHPV had an HSIL recurrence rate of 14% vs. 31% of unvaccinated patients. On multivariable analysis, qHPV was found to significantly reduce the risk of recurrent HSIL (hazard ratio 0.50). This promising retrospective finding suggested that patients beyond those at young ages with approved indications for vaccination may derive benefit in reducing recurrent HSIL.

This question was tested in the Acquired Immunodeficiency Syndrome (AIDS) Clinical Trials Group A5298 phase 3, double-blind, randomized, placebo-controlled trial [12]. It randomized 575 HIV-infected patients (including 103 females), age ≥27 years (median 47–48 years), to qHPV or placebo. With a median follow-up of 3.4 years, the study was stopped early for futility. They observed a vaccine efficacy of 22% for reducing persistent anal HPV infection and 0% efficacy in preventing new biopsy-confirmed HSIL. For patients with HSIL at diagnosis who underwent at least one treatment, vaccination did not reduce the risk of recurrence (63% qHPV vs. 57% placebo). They confirmed that qHPV increased seropositivity for all four HPV types by >97% in the vaccine group, without a significant change in the placebo group. These data do not support the routine use of vaccination in this population.

Taken together, the available data demonstrate the profound ability of HPV vaccines to increase immunity to oncogenic HPV types in patients without significant prior exposure. Currently, the Advisory Committee on Immunization Practices of the CDC recommends routine vaccination starting at age 11–12 (or as early as 9), as well as for females aged 13–26 and males aged 13–21. MSM, transgender people, and immunocompromised people are recommended to receive the vaccine through age 26.

HIV

It is estimated that 28% of men and 1% of women diagnosed with anal SCC have HIV infection [13]. As a group, HIV-infected patients have an increased incidence of anal dysplasia and invasive cancer and are typically diagnosed at a younger age [14, 15]. The estimated cumulative incidence of invasive anal cancer by age 75 for HIV-infected people is 1.5% vs. 0.05% for the general population [16]. Population-based cohorts and registries have provided valuable information on the risk of developing anal cancer in HIV-infected patients relative to the general population.

The trends in incidence have changed over time primarily due to the introduction of highly active antiretroviral therapy (HAART) around 1996. A meta-analysis by Machalek et al. [7] found that the incidence of anal cancer increased in HIV-infected MSM in the HAART era relative to pre-HAART era (Fig. 2.1) [7].

An analysis of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) multi-cohort of >34,000 HIV-infected and >114,000 HIV-uninfected individuals assessed from 1996 to 2007 found that HIV-infected MSM as a group were 80 times more likely to develop invasive anal cancer relative to

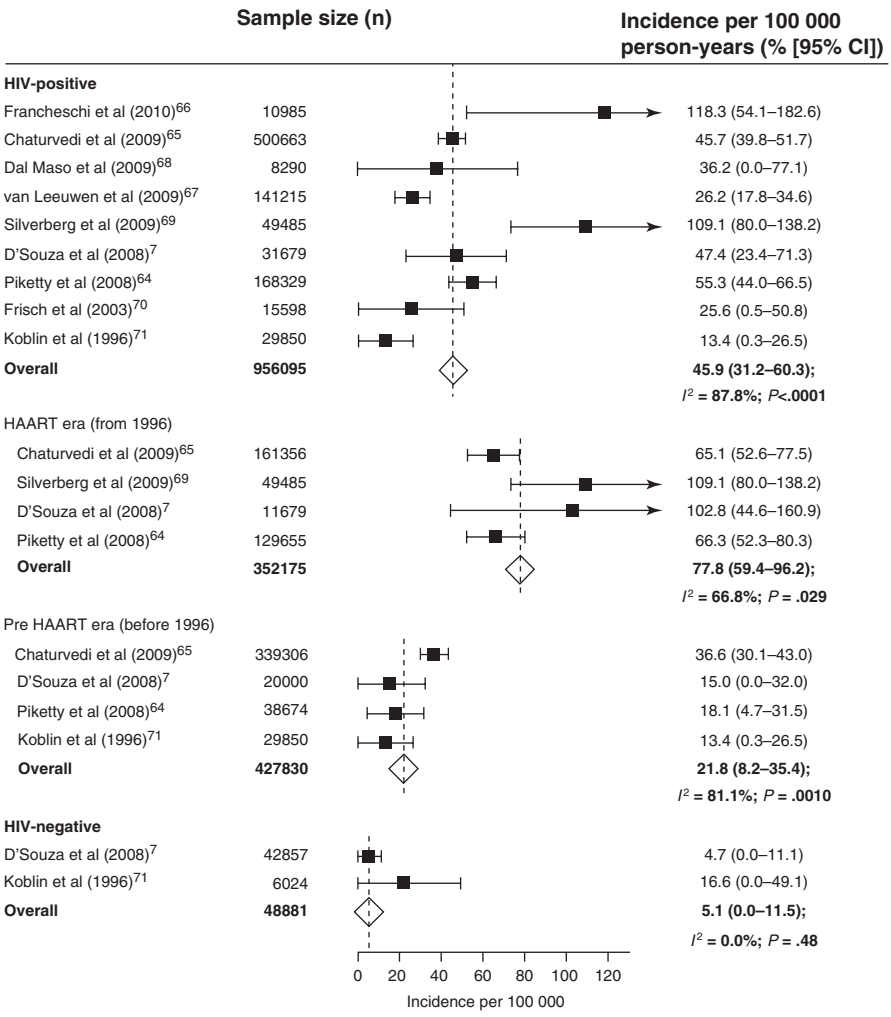

Fig. 2.1 Incidence of anal cancer in men who have sex with men, reported by HIV status. HIV-infected men had a higher incidence following the introduction of highly active antiretroviral therapy. (Used with permission of Elsevier from Machalek et al. [7])

HIV-uninfected men [14]. Other HIV-infected males (non-MSM) were at 27 times greater risk relative to HIV-uninfected men. In examining trends over time, there was an observed increase in anal cancer incidence between 1996–1999 and 2000–2003, though this appeared to stabilize by 2004–2007.

An investigation of the HIV/AIDS Cancer Match Study, which combines data from US HIV and cancer registries, assessed trends between 1996 and 2012 for ~448,000 HIV-infected patients [17]. As a group, HIV-infected people were found to have a standardized incidence ratio (SIR; the ratio of observed patients with cancer in the group divided by the expected rate of cancer in the general population) of 19.1. Further breakdown by sub-group found increased SIRs for MSM (33.2–38.7), non-MSM males (9.4–11.4), and females (7.9–13.5). Incidence increased with age, white race/ethnicity, and prior diagnosis of AIDS. When examining changes in incidence over time, between 1996 and 2000, there was an increase of 32.8%/year, from 2001 to 2008, there was a plateau with an increase of only 1.4%/year, and from 2008 to 2012, there was a decline in the incidence of 7.2%/year. These results are consistent with those of the NA-ACCORD in that the early HAART era saw an increase in anal cancer incidence in the HIV-infected population, particularly MSM, while by the mid-2000s, this appeared to stabilize or even decline.

Given the initial increase in the incidence of anal cancer in the early HAART era followed by a plateau or decline more recently, the effect of HAART on anal cancer development remains unclear. Following the introduction of HAART, HIV-infected patients began living much longer lives. Because of this, the natural history of HPV infection and progression to invasive disease over one to two decades is also more likely to occur as HIV-infected people live to older ages. Therefore, the increase in incidence in the initial post-HAART era may reflect those patients previously co-infected with HPV in the 1980s and early 1990s, with improved life expectancies following initiation of HAART, allowing for the natural history of progression to invasive disease to manifest.

Multiple studies have found that a low CD4 count <200/mm^3 or low CD4 nadir is associated with an increased progression from LSIL to HSIL or with an increased incidence of invasive anal cancer [17–21]. A study of the prospective French Hospital Database on HIV with >52,000 patients from 1998 to 2006, found that the duration of time with CD4 count <200 cells/mm^3 had a significantly increased relative risk of anal cancer of 1.3 per year [21]. Similarly, an analysis of the British Columbia Cancer Registry and HIV/AIDS Drug Treatment Program Registry examined records on ~1600 HIV-infected MSM treated with HAART between 1988 and 2008 (both pre- and post-HAART era year of 1996) [19]. Both CD4 count nadir <100 cell/mm^3 and duration of low CD4 count were associated with an increased incidence of anal cancer. Interestingly, patients treated in the pre-HAART era had a faster time between initial CD4 count or HIV RNA viral load test and development of anal cancer, while patients in the post-HAART era had a longer time to diagnosis of invasive disease. Collectively, these findings suggest that HAART may delay progression to invasive disease for patients who are started on treatment earlier in their course and thus potentially have spent less time immunocompromised.

HIV infection has unquestionably increased the risk of anal dysplasia and anal SCC for an entire population of people. Although the early post-HAART era provided the promise of longer life expectancies for patients living with HIV, the data clearly demonstrate that this also coincided with an increased incidence of anal dysplasia and invasive cancer. While more recent data suggest the upward trend in the incidence of anal SCC may have leveled off for this population, they remain at an increased risk of disease that warrants consideration in the establishment of primary and secondary prevention programs. Anal cancer screening and treatments for anal dysplasia are discussed below in sections "Screening for Anal Dysplasia and Anal Cancer" and "Management of Anal Dysplasia."

Non-HIV Immunosuppression

Chronic immunosuppression without HIV infection also carries an increased risk of development of AIN and invasive anal cancer, though the data supporting this are more limited due to lower prevalence relative to HIV infection. A cohort study linking the US Scientific Registry of Transplant Recipients with multiple state and regional cancer registries examined the incidence of multiple cancers in >175,000 solid organ transplant patients between 1987 and 2008 [22]. It found a significantly increased incidence of anal cancer with a SIR of 5.8. An analysis for the Swedish Cancer Registry of 5900 patients who received organ transplants between 1970 and 1997 found a SIR of 10 for anal cancer in this subpopulation [23]. The increased incidence associated with immunosuppression is thought to be related to decreased immunity or clearance of HPV in this population, as an estimated 47% of established renal transplant patients have HPV infection, while only 23% of new organ transplant patients test positive [24, 25]. Based on these findings, patients who have either inherited or acquired chronic immunosuppression are frequently included in algorithms for anal cancer screening.

Cigarette Smoking

Smoking is also associated with an increased risk of invasive anal cancer [6, 26, 27]. An early case-control study in the San Francisco Bay Area found that smoking increased the relative risk of anal cancer by 1.9 in smokers with at least 20 pack-years and up to 5.2 in smokers with >50 pack-years [26]. This study did account for sexual orientation but not HIV status. Another case-control study of patients from the Seattle area detected an odds ratio of developing anal cancer in current smokers of 3.9 in men and 3.8 in women, factoring out the effects of age, sexual orientation, and the number of sexual partners [6]. A similar association has been found when investigating subpopulations at higher risk for anal cancer. A study of 800 HIV-infected MSM who participated in a German anal cancer screening program between 2003 and 2014

were compared by smoking status [28]. At baseline, smokers were found to have greater high-risk HPV DNA (89% vs. 80%), dysplasia (58% vs. 52%), and HSIL (23% vs. 17%). Over the course of follow-up, smokers were also more likely to develop HSIL (40% vs. 33%). Finally, an analysis of 1.3 million women who enrolled in the United Kingdom's (UK) Million Women Study from 1996 to 2001 with a median of 13 years follow-up found that smokers (women with any history of tobacco use) had a relative risk of developing anal cancer of 1.49 [27]. This was primarily driven by squamous cell carcinoma (relative risk 1.66 for SCC vs. 0.89 for adenocarcinoma in smokers relative to non-smokers). For comparison, the same study found that prior cervical intraepithelial neoplasia grade 3 had a relative risk of 4.03, while living without a partner carried a relative risk of 1.82. Collectively, these findings suggest that cigarette smoking increases the risk of anal dysplasia and invasive cancer, though the mechanism remains unclear and is likely multi-factorial.

As noted above, many of the risk factors for the development of anal SCC are interrelated. The driving factor, HPV infection, is associated with sexual practices such as increasing number of sexual partners and anoreceptive intercourse, as well as facilitated by HIV infection, immunosuppression, and cigarette smoking. Additionally, patients with a prior HPV-related dysplasia or invasive cancer are more likely to develop anal SCC in the future. With the introduction of the HPV vaccine as primary prevention, there is great promise that the incidence of anal dysplasia and invasive cancer will decrease in the future; however, at this time, the data are merely suggestive and not yet mature enough to make that conclusion. The mechanisms by which HPV promotes carcinogenesis are discussed in the next section.

Pathogenesis

HPV-Positive Anal SCC

HPV is a double-stranded circular DNA virus capable of integrating into the host genome of squamous epithelium. Humans are the only known host for HPV. There are at least 200 HPV genotypes, of which high-risk types 16 and 18 are predominantly responsible for carcinogenesis, while low-risk types 6 and 11 are the predominant cause of benign genital warts. The viral genome encodes for two classes of genes: E (early) genes *E1–E2* and *E4–E7* encode for their respective proteins associated with viral replication, while L (late) genes *L1–L2* encode for proteins of the capsid shell. The L1 protein is a target of HPV vaccines.

HPV-induced carcinogenesis is driven primarily by E6 and E7 proteins. E6 binds to p53 and promotes its degradation by the ubiquitin pathway [29, 30]. The result of this is to inhibit the function of p53 to promote cell cycle arrest and apoptosis [31]. E7 protein binds to pRb and promotes its degradation [32, 33]. pRb is normally complexed with the E2F transcription factor, which prevents E2F from promoting progression through G1 to S phase of the cell cycle. pRb also negatively regulates the activity of the cyclin-dependent kinase inhibitor p16. Therefore, by binding to

pRb, E7 protein promotes cell cycle progression and proliferation as well as upregulation of p16. Collectively, these functions of E6 and E7 are necessary to promote progression to HSIL and invasive malignancy, but they are not sufficient on their own for the development of cancer. It is thought that repeated viral infection and cell proliferation leads to increased mutational burden of transformed cells over time, eventually resulting in the malignant phenotype.

The classical model for HPV infection and pathogenesis starts with exposure of the epithelium to the virus, most commonly by sexual contact. In the anal canal, the squamocolumnar transition zone is the most vulnerable region to infection. Viral particles first infect basal epithelium, following which early proteins are translated from viral episomal DNA in host cells (Fig. 2.2). Early following infection, E2 protein binds to *E6* promoter region and attenuates translation. At this time, E5 protein promotes viral replication and early cellular transformation via the Epidermal Growth Factor Receptor (EGFR) pathway [35]. Over time and when viral DNA integrates into the host genome, E5 expression decreases and breakage of the *E2* region causes decreased E2 translation with resultant upregulation of E6. The upregulation of E6 and E7 leads to cellular proliferation and high-grade dysplasia. As mutational burden builds within the cell, and in conjunction with environmental and host factors, progression to invasive malignancy occurs. The natural timeline of this progression from HPV infection to dysplasia to invasive cancer is likely on the

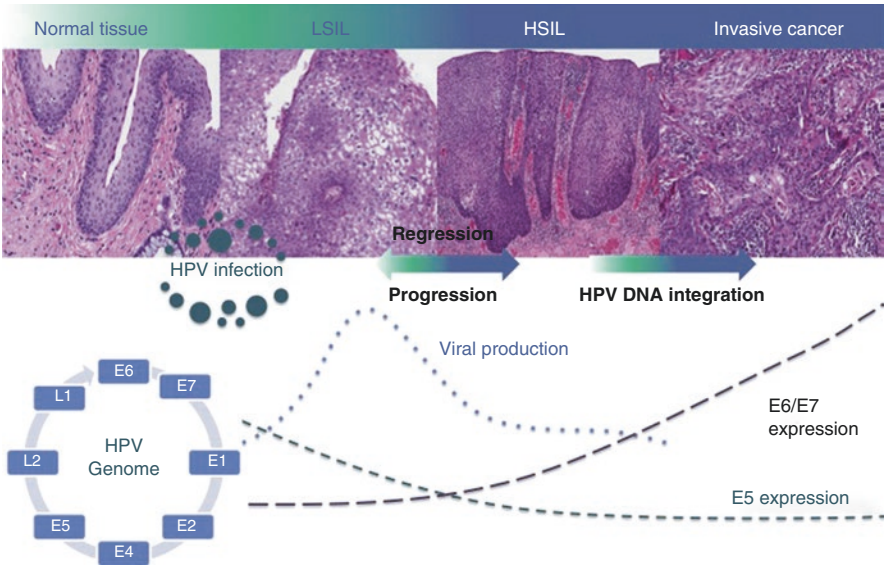

Fig. 2.2 Pathogenesis of HPV infection leading to anal intraepithelial neoplasia and invasive squamous cell carcinoma. Early E5 translation and viral replication co-occur with differentiation of infected epithelial cells. Following viral DNA integration into the host genome, E2 production is lost, leading to increased translation of oncogenic E6 and E7 proteins. LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion. (Used with permission of Elsevier from Hoff et al. [34])

order of years to decades, but multiple factors (including the risk factors listed above) influence how rapidly this develops.

Mechanisms of Immunity and Immune Evasion

Although the majority of AIN and anal SCC cases are associated with HPV infection, most patients infected with HPV clear the virus before developing progression. Even in cases where HSIL develops, the estimated progression to invasive disease is 2–13% for the general population, though this number is considered to be much higher for immunocompromised patients [36–38]. The exact mechanisms by which the host immune system clears HPV infection are not fully understood, but there is likely an initial inflammatory response by innate immune cells such as dendritic cells and natural killer cells, followed by T-cell infiltration. Following natural infection, HPV-directed antibody titers are generally low and do not appear to protect against subsequent infection, indicating poor humoral immunity [39].

The reproductive cycle of HPV allows for host immune evasion because it occurs within the epithelial cell only. Infection occurs in the basal epithelial layer, so as epithelial cells differentiate they become more superficial. It is only upon natural cell death and desquamation that viral particles are released and again exposed to superficial skin or mucosa to allow for re-infection. This lack of virus-induced cell death and of viremia allows for escape from antigen-presenting cells (APCs) and from a strong host antibody production, respectively. Additional ways that high-risk HPV genotypes have developed to evade the host immune system include downregulation of pro-inflammatory cytokines such as interferon and downregulation of cell surface proteins that promote expression of MHC-I and binding of APCs [40–42].

HPV-Negative Anal SCC

There are very limited data on the pathogenesis of HPV-negative SCC, likely due to the limited number of cases in an already rare cancer. One early review of 35 anal SCC samples (11 HPV-negative, 24 HPV-positive) found no differences in morphology but noted that HPV-negative tumors were more likely to arise from the anal margin rather than the anal canal (55% HPV-negative vs. 8% HPV-positive) [43]. A more recent study examined 107 anal SCC tumors (14 HPV-negative, 93 HPV-positive) and found an increased rate of disruptive TP53 mutations in HPV-negative tumors (80% vs. 6%) [44]. HPV-negative status was associated with worse locoregional control and survival. A similar study performing genomic profiling of 70 anal SCC (9 HPV-negative, 61 HPV-positive) found loss-of-function mutations in TP53 and CDKN2A (encoding for p16) significantly increased in HPV-negative tumors and rarely found in HPV-positive tumors [45]. Based on these data, it has been proposed that p53 suppression is a necessary step in anal SCC tumorogenesis, occurring by viral E6 protein in HPV-induced tumors or by the increased genomic mutational burden in HPV-negative tumors [46]. The steps that lead to the development of HPV-negative anal SCC remain unclear.

Screening for Anal Dysplasia and Anal Cancer

There are no randomized prospective trials that demonstrate a reduction in invasive anal SCC or improvement in mortality following anal cancer screening. At this time, most major professional societies do not make official recommendations for screening of anal intraepithelial lesions, nor does the US Preventive Services Task Force; however, the similar pathogenesis of cervical and anal cancers has caused some to advocate that the successful decrease in mortality following cervical cancer screening may lead to a similar outcome in patients at high risk of anal cancer. While there are much debate and ongoing research about when to screen, there is agreement that screening programs should have experienced personnel available to interpret anal cytology and have access to high-resolution anoscopy.

Due to the low prevalence of the disease, screening the general population is not considered to be effective, though patients at high risk for disease including HIV-infected individuals with genital warts, MSM, and women with prior HPV-related dysplasia or malignancy, may derive a benefit [47]. Currently, the standard for screening is high-resolution anoscopy (HRA), but other methods such as digital anorectal exam (DARE), anal Papanicolaou (Pap) test, and HPV co-testing are also in use (Table 2.1).

Screening Modalities

Digital Anorectal Examination

Until 1997, the American Cancer Society recommended DARE for screening of colorectal cancer, but this recommendation was discontinued based on lack of supportive evidence. One consequence of this decision may have been a reduction in screening evaluation of patients at high risk for anal cancer. While the American Society of Colon and Rectal Surgeons does not make specific recommendations for anal cancer screening, DARE is advised as a necessary component in the physical examination of patients

Table 2.1 Screening modalities to detect anal dysplasia and invasive cancer

Modality	Sensitivity	Specificity	Advantages	Limitations
DARE	Not tested	Not tested	Easy to perform	Can only identify gross, palpable lesions
Anal pap testing	63–93%	32–60%	Easy to perform	Interpretation varies by reader; higher false negatives in at-risk populations
HPV testing	94–100%	17%	Easy to perform	At-risk populations have high prevalence, limiting usefulness of test
HRA	Diagnostic standard	Diagnostic standard	Best test for making diagnosis	Requires more equipment and significant training, so is limited to higher volume centers

DARE digital anorectal exam, *Pap* Papanicolaou, *HPV* human papillomavirus, *HRA* high-resolution anoscopy

with anorectal complaints, especially those with anal cancer risk factors [48]. Although DARE carries minimal risk to the patient and is easily administered, there are no studies providing the sensitivity and specificity of DARE as a screening method.

Anal Papanicolaou Test

Pap testing for cervical cancer began in the 1960s and became utilized in screening for anal dysplasia in the 1990s [49]. It involves swabbing of the area of interest (for anal dysplasia, ideally including the squamocolumnar junction in the anal canal) followed by cytologic grading of the collected cells by a pathologist. One advantage of the Pap test is that it is easy to perform; however, the sensitivity and specificity of the test have a wide range from approximately 63–93% and 32–60%, respectively, based on variability in interpretation [49–52]. Additionally, the false-negative rates for anal Pap testing increase in higher risk groups, indicating that anal pap testing by itself is not an adequate screening test but must be used in combination with techniques that offer visualization [53]. A meta-analysis comparing the ability of cervical Pap testing to discriminate LSIL vs. HSIL to the ability of anal Pap testing to discriminate found that anal Pap testing was less discriminating than the cervical test (receiver operating characteristic area 0.700 vs. 0.834) [54]. For these reasons, most algorithms for anal cancer screening recommend HRA in patients with a finding of at least atypical squamous cells of undetermined significance (ASC-US).

HPV Testing

This method for screening may utilize the same sample collected during anal Pap testing, and is therefore easy for physicians to perform. Although HPV testing has shown clinical utility in cervical cancer screening, it has not been found to improve upon the detection of anal cancer when combined with anal Pap testing [55, 56]. Additionally, since no guidelines at this point recommend the use of HPV testing alone, insurance companies often will not cover the test.

High-Resolution Anoscopy

HRA makes use of high-magnification colposcopy coupled with a transparent anoscope that allows direct visualization of the anal canal. It is currently the diagnostic standard for AIN screening; however, the availability of HRA is limited compared to anal Pap and HPV testing, and requires more formal training than the previously mentioned screening modalities. Similar to colposcopy, upon visualization, 5% acetic acid is applied to distinguish areas of rapid cell growth, and Lugol's solution is then added to determine low- vs. high-grade dysplastic areas. HRA is the standard diagnostic procedure against which Pap and HPV testing are compared.

As discussed above, MSM regardless of HIV status are at increased risk of developing anal dysplasia and invasive cancer. The ANALOGY trial conducted in the UK was designed to determine the practicality of screening MSM for anal cancer and compared HPV testing, Pap testing, and HRA as screening modalities [57]. Over 280 MSM (~200 were HIV-infected) were followed for 3 years with HPV testing, anal Pap testing, and HRA for screening. High-risk HPV testing detected a high HPV prevalence of 88% in HIV-infected MSM and 78% in HIV-uninfected MSM. HPV testing for HSIL (AIN2 or AIN3) had a very high sensitivity of 94%, but a low specificity of 17%. Overall, 43% of MSM had abnormal cytology results on Pap testing, but one-third of HSIL cases found on HRA had negative cytological results. Pap testing sensitivity was 63% and specificity 60% for HSIL. Although the combination of anal Pap and HPV testing would have identified the majority of HSIL cases, only 10% of participants had a negative result for both tests and would have been spared a biopsy. HRA detected a prevalence of AIN3 in 7% of HIV-infected MSM and 4% in HIV-uninfected MSM, while the prevalence of HSIL was 27% and 21%, respectively. These results suggest that HRA may be the screening modality with the greatest ability to detect HSIL in this population. While recognized as the best available diagnostic modality, HRA is still infrequently used for primary screening due to its limited availability and technical demands. Screening algorithms for AIN and invasive cancer recommend HRA following abnormal pap result (Fig. 2.3).

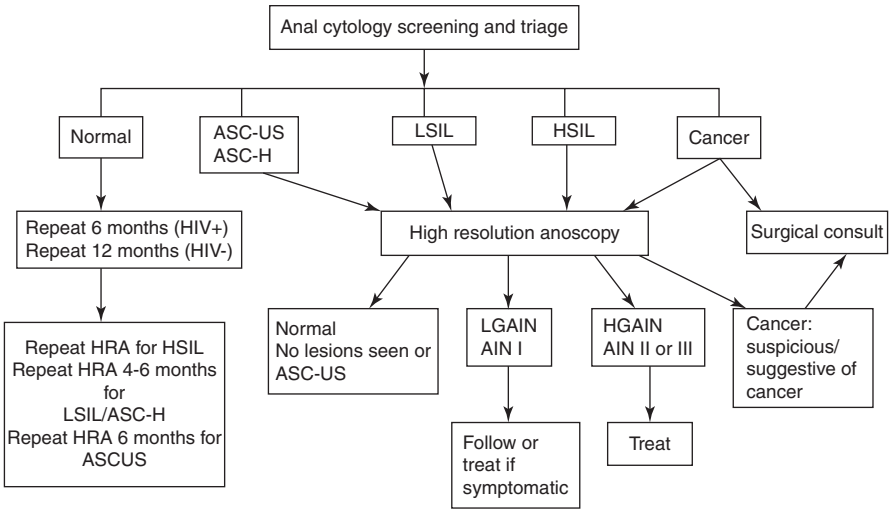

Fig. 2.3 Algorithm for anal cancer screening from the University of California San Francisco Anal Neoplasia Clinic. ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells cannot rule out high-grade lesion; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; LGAIN, low-grade anal intraepithelial neoplasia; HGAIN, high-grade anal intraepithelial neoplasia; HRA, high-resolution anoscopy. (Used with permission of Elsevier from Palefsky and Rubin [58])

At this time, most major professional societies and the US Preventive Services Task Force do not make specific recommendations for screening of anal dysplasia and SCC. While the prevalence in the general population is too low for screening to be cost-effective, certain high-risk populations should be followed more closely. High-risk groups including HIV-infected individuals, MSM, women with prior HPV-related dysplasia or cancer, and patients who have chronic immunosuppression may benefit from screening, though further studies are needed to determine the impact on anal cancer prevention or detection at an earlier stage.

Management of Anal Dysplasia

AIN, particularly AIN 2 and 3, is considered a precursor to invasive anal carcinoma. It is thought that the identification of these precancerous lesions may allow for treatment before progression to invasive cancer occurs. Patients diagnosed with LSIL or AIN 1 on biopsy do not require curative treatment because the rate of direct progression to invasive cancer is low, but they are candidates for local therapy options if symptomatic. Since they are at risk for progression to HSIL, follow-up at least every 6 months is advised to monitor for progression. Many modalities are available for treating AIN, though the clinical factor that dictates which treatment option to use is predominantly size. This section will discuss the different treatment modalities available and the studies assessing their efficacy (Table 2.2). There are no randomized data available at this time demonstrating a mortality or morbidity benefit from treatment over observation.

Topical Therapies

Trichloroacetic Acid (TCA)

TCA is a local ablative therapy performed by the provider in combination with HRA. It can require 4–5 office treatments before a lesion is cleared. A review of 54 patients including both HIV-infected and HIV-uninfected males found a clearance rate of 73% for AIN 1 and 64% for AIN 2/3 [59]. Recurrence rates were not reported.

Table 2.2 Treatment options for anal intraepithelial neoplasia

Treatment	Type	Response rate	Recurrence rate
TCA	Topical ablation	61–79%	21–28%
5FU	Topical	17–57%	50–58%
Imiquimod	Topical	24–74%	58–71%
Cidofovir	Topical	70–76%	35%
Infrared coagulation	Procedural	67–80%	36%
Electrocautery	Procedural	39–93%	15–79%
Cryotherapy	Procedural	60%	68%

TCA trichloroacetic acid, *5FU* 5-fluorouracil

A similar review of 72 HIV-infected patients with 98 HSILs treated with TCA found that 79% of lesions regressed either completely or to LSIL, with 76% requiring only one or two treatments [60]. Of the patients who were followed for at least 1 year, 21% of lesions recurred and 17 new lesions were diagnosed. TCA provides a low cost, practical treatment option with no long-term side effects, making it an attractive therapy for practices that provide HRA.

5-Fluorouracil (5FU)

5FU is a pyrimidine analog in which the position 5 ring of uracil is fluorinated. It inhibits DNA synthesis by blocking uracil conversion to thymine. It is typically used as 5% strength for topical treatment of HSIL. Potential side effects are skin irritation, erythema, pain, edema, and ulceration. An open prospective trial including 46 HIV-infected MSM with HRA-diagnosed AIN (74% HSIL) evaluated the efficacy and safety of self-administered 5FU twice weekly for 16 weeks. Repeat biopsies were performed at the end of the study. Based on intention-to-treat analysis, 57% of patients had either clearance or partial response to 5FU. Although 85% of patients had side effects, including local irritation and tenesmus, only two patients discontinued 5FU. At 6-month follow-up, 50% of complete responders developed recurrence. This study suggests that 5FU can be a practical treatment option offering high response rates with acceptable side effects, but it also requires close follow-up due to the high recurrence rate. A randomized trial comparing 5FU to imiquimod and electrocautery is discussed below.

Immune Modulating Therapy

Imiquimod is a topical therapy that acts as a Toll-like receptor agonist to activate the immune system. It stimulates the production of inflammatory cytokines locally, which in turn attracts T cells and natural killer cells. One prospective study of 19 HIV-infected MSM with AIN treated with imiquimod three times per week for 4 months reported 74% clearance at the initial site after a mean of 30 months [61]. During the follow-up period, 58% of patients developed new abnormalities in additional sites, with half of those being HSIL. This regimen was then tested in a double-blind, randomized controlled trial comparing imiquimod to placebo cream [62]. Fifty-three HIV-infected MSM with HSIL were randomized to the same protocol of imiquimod cream three times a week for 4 months or to placebo cream. Of the patients receiving imiquimod, 43% had either clearance or downgrade to LSIL. In contrast, only one patient receiving placebo had clearance.

Cidofovir

Cidofovir is an analogue of cytidine that has been demonstrated to have selective cytotoxicity against HPV-infected cells [63]. One small pilot study of 16 HIV-infected patients with HSIL administered 1% topical cidofovir cream applied three

times weekly for 4 weeks [64]. At 12 weeks follow-up, 62% of patients achieved complete response by HRA and biopsy. At 24 weeks, 70% achieved complete response. An additional study compared the effectiveness of cidofovir to electrocautery in HIV-infected patients with anal warts [65]. Seventy-four patients were randomized to electrocautery, cidofovir, or combined electrocautery followed by cidofovir 1 month later. The complete response rates were 93%, 76%, and 100%, respectively. Interestingly, relapse rates were 74%, 35%, and 27%, demonstrating the utility of cidofovir in reducing the recurrence of HPV-related anal dysplasia. Since cidofovir is only FDA approved for the treatment of cytomegalovirus retinitis, it is not covered by most insurance plans. It is also not commercially available without acquisition from a compound pharmacy.

Non-topical Therapies

Infrared Coagulation

This is an outpatient procedure utilized in lesions too large for topical therapy. Treatment consists of a 1.5 s pulse directly applied to the lesion that destroys tissue to a depth of 1.5 mm. Following tissue destruction, forceps can be utilized to debride the tissue. One report of 74 lesions in 68 HIV-infected MSM found 64% effectiveness in preventing recurrence [66]. A larger study of 96 MSM (44 HIV-infected) with HSIL treated with infrared coagulation observed recurrence in 62% of HIV-uninfected MSM and 91% of HIV-infected MSM [67]. After the first ablation, individual lesion local control was 80% for HIV-uninfected MSM vs. 67% for HIV-infected MSM, thus most recurrences were metachronous and more likely to occur in HIV-infected males. An alternative strategy of treating patients with HSIL up-front with surgical excision/cauterization followed by outpatient infrared coagulation was reported by Pineda and colleagues [68]. They reported on 246 patients treated over 10 years, with 78% of patients free of HSIL at last follow-up and 1.2% of patients progressing to invasive cancer during that period. These findings suggest that initial surgical excision/cauterization followed by ablation at recurrence may be a better strategy to prevent recurrence than up-front infrared coagulation alone.

Electrocautery Ablation

Lesions that are too large for either infrared coagulation or are poorly visualized are candidates for treatment with HRA guided electrocautery ablation. A retrospective review of 232 MSM with HSIL treated with electrocautery ablation observed local control rates after a single treatment of 85% and 75% in HIV-uninfected and HIV-infected MSM, respectively [69]. During the course of follow-up, 53% and 61% of HIV-uninfected and HIV-infected MSM, respectively, recurred. A prospective study of 37 patients with HSIL treated with initial excision/cauterization and followed for

a mean of ~30 months reported no HSIL recurrences in the eight HIV-uninfected patients but 79% HSIL recurrence rate in HIV-infected patients [70]. More recently, a propensity-scored retrospective analysis of HIV-infected MSM with HSIL treated with electrocautery ($N = 182$) compared with patients treated with TCA ($N = 56$) observed a complete response of 34% vs. 61%, respectively [71]. Cumulative incidence of recurrence during the first year was 15% for electrocautery and 28% for TCA. Treatments were equally well tolerated with reported good tolerance in 81% electrocautery vs. 83% TCA. Based on these findings, the authors recommended TCA as first-line treatment for most HSIL.

A prospective randomized trial conducted in the Netherlands assessed AIN response to treatment with imiquimod, 5FU, and electrocautery in HIV-infected MSM [72]. Patients were randomized to either 16 weeks of imiquimod with three doses per week ($N = 54$), 16 weeks of fluorouracil with two doses per week ($N = 48$), or monthly electrocautery for 4 months ($N = 46$). Response to treatment was assessed with HRA 1 month after completion, and in patients with resolution, follow-up was performed with HRA every 6 months up to 18 months to identify recurrence. After 4 months of treatment, electrocautery was statistically more effective at 39% complete response compared with imiquimod and 5FU at 24% and 17%, respectively. At 18-month follow-up, HSIL recurred in 68% of electrocautery, 71% of imiquimod, and 58% of 5FU groups. Grade 3–4 toxicity occurred in 18% of electrocautery, 43% of imiquimod, and 27% of 5FU groups. These findings support the initial effectiveness of electrocautery as well as continued surveillance regardless of the treatment given the high rates of recurrence across groups. TCA was not included as an arm on this trial, though the retrospective data discussed above suggest it may offer better first-line management in patients with less extensive HSIL.

Cryotherapy

Cryotherapy has long been used in the treatment of pre-malignant diseases of the skin. While cryotherapy has been proposed as an alternative approach for HSIL, there are very limited data regarding its effectiveness. A retrospective study of 58 HIV-infected MSM treated for either intra-anal or perianal HSIL with cryotherapy for up to five sessions observed a 60% response rate with 68% of responders eventually developing recurrence over 18 months [73].

Many treatment modalities exist for AIN ranging from topical applications to ablation therapies. Overall, they appear to provide a similar efficacy in resolving or downgrading HSIL, but all fail to successfully prevent recurrence in most patients. When treating patients with AIN, it is important to have close follow-up with HRA to detect recurrence early because most recurrences are amenable to treatment. Notably, there are still insufficient data to support that early intervention of AIN reduces the risk of progression to invasive disease or anal cancer mortality when compared to close observation. To that end, the Anal Cancer HSIL Outcomes Research (ANCHOR) study is an ongoing US phase 3 randomized trial of HIV-infected patients randomized to treatment (imiquimod, 5FU, electrocautery, or laser

coagulation decided by physician) or observation to assess whether early intervention reduces rates of invasive anal cancer (Clinicaltrials.gov ID: NCT02135419). In the UK, the Laser ablation vs. Observation to Prevent Anal Cancer (LOPAC) trial is a randomized trial comparing initial laser ablation of HSIL vs. close observation in HIV-infected MSM to determine whether early intervention reduces the incidence of invasive disease.

Conclusion

The past three decades have seen a steady increase in anal cancer incidence in the general population. Although there was a dramatic increase in anal SCC incidence in HIV-infected patients in the early HAART era, recent data suggest this may now have plateaued or even be declining for this population. The impact of recently introduced primary prevention with HPV vaccines remains to be determined, but early data are promising that this will also produce a decrease in anal cancer incidence in the coming years. Much has been learned about the pathogenesis of HPV-related anal SCC, which may allow for additional immune pathway targets in the future. Unfortunately, there remain very limited data on HPV-negative anal SCC pathogenesis. The rarity of anal SCC has limited the advocation of screening programs, but these may be useful in high-risk populations. Finally, though multiple treatment modalities exist for patients identified to have high-grade anal intraepithelial neoplasia, ongoing trials will provide randomized data to inform whether early intervention is successful in reducing rates of invasive cancer or reducing anal cancer mortality.

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Chapter 3
Staging and Initial Evaluation of Anal Cancer

Apar Gupta, Shang-Jui Wang, and Salma K. Jabbour

Abbreviations

AJCC	American Joint Committee on Cancer
BMP	Basic metabolic panel
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CT	Computed tomography
DRE	Digital rectal exam
HAART	Highly active antiretroviral treatment
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IV	Intravenous
LFTs	Liver function tests
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
OS	Overall survival
PET/CT	Positron emission tomography-computed tomography
PSA	Prostate-specific antigen
SEER	Surveillance, epidemiology, and end results
SLNB	Sentinel lymph node biopsy

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Initial Diagnosis

Anal cancer commonly presents as a slow-growing mass that involves the anal canal or the perianal skin. The interval from symptom onset to diagnosis can be quite prolonged, exceeding 1 month in 80% of patients and 6 months in 33% of patients [1]. Up to one-half of patients report rectal bleeding, which may be mistakenly attributed to hemorrhoids or other benign anal pathology, and about one-third of patients report pain or sensation of a mass [2]. Other common symptoms include obstruction, incontinence, discharge, change in bowel habits, pruritus, non-healing ulcer formation, and, in more advanced cases, inguinal pain or lymphadenopathy. Up to 20% of patients may display no symptoms and are diagnosed incidentally during hemorrhoid evaluation or removal of anal tags [2].

An overview of the diagnostic workup of anal cancer is given in Table 3.1. A thorough history and physical examination should be performed, including history of anal sphincter continence, change in stool caliber, tenesmus, immunosuppression, and human papillomavirus (HPV)-related disease or malignancy. A full sexual history including HIV risk factors should also be performed. Patients who are smoking should be counseled to quit as smoking increases the risk of acute and late treatment toxicity. DRE and anoscopy/proctoscopy with biopsy are critical for diagnosis. Size, extent, and location of the mass (including any skin extension beyond the anal verge to the perianal skin and any sphincter involvement) should be noted along with anal sphincter tone and the presence of any fixation or involvement of adjacent organs. In females, a thorough gynecological exam should assess the relationship of the tumor to the vagina, including rectovaginal septum examination to rule out a

Table 3.1 Diagnostic workup of anal cancer

	Required	Recommended	Optional
History and physical	Complete history and general exam	–Genital exam in males	–
	Digital rectal exam		
	Inguinal lymph node evaluation		
	Gynecologic exam in females		
Procedures	Anoscopy or proctoscopy	Biopsy of indeterminate inguinal lymph nodes	Colonoscopy
	Biopsy of primary tumor		
	Cervical Pap smear and/or HPV testing in females		
Laboratory evaluation	CBC	HIV screening	PSA
	LFTs		
	BMP including creatinine		
Radiographic evaluation	CT or MRI pelvis	Whole-body PET/CT	–
	CT abdomen/chest		

CBC complete blood count, *HIV* human immunodeficiency virus, *PSA* prostate-specific antigen, *LFTs* liver function tests, *BMP* basic metabolic panel, *CT* computed tomography, *MRI* magnetic resonance imaging, *PET/CT* positron emission tomography-computed tomography

possible fistula. Palpation of the inguinofemoral nodes is an essential component of the physical exam as well.

The subclassification of anal cancer as anal canal or perianal cancer guides definitive management. The anal canal is defined by a superior border at the palpable puborectalis muscles of the anorectal ring and an inferior border at the anal verge corresponding to the introitus, while the perianal area encompasses a region of five-centimeter radius around the anal verge. If a tumor in the perianal region has any extension into the anal canal, it would be more properly classified as an anal canal cancer. At our institution, for tumors with significant perianal skin involvement, we often consider a diverting colostomy to reduce the risk of infection from stool passing through non-healed skin during chemoradiation. Similarly, anovaginal or other fistulae may warrant diverting colostomy.

Pathologic Evaluation

Up to 80% of anal cancers are of squamous cell histology, including predominantly non-keratinizing, poorly differentiated tumors in the anal canal distal to the dentate line and keratinizing, well-differentiated tumors in the perianal region [3, 4]. Another histology of the anal canal includes adenocarcinomas, which most often occur in the transitional zone above the dentate line and are generally treated like rectal cancers. Rare entities of the anal canal include melanoma, sarcoma, lymphoma, neuroendocrine carcinoma, and undifferentiated cancer. Rare histologies of the perianal region include verrucous carcinoma (giant condyloma), basal cell carcinoma, Bowen's disease, and Paget's disease (perianal adenocarcinoma).

Although HPV is found in the majority of anal cancers and is prognostic of overall survival [5, 6], it is not standard to perform HPV testing on the tumor sample as it does not alter management. However, HPV testing may be recommended in cases in which it may inform additional workup, for example, if other anogenital lesions are found, or if a female has had normal cervical cancer Pap smear screening in the preceding 3–5 years and HPV testing on the tumor sample may direct if rescreening should be performed. Our preference is to perform a Pap smear at the time of workup for the anal cancer. Genetic sequencing of anal tumors is also not yet standard but may play a role in personalizing therapies in the future.

Laboratory Evaluation

Basic laboratory evaluation is required for workup of anal carcinoma, including a complete blood count (CBC), basic metabolic panel (electrolytes and creatinine), and liver function tests (LFTs). Creatinine is necessary to determine feasibility and need of any dose modification of concurrent chemotherapy. Abnormal LFTs may indicate the presence of liver metastasis, prompting further evaluation with various

imaging modalities (CT, MRI, and/or ultrasound). In pre-menopausal or peri-menopausal females, pregnancy testing should be performed, as is standard before commencing radiation treatment. Finally, as detailed below, HIV testing should at a minimum be pursued in those with risk factors for infection; the preferred initial test for screening is a fourth-generation antigen/antibody combination HIV-1/2 immunoassay, followed by confirmatory testing and CD4 level if positive.

Although carcinoembryonic antigen (CEA) is elevated in ~20% of patients with anal carcinoma, it has limited diagnostic ability to detect anal cancer due to low sensitivity [7]. Specificity of CEA is also limited, given that various nonmalignant conditions can cause CEA elevation, including gastrointestinal tract infection/inflammation, liver disease, chronic obstructive pulmonary disease, diabetes, and cigarette smoking. Unlike in colorectal cancer, CEA also has no role in the assessment of prognosis or posttreatment follow-up of anal carcinoma [7, 8].

Screening for Comorbid Conditions

Colorectal Cancer Screening

Although prior studies have shown no increased risk of colorectal cancer in patients diagnosed with anal cancer, colonoscopy is often performed in the workup of anal cancer [9, 10]. The recent clinical practice guidelines developed by the American Society of Colon and Rectal Surgeons endorse colonoscopy after diagnosis of anal cancer [11], although other societies, such as the European Society of Surgical Oncology, consider it optional [12]. At a minimum, history of and time interval between any previous screening colonoscopies should be considered when making the decision to offer or refer a patient for new colonoscopy.

HIV Screening

The risk of anal cancer is significantly increased in patients with HIV infection and has been increasing over time due to improved survival from highly active antiretroviral treatment (HAART) [13–15]. While some advocate HIV testing for all patients with unknown HIV status, others only recommend it for patients at high risk for HIV infection. Recent evidence has shown similar treatment response and overall survival for HIV-positive patients treated with HAART compared to HIV-negative patients [16–18].

Multidisciplinary management with patients' infectious disease or primary care physicians should be sought. For patients with a new diagnosis of HIV, referral to an infectious disease physician should be made for evaluation and initiation of HAART, as outcomes for those with low CD4 counts have generally been found to be inferior, although the data remain equivocal [17, 19, 20].

Gynecological Cancer Screening in Females

HPV is the common causative agent of most anogenital cancers, including 91% of cervical cancers, 75% of vaginal cancers, and 69% of vulvar cancers [21]. Field cancerization can occur leading to the synchronous or metachronous development of multiple malignant or premalignant lesions. Studies have found that a diagnosis of anal cancer carries increased risk of cervical cancer, vulvar or vaginal cancer, and cervical carcinoma in situ; likewise, invasive or in situ cervical cancer is associated with increased risk of anal cancer [22–24].

As previously mentioned, gynecological exam should be performed in females to assess for extent of the primary disease. Careful examination of the vulva, vaginal canal, and cervix is additionally warranted to assess for any suspicious premalignant or malignant lesions; cervical cancer screening with Pap smear and/or HPV testing should be performed at the same time.

Genitourinary Cancer Screening in Males

Similarly, HPV is found in 63% of penile cancers in males [21], and a field cancerization effect may lead to the development of multiple anogenital cancers. Indeed, condylomata acuminata (genital warts) has been found to increase the risk of both penile and anal cancers [25, 26]; as such, it may be prudent to examine the external genitalia in males for signs of papillomatous and/or malignant lesions.

Although there appears to be little etiological similarity between anal and prostate cancers, prostate cancer is the most common cancer in males, and thus, a considerable portion of male patients with anal cancer can be expected to harbor a simultaneous prostate cancer. This relationship has not been systematically studied due to the relative rarity of anal cancer and its predominance in females; however, in a prospective study of 20 male patients with colorectal cancer who were screened for prostate cancer, it was found that 16% had biopsy-proven prostate malignancy [27]. Given that any treatment of prostate cancer, whether surgical or radiotherapeutic, would be impacted by radiation treatment to the anal canal and pelvis, some consider it prudent to screen for prostate malignancy with PSA, although there are insufficient data to make this standard practice.

Radiographic Assessment of Primary Tumor

CT or MRI of the pelvis is an essential component of workup and provides additional characteristics of the primary tumor (e.g., involvement of adjacent organ or structures, such as vaginal canal or external anal sphincter). However, CT scan alone is often not sufficient in assessing the primary tumor due to limitations of CT in delineating the anatomy of the anal region. Studies have reported sensitivity of

CT scan in detecting the primary tumor of ~60%, in contrast to a detection rate of >90% with the addition of PET [28–30]. Similarly, MRI provides higher resolution of the location, size, and extent of disease of the primary tumor compared to CT, especially with regard to adjacent organ and soft tissue involvement (Fig. 3.1a, b) [31, 32]. As definitive chemoradiotherapy is the mainstay of treatment for anal carcinoma, more accurate tumor delineation with MRI may be beneficial in treatment planning, most notably for T4 disease (adjacent organ involvement). Lastly, there is generally no role for endoscopic ultrasound, as the depth of invasion is not used in anal cancer staging and does not dictate management, in contrast to that of other gastrointestinal cancers.

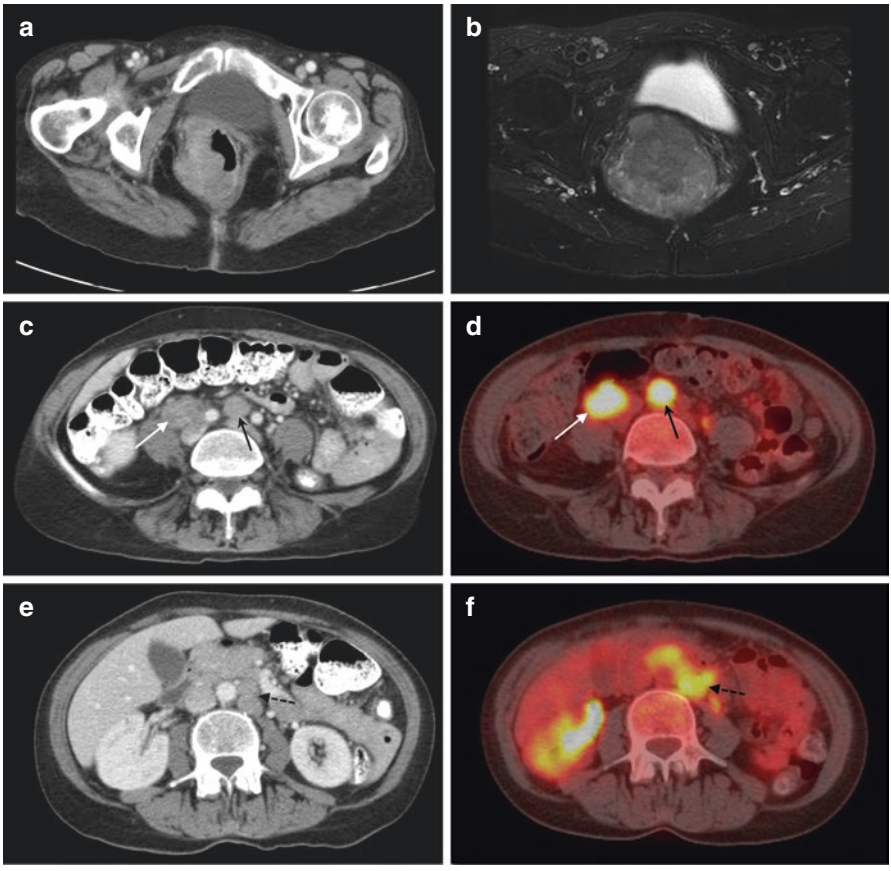

Fig. 3.1 (**a**–**f**) CT pelvis with IV contrast (**a**) demonstrating heterogeneously enhancing bulky mass with necrosis in the anal canal. T2-weighted axial pelvic MRI (**b**) depicting the same anal carcinoma, characterized by hyperintense diffusely enhancing anal mass with mild infiltration of the posterior perirectal soft tissue. Left (black arrow) and right (white arrow) common iliac lymph node metastases detected on CT pelvis with IV contrast (**c**) and PET/CT (**d**), with disease extension superiorly involving the para-aortic lymph nodes (black-dashed arrow) on CT pelvis with IV contrast (**e**) and PET/CT (**f**)

Assessment of Nodal Metastases

Anal carcinoma can metastasize to the perirectal and internal iliac lymph nodes if located superior to the dentate line and to the superficial inguinal and external iliac lymph nodes if located inferior to the dentate line. CT or MRI of the pelvis is an integral part of staging evaluation to assess both primary and nodal diseases. While older studies have demonstrated similar efficacy of CT and MRI in lymph node evaluation [33], improvement in MR technology has allowed greater sensitivity in detecting smaller lymph nodes (<5 mm) that may also harbor cancer cells [34]. Nevertheless, both techniques rely on nonspecific characteristics of size and morphologic criteria to differentiate between benign and malignant lymph nodes, which could often lead to false-positive or false-negative interpretations [35].

Increasingly, PET/CT has been used by clinicians as a complementary study to the staging pelvic CT/MRI. Multiple studies over the past decade have evaluated the value of PET/CT in the staging for anal cancer, which are summarized in Table 3.2. PET/CT allows for enhanced evaluation of the primary tumor and increased detection of inguinal lymph node involvement compared to CT and physical exam. As such, studies have reported significant upstaging of disease with the addition of PET/CT, with rates ranging from 5.1% to 37.5% [28–30, 36–40]. Interestingly, several of

Table 3.2 Selected studies and meta-analyses evaluating the role of PET/CT in anal cancer

		Primary site detection	Nodal evaluation by PET/CT				
	N	PET/CT vs. CT	Sensitivity	Specificity	Upstaging	Downstaging	Change in radiation plan
Selected studies							
Cotter et al. [28]	41	91% vs. 59%	–	–	15%	–	–
Nguyen et al. [29]	50	98% vs. 58%	–	–	17%	–	19%
Winton et al. [36]	61	–	89%	–	18%	13%	31%
Mistrangelo et al. [37]	53	98% vs. 83%	–	–	38%	25%	13%
Sveistrup et al. [38]	95	–	–	–	14%	–	23%
Meta-analyses							
Caldarella et al. [39]	–	–	56%	90%	–	–	–
Jones et al. [30]	–	99% vs. 60%	–	–	15%	15%	–
Mahmud et al. [40]	–	99% vs. 67%	93%	76%	5–38%	8–27%	13–59%

these studies also demonstrate downstaging of nodal disease in some patients, wherein enlarged lymph nodes detected on CT or MRI are not metabolically active on PET; however, the overall changes in staging with PET/CT still distinctly trend toward upstaging [30, 36, 37, 40]. Additionally, various studies report changes in the radiation planning (prescribed dose and treatment field) due to changes in nodal staging from PET/CT, ranging from 12.5% to 59.3% of patients treated [29, 36–38, 40].

The degree of true sensitivity and specificity of PET/CT in detecting nodal metastases in anal cancer remains controversial. A meta-analysis of seven retrospective and five prospective studies demonstrated pooled estimates of sensitivity of 56% and specificity of 90% [39]. The low sensitivity may be at least partially attributed to decreased sensitivity of PET for lymph node sizes of <8 mm [41]. However, a more recent meta-analysis of 17 studies reported pooled sensitivity and specificity of 93% and 76%, respectively, for the detection of nodal metastases [40]. Overall, PET/CT appears to provide valuable assessment of nodal status in anal cancer, and should be used in conjunction with, rather than as a replacement of, pelvic CT or MRI, as per NCCN guidelines.

While PET/CT has higher rates of lymph node detection than CT, there is also concern regarding its high false-positive rates, which is likely in part due to increased FDG uptake from inflammatory reaction. Histological confirmation with needle biopsy of FDG-avid inguinal nodes is recommended if the lymph node is of sufficient size and is otherwise indeterminate on radiographic or clinical assessment; biopsy is also recommended for any suspicious inguinal nodes that lack FDG avidity. However, surgical data demonstrate that pelvic lymph node metastases for anal cancer are often <5 mm in diameter, suggesting that many early inguinal node metastases may not be amenable to biopsy [42]. Demonstrating the false positivity of PET/CT, Mistrangelo and colleagues compared PET/CT to sentinel lymph node biopsy (SLNB) in the detection of inguinal node metastases in 27 patients with anal cancer and showed that of seven patients with positive PET scans, four had negative SLNBs [43]. This evidence suggests that PET/CT may lead to overdiagnosis of nodal metastases, and thus, overtreatment of the nodal regions. Indeed, a recent meta-regression and simulation study observed that modern clinical series of anal cancer reported much higher rates of lymph node positivity than predicted, which is likely attributable to overdiagnosis by modern imaging studies [44]. Notably, nodal stage migration with the advent of PET/CT staging was associated with improved survival in both node-positive and node-negative patients and decreased survival differences by nodal status, while proportions of T staging remained unchanged, suggesting misclassification of node-negative patients to the node-positive cohort [44].

The false positivity of PET/CT in nodal staging is especially important to consider when assessing an HIV-positive patient. Patients with HIV often have diffuse lymph node activation resulting in low-level uptake of FDG in lymph nodes at baseline, likely driven by inflammatory changes [45]. Correspondingly, Cotter and colleagues showed that HIV-positive patients were more likely to have positive PET findings in the inguinal (44% vs. 34%) and pelvic lymph nodes (44% vs. 16%) compared to HIV-negative patients, although the number of patients studied was small [28]. Of the four HIV-positive patients with FDG-avid inguinal lymph nodes, two underwent biopsy which revealed only diffuse inflammatory changes. There

was also a higher rate of FDG-avid distant lymph nodes, which were again felt to be reflective of the heightened inflammatory state rather than distant metastatic deposits. Thus, biopsy of suspicious FDG-avid lymph nodes in HIV-positive patients is of particular importance before making management decisions.

To circumvent the overdiagnosis and overtreatment of inguinal lymph nodes, further efforts have been made to investigate the efficacy of inguinal SLNB. As most studies that evaluated SLNB had small sample sizes, two meta-analyses were carried out to provide important insight. Noorani and colleagues showed that SLN detection rate ranges from 47% to 100% across 17 studies [46], while Tehranian and colleagues demonstrated pooled inguinal SLN detection rate of 86.2% among 16 studies [47]. In seven studies of the former meta-analysis, patients with negative inguinal SLNB underwent inguinal-sparing radiotherapy and the rate of inguinal nodal recurrence (a surrogate of false-negative rate of SLNB) ranged from 0% to 18.75% [46]. Although inguinal SLNB prior to definitive chemoradiotherapy appears to be a promising strategy, it is unclear if it will change practice, as the toxicity of overtreating questionable lymph nodes with chemoradiation is currently low with modern techniques such as intensity-modulated radiation treatment.

Assessment of Distant Metastases

Anal carcinoma can spread via both the portal venous system and systemic circulation to result in distant metastases. The blood supply of anal lesions located above the dentate line drains into the portal venous system and provides a direct conduit for metastases to the liver, which is the most common site of distant spread for anal carcinoma. Conversely, lesions below the dentate line drain directly into the systemic circulation, which can lead to lung metastases. As such, proper workup for anal cancer includes CT abdomen with intravenous (IV) and oral contrast for evaluation of liver and abdominal metastases as well as CT chest for pulmonary metastases. An additional benefit to CT chest is the potential detection of new primary lung cancers, which occur at increased rates in patients with anal cancer due to the common risk factor of smoking. Whole-body PET/CT, which is increasingly utilized for nodal evaluation, will also further increase the sensitivity of detecting distant disease.

Para-aortic lymph node spread may also occur. Although spread of disease to the para-aortic lymph nodes is staged as distant metastases, recent retrospective studies have shown that patients with distant disease limited to the para-aortic nodes can be treated curatively with extended-field chemoradiation (Fig. 3.1c–f) [48, 49].

Staging

The AJCC anal cancer staging manual (eighth edition) is used to stage all anal cancers, including anal canal and perianal cancers [50], and is outlined in Box 3.1. All histologies are staged as anal cancers, except for melanoma, sarcoma, and

well-differentiated neuroendocrine carcinoma. Assessment of the primary tumor (T) focuses on tumor size, rather than depth of invasion as in the remainder of the luminal gastrointestinal tract. Assessment of nodal involvement (N) is based on the nodal region involved rather than the number of lymph nodes involved. Assessment of distant metastasis (M) evaluates for the presence or absence of distant spread.

Box 3.1 AJCC Staging for Anal Cancer, Eighth Edition (2017)

Primary tumor (T)			
TX	Primary tumor (T)		
T0	No evidence of primary tumor		
Tis	High-grade squamous intraepithelial lesion		
T1	Tumor ≤2 cm		
T2	Tumor >2 cm but ≤5 cm		
T3	Tumor >5 cm		
T4	Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes		
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes		
N1b	Metastasis in external iliac lymph nodes		
N1c	Metastasis in external iliac with any N1a nodes		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Prognostic stage groups			
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T1-2	N1	M0
IIIB	T4	N0	M0
IIIC	T3-4	N1	M0
IV	Any T	Any N	M1

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Changes were made from the AJCC staging manual seventh edition (2009) to the eighth edition (2017), including removal of N1, N2, and N3 categories and addition of N1a, N1b, and N1c categories, based on similar prognosis with any level of nodal involvement [50]. The stage groups were also revised to accommodate the new N categories. Additionally, perianal cancers were previously termed anal margin cancers and staged as skin cancers, but because many of these tumors involve the anal canal, they are now staged as anal cancers.

The TNM staging assessment carries prognostic significance. In a secondary analysis of 620 patients on the Radiation Therapy Oncology Group 98-11 trial, the best overall survival (OS), disease-free survival, and locoregional failure outcomes were found in those with T2-3N0 tumors and the poorest outcomes were found in those with T4N0 and T3-4N+ tumors [51]. Similarly, the need for future colostomy, a surrogate for local recurrence, was lowest for patients with T2N0 and T2N+ tumors and highest in those with T4N0 and T3-4N+ tumors.

In a Surveillance, Epidemiology, and End Results (SEER) study, between 2008 and 2014, 48% of anal cancers were localized at initial diagnosis, 32% had spread to the regional lymph nodes, and 13% presented with distant metastases; 5-year OS was 82%, 64%, and 30%, respectively [52]. By stage, the AJCC has reported 5-year OS of 77% and 71% for Stage I squamous and non-squamous anal cancers, respectively, 67% and 59% for Stage II cancers, 58% and 50% for Stage IIIA cancers, 51% and 35% for Stage IIIB cancers, and 15% and 7% for Stage IV cancers [50].

Conclusion

Initial evaluation of anal cancer consists of a comprehensive history and physical examination, including digital rectal exam and palpation of inguinofemoral lymph nodes, followed by tumor biopsy with or without biopsy of any suspicious inguinal lymphadenopathy. CT or MRI of the pelvis and CT of the chest/abdomen are required to complete staging; PET/CT has also become widely implemented as it provides valuable additional information and guides radiation therapy planning to better delineate the primary tumor. Anal cancer is clinically staged primarily using primary tumor size and extent of regional lymphadenopathy according to AJCC guidelines with an overall very favorable prognosis. Subclassification of anal cancer as anal canal or perianal cancer has implications for definitive management.

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Chapter 4
Treatment of Localized Anal Cancer: Chemoradiotherapy

James Byrne and Jennifer Y. Wo

Introduction

Anal cancer is estimated to account for approximately 8300 new cases and 1280 deaths in the United States in 2018 [1]. Previously thought to be a condition of chronic inflammation, anal cancer has been found to be associated with human papillomavirus (HPV) infections in up to 90% of cases and is pathologically similar to cervical cancer [2–4]. Furthermore, immunosuppression is another major risk factor for the development of anal cancer [5, 6]. In localized anal cancer, the primary treatment aim is to achieve locoregional control while maintaining organ function. Chemoradiotherapy with fluoropyrimidines and mitomycin C has supplanted abdominoperineal resection (APR), a surgery that involves removing the anorectum and creating a permanent colostomy, as the standard-of-care treatment for anal cancer patients and has allowed the majority of patients to undergo organ-sparing curative therapy. The use of modern radiation techniques, including intensity-modulated radiation therapy (IMRT) and image guidance, has improved treatment delivery and reduced side effect profiles compared to historical data. In this chapter, we describe the evolution of the treatment of localized anal canal cancer from surgery to standard-of-care chemoradiotherapy.

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Role of Surgery: Prior to and After the Introduction of Chemoradiotherapy

Prior to 1980, surgical resection of the tumor in the form of an APR had been the primary treatment for anal canal cancers. An APR involves removal of the anus and rectum and creation of a permanent colostomy and was considered to be an extremely complicated procedure [7]. The major surgical series prior to 1980 found that the 5-year survival after an APR ranges from 40% to 70% [8–13]. It was determined that patients with large tumors and nodal metastases had worse overall survival [8]. In addition, lymphovascular invasion predicted for worse overall survival [8]. To convert inoperable cases into surgical candidates, Norman Nigro and his colleagues proposed a neoadjuvant chemoradiotherapy approach. They found that neoadjuvant therapy resulted in complete response in their first three patients [14]. With increasing success using chemoradiotherapy, Nigro began to recommend local excision of the primary tumor instead of a planned APR, and then later dropped the use of local excision [14–16].

There does remain a role for surgical excision in this disease. Currently, local excision is reserved for superficially invasive anal cancer and T1 N0 well-differentiated perianal cancer. Superficially invasive anal cancer is defined as anal cancer that invaded <3 mm of the basement membrane with horizontal spread of <7 mm (T1NX) determined after complete excision [17]. As high-risk populations are being screened more frequently for anal cancer, superficially invasive anal cancers are being diagnosed more often. In addition, most of these lesions are completely excised at the time of biopsy. Excellent outcomes were noted in a retrospective analysis of 17 patients with completely excised anal cancers, where seven patients met criteria for superficially invasive anal cancer. Patients with positive margins underwent radiation alone. All patients subsequently underwent surveillance. The 5-year overall survival was 100%, and 5-year recurrence-free survival was 87% [18]. Patients with T1 N0 well-differentiated perianal cancers are also managed with local excision where a 1 cm margin is recommended. A National Cancer Data Base study of patients with T1 N0 anal cancers noted that the frequency of local excision as the main treatment rose from 2002 to 2012, and that there was no major difference in overall survival between local excision compared to chemoradiotherapy (85.3% vs. 86.6%, respectively) [19].

Radical surgery involving an APR and colostomy is reserved as salvage therapy after disease progression through chemoradiotherapy and for local recurrence. A Danish retrospective cohort study looked at 5-year cause-specific colostomy rates in 235 patients with anal cancer who underwent radiation therapy or chemoradiotherapy between 1995 and 2003. The tumor-specific colostomy rate was found to be 26% (95% CI, 21–32%), and the therapy-specific colostomy rate was 8% (95% CI, 5–12%) [20]. The major predictor for tumor-specific colostomy was tumor size >6 cm. Limitations of the study included older chemotherapy and radiation therapy [21]. In general, for anal cancer patients able to undergo salvage APR, the 5-year overall survival is 39–66% [22–25].

The technique for an APR after radiation therapy or chemoradiotherapy is similar to rectal cancer, except for the need for wider lateral perianal margins. One major complication to the APR in this setting is poor wound healing. Alternative methods for perineal wound closure have been recommended [26, 27]. Lastly, intraoperative radiation therapy was not found to confer a benefit in local control or overall survival for patients with recurrent anal cancer [28].

Results of Nigro and Colleagues

In the early 1970s, Nigro and his colleagues at Wayne State University Hospital intended to use neoadjuvant chemoradiotherapy to reduce the local failure rates from surgery, especially in the locally advanced disease setting [14]. For their chemoradiotherapy regimen, which was later affectionately termed the Nigro regimen, they used two cycles of 5-fluorouracil (5FU) at 1000 mg/m^2 continuous infusion on days 1–4 and 29–32 and mitomycin C (MMC) at 10–15 mg/m^2 on day 1, in addition to external beam radiation therapy at 30 Gy. As noted above, the first three patients who underwent this therapy experienced complete responses, which suggested the ability to provide cure with chemoradiotherapy and avoid an APR with colostomy.

Subsequently, Nigro continued to use chemoradiotherapy and reserved APR for only residual or progressive disease after initial chemoradiotherapy. In a follow-up study, patients who were treated with chemoradiotherapy did not require an APR, and the 5-year overall survival was 67% with a colostomy-free survival rate of 59% [29]. Chemoradiotherapy became adopted by others who reported a colostomy-free survival rate of between 66% and 70% [29]. For patients who developed recurrence of their disease, an APR was a viable treatment option with a 5-year survival rate up to 92% [15, 17, 29–44]. Additionally, chemoradiotherapy has achieved excellent success rates in HIV-positive patients with anal cancer. Side effects of such therapy are found to be slightly higher in this population, particularly in those patients with CD4 counts <200 mm^3 and >30 Gy of radiation [45–47].

Chemoradiation Versus Radiation Therapy Alone

The use of radiation therapy alone to treat localized anal cancer had been proposed to avoid the side effects that accompany the concurrent use of 5FU and MMC with radiation therapy. Retrospective studies showed that radiation alone led to a 3-year overall survival of 75%, with brachytherapy resulting in lower control rates between 40% and 50% [48–50]. For patients treated with external beam radiation therapy or brachytherapy alone, the 5-year overall survival was found to be approximately 66%. In addition, adequate sphincter function was maintained [51]. The benefit of chemotherapy was debated in the 1980s given that similar local control and overall

Table 4.1 Outcomes from UKCCCR and EORTC trials evaluating radiation alone compared to chemoradiotherapy

Study	Arms	N	3-year local control		3-year overall survival	
UKCCCR	RT alone	200	39%	$p < 0.001$	58%	$p = 0.25$
	RT + chemo	295	61%		65%	
EORTC	RT alone	52	39%	$p = 0.02$	65%	$p = 0.17$
	RT + chemo	51	58%		72%	

survival could be achieved with radiation therapy alone [52]. A nonrandomized comparison of chemoradiotherapy and radiation alone demonstrated an improvement in local control with the use of chemoradiotherapy (81% vs. 66%) [51]. Others had evaluated chemoradiotherapy vs. radiation therapy alone and found a 6-month local control of 94% and 60%, respectively [44]. Prospective randomized trials, including two major phase III studies performed by the United Kingdom Coordination Committee on Cancer Research (UKCCCR) and European Organization for Research and Treatment of Cancer (EORTC), were subsequently proposed to evaluate the additional benefit of chemotherapy with radiation therapy. Table 4.1 provides a summary of the results of these two trials.

The trial conducted by the UKCCCR involved 585 patients with anal cancer who were randomized to radiation therapy (45 Gy with external beam and either a 15 Gy external beam boost or 25 Gy brachytherapy boost) or chemoradiotherapy (same radiation regimen and combination with concurrent 5FU at 1000 mg/m^2 continuous infusion for 4 days or 750 mg/m^2 continuous infusion for 5 days during the first and last week of radiation therapy and mitomycin at 12 mg/m^2 on day 1) [53]. The local control for radiation therapy alone was inferior to chemoradiotherapy (39% vs. 61%, $p < 0.001$). However, the 3-year overall survival was not significantly different (58% vs. 65%, $p = 0.25$) between radiation therapy and chemoradiotherapy.

In a similar fashion, the trial conducted by EORTC randomized 110 patients with anal cancer to radiation therapy (45 Gy of EBRT with either a 15 Gy or 30 Gy external beam boost) or the same radiation therapy in combination with concurrent 5FU (750 mg/m^2 continuous infusion on days 1–5 and 29–33) and mitomycin (15 mg/m^2 day 1) [54]. The local control for radiation therapy was inferior to chemoradiotherapy (58% vs. 39%, $p = 0.02$). The colostomy-free survival rate was 32% higher for patients treated with chemoradiotherapy. The 3-year overall survival was not significantly different between the two arms (65% vs. 72%, $p = 0.17$). It is worth noting that negative prognostic factors for local control were skin ulceration and lymph node involvement.

Overall, both trials evaluated the impact of concurrent chemotherapy with radiation for the treatment of anal cancer patients and found that chemoradiotherapy was superior to radiation alone for local disease control, colostomy-free survival, and disease-specific survival. However, they were unable to prove a benefit to overall survival, as salvage therapy with an APR is successful at controlling and eliminating disease. Based upon the results of these studies, chemoradiotherapy was established as the standard-of-care therapy.

Role of Cisplatin as an Alternative to Mitomycin C

The optimal chemotherapy regimen used to treat anal cancer has always been a major question posed by members of the oncology community. Many of the side effects of the initial Nigro regimen have been attributed to MMC. In addition, MMC is not a known radiosensitizer. For this reason, the Radiation Therapy Oncology Group (RTOG) and Eastern Cooperative Oncology Group (ECOG) developed RTOG 87-04/ECOG 1289 to evaluate the need for MMC in concurrent chemotherapy and radiation. The trial involved 310 patients randomized to external beam radiation therapy (45–50.4 Gy) with 5FU alone (continuous infusion 1000 mg/m^2 days 1–4 and 29–32) vs. 5FU at the same scheduled with MMC 10 mg/m^2 for two doses [55]. They found that the addition of MMC leads to higher colostomy-free survival (71% for 5FU and MMC vs. 59% for 5FU alone; $p = 0.014$) and disease-free survival (73% for 5FU and MMC vs. 51% for 5FU alone; $p = 0.0003$). However, overall survival and disease-specific survival were not significantly impacted by the exclusion of MMC. Toxicity was significantly higher in the patients who received MMC with grade 4 and 5 toxicities of 23% compared to 7% for 5FU alone ($p < 0.001$). Despite the additional toxicities, it was concluded that MMC plays a significant role in improving outcomes and remained a part of the standard-of-care therapy for anal cancer.

Additional agents have been investigated to replace MMC in the treatment of anal cancer. Platinum agents, which were not available at the time of the initial trials for chemoradiotherapy, are known to be especially active against squamous cell cancers of the head and neck, lung, and cervix [56]. There were numerous preliminary studies that combined cisplatin with 5FU and radiation therapy and demonstrated excellent results [36, 57, 58]. Based upon these studies, the RTOG 98-11 trial was developed. This trial randomized 682 patients to either 5FU 1000 mg/m^2 days 1–4 and 29–32, MMC 10 mg/m^2 days 1 and 29, and radiation therapy or an induction course of chemotherapy with 5FU 1000 mg/m^2 on days 1–4 and 29–32 with cisplatin 75 mg/m^2 on days 1 and 29, with radiation therapy starting day 57 and 5FU 1000 mg/m^2 on days 57–60 and 85–88 and cisplatin 75 mg/m^2 on days 57 and 85. The minimum radiation dose was 45 Gy, which was delivered to the primary tumor and perirectal nodes in 25 daily fractions, with an additional boost of 10–14 Gy for more advanced disease. The initial published results at 5-years demonstrated no difference in disease-free survival or overall survival between the two groups. There was a higher colostomy rate for the cisplatin arm compared to the MMC arm (19% vs. 10%, $p = 0.02$). In addition, the MMC arm had significantly higher rates of grade 3 or 4 toxicities (61%) compared to the cisplatin arm (42%, $p < 0.001$) [59]. An update of the trial was subsequently published with a longer median follow-up time and demonstrated that the MMC arm resulted in significantly improved 5-year disease-free survival (68 vs. 58%, $p < 0.005$) and 5-year overall survival (78% vs. 70%, $p < 0.02$). Although not significant, there was also a trend toward lower rates of locoregional recurrence (20% vs. 27%, $p = 0.092$) and colostomy rates (12% vs. 17%, $p = 0.075$) [60]. One major issue with the trial was

Table 4.2 Outcomes from RTOG 98-11 and ACT II evaluating cisplatin compared to MMC in chemoradiotherapy

Study	Arms	N	Colostomy-free survival		Disease-free survival		Overall survival	
RTOG 98-11	RT plus FU/MMC	325	72% at 5 years	$p = 0.05$	67.8% at 5 years	$p = 0.006$	78.3% at 5 years	$p = 0.026$
	RT plus FU/CDDP	324	65% at 5 years		57.8% at 5 years		70.7% at 5 years	
ACT II	RT plus FU/MMC	472	68% at 3 years	$p = 0.94$	69% at 3 years	$p = 0.63$	79% at 3 years	$p = 0.7$
	RT plus FU/CDDP	468	67% at 3 years		69% at 3 years		77% at 3 years	

that the investigators were asking two questions, including substitution of MMC with cisplatin and the use of induction chemotherapy. Induction chemotherapy prolonged the overall treatment time compared to standard therapy. An analysis of RTOG 87-04 and 98-11 demonstrated that longer overall treatment time predicted for worse outcomes, including higher rates of colostomy failure, locoregional failure, and worse disease-free survival [61].

A subsequent trial, ACT II, investigated whether replacing mitomycin with cisplatin in chemoradiation improves clinical complete response at 6 months, and whether maintenance chemotherapy after chemoradiation improves progression-free survival. ACT II was a 2 × 2 randomized trial that evaluated 5FU 1000 mg/m^2 d1-4 and d29-32 with cisplatin 50 mg/m^2 d1 and 29 vs. MMC 12 mg/m^2 d1. These patients underwent a second randomization with observation vs. maintenance chemotherapy with 5FU/cisplatin for two cycles. There was no significant difference in clinical complete response at 6 months (91% for MMC arm and 90% for cisplatin arm, $p = 0.64$) and grade 3–4 toxicity (71% for MMC arm vs. 72% for cisplatin arm). In addition, there was no difference in 3-year progression-free survival with maintenance chemotherapy (74% with maintenance chemo vs. 73% with observation, $p = 0.7$). It was concluded that neither cisplatin nor maintenance chemotherapy was more effective than the standard-of-care of therapies and that 5FU and MMC with radiation therapy should continue to be the standard of care for the treatment of localized anal cancer. As there was no difference between the MMC and cisplatin arms in ACT II, it was suggested that the experimental arm in RTOG 98-11 failed due to the induction chemotherapy [60]. Table 4.2 summarizes the results of RTOG 98-11 and ACT II.

Role of Capecitabine as an Alternative to Infusional 5FU

Many investigators have proposed replacing 5FU with capecitabine due to ease of administration and the potential benefits of continuous radiosensitization. Two single-arm phase II trials and one phase I trial have evaluated the use of capecitabine

for anal cancer. In particular, one of the phase II trials by Oliveira and colleagues evaluated the use of capecitabine 825 mg/m^2 twice daily and MMC 15 mg/m^2 on day 1 during radiation therapy in 51 patients. The response to therapy was excellent, where they found that 86% of patients had a complete response, 7% of patients had a partial response, and 7% of patients had progressive disease at 6 months. At 6 months, the locoregional control rate was 86% [62]. Another phase II study using the same dose of capecitabine but lower dose of mitomycin C (12 mg/m^2) with radiation therapy found a complete response rate of 77%, partial response rate of 16%, and progressive disease in 7%. There was a locoregional relapse rate of 14% [63].

Furthermore, the use of capecitabine in lieu of 5FU has gained acceptance in the treatment of rectal cancer based on NSABP R-04. This trial was a 2 × 2 randomized phase III trial involving 1608 patients with stage II or III rectal cancer. These patients were randomized to concurrent radiation therapy with continuous infusion 5FU (225 mg/m^2/day for 5 days per week) +/− oxaliplatin or capecitabine (825 mg/m^2 BID for 5 days per week) +/− oxaliplatin. There was no difference in pathologic complete response, sphincter-sparing surgery, and surgical downstaging for patients treated with capecitabine compared to 5FU [64]. As such, there may be rationale for replacing 5FU with capecitabine in select compliant patients [65].

Roles of Dose Escalation and Dose De-Escalation

There has been much interest in radiation dose escalation to increase the effectiveness of therapy, especially in locally advanced anal cancer. An analysis of RTOG 98-11 demonstrated that patients with tumor diameters >5 cm predicted for worse 5-year disease-free survival and overall survival [66]. It was also found that 3-year colostomy failure rates by stage in the same trial were 12% (T3N0), 20% (T4N0), 19% (T3N1-3), and 28% (T4N1-3) for larger tumors versus only 9% (T2N0) and 4% (T2N1-3) for smaller tumors [67]. These analyses provide further justification for dose escalation in the management of locally advanced anal cancer.

There are older studies that have investigated radiation dose escalation. In RTOG 92-08, a total radiation dose of 59.4 Gy delivered in 1.8 Gy fractions was attempted with a 2-week treatment break in the middle of treatment. Patients treated on this trial had a higher colostomy rate of 30% compared to 9% in trial RTOG 87-04, where patients were treated with continuous 45 Gy radiation dose regimen and the same chemotherapy. The late effects of dose escalation were not presented in this study [32, 55, 68].

Other teams have explored the use of adapted radiation dose escalation. The ACCORD-03 trial was a 2 × 2 randomized controlled trial that investigated the use of a high-dose radiation boost per the response to initial therapy with an additional evaluation of induction chemotherapy. Patients who responded to treatment were scheduled to receive either standard boost (15 Gy) or higher-dose boost (20–25 Gy), which started 3 weeks after the chemoradiotherapy course. The higher boost arm

involved either external beam radiation therapy or LDR brachytherapy with Ir-192. If a patient had a complete response or tumor reduction >80%, the radiation dose was 20 Gy; otherwise, a 25 Gy boost was used if <80% partial response. There was no difference in the primary endpoint of colostomy-free survival for standard vs. high boost dose radiation therapy (78% vs. 74%, $p = 0.067$). However, there was a small nonsignificant improvement in 5-year local control for higher-dose boost of 83.1% compared to standard boost of 78.2% [69]. It is believed that overall treatment time is a major factor with the risk of accelerated tumor repopulation, which was impacted by induction chemotherapy and the 3-week break prior to boost therapy [70].

In the IMRT era, dose escalation has been re-examined as a possibility for the management of locally advanced anal cancers [71]. A review on the use of IMRT for anal cancer found that based upon the linear quadratic model, a > 5 Gy increase in radiation dose may result in >10% improvement in local control [72]. Ongoing trials in the United Kingdom trial portfolio that includes ACT IV–V will be examining radiation dose intensification in patients with tumor larger than 4 cm [73, 74]. Doses up to 61.6 Gy will be examined with a primary endpoint of 3-year locoregional failure. However, a major concern for dose escalation is the increased risk of fecal incontinence [75]. In addition, damage to the anal sphincter and lamina propria at very high doses could also result in stenosis and stricture formation. This risk must be balanced with the potential for improved local control [75]. A study from Norway found that radiation doses of 56 Gy in anal cancer patients resulted in fecal incontinence in a third of their patients [75–77].

The role of dose de-escalation is also still being determined. There are older retrospective studies that have concluded lower radiation doses than 50 Gy resulted in higher local failure rates compared to radiation doses >54 Gy [70]. The results of these studies are complicated by patient and tumor characteristics, chemotherapy, field size, and elective treatment of inguinal lymph nodes. A clinical study in patients with T1–T2 tumors with close or involved margins treated with chemoradiotherapy to radiation doses as low as 30 Gy demonstrated excellent local control (90%) [29]. An ongoing clinical trial, ACT III, has been initiated to evaluate the strategy of dose de-escalation in patients with T1–T2 tumors [78]. Similarly, within the United States, ECOG-ACRIN has recently approved the Decrease Trial, which will look at dose de-intensification for low-risk anal cancer. Table 4.3 summarizes the major trials that have evaluated radiation dose escalation and de-escalation.

The Role of Intensity-Modulated Radiation Therapy

IMRT has generated significant interest in shaping the radiation treatment field to cover the clinical target and avoid organs at risk. There have been multiple retrospective datasets showcasing the benefits of IMRT for reduction in toxicity, which provided the evidence for initiating RTOG 05-29 [71, 79, 80]. RTOG 05-29 was a prospective phase II trial that evaluated the benefit of dose-painted IMRT with

Table 4.3 Completed and ongoing trials evaluating dose escalation and de-escalation

Trial	Stage included	Design	RT dose	Complete response	Follow-up data
RTOG 92-08	Any except T1N0	Single-arm phase II: standard chemotherapy (5FU/ MMC) + high-dose RT	2 weeks of RT, then mandatory gap Total radiation dose of 59.4 Gy	81% biopsy confirmed pathologic complete response at 4–6 weeks	Median follow-up duration 12 years, estimated 5-year DFS 53%; estimated 5-year CFS 58%; estimated 5-year OS 85%
ACCORD-03	T1/T2, N0 excluded	Randomized 2 × 2 factorial: Neoadjuvant chemotherapy and chemoRT (5FU/cisplatin) +/− high-dose RT	45 Gy in 25 fractions over 5 weeks, with either standard-dose boost (15 Gy) or high-dose boost (20–25 Gy) using external beam or brachytherapy	79% overall achieved. 82%, 97%, 86%, and 94% for arms A, B, C, and D, respectively, were kept in the sphincter preservation program	–
ACT III	T1N0	Single-arm phase II: dose-reduced chemoRT	No radiation for >1 mm margin; for <1 mm margin received 41.4 Gy in 23 fractions	–	–
ACT IV	T1-2, N0	Randomized phase II: standard chemotherapy (5FU/MMC) and standard vs. de-intensified RT	Standard RT arm of 50.4 Gy in 28 fractions or de-intensified radiation arm of 41.4 Gy in 23 fractions	–	–
ACT V	T3-4, N0-X	Randomized phase II/III: standard chemotherapy (5FU/MMC) with standard vs. two escalated radiation doses	53.2 Gy, 58.8 Gy, or 61.6 Gy all in 28 fractions with standard concurrent chemo. One of the dose escalation arms will move onto phase III	–	–

concurrent chemotherapy (5FU and MMC). The primary endpoint was a reduction in treatment-related grade 2+ GI/GU toxicity by 15% compared to the conventional 5FU/MMC chemoradiation arm in RTOG 98-11. The radiation dose was adapted to the staging of the patient, where T2N0 patients received 42 Gy elective nodal and 50.4 Gy anal tumor PTVs in 28 fractions, and T3-4N0-3 received 45 Gy elective nodal and 50.4 Gy < 3 cm or 54 Gy > 3 cm metastatic nodal and 54 Gy anal tumor PTVs in 30 fractions. Fifty-two patients were treated with dose-painted IMRT, and these patients experienced reduced grade 3+ genitourinary and gastrointestinal toxicity (22% vs. 36%, $p = 0.014$), and grade 3+ dermatologic toxicity (20% vs. 47%, $p < 0.001$) when compared to the MMC arm of RTOG 98-11. IMRT resulted in a shorter median treatment duration (43 days vs. 49 days, $p < 0.001$) and shorter median duration of treatment breaks due to toxicity (0 vs. 3 days, $p < 0.001$) compared to prior results. The results of this study prompted investigators to conclude that IMRT should be the primary radiation modality for the treatment of anal cancer.

Details of Chemoradiation Treatment: Simulation

The radiation simulation is an important component of treatment planning and administration. Attention to a patient's prior exams, including digital rectal, gynecologic/genital, inguinal node, and radiographic studies are critical to determining the optimal treatment position. Bimanual gynecologic examination is also critical to rule out the presence of a precancerous or synchronous cancer, which may impact management or radiation coverage. In addition, patient factors, such as comfort and adherence to the treatment positioning and instructions, are critical for quality of the treatment and reduction in side effects [70].

The prone position on a belly board is typically preferred for sparing bowel but comes at a cost of interfraction variability. The placement of the belly board aperture depends on the patient's anatomy and the degree of bladder filling [81]. Bladder distention is another technique for bowel sparing that can be used in conjunction with the belly board [82]. Historically, it was helpful to consider placing patients with gross inguinal lymphadenopathy in a supine position instead of prone due to reproducibility; this is less important in the era of image-guided radiation therapy. Regardless of prone vs. supine position, patients should undergo simulation and treatment with their arms up or arms on chest. Immobilization devices, such as vaclock bags, can improve reproducibility of treatment. An additional consideration is the use of vaginal dilators, a marker at the verge, and anal markers or wires near the gross tumor or lymphadenopathy [83]. With the use of volumetric arc therapy (VMAT), there have been increasing data suggesting that bolus may not be necessary [84]. For patients with perianal skin involvement treated on trial RTOG 05-29, bolus was placed at a minimum of 2.5 cm circumferentially around the anal verge tumor. Vaginal dilators have found to reduce radiation dose to vagina. When combined with IMRT treatment planning, it has been proposed that vaginal dilators could enable maximum sparing of female genitalia [83]. Intravenous and oral contrast may also assist in delineation of normal structures [85].

Details of Chemoradiation Treatment: Planning and Daily Treatments

Accurate delineation of the target and organs at risk are critical to the effectiveness of therapy. The use of PET-CT and MRI-CT fusion-based planning is helpful to adequately define target margins. Moreover, PET-CT has been shown to improve target delineation, treatment volume, and management of nodal disease [86]. As there is much variability in contouring among radiation oncology experts, there have been contouring atlases set up by the various governing bodies, including RTOG, European Society for Therapeutic Radiotherapy and Oncology (ESTRO), and Australian Gastro-Intestinal Trials Group (AGITG), for target delineation, prophylactic nodal irradiation, and normal pelvic tissues [87–90].

RTOG 05-29 evaluated the use of IMRT for the treatment of anal cancer, as mentioned above. In the trial, they required CT-based planning with oral and IV contrast, anal marker, and immobilization. All targets were contoured on the CT, with the GTV based upon exam, endoscopy, and radiographic findings. They created multiple GTVs for the primary tumor and metastatic lymph node regions (<3 cm and >3 cm). The primary CTV included the GTV and the entire anal canal and nodal GTVs with additional editing from certain muscles and bones. The elective nodal CTV covered the mesorectum, presacrum, bilateral internal and external iliac, and bilateral inguinal lymph nodes with a 1 cm margin around vessels. Furthermore, the trial used a 1 cm expansion on the CTV to generate a PTV, and the PTV was pulled back under the skin if not involved by tumor.

As one of the secondary objectives of RTOG 05-29 was to establish feasibility of IMRT, defined as <5 cases with major deviation, the trial was designed with generous clinical and planning target expansion to ensure adequate target coverage. However, in the era of image-guided radiation therapy, at our institution, we have generally adopted tighter clinical target margins. CTV of the primary tumor/anal canal is generated typically with a 1–1.5 cm margin radially and coverage of the lower presacral space. The elective nodal CTV covered the mesorectum, presacrum, bilateral internal and external iliac, and bilateral inguinal lymph nodes and is now generated with a 7 mm margin around vessels. Additionally, per institutional standards, we generally employ a 5 mm PTV margin expansion in the setting of daily IGRT. Figure 4.1a, b demonstrates a representative image of target volumes and doses in a patient with cT3N3 anal cancer, as well as correct contouring of the mesorectum. Per RTOG guidelines, the radiation dose recommended is adapted to the staging of the patient, where T2N0 patients received 42 Gy elective nodal and 50.4 Gy anal tumor PTVs in 28 fractions, and T3-4N0-3 received 45 Gy elective nodal and 50.4 Gy < 3 cm or 54 Gy > 3 cm metastatic nodal and 54 Gy anal tumor PTVs in 30 fractions. At our institution, patients are routinely treated with dose-painted IMRT per RTOG 05-29; however, given excellent outcomes from sequential boost strategies, many institutions have continued with sequential dose escalation with IMRT to doses of 59.4 Gy as published in RTOG 98-11 [59]. See Table 4.4.

In terms of lymph node coverage, at our institution, we have not routinely obtained inguinal lymph node biopsy for pathologic confirmation of involvement. If

PET/CT or imaging is concerning for lymph node involvement, we would plan to treat clinically involved lymph nodes, as stated above, to 50.4 Gy < 3 cm or 54 Gy > 3 cm. Additionally, while RTOG 05-29 has traditionally recommended doses of 50.4 Gy and 54 Gy to the involved nodal regions and not simply the involved lymph nodes, we have modified this prescription to include only the involved lymph nodes, and dose elective uninvolved lymph nodes to 45 Gy.

For normal structures, small bowel, large bowel, bladder, femoral heads, iliac bones, perianal skin, and genitalia should be contoured. Table 4.5 lists the dose constraints for normal tissues in the order of decreasing priority. Given the inverse

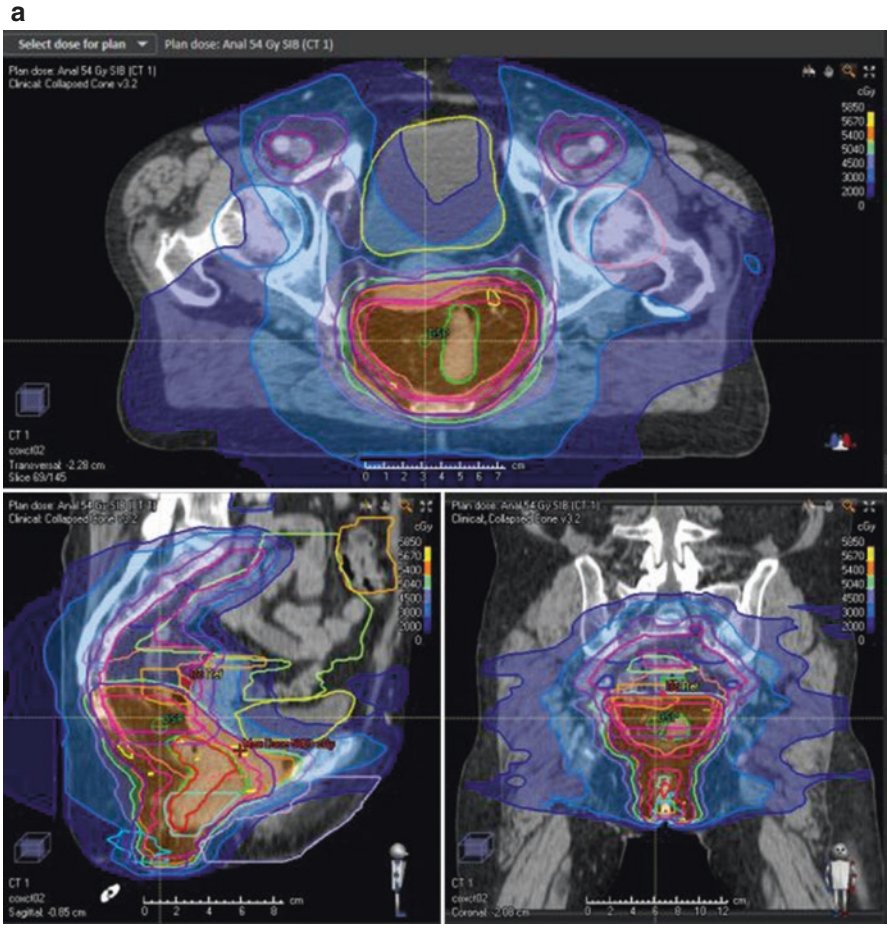

Fig. 4.1 (**a**) A representative image of target volumes and doses in a cT2N0M0 case treated with IMRT. The primary tumor PTV receives 50.4 Gy (orange) and the elective nodes receive 42 Gy (blue). (**b**) Representative contour for patient plan shown above. Pink line delineates PTV4200, blue line delineates PTV5400, and red line represents clinically involved disease. Superior aspect of field is at the bifurcation of the common iliac vessels into internal and external iliacs vessels

Fig. 4.1 (continued)

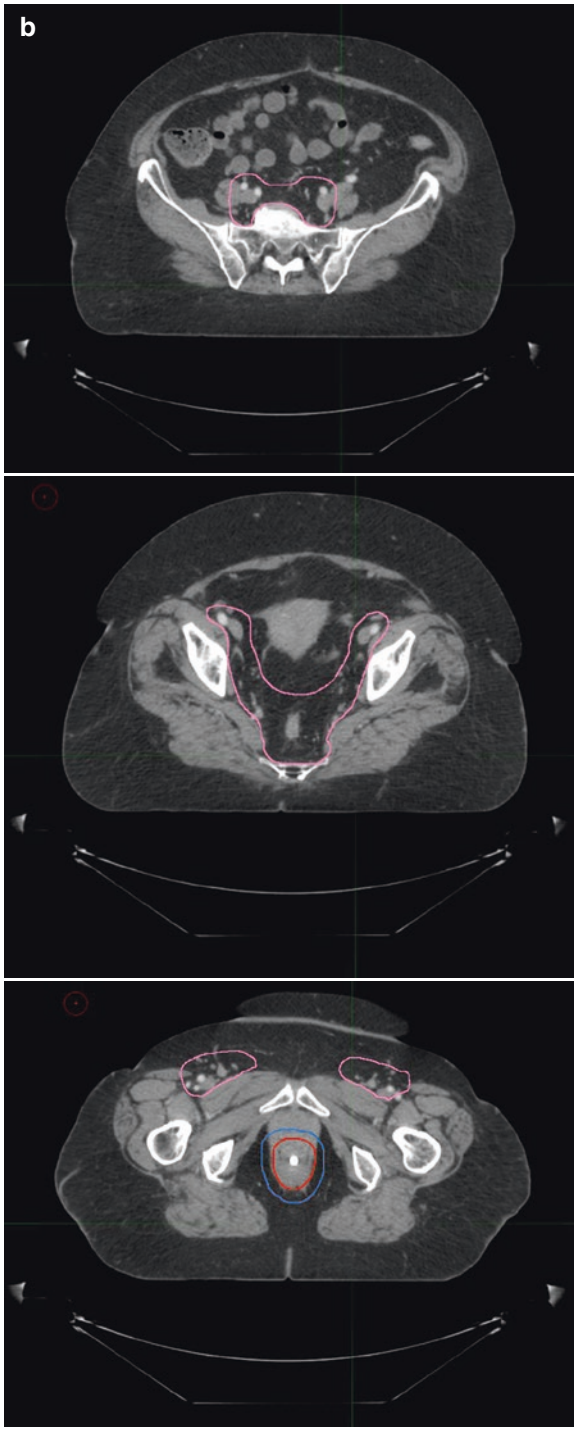

Table 4.4 IMRT dosing recommendations per RTOG 05-29

Stage	Primary	Elective nodal	Nodal ≤ 3cm	Nodal > 3 cm
T2 N0	50.4 Gy	42 Gy	–	–
T3-4 N0-3	54 Gy	45 Gy	50.4 Gy	54 Gy

Table 4.5 IMRT dose constraints for normal tissues in RTOG 05-29. Organs were listed in order of decreasing priority

Organ	Dose (Gy)	Dose (Gy)	Dose (Gy)
Small bowel	$V_{45} < 20$ cc	$V_{35} < 150$ cc	$V_{30} < 200$ cc
Femoral heads	$V_{44} < 5\%$	$V_{40} < 35\%$	$V_{30} < 50\%$
Iliac crest	$V_{50} < 5\%$	$V_{40} < 35\%$	$V_{30} < 50\%$
External genitalia	$V_{40} < 5\%$	$V_{30} < 35\%$	$V_{20} < 50\%$
Bladder	$V_{50} < 5\%$	$V_{40} < 35\%$	$V_{35} < 50\%$
Large bowel	$V_{45} < 20$ cc	$V_{35} < 150$ cc	$V_{30} < 200$ cc

planning, the planning priority was placed on maximal PTV coverage with the prescription dose covering at least 90% of the primary and involved nodal PTVS and 85% of elective nodal PTVs. Tissue heterogeneity corrections were also used. At our institution, we employ the RTOG 05-29 dose constraints; however, we recognize that adequate target coverage often is difficult if not impossible to achieve without violating dose volume constraints for organs at risk. This is particularly true for larger, T4 tumors or among patients with significant volumes of small bowel in the treatment field. In these situations, we always prioritize target coverage given the definitive nature of the treatment intent. Once-daily treatments were planned with five fractions per week. Daily image guidance was also highly recommended, but not required, for prone delivery [91]. This trial has established some of the major radiation therapy treatment planning guidelines for anal cancer [70].

There are other sophisticated radiation techniques that may be used for treatment, including VMAT, image guidance, MRI-based planning, and adaptive planning. The use of VMAT and other rotational techniques reduces treatment time compared to static IMRT. In addition, by combining IMRT with image guidance, major organs at risk are exposed to lower radiation doses, which results in reduced side effects. Use of PET- and MRI-based planning may offer improvement target delineation, as both modalities provide improved spatial resolution, although we do not routinely obtain baseline MRI imaging unless there is a concern for T4 disease. Lastly, adaptive planning involves adjusting the radiation plan based on patient-specific changes not accounted for on the initial plan. As the tumor shrinks, the PTV or OARs can be adjusted based on a cone beam CT (CBCT). Although adaptive planning is not yet a validated standard, this may allow for maintaining tight margins, accurate radiation administration, and reduced toxicities compared to conventionally planned radiation therapy [70].

All components of daily radiation treatments are arranged for accurate, reproducible, and safe administration of the established radiation plan. Patients will undergo multiple identification steps to ensure correct administration of radiation therapy. As a part of daily treatments, patients should be able to maintain the proper positioning for the length of treatment. Patient setup and immobilization should use the same devices from the simulation. Additional measures, such as belly board and bladder distention, will need to be accurately assessed on a daily basis. Imaging guidance, as mentioned above, has become standard in the treatment of anal cancer to reduce setup error [92]. Radiation treatment may be held in the case of certain toxicities. In RTOG 05-29, treatment was stopped for patients with grade 3–4 non-hematologic acute toxicity (per the National Cancer Institute Common Terminology Criteria for Adverse Events version 3) until the toxicity improved to grade <2, except for dermatitis. For patients with grade 4 dermatitis, treatment was held until the dermatitis improved to grade <3. Lastly, radiation was held for hematologic toxicity including grade >3 neutropenia and thrombocytopenia, until the absolute neutrophil count improved to >500/μL and platelets >50,000/μL [91].

Proton and Charged Particle Therapy

There have been no published prospective studies about the use of proton or charged particle therapy in anal cancer. Protons deposit their energy at defined depths and enable a low radiation entry dose and no exit dose. There may be benefits to using this type of therapy given the low integral dose that could be achieved [93]. Multiple retrospective reviews have suggested that proton beam therapy could be used to limit bone marrow toxicity in GI malignancies, which is beneficial in the setting of concurrent chemotherapy use [93, 94]. In addition, other organs at risk have lower dose exposures using proton therapy [93].

In a comparison of radiation plans between patients treated with proton pencil beam therapy to IMRT, it was found that the proton therapy reduced radiation exposure to nearly all organs at risk compared to IMRT (Fig. 4.2). Using a posterior oblique beam arrangement, they found that the total pelvic marrow was better spared with proton therapy. As grade >2 diarrhea has been associated with volume of bowel receiving between 5 and 40 Gy, proton beam therapy demonstrated reduction in small bowel dosing up to 35 Gy when compared to IMRT. Other nearby organs, including genitalia, femoral heads, and bladder, were also spared dose using proton therapy [93].

There are ongoing clinical prospective clinical trials, such as NCT01858025 and NCT03018418, evaluating the use of proton pencil beam radiation therapy in combination with 5FU and MMC for the management of anal cancer [95]. The data for these trials have not yet matured.

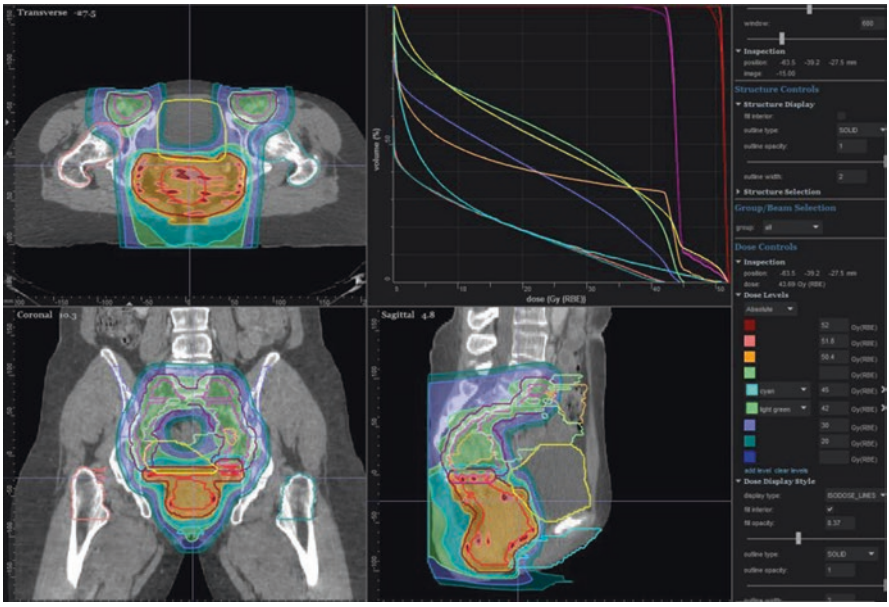

Fig. 4.2 Representative pencil beam scanning proton plan. Dose color wash images of proton therapy for a patient with T2N0 anal cancer prescribed 42 Gy to elective lymph nodes and 50.4 Gy to the primary tumor bed

Treatment of Persistent Disease

Anal squamous cell carcinoma takes weeks to months to fully regress after the completion of therapy. The assessment of disease typically occurs in 4-week intervals after completion of therapy and involves digital rectal exam. Anoscope is often performed at 3 months post therapy completion. Biopsy is reserved for progressive disease at any time or residual disease at 6 months based on time to clinical response data from the ACT II trial (discussed below). In RTOG 87-04, patients underwent repeat biopsies 6 weeks after therapy to assess degree of response. There were 12.0% of patients who had positive biopsy results after initial treatment. Salvage chemoradiotherapy with one dose of 5FU and cisplatin (100 mg/ml^2 on day 2) was administered with a radiation therapy boost to an additional 9 Gy to the area of residual disease. Of those patients treated with salvage chemoradiotherapy, 55% achieved a complete response. As such, it is uncertain whether the patients treated with salvage therapy were slow or nonresponders [55]. Many patients who do not have a complete clinical response when assessed at 11 weeks after chemoradiotherapy do in fact respond by 26 weeks, and the earlier assessment could lead to some patients having unnecessary surgery. A post hoc analysis of ACT II evaluated time to complete clinical response. Three assessments were performed at 11 weeks, 18 weeks, and 26 weeks after chemotherapy, and it was found that of the patients who underwent all three assessments, 52% of patients had a complete response at week 11, 71% at week 18, and 78% at week 26. In the patients who had completed

all three assessments, they found that the 5-year overall survival in patients with complete response at assessments 1, 2, and 3 was 85% (95% CI, 81–88%), 86% (95%, 82–88%), and 87% (95% CI, 84–90%), respectively. Patients with less than a clinical complete response had significantly lower rates of 5-year overall survival [96]. These data suggest that the most appropriate time to assessment is 26 weeks after chemoradiotherapy.

The primary treatment for persistent/recurrent disease is an APR [97]. In the UKCCCR trial that involved chemoradiotherapy versus radiation therapy alone, patients who achieved less than a 50% response underwent a salvage APR [53]. Of the patients who underwent a salvage APR, 60% were free of locoregional recurrence. Furthermore, salvage chemoradiotherapy has been explored in this population. After salvage chemoradiotherapy in RTOG 87-04, 9 of 10 patients who had persistent disease underwent an APR. Unfortunately, six of the nine patients developed disease recurrence [55]. Other investigators have looked at combined modality therapy including salvage chemoradiotherapy with APR to improve the local control. In general, there are higher rates of adverse events in this patient population.

Role of Targeted Therapies in Combination with Definitive Chemoradiation

There are other recently completed and ongoing studies in locally advanced anal cancer patients testing the use of targeted agents in combination with chemoradiotherapy. A secondary analysis of pathologic samples from RTOG 98-11 found that EGFR mutations predicted for inferior outcomes [98]. Trials by the AIDS Malignancy Consortium (AMC) and ECOG completed two companion phase II trials (AMC045 and E3205) that evaluated the addition of cetuximab (400 mg/m^2 loading, then 250 mg/m^2 per week IV for 6–8 weeks) to concurrent 5FU (1000 mg/m^2 per day IV infusion on days 1–4 and 29–32), cisplatin (75 mg/m^2 IV every 28 days × 2), and radiation therapy (45–54 Gy) starting with the second dose of cetuximab [99, 100]. Trial E3205 included induction chemotherapy with two cycles of cisplatin and 5FU, but after the results of RTOG 98-11 were published, induction chemotherapy was dropped. Similar to ACT III–V, the primary endpoint for these studies was 3-year locoregional failure. In AMC045, the 3-year locoregional failure was 20% (95% CI, 10–37%) by Kaplan-Meier estimate in post hoc analysis. The study also revealed a 3-year PFS, and overall survival were 72% (95% CI, 56–84%) and 79% (95% CI, 63–89%). The trial was also notable for a grade 4 toxicity of 26%, and treatment-associated death rate was 4% [100]. The 3-year locoregional failure rate in trial E3205 was 21% (95% CI, 7–26%) by Kaplan-Meier estimate in post hoc analysis. The study revealed a 3-year PFS of 68% (95% CI, 55–79%) and overall survival of 83% (95% CI, 71–91%). The grade 4 toxicity was 32%, and treatment-associated death was 5% [99]. Both trials resulted in no additional locoregional control benefit. In addition, the addition of cetuximab resulted in significant toxicity.

Ongoing and Developing Trials

The PLATO (Personalising Anal Cancer Radiotherapy Dose) trial portfolio from the United Kingdom has three ongoing clinical trials for the treatment of anal cancer, including ACT III, ACT IV, and ACT V [78]. These trials will evaluate risk-adapted therapy based on pathologic characteristics, and the primary endpoint for each of these trials is 3-year locoregional failure. ACT III is a nonrandomized phase II study evaluating dose-reduced chemoradiotherapy in patients having undergone local excision and found to have T1 N0 anal tumors, where patients with >1 mm margin will undergo observation and those with <1 mm margin will be treated with chemoradiotherapy to a dose of 41.4 Gy in 23 fractions with capecitabine. Reduced dose chemoradiotherapy will also be evaluated in the ACT IV trial, a phase II study in clinical T1–T2 (up to 4 cm), node-negative anal cancer patients. Patients will be randomized to the standard radiation arm of 50.4 Gy in 28 fractions or the de-intensified radiation arm of 41.4 Gy in 23 fractions. Lastly, the ACT V trial is a phase II/III trial in locally advanced anal cancer patients with primary tumors greater than 4 cm or node-positive disease. They will be testing dose escalation of 53.20 Gy, 58.8 Gy, or 61.6 Gy, all in 28 fractions with standard concurrent chemotherapy. During interim analysis, one of the dose-escalated arms (58.8 Gy or 61.6 Gy) will move onto the phase III component [101].

Most anal cancers are a result of HPV infections. For this reason, there is interest in evaluating an immunotherapy treatment approach to treating locally advanced anal cancer. A phase I/II trial is underway in patients with a tumor size >4 cm or node-positive disease that combines standard-of-care chemoradiotherapy with a listeria-based HPV vaccine. Patients received four infusions of the vaccine with chemoradiotherapy. All patients treated on trial had complete responses, and the toxicity profile was deemed acceptable [102]. Additionally, a multicentre, cooperative group study is currently underway to evaluate adjuvant nivolumab for 6 months in high-risk anal cancer patients after definitive chemoradiation (NCT03233711).

Conclusions

The treatment paradigm for anal cancer has remained largely unchanged over the past 40 years. Attempts have been made to change or eliminate the chemotherapy used in the original Nigro regimen with no significant improvement in outcomes. However, there have been marked advancements in the delivery of radiation therapy using intensity-modulated radiation therapy and image guidance, where dose escalation is possible as a result of reduced side effect profile. There are multiple upcoming and developing clinical trials attempting to improve the efficacy of treatment for locally advanced disease, as well as evaluating descalation of therapy for lowrisk disease.

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Chapter 5
Anal Cancer: Toxicities and Management

Shalini Moningi and Prajnan Das

Introduction

Anal cancer is a rare malignancy, comprising approximately 1% of all GI cancers [1]. However, rates continue to rise every year in the United States, in large part due to high-risk HPV transmission [2]. For the last half-century, definitive chemoradiation with sphincter-sparing intent has been established as the primary, curative treatment option for this disease [2, 3]. While chemoradiation has been shown to be highly effective in terms of disease-free survival outcomes, it is associated with notable acute and late toxicities, even with the advent of intensity-modulated radiation therapy (IMRT). This chapter will discuss these morbidities and ways to mitigate and manage them.

Toxicities from Surgery

Prior to the 1970s, surgery was the mainstay of treatment for patients with anal cancer. The surgery involved an abdominal perineal resection (APR). An APR involves removal of the anus and rectum and placement of a permanent colostomy. An APR procedure alone resulted in approximately 40% recurrence rates. Additionally, there were significant morbidities associated with this procedure. There are high rates of urinary and sexual dysfunction and wound-related morbidities and high rates of perioperative morbidity and mortality, in addition to the issues related to a permanent colostomy [4, 5].

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Toxicities from Chemotherapy

Significant toxicity profiles exist with the usage of chemotherapy for anal cancer, specifically when using the two most common regimens: 5-fluorouracil (5-FU) and mitomycin C (MMC). The toxicity profile associated with the use of 5-FU and its oral prodrug, capecitabine, includes diarrhea, nausea, oral mucositis, and hand-foot syndrome. Common toxicities associated with MMC include myelosuppression and dermatitis. MMC can also be associated with rare side effects such as pulmonary fibrosis, hemolytic-uremic syndrome, and nephrotoxicity [4]. The risk of hematologic toxicity may depend on the number of doses of MMC. In the Radiation Therapy Oncology Group (RTOG) 98-11 trial, patients in the 5-FU/MMC arm (10 mg/m^2 MMC on days 1 and 29 and 1000 mg/m^2 5-FU on days 1–4 and 29–32) experienced 61% grade 3–4 hematologic and 74% grade 3–4 non-hematologic toxicity from the combination of 5FU/MMC and radiation [6]. In contrast, in the ACT II trial, patients in the 5-FU/MMC arm (single dose of 12 mg/m^2 MMC on day 1 and 1000 mg/m^2 5-FU on days 1–4 and 29–32) experienced only 26% grade 3–4 hematologic and 62% grade 3–4 non-hematologic toxicity. Lower rates of hematologic toxicity have been reported by prospective and retrospective studies that have used IMRT (Table 5.1) [7]. In the RTOG 0529 trial discussed below, the risk of grade 2+ hematologic toxicity was significantly lower compared to that in the RTOG 98-11 trial (73% vs. 85%) [8, 9].

Acute Toxicities from Radiation Therapy

The current treatment for anal cancer, a combination of radiation therapy, 5-FU, and mitomycin-C, can lead to significant toxicity. Acute side effects from chemoradiation include dermatitis, diarrhea, anorectal pain, neutropenia, nausea, tenesmus, vaginitis, and urinary dysfunction. We will review management options for each of these side effects. In the early years, toxicity was largely due to large fields associated with conventional 2D or 3D-conformal radiation treatment. With improved technology, we now are able to provide highly conformal treatments with the use of intensity-modulated radiation therapy (IMRT), which has reduced acute toxicity.

Multiple studies have shown a reduction in toxicity rates with the use of IMRT. Most notable of these was RTOG 0529, a multi-institutional phase II trial that investigated the use of IMRT for patients with T2–T4, N0-3 anal cancer and its utility in decreasing rates of toxicity. T2N0 patients received 42 Gy to the elective nodal regions and 50.4 Gy to the primary anal tumor in 28 fractions and T3-4, N0-3 patients received 45 Gy to the elective nodal region and 54 Gy to the primary anal tumor in 30 fractions. Seventy-seven percentage of patients experienced grade 2 or higher acute GI and/or GU toxicity, which was not significantly different from the rates seen in RTOG 98-11 which delivered standard conventional radiotherapy to patients. There was, however, a significant decrease in acute grade 2+ hematologic (73% vs. 85%), grade 3+ gastrointestinal (21% vs. 36%), and grade 3+ dermatologic

Table 5.1 Acute toxicity profiles in prospective and retrospective studies investigating IMRT for the treatment of anal cancer

Study	Study details	Total number of patients	Acute grade 3–4 toxicity (%)			Toxicity scoring system used
			Hematologic	Dermatologic	Gastrointestinal	
RTOG 05–29 [8]	Prospective trial	52	58	23	21	[a]CTCAE v3.0
Milano [48]	Retrospective	17	53	0	0	CTCAE v2.0
Salama [49]	Retrospective	53	59	38	15	CTCAE (version not specified)
Pepek [50]	Retrospective	45	24	0	15	CTCAE v3.0
Bazan [51]	Retrospective	54	21	21	7	CTCAE v3.0
Vieillot [52]	Retrospective	39	27	42	10	CTCAE v3.0
Kachnic [10]	Retrospective	43	51	10	7	CTCAE v3.0
Chuong [53]	Retrospective	52	63	12	10	CTCAE v4.0
Mitchell [38]	Retrospective	65	3	17	9	CTCAE v4.0
Call [54]	Retrospective	148	41	20	11	CTCAE v3.0
Belgioia [55]	Retrospective	41	5	5	7	CTCAE v3.0
Han [56]	Prospective	58	41	46	9	CTCAE v3.0
Janssen [57]	Retrospective	25	19	24	0	CTCAE v4.0
DeFoe [58]	Retrospective	78	13	29	28	CTCAE v3.0

[a]*CTCAE* common terminology criteria for adverse events

(23% vs. 49%) toxicities in the IMRT group compared to the conventional mitomycin group treated in RTOG 98-11 [10]. Table 5.1 shows acute toxicity rates from this trial and selected retrospective studies using IMRT for the use of anal cancer.

Dermatologic Toxicity

Dermatitis is usually present in the region receiving radiotherapy. Radiation therapy usually causes injury because it targets rapidly dividing cells, such as cancer cells, but also cells present in the epidermis, hair follicles, and sebaceous glands. The

degree of radiation-associated dermatitis is dependent on dose delivered, concomitant chemotherapy, comorbidities (such as diabetes, obesity, and age), and body location to which the treatment is delivered. The inguinal fossa and perianal/perineal regions are more susceptible to dermatitis due to skin folds present that can lead to "hot spots" [11, 12].

There are different degrees of radiation dermatitis described in detail by the National Cancer Institute's Common Toxicity Criteria for Adverse Events (the current version that is used nationwide is CTCAE v5.0). Grade 1 dermatitis includes faint erythema and dry desquamation.

The perianal and perineal region should be carefully assessed weekly during chemoradiation for skin erythema and integrity when patients are undergoing radiotherapy. Grade 1 dermatitis (erythema) is usually treated with topical therapy. Topical therapy includes lotions, ointments, and creams that are alcohol-, perfume-, and menthol-free. They can either be hydrating such as Aquaphor and aloe vera or antipruritic such as low-dose corticosteroid creams.

Data on topical treatments for radiation-induced dermatitis (RID) are sparse [13]. There are conflicting data on the use and benefit of aloe vera for RID. One self-controlled trial study has shown benefit with the use of topical aloe vera prophylactically for 60 patients undergoing irradiation for breast, head and neck, and pelvic tumors. Patients received a total dose ranging from 40 to 70 Gy and they found significantly lower mean dermatitis grade at 4 weeks following the completion of radiation treatment (0.05 vs. 0.21, $p = 0.002$) [14].

Hoopfer and colleagues performed a phase III trial comparing powder (nonmetallic baby powder or cornstarch), aloe cream and placebo cream applied during breast radiation therapy. They found that the prophylactic aloe formulation did not reduce acute skin toxicity or symptom severity. Their results showed worsening dermatitis, measured with a Catterall Skin Scoring Profile (CSSP) score, of 0.59 for placebo cream and 0.82 for aloe regimen after radiation. Their results support a dry skin care regimen of powder during radiation therapy [15]. Geara and colleagues conducted a prospective open-label randomized phase III study comparing the effect of β-sitosterol ointment to trolamine cream for the management of radiation dermatitis in breast cancer patients receiving radiation therapy. They found no significant difference in grades 2 and 3 dermatitis between the two groups. However, the incidences of severe pruritus and severe local skin pain were both significantly reduced in patients receiving β-sitosterol (14.1% in trolamine vs. 2.9% in β-sitosterol, $p = 0.016$ for pruritus, and 11.5% vs. 1.4%, respectively, $p = 0.02$ for severe pain) [16].

Finally, Ho and associates conducted a two-arm, double-blinded randomized trial evaluating the efficacy of 0.1% mometasone furoate compared to Eucerin Original cream in preventing the development of acute radiation dermatitis in breast cancer patients receiving radiation in the post-mastectomy setting. They found a significantly lower rate of moist desquamation in patients receiving mometasone furoate compared to patients receiving Eucerin cream (43.8% vs. 66.7%; $p = 0.012$) [17]. Patients receiving mometasone furoate also were found to have a lower incidence of maximum skin toxicities ($p = 0.036$) and longer time to development of grade 3 dermatitis (46 vs. 35.5 days; $p \leq 0.001$) [17, 18]. Topical steroid agents have

also shown to significantly reduce acute skin reactions and rates of moist and dry desquamation [19–21].

Grade 2 dermatitis involves a moderate to brisk erythema and/or dry or moist desquamation often seen in the inguinal and gluteal folds in patients receiving pelvic radiation. Patients with grade 2 dermatitis are also at a higher risk for local infections and worsening pain. In addition to topical treatments, patients with grade 2 dermatitis can be given Domeboro's solution and topical creams containing zinc oxide or silver sulfadiazine (Silvadene) in order to help cleanse the wound and reduce the risk of infections. Patients with grade 3 dermatitis have moist desquamation in areas other than skin folds and creases, and are at a higher risk for bleeding from minor trauma to the affected area. A variety of dressings can be used for moist desquamation.

Niazi and colleagues led a phase III randomized trial looking at patients with GI malignancies, primarily rectal and anal cancer, undergoing chemoradiation comparing the efficacy of silver clear nylon dressing (SCND) with that of standard skin care (sulfadiazine cream). They found that patients receiving SCND had a lower mean dermatitis score (1.67) on the last day of RT compared to patients receiving sulfadiazine cream (2.53, $p = 0.01$) [18].

For infections, which are uncommon, oral antibiotic therapy can be considered. Oral and/or topical antifungal medications should be used if there is evidence of candidal infection. Routine sitz baths are also recommended in order to keep the area clean and free of debris. Patients should also be educated on wearing looser clothing and to avoid tight clothing that can cause additional friction in the pelvic region [12, 22]. Finally, grade 4 dermatitis can cause life-threatening consequences including skin necrosis and full thickness dermal ulceration which might require skin grafting. Patients with severe dermatitis may require radiation treatment breaks to allow skin healing; however, such incidents are rare in the IMRT era.

Since the advent of IMRT, grade 2 and higher desquamation may not be seen until after the second week of chemotherapy. As such, it is recommended that patients return for skin checks after IMRT completion.

Diarrhea

Diarrhea is commonly seen a frequent acute toxicity associated with radiation treatment to the pelvis.

Studies have shown a dose response for the amount of radiation dose delivered to small bowel and the degree of GI toxicity in patients treated with rectal cancer. Robertson and colleagues found a highly significant correlation between small bowel volumes (bowel loops) receiving at least 15 Gy and toxicity, in terms of acute grade 3 diarrhea, occurring during and following radiotherapy treatment [23]. Furthermore, in the RTOG 0529 trial, small bowel volume (bowel loops) receiving radiation therapy was associated with grade 2+ gastrointestinal toxicity [24]. Higher rates of acute grade 2+ GI toxicity were seen for small bowel $V_{25Gy} > 186$ cc, $V_{30Gy} > 155$ cc, $V_{35Gy} > 41$ cc, and $V_{40Gy} > 30.4$ cc.

Table 5.2 Steps in escalating management for acute diarrhea during radiotherapy treatment

Step 1	Imodium 1–2 PO titrating to max of 8/day low fiber diet; 8 glasses fluid/day
Step 2	Imodium 2 PO q 4 h to max of 8/day
Step 3	Alternate Lomotil 2 PO with Imodium 2 PO q 3 h to max of 8/day each
Step 4	Evaluate need for IV fluid replacement; add tincture of opium
Step 5	Consider inpatient admission

Diarrhea is commonly managed with oral medications such as loperamide or lomotil. These can be used as needed and slowly titrated up to the maximum dose depending on the frequency of stools. A stepwise approach to the management of diarrhea is often helpful and is exemplified in Table 5.2.

Hematologic Toxicity

In addition to the myelosuppressive effect of MMC, pelvic radiotherapy also contributes to the suppression of bone marrow function, leading to hematologic toxicity. Mell and associates showed that the volumes of pelvic bone marrow receiving 5, 10, 15, and 20 Gy were significantly associated with white blood cell (WBC) counts and absolute neutrophil count (ANC) nadirs in patients treated with IMRT for anal cancer [25]. Normal tissue complication probability (NTCP) models have indicated that mean pelvic bone marrow dose of <22.5 Gy and <25 Gy were associated respectively with 5% and 10% risks of hematologic toxicity in patients treated with IMRT for anal cancer [26]. A subsequent study showed that radiation doses to total bone marrow, lumbosacral bone marrow, and iliac bone marrow were individually associated with hematologic toxicity [27]. Hence, efforts should be made to reduce the dose of bone marrow exposed to radiation therapy. Patients that do develop myelosuppression may need supportive therapy. Dose modification of MMC, such as omitting the second dose, is often needed when patients develop myelosuppression. Patients with myelosuppression may be at higher risk of skin infections, and increased attention needs to be paid to managing dermatologic toxicities in these patients. In selected cases, hematopoietic growth factors such as G-CSF and GM-CSF might be indicated.

Nausea

Nausea and emesis are common side effects of chemoradiation. There are multiple classes of medications that can be used for nausea. Commonly used anti-emetics include 5-HT3 receptor antagonists, such as ondansetron (Zofran), antihistamines such as promethazine (Phenergan), and dopamine antagonists such as prochlorperazine (Compazine). Patients with refractory nausea can also be treated with benzodiazepines such as lorazepam (Ativan) or with low-dose dexamethasone. Supportive care may include IV rehydration and electrolyte repletion [4, 12].

Fatigue

Cancer-related fatigue is a common phenomenon. Additionally, fatigue has also been documented in patients receiving radiotherapy. Even with being such a well-known side effect of radiotherapy, causes of radiation-related fatigue are still not completely clear.

First-line therapy can include non-pharmacologic interventions such as exercise, improved sleep hygiene, cognitive behavioral interventions, meditation, and acupuncture. Non-pharmacologic approaches have been shown to improve quality of life, fatigue, and the quality of sleep in patients [12].

Second-line therapy can include pharmacologic agents such as methylphenidate or dexamethasone.

Urinary Dysfunction

Urinary dysfunction usually manifests as cystitis or urinary tract infections (UTI) during radiotherapy treatment, often in the third to fourth week of radiation. Oral antibiotics can be used to treat UTIs, and if a UTI is ruled out, phenazopyridine (Pyridium) can be used for radiation cystitis. Men receiving pelvic radiation therapy can sometimes develop urinary obstructive symptoms; such symptoms can be treated with the alpha-adrenergic blocker tamsulosin (Flomax) [22].

Pain

Patients undergoing chemoradiation for anal cancer can present with or develop severe pain, especially with bowel movements. First-line management of pain should include over-the-counter medications such as acetaminophen and/or nonsteroidal anti-inflammatory drugs, such as ibuprofen. Patients with refractory pain may need opioid pain medications; however, such medications should be used judiciously, given the potential for opiate addiction [28].

Anorectal Dysfunction and Proctitis

Pelvic radiotherapy can commonly affect the rectum and anal canal. Radiation-associated proctitis is a result of epithelial damage to the rectum leading to inflammation. Acute radiation proctitis occurs within 6 weeks of RT and chronic radiation-associated proctitis can occur 9–14 months following the completion of radiation treatment. Acute proctitis can be managed with steroid agents, hydration and antidiarrheal medications, and pain medications as needed. Severe tenesmus and/or rectal pain can be managed with steroid suppositories or proctofoam. Severe and persistent bleeding can be

managed with a trial of the various treatments discussed above and possible endoscopic intervention for patients with persistent symptoms [29–32].

Late Toxicities from Chemoradiation

Long-term side effects include gastrointestinal dysfunction, anorectal dysfunction, chronic dermatitis, sexual dysfunction, infertility, fistulas, ulcers, and pelvic fractures.

Gastrointestinal Dysfunction

Many patients will develop long-term gastrointestinal dysfunction after chemoradiation, with symptoms such as chronic diarrhea, bowel urgency, and anorectal dysfunction leading to fecal leakage and incontinence [33]. These symptoms can be treated with low-fiber diet and long-term use of antidiarrheal medications such as Imodium. Conversely, in some patients, stool bulking agents such as psyllium (Metamucil) can promote anorectal emptying, and thereby reduce stool leakage and incontinence. Fecal incontinence can also be managed with pelvic floor muscle exercises [22].

Das and associates assessed long-term quality of life after 3DCRT for anal cancer patients by using the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) score. The FACT-C score has been validated in patients with colorectal cancer. They found that the median colorectal subscale was 21 out of a maximum 28; 23% (7 patients) reported having very little control of bowels and 31% (10 patients) reported having "quite a bit" of diarrhea [33]. Additionally, Tang and associates from the same institution reported FACT-C scores in anal cancer patients who received IMRT. They found similar FACT-C median Colorectal subscores of 21 out of a maximum of 28 [34].

Additionally, patients who suffer from chronic radiation proctitis can present with bleeding, rectal pain, and tenesmus. Similar treatment strategies as discussed in the acute toxicities section can be used for chronic radiation proctitis.

Chronic Skin Changes

Chronic radiation dermatitis can develop months to years following radiation therapy. Unlike acute dermatitis, chronic changes will likely be irreversible. Chronic dermatitis manifests in multiple ways and is usually seen in the radiation treatment field. First textural changes can be seen like xerosis, scaling of the skin, and

hyperkeratosis. Persistent toxicities like changes in pigmentation, atrophy of the skin, and telangiectasias can also be seen. Hair follicle and sweat gland changes and decreased rates of sweating within the treatment field are also possible. Cutaneous and subcutaneous tissue fibrosis can also occur. Radiation can also cause acute and chronic alopecia in the treatment field. We expect that the use of IMRT will result in a reduction in the incidence and severity of such chronic skin changes, just as IMRT has reduced acute dermatologic toxicities [35].

Sexual Dysfunction

Sexual dysfunction can also be seen as a late side effect following radiotherapy treatment. A long-term quality of life study reported poor sexual function scores after conventional radiotherapy for anal cancer [33, 34]. Patients had a median score on the Medical Outcomes Study (MOS) Sexual Problems Scale of 67 out of a maximum possible score of 100. Among 6 men, 4 (67%) had difficulties maintaining an erection and among 20 women, 14 (70%) reported difficulty having an orgasm [33]. A subsequent study from the same institution showed poorer sexual function scores, with a median of 63 out of a maximum value of 100, even after IMRT for anal cancer [33, 34]. Vaginal stenosis is a recognized toxicity seen in patients who have received pelvic radiotherapy. A study on patients undergoing radiation for anal and rectal cancer showed that women who had a mean vaginal dose of <43 Gy had significant decreases in severe vaginal stenosis [36]. The rate of vaginal stenosis has been shown to be associated with younger age and higher tumor dose [37]. The use of a vaginal dilator during treatment can displace the anterior vagina from the high-radiation dose area and thereby reduce vaginal toxicity [38]. Das and colleagues found significantly better FACT-C scores in women who have used vaginal dilators during RT simulation and treatment (26 vs. 24; $p = 0.031$). Additionally, these women also had an improved MOS sexual subscale score [33]. Long-term and regular use of vaginal dilators should be recommended for the prevention and mitigation of vaginal stenosis [39]. Men can develop erectile dysfunction after pelvic radiotherapy (up to 67% of men experiencing sexual dysfunction in some studies [33]), and may benefit from pharmacologic interventions with phosphodiesterase type 5 inhibitors, such as sildenafil (Viagra) or tadalafil (Cialis). Interventional urologic procedures can also be considered for the treatment of sexual dysfunction in men. The likelihood of pregnancy following pelvic RT is low based on the current literature. However, options for fertility preservation must still be discussed with the patient. There are some data supporting the use of laparoscopic ovarian transposition as a safe and viable option for women who aim to undergo fertility preservation prior to receiving pelvic RT [40]. For younger patients, it is important to discuss fertility preservation options prior to initiation of radiotherapy; such options may include oophoropexy, egg harvesting, and sperm banking. Patients may also benefit from referral to a sexual counselor.

Fistulas and/or Ulcers

Anal fistulas and/or ulcers were reported in 8% of patients in ACT I. Rarely, patients may need permanent colostomy due to chronic ulceration and/or fistulae formation [41].

Pelvic Fractures

Pelvic fractures are occasionally seen as a long-term toxicity following pelvic radiotherapy. A landmark study conducted by Baxter and colleagues looked at SEER data and the effect of pelvic irradiation on the incidence of pelvic fractures over time [42]. The authors found that treatment for anal cancer was associated with a higher risk of pelvic fractures compared to women who received radiotherapy for cervical and/or rectal cancer. However, the risk of pelvic fractures is likely to be much lower with the use of IMRT.

Additionally, elderly women are at a higher risk based on a few studies. Herman and colleagues looked at 562 patients with non-metastatic rectal adenocarcinoma who received preoperative chemoradiation followed by a mesorectal excision. They found that women and Caucasians had a higher rate of sacral insufficiency fractures compared to men and non-Caucasians respectively (5.8% vs. 1.6%, $p = 0.014$; 4% vs. 0%, $p = 0.031$) [43]. Additionally, Kim and associates found an even higher risk of SI fractures (7.1%) in patients receiving adjuvant chemoradiation following surgical excision for locally advanced rectal cancer. They also found that patients >60 years of age, women, and patients with a history of osteoporosis were at a significantly higher risk for developing sacral fractures [44].

Early identification of osteoporosis is crucial in patients receiving pelvic RT for lower GI malignancies.

For postmenopausal women, a bone density test should be obtained, and vitamin D and calcium supplementation should be recommended. Existing data show that fractures occur 2–2.5 years following completion of RT; therefore, screening for fractures shortly after completion of RT is also of utmost importance. Finally, treatment for pelvic and sacral fractures includes rest and nonsteroidal pain management. Additionally, there have been some data supporting pentoxifylline and sacroplasty as possible treatment options in addition to adequate pain management [45]. It is also important to differentiate sacral insufficiency fractures from pelvic recurrences early in the postradiation period in order to avoid unnecessary biopsies and manipulation in the pelvic region.

Secondary Malignancies

An adverse late side effect from radiation therapy delivered to any region of the body is the increased risk of secondary malignancies in the radiation field. There have been conflicting reports on the increased risk of secondary malignancies

following pelvic RT. Gonzalez and associates investigated the rates of secondary cancers by investigating national US Surveillance, Epidemiology and End Results (SEER) data. They estimated that a small proportion of patients, 8% of all patients receiving RT, experienced secondary solitary malignancies by 15 years after diagnosis. Their data suggest that in large most secondary malignancies are due to genetic and lifestyle factors and less likely due to radiation-related causes [46]. Rombouts and colleagues looked at a cohort of over 29,000 patients with rectal cancer, of which approximately 15,000 patients underwent RT and approximately 4300 patients were diagnosed with secondary primary tumors; one-fourth of those patients had secondary tumors in the pelvis. Gynecological tumors were more frequently observed in female patients who received RT; however, RT reduced the cumulative incidence of second pelvic tumors compared with patients who did not receive RT. Specifically, RT reduced rates of prostate tumors [47].

Conclusion

Chemoradiation can lead to dermatologic, gastrointestinal, sexual, and other toxicities during and after chemoradiation. While IMRT has enabled us to reduce the risk of acute toxicities, long-term gastrointestinal and sexual toxicities remain a concern. Appropriate management of acute and chronic toxicities is a critical part of the clinical care of patients with anal cancer.

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Chapter 6
Management of Local-Regional Anal Cancer Recurrence

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Abbreviations

5-FU	5-Fluorouracil
APR	Abdominoperineal resection
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
MRI	Magnetic resonance imaging
SCC	Squamous cell carcinoma

Introduction

Anal cancer, a rare gastrointestinal disease, accounts for 1–2.5% of GI cancers [1, 2]. Its epidemiologic rise is a result of an increase in the incidence of human papillomavirus (HPV), improved survival of patients with autoimmune disorders, and immunosuppressed patients (organ transplant and human immunodeficiency virus (HIV)-positive patients) [1, 2]. Squamous cell carcinoma (SCC), the most common pathologic subtype, is treated primarily with chemoradiation [3–9]. Salvage surgery is the second line of treatment for those 10–30% of patients who experience local relapse, usually within the first 3 years after chemoradiation treatment [10–14]. Locoregional failure is defined as a persistent or recurrent disease. The persistent disease is diagnosed within 6 months of chemoradiation treatment, and locoregional failure due to recurrent disease presents beyond 6 months after completion of chemoradiation [12, 15].

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Studies suggest tumor regression continues several months after completing chemoradiation [16, 17]. Current guidelines recommend physical examination 8–12 weeks after treatment to evaluate tumor response [18]. However, post hoc analysis of the ACT II trial showed that patients who do not have a complete response when assessed at 11 weeks post chemoradiation therapy may in fact have a complete response after 26 weeks [16–18]. This delay has to be weighed against delaying salvage surgery for patients who are at high risk for failure of chemoradiation treatment.

Patients who present with higher T and N stages, poorly differentiated SCC, HIV and solid organ transplant patients who poorly tolerate chemoradiation are more likely to fail primary chemoradiation [11, 12, 19–21]. One-third of patients with T4 or N3 disease develop local recurrence [11, 12]. Of patients with relapsed disease, 75% of recurrences are in the anus or rectum, 20% recur elsewhere in the pelvis, 5–10% recur in inguinal nodal basins, and 10–20% relapse with distant metastases, with liver being the most common site of metastatic disease [11, 12, 22–27].

Locoregional Failure

When the disease remains persistent or local recurrence occurs, restaging studies are required—multidisciplinary tumor board discussions and salvage surgery should be considered. Cross-sectional CT imaging of the chest, abdomen, and pelvis or fluorodeoxyglucose [18F] positron-emission tomography with CT (PET/CT) can evaluate the burden of local disease, but more importantly, the presence of distant metastatic disease. High-resolution MRI with or without diffusion evaluates pelvic resectability and nodal status [12, 17]. In the absence of metastatic disease on imaging, curative surgery should be pursued. Surgical options include wide local excision, which is rarely implemented, abdominoperineal resection (APR), pelvic exenteration with or without sacrectomy, and/or inguinal node dissection.

Wide local excision with or without flap closure is appropriate for recurrence that is localized without significant anal sphincter involvement for low-grade disease. However, if there is any concern for advanced disease, then APR is pursued. Compared to APRs performed for rectal cancer, salvage APR for anal SCC involves wide lateral margins that extend to the ischial tuberosities. Five-year disease-free survival rates for salvage APR range from 24% to 75% [12, 28–40]. Median survival has been reported at 22 months [41]. The presence of positive surgical margins, T stage, perineural and/or lymphovascular invasion, tumors involving other organs, HIV positivity, and positive lymph nodes are independent predictors of recurrence and survival after APR [15, 30, 42].

Pelvic exenteration surgery is possible in 20% of patients with recurrence in the pelvis [31, 43]. This approach is appropriate for medically fit patients who have tumors that abut or infiltrate pelvic organs such as the prostate, urethra, bladder, seminal vesicles, or vaginal septum. Pelvic exenteration is only offered if distant

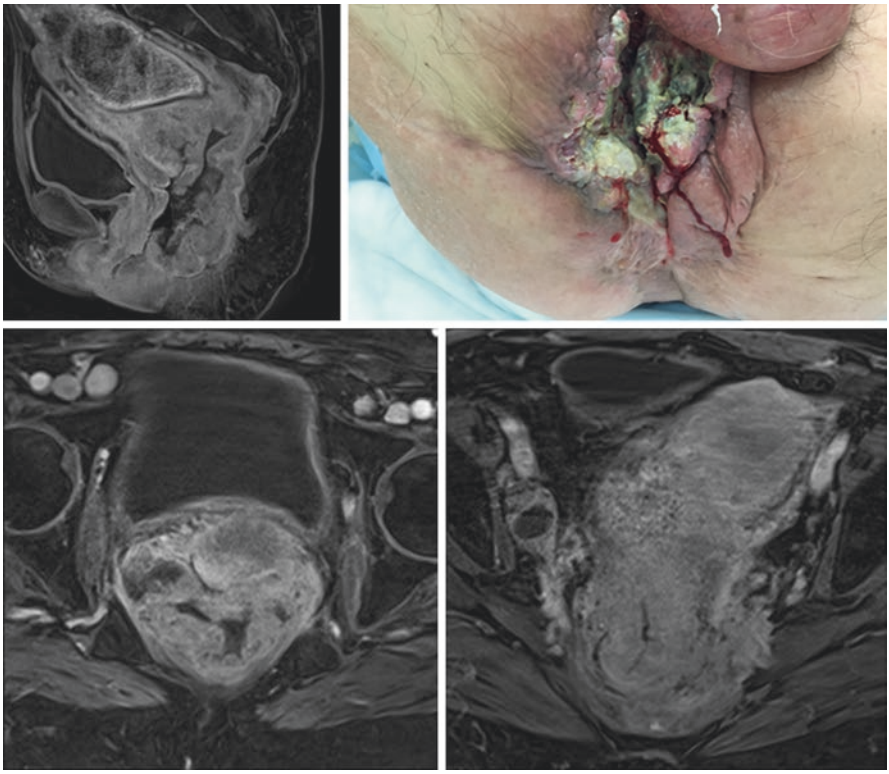

Fig. 6.1 Unresectable disease. MRI of partially obstructing mass with extensive inguinal, iliac, and pelvic adenopathy

metastatic disease is absent on imaging and R0 resection is possible. Sacrectomy en bloc is performed if there is concern for tumor abutment or infiltration of the sacrum; this procedure is usually performed in collaboration with orthopedic surgeons [44]. Absolute contraindications to pelvic exenteration are para-aortic node involvement, bilateral sciatic nerve involvement, circumferential pelvic bone involvement, and lumbar spine involvement (Fig. 6.1). Relative contraindications include tumor extension through the sciatic notch, encasement of external iliac vessels, and high sacral involvement [12].

Perineal defects, particularly after radiation treatment, are at high risk of wound complications, if closed primarily. Flap closures mitigate this risk. Vertical rectus abdominis myocutaneous flaps are the most common flaps performed [45–48]. Other options include anterolateral thigh flaps, gracilis muscle flaps, inferior gluteal artery myocutaneous flaps, full thickness local advancement flaps, and gluteal fold flaps [49–53]. If inguinal node dissection is performed, a sartorius muscle flap can be utilized for wound coverage. Vaginal reconstructions can also be performed with the flaps mentioned above or with local rotational flaps [12, 53].

For patients who are poor surgical candidates or ones who refuse colostomy, there is a paucity of data on salvage chemotherapy, radiation, or chemoradiation. Studies demonstrate that 5-FU, cisplatin, or mitomycin and re-irradiation can be considered, although there may not be a significant increase in overall survival [6]. A study by Flam and colleagues demonstrated that 26 of 30 patients attained biopsy complete remission and were disease-free for 9–76 months. Patients in this study were treated with salvage chemoradiation consisting of 5-FU, mitomycin-C, and whole pelvis irradiation and had only mild acute toxicities like diarrhea [54]. Additional studies that are powered appropriately need to be performed to determine whether a true survival or palliative benefit exists.

Table 6.1 reports the results of the selected series of salvage surgery for patients with anal cancer.

Table 6.1 Results of selected series of salvage surgery for patients with anal cancer

Authors and year	Number of cases (N)	Survival
Ellenhorn et al. [32]	38	5 years actuarial: 44%
		DFS: 44%
Pocard et al. [33]	21	3 years overall: 58%
Allal et al. [34]	26	5 years actuarial: 44.5%
Van der Wal et al. [35]	17	5 years actuarial:47%
		DFS: 44%
Smith et al. [36]	22	5 years overall: 23%
Nilsson et al. [37]	35	5 years: 52%
Akbari et al. [30]	57	5 years: 33%
Ghouti et al. [38]	36	5 years: 69.4%
Renehan et al. [28]	73	3 years overall: 55%
		5 years overall: 40%
Mullen et al. [29]	31	5 years actuarial: 64%
Schiller et al. [39]	40	5 years overall: 39%
		DFS: 30%
Mariani et al. [40]	41	3 years actuarial: 62.8%
		5 years actuarial: 56.5%
		DFS at 3 years: 79.9%
		DFS at 5 years: 75.5%
Sunesen et al. [45]	49	5 years overall: 61%
Lefèvre et al. [31]	105	5 years overall: 61%
		DFS: 48%
Correa et al. [42]	111	2 years overall: 60%
		5 years overall: 24.5%
		DFS: 29.5%
Severino et al. [15]	36	3 years overall: 46%
Guerra et al. [10]	41	5 years overall: 51%
		DFS:47%

Inguinal Nodes

Anal cancer spreads through lymphatic channels, hematogenously, and through the direct invasion of adjacent organs. Tumors above the dentate line spread to perirectal (N1) lymph nodes, and tumors below the dentate line metastasize to inguinofemoral lymph nodes (N2). About 0–10% of T1 and T2 tumors metastasize to lymph nodes, and 40–50% of T3–T4 tumors present with inguinal node metastases [55–57]. Seven to 16 % of patients who are initially node negative and are not treated with prophylactic inguinal radiation recur with a positive node, and as many as 30% of T3–T4 patients recur in the inguinal lymph node basin [57–59]. Individuals who receive prophylactic radiation to the inguinal node region have a 2% recurrence rate in the inguinal nodes [57, 58]. Patients with inguinal recurrence who did not have radiation to the inguinal region can be managed with chemoradiation. If the inguinal disease is present after groin irradiation, then inguinal lymph node dissection is indicated. If recurrence is absent in the anus, an APR does not necessarily need to be performed in concurrence with the inguinal lymph node dissection [31, 43].

Salvage Surgery for HIV-Positive Patients

Over the last decade, with the discovery of highly active antiretroviral therapy (HAART), the survival of HIV-positive patients taking HAART approaches that of the non-HIV population [60]. Patients diagnosed with HIV have a 55-fold increased prevalence of invasive anal carcinoma and are younger in age compared to the non-HIV population [61, 62]. Primary chemoradiation treatment in HIV-positive individuals results in a 75% 5-year survival, similar to that demonstrated in non-HIV patients. However, chemoradiation reduces CD4 counts in HIV patients which could be the cause of increased morbidity such as wound healing after surgery. There is an absence of studies for HIV-positive patients undergoing salvage surgery. Cunnin and colleagues reported that overall survival was 25% at 2 years from salvage surgery [63]. Complete perineal healing did occur, but it could take up to 11 months with a median time of 4 months from the time of operation, even though flaps were utilized. Theories that HIV-positive patients are at greater risk for flap ischemia due to HIV-related microvascular disease may explain the prolonged time for perineal wound healing. Although survival was similar to salvage surgery for patients with non-HIV anal carcinoma, patient morbidity may be worse for HIV-positive patients [63].

Conclusion

Salvage surgery improves survival for selected patients with persistent or recurrent disease after chemoradiation. It can improve the quality of life for symptomatic palliative patients or lead to curative resection. Further research needs to be performed

to determine the overall benefit of salvage chemoradiation and treatment options for HIV-positive patients.

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Chapter 7
Treatment of Advanced Anal Cancer

Satya Das and Kristen Keon Ciombor

Abbreviations

5-FU	5-fluorouracil
AE	Adverse event
ASCC	Anal squamous cell carcinoma
CC	Cervical cancer
CI	Continuous infusion
CP-5-FU	Cisplatin plus 5-fluorouracil
CPAC	Carboplatin plus paclitaxel
CP	Carboplatin
CR	Complete response
D	Day
DCF	Docetaxel, cisplatin, fluorouracil
DCR	Disease control rate
DFS	Disease-free survival
EGFR	Epidermal growth factor receptor
FOLFOX	5-FU, oxaliplatin and leucovorin
FOLFIRI	5-FU, irinotecan and leucovorin
G	Grade
GGT	Gamma-glutamyltransferase
Gy	Gray
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IV	Intravenous
MAP	Mitomycin C, adriamycin and cisplatin
mASCC	Metastatic anal squamous cell carcinoma
m^2	Meters squared
mg	Milligram

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NCCN	National Comprehensive Cancer Network
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
RFA	Radiofrequency ablation
SD	Stable disease
TIL	Tumor-infiltrating lymphocytes
TRAE	Treatment-related adverse event
WT	Wild-type

Introduction

Metastatic anal squamous cell carcinoma (mASCC) is a rare disease whose incidence is rising annually in the United States. Patients with anal squamous cell carcinoma (ASCC) are diagnosed de novo with metastatic disease in 5–10% of cases, and another 10–20% of patients initially diagnosed with local disease ultimately relapse distantly [1, 2]. Five-year survival rates for mASCC patients are less than 30%, and there are few systemic treatment options which have been validated prospectively or in a comparative fashion. Most patients with adequate performance status receive platinum-based doublet therapy based on results from case reports or small case series, with cisplatin plus 5-fluorouracil (CP-5-FU), oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) or carboplatin plus paclitaxel (CPAC). After progression on first-line therapy, the later-line treatment options become even more limited. Recently, given the success of immunotherapy in other malignancies with human papillomavirus (HPV)-mediated oncogenesis, immune-modulating agents have become an area of great interest in mASCC [3, 4]. We will discuss existing chemotherapy, targeted therapy, and immunotherapy data along with promising new treatments in development for mASCC in the subsequent paragraphs of this chapter.

Chemotherapy

Platinum-Doublet Therapy for Metastatic Anal Squamous Cell Carcinoma

One of the initial descriptions of the activity of CP-5-FU in mASCC was published by Khater and colleagues in the form of a two-patient case report [5]. Ajani and colleagues described three patients with hepatic metastases from anal primaries who were treated with intra-arterial floxuridine (5-FU being the catabolic end product of this drug) 100 mg/m^2 daily and cisplatin 30 mg/m^2 daily for 3 days per treatment cycle [6]. Two of the three patients had ongoing responses at 17 and 20 months,

respectively, while one patient had tumor progression after 4 months. Jaiyesimi and colleagues reported another case of patient with mASCC with necrotic inguinal lymph node recurrence who was treated with continuous infusion (CI) 5-FU 1000 mg/m^2 on days 1–5 (D1–D5) and cisplatin 100 mg/m^2 D1 every 21–28 days for 12 cycles [7]. The patient remained free of disease as of last reporting in 1992.

Faivre and colleagues described a single institution experience from the Institut Gustave Roussy in which 19 mASCC patients (10 with liver metastasis, 11 with lymph node metastasis, and 3 with pulmonary metastasis) received CI 5-FU 1000 mg/m^2 D1-D5 and cisplatin 100 mg/m^2 D2 every 28 days [8]. The median number of cycles patients received was 4, and 18 patients were evaluable for response. Overall response rate (ORR) was 66% with 1 complete response (CR) and 11 partial responses (PR). Disease control rate (DCR) was 89%. One-year survival was 62.2%, 5-year survival was 32.2% and median overall survival (OS) was 34.5 months. Patients developed grade 3/4 (G3/4) nausea in 30% of cases and neutropenia in 13% of cases. Haydon and colleagues published a case of a mASCC patient with extensive lung and liver metastases who achieved a CR with CP-5-FU [9]. The patient had treatment-naive p16-positive disease encompassing >50% of her liver, multiple pulmonary metastases, and intra-abdominal lymph nodes, along with an intact anal primary. She received 6 cycles of CP-5-FU with a CR seen on post-treatment CT scan. The patient remained disease free after 7 years at the time of publication.

Eng and coworkers presented a large single institution retrospective experience from MD Anderson Cancer Center looking at mASCC patient outcomes with systemic chemotherapy followed by either multidisciplinary management for curative intent or continuation of palliative chemotherapy. A total of 77 patients (4 with HPV, 3 with HIV) received 5-FU (CI 750 mg/m^2 D1-D5) plus cisplatin (75 mg/m^2 D1) every 4 weeks (42 patients), carboplatin (AUC 5 D1) plus paclitaxel (175 mg/m^2 D1) every 3 weeks, or a regimen not otherwise specified [10]. After a median follow-up of 42 months, median progression-free survival (PFS) was 7 months, and median OS was 22 months. When stratified by regimen, a non-statistically significant difference in median PFS was observed in favor of CP-5-FU compared to CPAC (8 months versus 4 months). ORR was 57% (all PRs) in the CP-5-FU treated patients, and DCR was 86%. ORR was 33% (all PRs) in the CPAC treated patients, while DCR was 54%. The experience of the mASCC patients treated with curative intent is described below in the oligometastatic disease section.

Kim and coworkers published a retrospective single-center experience from Moffitt Cancer Center in which 18 mASCC patients received CPAC (carboplatin AUC 5 or 6 on D1 and paclitaxel 175 mg/m^2 D1 every 3 weeks); 12 received this regimen in the first-line setting and 6 in the second-line setting [11]. Among patients who received this regimen first line, median OS was 12.1 months. ORR was 53% in all patients (3 CRs) and 69% among patients receiving first-line therapy. Grade 3 or 4 toxicities were observed in six patients with the most common ones being neutropenia and anemia. The EA2133/InterACCT study is a recently completed randomized phase II trial comparing first-line CP-5-FU versus CPAC in mASCC patients with a primary endpoint of ORR [NCT02051868]. This study was recently pre-

Table 7.1 Select published trials or retrospective patient series about the platinum-doublet chemotherapy experience in mASCC patients

Trial name or study authors	Treatment	P or R	Ongoing or completed	Number of patients	ORR (percent)	PFS (months)	OS (months)
Eng et al. [10]	CP-5-FU	R	Completed	42	57%; all PR	8	22 (entire cohort)
	CPAC	R	Completed	24	33%; all PR	4	22 (entire cohort)
Faivre et al. [8]	CP-5-FU	R	Completed	19	65%; all PR	4	N/A
Kim et al. [11]	CPAC	R	Completed	18	53%; 17% CR	N/A	12.1
EA2133	CP-5-FU vs CPAC	P	Ongoing	91	NA	N/A	N/A
Matsunaga et al. [13]	FOLFOX	R	Ongoing	1	100%; PR	N/A	N/A

CR complete response, *N/A* not applicable, *NR* not reached, *ORR* overall response rate, *OS* median overall survival, *P* prospective, *PFS* median progression-free survival, *PR* partial response, *R* retrospective, *vs* versus

sented and demonstrated an ORR of 57.1% for cisplatin/5-FU versus 59.0% for carboplatin/paclitaxel; however, OS was improved in the carboplatin/paclitaxel arm (mOS 20 vs 12.3 months, $p = 0.014$). With these results, investigation of the addition of targeted agents and/or immunotherapy for mASCC patients is anticipated [12].

Matsunaga and coworkers reported a single-patient case of a KRAS-mutant mASCC patient with liver and lung metastases who was treated with FOLFOX and bevacizumab every 2 weeks [13]. The patient received 22 doses of the combination and achieved a PR. At the time of the publication, the patient remained progression free. FOLFOX is a National Comprehensive Cancer Network (NCCN) category 2A recommendation for mASCC based on this report and extrapolation from data in metastatic rectal cancer.

Results from these series are summarized in Table 7.1.

Beyond Platinum-Doublet Therapy in Metastatic Anal Squamous Cell Carcinoma

Another studied chemotherapeutic regimen for the treatment of metastatic anal squamous cell carcinoma has been mitomycin C, adriamycin, and cisplatin (MAP) followed by bleomycin-CCNU, which was assessed in the ECOG 7282 trial (Table 7.2). Jhawer and coworkers reported the results from the phase II study where 20 patients with mASCC (15% treatment-naïve, 60% unknown prior treatment, if any) received MAP (mitomycin C 10 mg/m^2 D1, adriamycin 30 mg/m^2 D1, cisplatin 60 mg/m^2 D1) every 4 weeks for two cycles [14]. Thereafter, mitomycin C

Table 7.2 Select published trials and retrospective patient series about the platinum-doublet chemotherapy experience in mASCC patients

Trial name or study authors	Treatment	P or R	Ongoing or completed	Number of patients	ORR (percent)	PFS (months)	OS (months)
ECOG 7282 [14]	MAP plus BCNU	P	Completed	20	60%; all PR	8	15
Kim et al. [17]	DCF	P	Completed	66	89%; 45% CR	11	NR
Hainsworth et al. [16]	CPAC plus 5-FU	R	Completed	4	65%; 25% CR	26	NR
Alcindor et al. [18]	Paclitaxel	R	Completed	5	60%; all PR	3–8	4–20
Abbas et al. [19]	Paclitaxel	R	Completed	7	57%; all PR	NR	NR
Evans et al. [20]	Carboplatin	R	Completed	1	100%; PR	9	N/A

CR complete response, *N/A* not applicable, *NR* not reached, *ORR* overall response rate, *OS* median overall survival, *P* prospective, *PFS* median progression-free survival, *PR* partial response, *R* retrospective

was administered every 10 weeks, while adriamycin and cisplatin were administered every 5 weeks. Patients who developed progressive disease on MAP were eligible for bleomycin-CCNU; however, only two patients received this latter treatment. ORR was 60% (all PRs), median OS was 15 months and median PFS was 8 months. Fifty percent of patients experienced G3 hematologic adverse events (AEs), while 55% experienced G2 vomiting.

Kim and coworkers retrospectively assessed the efficacy of docetaxel 75 mg/m^2 D1, CP 75 mg/m^2 D1, and 5-FU 750 mg/m^2 D1-D5 (DCF) every 3 weeks in eight recurrent mASCC patients [15]. Six of the eight patients were HPV-positive, and all patients had initially received curative intent concurrent chemoradiation (CCR) with 5-FU and mitomycin C. Fifty percent of patients achieved an objective response, with four patients achieving a CR; the responding patients remained disease free as of the time of case series publication. Four patients experienced G3 toxicities but no patients experienced G4 toxicities. The most common G3 hematologic toxicities were anemia and neutropenia.

Hainsworth and coworkers assessed the combination of CPAC and 5-FU in metastatic squamous cell carcinoma patients of various origins in a phase II study [16]. Eighty percent of patients were treatment-naïve, while 20% received treatment in the second-line setting. Out of 60 patients, four had mASCC. Each patient received carboplatin AUC 6 on D1 and D22, 5-FU 225 mg/m^2 D1-D35 and paclitaxel 200 mg/m^2 D1 and D22 every 6 weeks for a maximum of four treatments. ORR was 65% (CR in 25%; CR 25% in the mASCC cohort), median PFS was 26 months and median OS was not reached in the entire cohort. The most frequent grade 3/4 toxicities experienced by patients in the study included leukopenia (48%), mucositis (28%) and diarrhea (17%).

Recently, Kim and associates published results from the Epitopes-HPV02 study [17]. In this single-center phase II study, mASCC patients or those with recurrent unresectable disease were treated with two different regimens of docetaxel, cisplatin and fluorouracil (DCF). Sixty-six patients were randomized to either standard DCF (75 mg/m^2 docetaxel D1, 75 mg/m^2 cisplatin D1 and 750 mg/m^2 of 5-FU D1-D5 every 3 weeks) or modified DCF (40 mg/m^2 docetaxel D1, 40 mg/m^2 cisplatin D1 and 1200 mg/m^2 of 5-FU D1-D2 every 2 weeks). The choice of which regimen to give patients was guided by age; patients >75 years old received modified DCF, and patients <75 years old received standard dosing DCF. The primary endpoint of the study was 12 month PFS post-cycle 1 of DCF. This primary endpoint of this study was met, with 47% of patients alive and progression-free at 12 months (minimum threshold for study to be deemed positive was 17%). A total of 61% of the patients who received standard DCF were progression-free at 12 months, while 60% of patients treated with the modified regimen were progression free at that timepoint. Median PFS and OS in all patients were 11 months and not reached, respectively. ORR in the entire cohort was 89%, with 45% of patients achieving CR. Adverse event profile clearly favored the modified regimen with reduced incidence of G3 neutropenia, anemia, vomiting, mucositis, diarrhea, or asthenia. No patients in the modified DCF arm experienced G4 febrile neutropenia events or non-hematologic events, compared to 14% and 8%, respectively, in the standard DCF arm.

Single-agent chemotherapy approaches that have been utilized in mASCC patients, either in the first-line setting for poor risk patients or after disease progression with first-line therapy, include paclitaxel, irinotecan and carboplatin [18–20]. Alcindor and associates reported findings from a five-patient mASCC case series from McGill University Health Centre [18]. Three patients were treated with paclitaxel 175 mg/m^2 every 3 weeks in the second-line setting after progression on CP-5-FU, while the other two patients received the agent in the first-line setting. Sixty percent of patients experienced PR, with disease control lasting from 3 to 8 months. Survival for these patients ranged from 4 to 20 months. Another case series from Abbas and associates looked at the experience of seven mASCC patients treated with weekly paclitaxel 80 mg/m^2 (3 out of 4 weeks) post-progression on CP-5-FU [19]. Fifty-seven percent of patients achieved radiographic response with duration of disease control between 4 and 6 months in responding patients. Patients who achieved PR had a median OS between 12 and 14 months. Evans and associates reported activity of single-agent carboplatin in a mASCC patient who progressed with pulmonary involvement 5 months after completing primary therapy with 5-FU-/mitomycin-based chemoradiation [20]. The patient received 600 mg of carboplatin every 4 weeks for six treatments. He achieved a PR after three treatments which persisted for 9 months.

Results from these series are summarized in Table 7.2.

Targeted Therapy

Anti-EGFR Antibodies in the Treatment of Metastatic Anal Squamous Cell Carcinoma

RAS (KRAS and NRAS) and BRAF mutations have been reported in 4–5% of ASCC patients, while other retrospective analyses suggest the frequency of these mutations is even lower [21, 22]. Given the rarity of RAS and BRAF mutations, along with the prevalence of epidermal growth factor receptor (EGFR) overexpression (roughly 90%) in ASCC, there appears to be a biologic rationale for EGFR inhibitors such as cetuximab or panitumumab in this disease [23].

Phan and Hoff reported their experience of a single mASCC patient treated with irinotecan plus cetuximab [24]. This patient was initially treated with concurrent CP-5-FU and radiation in the local setting but recurred distantly in multiple lymph node stations both within and outside of the pelvis. She received carboplatin and docetaxel with a mixed response and then was switched to single agent irinotecan 350 mg/m^2 every 3 weeks. She progressed in her right inguinal lymph node basin with worsening lower extremity edema and was subsequently switched to irinotecan 180 mg/m^2 every 2 weeks and cetuximab 250 mg/m^2 weekly (after a loading dose of 400 mg/m^2). She experienced PFS of 8 months with the regimen. Lukan and colleagues published their experience in seven mASCC patients treated with cetuximab; six of these patients received it weekly (250 mg/m^2 after a loading dose of 400 mg/m^2) along with irinotecan (100 mg/m^2), while one received cetuximab alone [25]. Tissue from all seven patients was retrospectively assessed for RAS mutational status. Among the five cetuximab-treated wild-type (WT) RAS patients, mean PFS was 7.5 months. Three of the five patients achieved a PR with one patient still in PR after 3.5 months of follow-up. All five patients who achieved disease control developed at least a grade 1 skin rash, while both nonresponders did not have any rash. No patients experienced G3/G4 toxicities. Both patients treated with cetuximab whose tumors were RAS mutant progressed rapidly.

Klimant and Markman also document the experience of two other mASCC patients who were treated with the combination of irinotecan and cetuximab with the same dosing schedule as above [26]. The first patient initially had locoregional disease treated with cisplatin plus capecitabine-based radiation. After two local recurrences, the patient recurred distantly at the ureter. Molecular profiling was performed; once WT RAS and BRAF status were confirmed, she was treated with irinotecan and cetuximab. The patient experienced a PFS of 17 months with the regimen. The second patient was initially treated with 5-FU-/mitomycin-based chemoradiation for locally advanced ASCC. At her first recurrence, she received cisplatin and paclitaxel for 7 months and achieved PFS for 5 years. After another

inguinal recurrence that was managed surgically, at the time of her third recurrence (also in inguinal lymph nodes), she was treated with irinotecan plus cetuximab which resulted in PFS of 14 months.

The largest series of mASCC patients treated with cetuximab was published by Rogers and colleagues [27]. Seventeen patients received cetuximab or panitumumab in the second- or third-line setting in combination with a variety of chemotherapy backbones including CP-5-FU, CP-vinorelbine, irinotecan, CPAC, CP-capecitabine or docetaxel. Seventy-one percent of patients had been treated with concurrent chemoradiation for locally advanced disease initially, while 29% presented with metastatic disease at diagnosis. Ninety-four percent of patients had received CP-5-FU or CPAC in the first-line setting. Thirty-five percent of patients achieved a PR and 59% of patients achieved disease control with the addition of either anti-EGFR antibody. Median PFS was 7.3 months and median OS was 24.7 months in all patients; patients who achieved disease control had a median PFS of 12.7 months and a median OS of 33.7 months.

Other published series have reported mASCC patient outcomes with later line cetuximab pairings including with mitomycin or 5-FU, leucovorin and irinotecan (FOLFIRI) [28, 29]. Based on the preceding retrospective data, there may be a role for anti-EGFR directed antibodies in RAS WT mASCC after progression on first-line platinum-doublet chemotherapy. The question of whether cetuximab or panitumumab can prospectively demonstrate benefit in the later-line settings and then potentially be evaluated in the first-line setting remains to be determined.

Results from these series are summarized in Table 7.3.

Table 7.3 Select retrospective patient series about the anti-epidermal growth factor receptor (EGFR) antibody experience in mASCC patients

Trial name or study authors	Treatment	P or R	Ongoing or completed	Number of patients	ORR (percent)	PFS (months)	OS (months)
Lukan et al. [25]	Cetuximab plus irinotecan	R	Completed	5	60%; all PR	7.5 (mean)	NR
Klimant et al. [26]	Cetuximab plus irinotecan	R	Completed	2	100%; all PR	15.5	N/A
Rogers et al. [27]	Cetuximab or Panitumumab ± various chemotherapy	R	Completed	17	35%; all PR	7.3	24.7

N/A not applicable, *NR* not reached, *ORR* overall response rate, *OS* median overall survival, *P* prospective, *PFS* median progression-free survival, *PR* partial response, *R* retrospective

Immunotherapy for the Treatment of Metastatic Anal Squamous Cell Carcinoma

There is a strong basis for immunotherapy in mASCC as the disease is characterized by immune dysregulation, which promotes unchecked HPV-driven oncogenesis (85–90% of cases) [30]. The HPV oncoproteins E6 and E7 promote anti-tumor host responses and stimulate infiltration by T lymphocytes. Circumstances such as receipt of organ transplant, autoimmune disease and HIV positivity are all well-known risk factors for ASCC development [31].

Checkpoint Inhibitors

The success of checkpoint inhibitors in other HPV-mediated metastatic squamous cell cancers incited efforts to investigate the efficacy of nivolumab or pembrolizumab in mASCC patients. Morris and colleagues reported findings from NCI 9673, a multicenter phase II study of nivolumab in progressive mASCC patients [32]. A total of 37 patients with a median of two prior therapies (86% with prior platinum-based therapy, 81% with prior chemoradiation in the localized disease setting) received nivolumab 3 mg/kg every 2 weeks. Patients received a median of six cycles of nivolumab with a median follow-up time of 10.1 months. Four out of 12 patients demonstrated a PR in the first phase of the two-stage design, meeting the prespecified threshold for minimal efficacy and allowing the trial to proceed. An additional 25 patients were recruited for the second phase of the trial. Nine of 37 patients (24%) achieved ORR with 2 CRs and 7 PRs. Seven of these patients achieved durable responses with a median duration of response (DOR) of 5.8 months. At the time of publication, the longest DOR for a patient was 10.4 months. Seventeen (47%) of patients achieved SD. Median PFS was 4.1 months and median OS was 11.5 months. Fourteen percent of patients experienced G3 AEs; however, no patients discontinued nivolumab due to drug-related toxicity. No HIV-positive patients experienced any G3 or G4 AEs. Thirteen patients (four responders, nine non-responders) underwent pre-treatment tumor biopsies. By immunohistochemistry, responding patients had higher baseline levels of CD8 T-cells, granzyme B and PD-L1 than non-responders. NCI 9673 has recently reopened to investigate the efficacy of nivolumab versus nivolumab plus the CTLA-4 inhibitor ipilimumab in mASCC patients.

Keynote-028 was a multi-cohort phase Ib study of single agent pembrolizumab in patients with tumors expressing PD-L1 >1%. In the anal cancer cohort, 43 mASCC patients were screened and 32 were found to have requisite PD-L1 expres-

sion, but eight were found to be ineligible. A total of 24 patients received pembrolizumab 10 mg/kg every 2 weeks, as reported by Ott and colleagues [33]. The primary endpoints for the study were safety and ORR. Fifty-two percent of enrolled patients had received two or more prior lines of therapy. Duration of median follow-up was 10.6 months, and median duration of therapy overall was 3.1 months. ORR was 17% (all PRs), while DCR was 59%; median duration of response was not reached. Two responders had ongoing responses at 9 months at the time of publication. Median PFS was 3 months and median OS was 9.3 months. Four G4 treatment-related AEs were observed, and there were no treatment-associated drug discontinuations.

Given the potential interest of utilizing checkpoint inhibitors in HIV-positive patients, the EUDRACT trial is an ongoing phase II study exploring the utility of the PD-L1 inhibitor durvalumab (administered 1500 mg IV every 4 weeks) in HIV-positive patients with rare tumors, including mASCC [NCT03094286]. The primary endpoint of the study is the number of patients who remain on durvalumab at 4 months, with secondary endpoints of ORR, PFS, and OS. Given the success of combining different classes of checkpoint inhibitors (i.e., CTLA-4 plus PD-1 inhibitors) in other tumors, nivolumab and ipilimumab are also being investigated in the HIV-positive population in an ongoing phase I trial through the AMC 095 consortium [NCT02408861]. In this study, HIV-positive patients, stratified by CD4 count >200 or between 100 and 200 with HIV-associated solid tumors (mASCC, Kaposi's sarcoma, and others) or classical Hodgkin lymphoma, will receive nivolumab at escalating doses along with ipilimumab at various frequencies. The primary endpoint of the study is safety, with an intent to determine the maximal tolerated dose (MTD) of the combination in this population. To our knowledge, combinations of PD-1 inhibitors and other checkpoints such as OX-40, LAG-3, or TIM-3 have not been prospectively studied in mASCC yet.

Adoptive T-Cell Transfer

Adoptive T-cell transfer involves the transfer of ex-vivo expanded antigen-specific lymphocytes, either autologous or engineered, into patients [34]. Some very encouraging results have been seen in metastatic cervical cancer, where nine refractory patients treated with a single infusion of autologous HPV tumor-infiltrating lymphocytes (TILs) (preceded by lymphodepleting cyclophosphamide and fludarabine) demonstrated an ORR of 33% [35]. Remarkably, two out of the three responses were CRs. Each enrolled patient underwent metastatic tumor biopsy, followed by TIL culturing with IL-2 based media. TIL cultures were then selected for optimal E6 and E7 reactivity and the chosen cultures were infused into patients following the lymphodepleting therapy.

Hinrichs and colleagues reported findings from a phase I/II study where the investigators engineered TIL to express a T-cell receptor targeting an HLA-A∗02:01-restricted epitope of E6 for patients with metastatic HPV16-positive carcinoma

[36]. Of 12 patients who received escalating doses of cells, four had mASCC. No patients suffered from dose limiting toxicities (DLT) or cytokine storm, and two of the mASCC patients achieved PRs lasting 6 and 3 months, respectively.

Vaccines

Therapeutic vaccines for mASCC remain an area of promise given the central role humoral immunity plays in stimulating T-cell-mediated responses which can clear HPV. The E6 and E7 oncoproteins in HPV are expressed constitutively, unsuccessfully masked and represent an ideal target [37]. A *Listeria*-based vaccine Lm-LLO-E7, which secretes the HPV16 E7 antigen fused to a non-hemolytic piece of the protein listeriolysin O (LLO), demonstrated promise in a phase I study in metastatic cervical cancer (mCC) patients [38]. In this study, 15 patients with recurrent or progressive mCC received escalating doses of the vaccine given at week 1 and week 4 intervals. All patients experienced flu-like symptoms and 40% experienced G3 treatment-related AEs (TRAEs). The most common G3 TRAEs were pyrexia, elevated GGT and elevated liver enzymes; however, no patients discontinued treatment due to AE. Although this study was not designed to assess efficacy, seven patients experienced SD. Of these seven patients, four had a decrease in tumor size which did not meet criteria for PR. Three patients underwent pre- and post-vaccination quantification of E7-specific T-cell responses via the ELISpot assay; only one of these patients demonstrated a specific T-cell response after the second vaccine dose. Based on these results, a phase II trial with the trademark Advaxis Lm-LLO-E7 vaccine (ADXS11-001) in persistent or recurrent ASCC and mASCC is underway [NCT02399813]. The framework of this study, also known as the FAWCETT trial, has been presented [39].

DPX-E7 represents another peptide-based vaccine composed of amino acids 11 through 19 of the viral oncoprotein HPV subtype 16 E7 (HPV16-E7 11-19). It is being explored in a phase Ib/II study in combination with cyclophosphamide in HLA-A∗02 positive patients with refractory or metastatic HPV-positive cervical cancer, ASCC and head and neck cancer [NCT02865135]. Cyclophosphamide depletes CD4 positive Foxp3 positive Treg cells, which play a crucial role in dampening anti-tumor response mediated by other effector lymphocyte subsets [40].

Another vaccine approach being explored in metastatic squamous cell cancers, including mASCC, is the combination of an mRNA-based vaccine against HPV16 antigens and an agonist antibody targeting CD40 [HARE-40]. CD40 is a member of the TNF superfamily expressed of several antigen-presenting cells (APC); preclinical work suggests activating CD40-positive dendritic cells greatly stimulates the amplitude of vaccine induced T-cell responses [41]. A phase I study previously demonstrated the safety of the anti-CD40 agonist (Anti-CD40 IS-Ab ChiLob7/4) [42]. The personalized cancer vaccine RO7198457 is being explored as monotherapy or in combination with the PD-L1 inhibitor atezolizumab across several disease sites, including mASCC, in a phase Ia/Ib study [NCT03289962].

Results from these series are summarized in Table 7.4.

Table 7.4 Select published trials and ongoing studies about utilizing immunotherapy (checkpoint inhibitors, TIL therapy, vaccines) in mASCC patients

Trial name or study authors	Treatment	P or R	Ongoing or completed	Number of patients	ORR (percent)	PFS (months)	OS (months)
NCI 9673	Nivolumab	P	Completed	37	24%; 3% CR	4.1	11.5
Keynote 028	Pembrolizumab	P	Completed	24	17%; all PR	3	9.3
EURDACT	Durvalumab	P	Ongoing	N/A	N/A	N/A	N/A
NCT02408861	Nivolumab plus Ipilimumab	P	Ongoing	N/A	N/A	N/A	N/A
Hinrichs et al. [36]	TIL targeting HLA-A∗02:01-restricted epitope of E6	P	Completed	4	50%; all PR	NR	NR
FAWCETT	ADXS11–001 (lm-LLO-E7) vaccine	P	Ongoing	55	N/A	N/A	N/A
HARE-40	mRNA vaccine against HPV16 antigens ± anti-CD40 antibody	P	Ongoing	44	N/A	N/A	N/A
NCT03289962	RO7198457 ± atezolizumab	P	Ongoing	567 (multiple disease sites)	N/A	N/A	N/A

CR complete response, *N/A* not applicable, *NR* not reached, *ORR* overall response rate, *OS* median overall survival, *P* prospective, *PFS* median progression-free survival, *PR* partial response, *R* retrospective

Oligometastatic Disease in Anal Squamous Cell Carcinoma

Local management of limited oligometastatic disease from lower gastrointestinal tumors such as colorectal adenocarcinoma has changed the trajectory of the disease and improved OS for many patients. Whether this same principle can be utilized for patients with mASCC with limited sites of involvement remains unclear. Several studies suggest the potential benefit from such an approach. Eng and colleagues reported 33 patients who underwent curative intent multidisciplinary management after systemic therapy for their metastatic disease. Of these patients, 58% either underwent resection of their metastasis or radiofrequency ablation (RFA), while 42% underwent chemoradiation [10], with extent of metastasis to qualify for this approach not detailed. Overall, 50% of the radiation-sensitizing regimens involved CP-5-FU, while 28% involved CPAC or 5-FU/capecitabine alone. Of the 19 patients who underwent resection or RFA, 16 underwent surgical resection (9 in the liver, 2 in the lungs, 5 in the lymph nodes). Median PFS in mASCC patients treated with curative intent after initial systemic therapy was 16 months compared to 5 months in patients treated with palliative chemotherapy alone ($p < 0.001$). Median OS was 53 months for mASCC patients treated with curative intent and 17 months for mASCC patients treated with palliative intent ($p < 0.001$).

Rogers and associates presented a case series of five mASCC patients with oligometastatic disease (four metachronous, one synchronous) who were managed with concurrent chemoradiation (CCR) and other locoregional treatment approaches (radiofrequency ablation, surgery) [43]. Four of the five patients received systemic therapy with single agent 5-FU (one patient) or multi-agent combinations (1 with CPAC, 2 with CP-5-FU) with or without anti-EGFR antibodies and achieved treatment response prior to chemoradiation. The five patients achieved disease-free intervals ranging from 14 to 32 months. Hodges and associates presented another case series of six newly diagnosed mASCC patients with para-aortic and inguinal-node-only distant involvement treated with CCR [44]. Patients received 6 weeks of intensity-modulated radiation along with CP-5-FU 5 days per week. The primary tumor was treated to 57 Gy, while involved lymph nodes were treated to 55 Gy. After a median follow-up of 25 months, none of the patients had any local recurrence at sites initially involved with disease. Two patients developed metastatic disease in the liver, one at 4 months and one at 34 months after completing CCR. Three-year OS for all patients was 63%. A total of four patients developed nausea/vomiting and diarrhea which required hospitalization, and five patients developed G2 skin toxicity.

Pawlik and associates published a retrospective analysis from eight large hepatobiliary centers which explored the impact of liver metastasectomy and/or RFA on OS and disease-free survival with metastatic squamous carcinomas [45]. A total of 52 patients, 27 of who had mASCC, were included in the analysis. Sixty-seven percent of the mASCC patients presented with metachronous metastatic disease to the liver; median number of metastases was one, and the median size of the metastases was 5.8 cm in this group. Seventy percent of patients with mASCC were

treated with CCR in the local setting. Eighty-nine percent of mASCC patients underwent resection of their liver lesions, while 7.4% underwent surgery plus RFA and 3.7% underwent RFA alone. Seventy-four percent of the mASCC patients received pre-resection chemotherapy (regimens and frequency unspecified), with 80% of patients achieving disease control (40% PR, 40% SD). Sixty-three percent of mASCC patients received postoperative adjuvant therapy. Patients with mASCC had a median DFS of 9.6 months compared to 9.8 months in the non-mASCC cohort ($p = 0.43$). Twenty-two percent of patients experienced recurrent disease in the liver, 19% experienced both intrahepatic and extrahepatic recurrences, and 15% of patients in the mASCC cohort recurred elsewhere. There was no difference in 5-year survival between mASCC and non-mASCC cohorts (22.9% and 18.4%, $p = 0.75$). Median OS of all patients was 22.3 months.

Joe and associates describe the case of a p16-positive mASCC patient with bulky local disease along with liver, bone, and lymph node metastases where palliative CCR to the primary site elicited an abscopal immune effect leading to CR of all other tumor sites [46]. The patient received 54 Gy in radiation to the primary tumor and 50.4 Gy to the nodal and bony metastases, along with sensitizing chemotherapy with capecitabine (750 mg/m^2 twice daily on days of radiation) and mitomycin 10 mg/m^2 (D1 and D28). Within 6 weeks, the patient's bulky primary disease and mesorectal nodes were no longer clinically appreciated. Four weeks after completion of CCR, CT imaging demonstrated regression of the original 16 liver masses with only one 5 mm liver mass visible. At 4 months, no visible disease was noted on surveillance CT scans. Although the patient did receive chemotherapy and this may have influenced the disease response in the liver, the treatment effect was thought to exceed what would have been expected from chemotherapy alone. Retrospective staining of the patient's tumor tissue was performed to assess its immune signature and investigate the nature of the patient's complete response. Multiple regions of her tumor were infiltrated by CD8 and CD4 TILs. Intra-tumoral TILs expressed PD-1 more robustly than TILs found along the stromal interface.

Summary

Treatment of mASCC remains a challenge both in the United States and globally. The dearth of prospective evidence regarding chemotherapy, biologic and immunotherapy options, as well as a rising incidence of disease highlights the importance of ongoing investigative efforts to improve clinical outcomes for patients with mASCC. Platinum-doublet-based chemotherapy remains a fixture in treatment of this disease, and results from the InterAACT study demonstrate that the carboplatin/paclitaxel likely should serve as the optimal platinum-doublet backbone for future combination studies. Recent findings from the Epitopes-HPV02 study suggest DCF might be the most potent initial regimen in mASCC patients with more tolerable AEs utilizing a modified dosing regimen instead of standard dosing. A prospective study comparing DCF with the optimal platinum-doublet regimen would naturally be the next step to determine whether platinum-triplet or

platinum-doublet therapy is standard of care for mASCC patients. Anti-EGFR therapies such as cetuximab and panitumumab have a potential role in mASCC patients, given the limited number of RAS and BRAF mutations seen in this group. Furthermore, the efficacy signal suggested from retrospective data with biologics in the later-line setting raises the question of whether these therapies would be tolerable and effective in earlier lines of therapy. Immunotherapy with checkpoint inhibitors has demonstrated great promise in patients with other metastatic HPV-associated squamous malignancies as well as mASCC. Given the potential for durable responses and often tolerable side effects, checkpoint inhibitors are a welcome addition to treatment of mASCC patients who have previously received systemic therapy. The prospective data with nivolumab and pembrolizumab are encouraging, and ongoing studies with checkpoint inhibitor combinations and earlier lines of therapy will inform how benefit can be maximizes with these agents. Beyond checkpoint inhibitors, other immune-modulating strategies such as vaccines and adoptive T-cell transfer have demonstrated early promise in the treatment of mASCC. Oligometastatic ASCC patients are also a subset of great interest due to the potential ability to change their disease trajectory with durable responses after systemic therapy followed by locoregional treatment. Based on the data presented above, there appears to be potential to markedly improve PFS and OS in carefully selected patients within this group. Better understanding of the biological, genomic and immunological underpinnings of mASCC, as well as ongoing and anticipated prospective clinical trials, promise to move the field forward to improve clinical outcomes for patients with this disease.

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Chapter 8
Treatment of Non-squamous Histologies in Anal Cancer

Matthew T. Ballo

Epidemiology

Anal cancer accounts for 0.5% of all malignancies diagnosed in the United States in 2017 with 8200 new diagnoses and 1100 deaths [1]. While 97% of these cases are of squamous histology, just over 3% are divided between non-squamous histologies such as melanoma, large-cell neuroendocrine tumors, classic small-cell carcinoma, and adenocarcinoma [2]. Similar to squamous cell carcinoma, the median age at diagnosis is 55 years for most non-squamous histologies, and these afflict men and women equally, except for melanoma which occurs in a slightly older population and is more frequent in women [3]. Stage at diagnosis also differs from squamous histology in that melanoma presents more frequently with nodal disease, while the classic small cell subtype of neuroendocrine tumor presents more frequently with distant disease. These distinct differences in natural history are reflected in the rate of overall survival where patients with small-cell neuroendocrine tumor or melanoma have a 10-year survival in the single digits, while patients with large-cell neuroendocrine tumor have a survival rate similar to that of squamous histology.

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Treatment of Specific Histologies

Anal Melanoma

Primary anal melanoma is an aggressive malignancy characterized by early nodal and systemic spread and a generally poor prognosis. Patients typically present with rectal bleeding, pain, or a palpable anal mass that is often clinically amelanotic and not surprisingly misdiagnosed as a hemorrhoid [3–5]. Diagnosis is obtained by pathological examination of a biopsy specimen showing a combination of epithelioid and spindle cell morphology and almost uniform immunohistochemical positivity for S-100, HMB-45, and Melan A [5]. Patients are typically staged according to the extent of their disease as there is no official AJCC staging system for non-head and neck mucosal melanomas. Stage I disease is limited to the primary site; stage II is disease involving the regional lymphatics, and stage III represents distant spread.

Historically, therapy consisted of complete surgical resection via radical abdominoperineal resection (APR) with systemic therapy reserved for treatment of patients with documented distant metastatic disease. The rationale behind a radical procedure, as opposed to conservative sphincter-sparing local excision (LE), is that inguinal nodal failure rates of 27–47% and a perirectal lymph node involvement rate of nearly 80% are reported [5–7]. APR also results in a local-regional control rate of 82% compared to only 53% after LE alone, which then leads to local morbidity and the need for palliative surgery (Table 8.1) [6–15]. However, while APR clearly improves local-regional control, there is no improvement in overall survival, and many patients succumb to metastatic disease shortly after diagnosis bringing into question the wisdom of performing such a functionally debilitating surgical procedure.

In an effort to provide superior local-regional control while avoiding the functionally debilitating effects of APR, we combined a sphincter-sparing surgical approach with adjuvant radiation therapy reserving APR for patients in whom local excision would transect gross disease [16]. Twenty-three patients with invasive anal-rectal melanoma were managed with sphincter-sparing surgical resection and adjuvant radiation. Surgery consisted of primary local excision and nodal dissection for patients with documented regional nodal disease. Adjuvant radiation was delivered using a hypofractionated regimen of 30 Gy in 5 fractions over 2.5 weeks. The 5-year overall survival rate was 31% and the 5-year local and regional nodal control rates were 74% and 84%, respectively. No patient failed local-regionally as the sole site of failure and no patient required salvage abdominoperineal resection (APR). This series confirmed that adjuvant radiation therapy could be successfully combined with a sphincter-sparing surgical approach.

In the initial report, it was thought that comprehensive adjuvant irradiation was needed to address the propensity for submucosal spread and frequent lymphatic involvement. However, Kelly and colleagues updated our experience with combined modality therapy and found that, while inguinal nodal irradiation did not improve outcomes, it clearly resulted in an increased risk of lymphedema [17].

Table 8.1 Series reporting local control and overall survival rates for anorectal melanoma after abdominoperineal resection or local excision

	LE		APR	
Series	Local disease control[a]	5-year survival (median)	Local disease control[a]	5-year survival (median)
MDACC [6]	5/12 (42%)	3%	10/14 (71%)	0%
Stockholm [9]	9/18 (50%)	13 months	11/15 (73%)	12 months
Duke University [10]	0/7 (0%)	–	3/6 (50%)	–
Roswell Park [7]	3/6 (50%)	0%	7/9 (78%)	25%
Mexico [11]	0/1 (0%)	0%	1/6 (17%)	0%
Netherlands [12]	4/16 (25%)	30%	17/18 (94%)	25%
Gustave Roussy [13]	11/21	16%	7/9	33%
NCI Milano [14]	10/18	17 months	13/13	17 months
Guangxi Medical [15]	9/15 (60%)	16%	35/39 (90%)	30%
MSKCC [8]	31/40 (78%)	–	22/25 (88%)	–
Total	**82/154 (53%)**		**126/154 (82%)**	

Studies routinely incorporating radiation therapy are excluded
MDACC M.D. Anderson Cancer Center, *MSKCC* Memorial-Sloan Kettering Cancer Center, *MS* median survival, *APR* abdominoperineal resection
[a]Crude

As for adjuvant systemic therapy, it is difficult to make general recommendations in light of the rarity of this disease, but many of the same targets identified in cutaneous melanoma have been tested in mucosal sites including the anus [18].

The current recommendation is to reserve APR for patients in whom local excision would transect gross disease and instead perform sphincter-preserving local excision with adjuvant local only radiation. It is recommended that regional lymphatics only be dissected surgically if they are clinically involved and only radiated if they are pathologically involved. The radiation dose and fractionation schedule of 30 Gy in 5 fractions (doses delivered twice a week on Monday/Thursday or Tuesday/Friday) is well tolerated, results in satisfactory local and regional control, and can be conveniently delivered to a group of patients with poor overall survival. After local excision the target volume should encompass the primary lesion and the surrounding mesorectum, while radiation may be avoided after APR. This fractionation is traditionally used for patients with melanoma, because melanoma cells tend to be more sensitive to large dose per fraction radiation and there is substantial clinical experience with this regimen for both mucosal and non-mucosal sites [19, 20].

Adenocarcinoma of the Anal Canal

Adenocarcinomas of the anal canal are subclassified into a colorectal-type, an anal gland/transitional-type, and those associated with anal fistula. While the colorectal-type is morphologically indistinguishable from adenocarcinomas located in the

rectum, the anal gland/transitional-type is a distinct entity associated more frequently with inflammatory bowel disease and high-risk HPV infection [21].

Clinically, patients present with anal pain and/or bleeding and the diagnosis is obtained via biopsy. Physical exam, MRI scan, and ultrasound imaging can often times distinguish between downward spread of true rectal cancers and de novo tumors of the anal canal. Approximately 50% of patients will present with lymphatic spread and 10% with distant spread, primarily to the liver [21].

Treatment recommendations are based upon small retrospective studies and collections of case studies, but generally mirror the combined modality approach used for adenocarcinoma of the rectum (preoperative capecitabine and concurrent pelvic radiation, with consideration of coverage of the inguinal and external iliac nodes, followed by radical surgery and then additional chemotherapy) (Fig. 8.1a, b). A large multicenter study reported on a total of 82 patients; 45 treated with pre- or postoperative radiotherapy, 31 treated with chemoradiation alone, and 6 treated with APR alone [22]. Despite local recurrences being more common in the surgery/radiation and chemoradiation groups (37 and 36%, respectively) compared to the APR alone group (20% recurrence rate), the authors recommended chemoradiation because their analysis of overall survival favored the chemoradiation approach. In contrast, investigators from M.D. Anderson Cancer Center reviewed their experience with anal adenocarcinoma and reported an unacceptably high local recurrence rate after chemoradiation alone leading them to recommend neoadjuvant chemoradiation followed by surgical resection [23]. In an update of this experience, Chang and colleagues compared 13 patients treated with local excision and either radiation or chemoradiation to 15 patients treated with radical resection (APR being the most common procedure) and pre- or postoperative chemoradiation [24]. The 5-year overall survival was 43% after local excision and 63% after radical surgery. On multivariate analysis, radical resection was associated with improved survival confirming their recommendation made years earlier for a combined modality approach that includes radical surgical resection. The treatment for patients with anal adenocarcinoma associated with anal fistula (usually from Crohn's disease) is also a combined modality approach with perioperative chemoradiation and radical resection [25].

Previously no treatment distinction has been made between the colorectal-type and anal gland/transitional-type tumors. However, Herfs and colleagues noted some differences in a recent multi-institutional study of 65 patients receiving various local and systemic therapies [21]. For patients with anal gland/transitional zone tumors, the rate of local or distant recurrence was 41.7% compared to 31.7% for those with colorectal-type tumors, and the 5-year DFS rate was 33.1% compared to 52.6%, respectively. Although these differences were not statistically significant, the data suggest that the anal gland/transitional-type tumors may have a worse outcome and in light of other distinctions discussed below future study may point to different treatment strategies.

As seen in other tumors of the anal canal, prognosis is dependent upon the primary tumor size and the extent of nodal spread. Although tumor size and extent of nodal spread does not differ between the two subtypes, Herfs and colleagues clearly show that the anal gland/transitional-type tumors are associated with HPV infection and have a distinct molecular profile marked by high EGFR expression, a collection

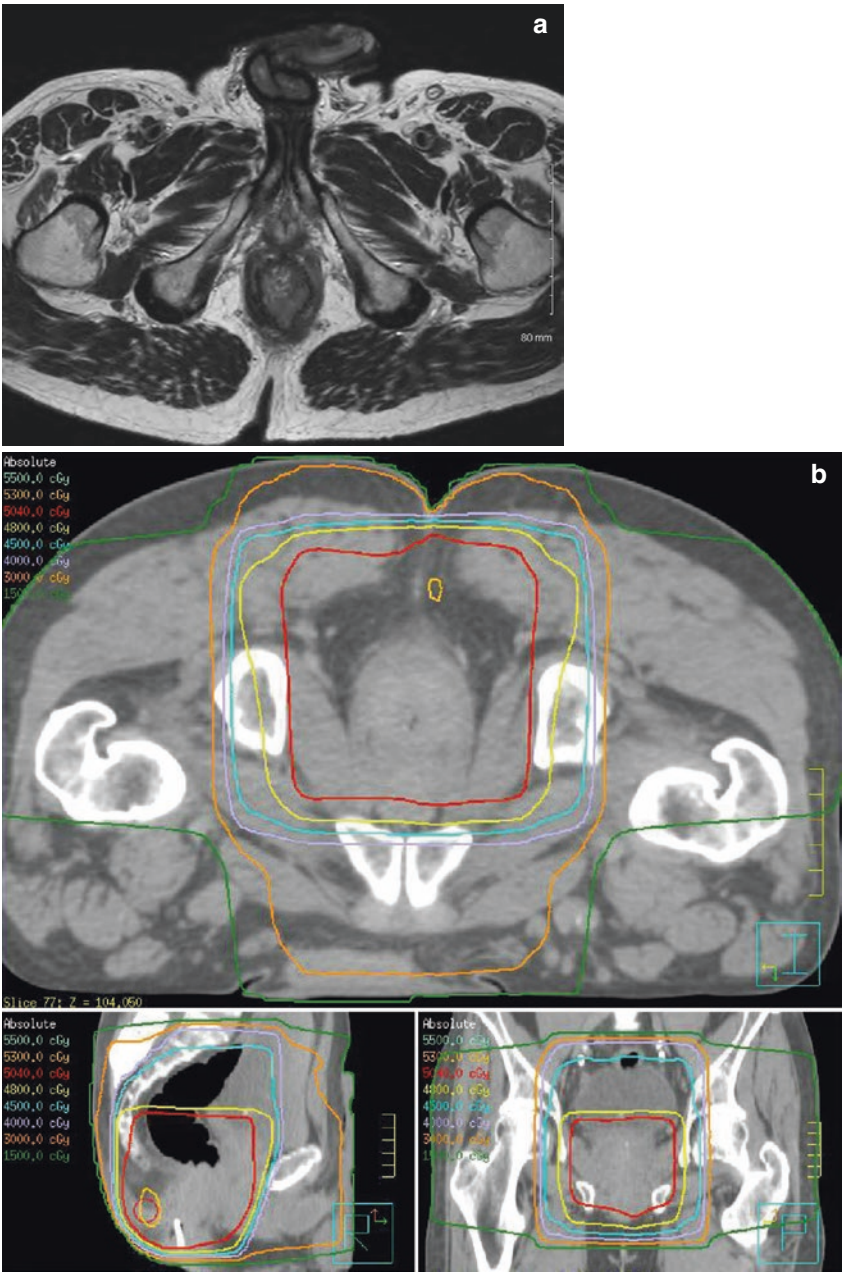

Fig. 8.1 (**a**) Magnetic resonance imaging (MRI) of the pelvis from a 60-year-old man presenting with anal pain. Physical exam revealed a 4 cm anal canal mass, and biopsy showed mucin-producing colorectal-type adenocarcinoma. Tumor extended through the muscularis and several surrounding lymph nodes were radiographically suspicious for involvement (cT3N1). (**b**) He was treated with external beam radiation to a dose of 50.4 Gy in 28 fractions with concurrent oral capecitabine chemotherapy. The radiation treatment plan is shown. The patient then lost health insurance and did not undergo abdominoperineal resection until 6 months later. At that time there was no residual disease and no involved lymph nodes (ypT0N0). Five years later, he remains free of disease

of wild-type downstream effectors (NRAS, BRAF, PIK3CA, and PTEN), and a highly inflammatory tumor microenvironment with high PD-L1 expression [21]. Given the rarity of these tumors, it is too premature to vary local regional treatment by histological subtype, but the combination of these unique features may have implications for patients with metastatic disease from the anal gland/transitional-type tumors as they may respond to anti-EGFR drugs and immune checkpoint inhibitors [21].

Neuroendocrine Tumors

Neuroendocrine cancers are divided into two groups based on grade: carcinoid or neuroendocrine tumors (grades 1 and 2) and high-grade neuroendocrine carcinomas, including small-cell neuroendocrine carcinoma [26]. Neuroendocrine tumors are graded according to rate of cellular proliferation (mitotic count and Ki-67 labeling index) into either well-differentiated tumors with benign or low malignant potential or poorly differentiated carcinomas which carry a very poor prognosis. Fifty percent of carcinoid tumors occur in the midgut (small intestine, appendix, or proximal colon), while only 15% occur in the distal colon or rectum. Within this latter group of hindgut carcinoids, only a very small fraction actually occur in the anal canal. In a single institutional review of 22 patients of either rectal or anal canal neuroendocrine tumors, only 4 were in the anal canal and all of them were poorly differentiated [27].

Given their rarity, treatment recommendations mirror those used for rectal carcinoid where size and extent of local regional growth primarily determine treatment [28]. Tumors less than 1 cm in size without muscularis propria involvement may be managed with local excision alone, while larger lesions and those involving the muscularis have at least a 30% incidence of nodal involvement and are better treated with anal resection and lymph node dissection. No series have addressed the role of chemoradiation alone for anal carcinoid. Treatment for patients with metastatic disease includes either radiolabeled or non-labeled somatostatin analogs and more recently mTOR inhibitors and anti-angiogenic therapies [29]. The role of cytotoxic chemotherapy is typically reserved for the poorly differentiated tumors.

Small-cell carcinomas of the anal canal will have typical small-cell histomorphological features including a markedly enlarged nuclear-to-cytoplasmic ratio, hyperchromatic nuclei with finely granular cytoplasm, and increased mitotic activity as well as positive neuroendocrine markers by immunohistochemistry such as synaptophysin, chromogranin, or CD56 [30]. As has been shown for small-cell carcinoma of the uterine cervix and head and neck, small-cell carcinoma of the anal canal is associated with HPV infection suggesting a role for viral replication in the oncogenesis of these tumors [30–32]. There are no large retrospective series, but most case reports have applied a treatment strategy similar to small-cell carcinoma of the lung with doses of radiation ranging from 45 to 55 Gy combined with cisplatin and etoposide [33].

Sarcomas

Sarcomas are tumors of mesenchymal origin and can therefore occur within any location. Histopathological subtype generally depends upon the bulk of cells occurring in that location such that sarcomas of skeletal muscle occur most frequently in the thigh, while sarcomas of fat occur most frequently in the retroperitoneum. It follows, therefore, that the most frequently reported sarcomas of the anal canal in adults are either gastrointestinal stromal tumor (GIST) or leiomyosarcoma (a sarcoma of smooth muscle origin) [34–37]. There is, however, at least one case report of a malignant fibrous histiocytoma (a high-grade pleomorphic sarcoma) of the anal canal [38].

As stated for the other unusual and rare tumors of the anal canal, it is nearly impossible to claim that one treatment is clearly better than another. There is general consensus, however, that APR results in better local control than local excision alone and that overall survival is independent of local therapy [37]. First principles would then dictate that local excision is reserved for patients with smaller tumors amenable to resection with negative margins and radiation is added for histologies where it is known to improve local control in other locations such as for leiomyosarcoma or a pleomorphic undifferentiated sarcoma. Grann and colleagues reported on eight patients treated with local excision and postoperative low-dose rate brachytherapy for rectal (seven patients) or anal (one patient) leiomyosarcoma [35]. Only two patients developed local failure, and sphincter function was excellent in the four evaluable patients. Although these investigators used brachytherapy to deliver 45 Gy to 1 cm from the plane of the implant, others have used maximally tolerable doses of external beam radiation [36].

For rectal or anal GIST, the treatment was traditionally surgical resection alone; however, because these tumors are driven by activated mutations in KIT (75%) or PDGFRα (10%), they usually respond to the oral tyrosine kinase inhibitor imatinib mesylate (Gleevec®, Novartis, Basel, Switzerland). Imatinib has been used in both the neoadjuvant and adjuvant setting and shown to improve survival and resectability [39, 40]. In a large retrospective series of patients with a mixture of rectal and anal GIST, Cavnar and colleagues reported on outcomes before and after the era of imatinib use [41]. They compared 17 patients treated with surgery +/− perioperative radiation to 30 patients treated in the imatinib era with surgery +/− imatinib, none of whom received radiation. Overall, disease-specific, relapse-free, local relapse-free, and distant relapse-free survivals were all significantly higher in the group of patients treated in the imatinib era. Importantly only 3% of the patients treated in the imatinib era required a functionally debilitating surgical procedure compared to 59% in the pre-imatinib era [41].

Metastatic Tumors to the Anus

Tumors of any type can metastasize to the anal canal, but as one might expect, those that do so most frequently are common themselves such as lung cancer, breast cancer, or melanoma [42–44]. Less common tumors have also been reported to

metastasize to the anal canal such as renal cell carcinoma, pancreaticobiliary tumors, and rectal cancers [45–47]. All series to date include only individual case reports with or without an accompanying review of the literature making generalizable recommendations nearly impossible. As most of the reports recognize this event as a late one carrying a poor prognosis, the treatment is usually palliative radiation therapy with or without systemic therapy, and surgery is reserved for situations resistant to other modes of palliation [43, 44].

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Chapter 9
Diagnosis and Management of Perianal Skin Tumors

Monica Polcz, A. Bapsi Chakravarthy, and Christina Edwards Bailey

Introduction

Malignancies of the anus and anoderm reflect a small proportion of cancers of the lower gastrointestinal (GI) tract. In 2018, an estimated 5.7% of newly diagnosed lower GI cancers will arise from the anus, resulting in approximately 2.2% of deaths related to lower GI cancers [1]. Squamous cell carcinoma (SCC) of the anal canal accounts for many of these cases, and it is discussed elsewhere in this book; however, several distinct tumor types arising in this area dictate the need for awareness and appropriate workup as they may easily be mistaken for a myriad of more common benign lesions.

Anatomy and Histology of the Anoderm

The anal region is composed of the anal canal, the anal verge, and the perianal region (also known as the anal margin). The anal canal is described as the space between the anorectal junction and anal verge. The anorectal junction is

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approximately 1–2 cm proximal to the dentate line at the level of the pelvic floor, specifically the superior border of the puborectalis muscle. The anal canal is typically 3–5 cm in length [2]. Histologically, the anal canal is comprised of three zones: the colorectal-type columnar epithelium proximally, the stratified non-keratinizing squamous epithelium distally below the dentate line (anal pecten), and the anal transition zone (ATZ) in between containing a mixture of columnar, cuboidal, and flattened epithelial cells. Embryologically, the ATZ represents the fusion of two different germ layers, the endodermal hindgut above and the ectoderm below. The ATZ can extend anywhere between 0.5 cm below to 2.0 cm above the dentate line [3]. The anal pecten lacks skin adnexa including hair follicles. The perianal region, which is the focus of this chapter, extends from the anal verge to a radius of approximately 5 cm. This region is characterized by keratinized squamous epithelium. The skin appendages of this area consist of hair follicles, sebaceous glands, and apocrine glands. Papillae and melanocytes are prominent [4].

The upper two-thirds of the anal canal receive its blood supply from terminal branches of the superior rectal artery, a branch of the inferior mesenteric artery. The lower third of the anal canal receives its blood supply from the inferior rectal artery, a branch of the internal iliac artery. Lymphatic drainage is generally to the perirectal and internal iliac lymph nodes above the dentate line, and to the inguinal and femoral lymph nodes below the dentate line [5].

Perianal Skin Tumors

Initial Evaluation

Perianal lesions can be defined as those that are completely visible with gentle traction of the buttocks and within a radius of 5 cm from the anal verge [6]. Malignancies in this area are easily confused with benign lesions such as polyps or hemorrhoids, and appropriate workup is of utmost importance to prevent delays in diagnosis.

Squamous Cell Carcinomas of the Perianal Skin

Squamous cell carcinoma (SCC) of the perianal skin was previously staged similarly to cutaneous SCC, but the most recent AJCC guidelines (8th edition) stage perianal SCC similarly to those of the anal canal [2] (Table 9.1). However, treatment differences exist and thus it remains important to distinguish SCC of the perianal skin from those of the anal canal. SCC of the perianal skin is most often keratinizing and well or moderately differentiated [7]. Evaluation consists of digital rectal exam (DRE) and examination of the inguinal lymph nodes. Diagnosis is confirmed by incisional or excisional biopsy. Clinically suspicious lymph nodes should be biopsied. Computed tomography (CT) with or without positron emission tomography

Table 9.1 Staging of perianal cancers

T category	T criteria
TX	Primary tumor not assessed
T0	No evidence of primary tumor
Tis	High-grade squamous intraepithelial lesion (previously termed carcinoma in situ, Bowen disease, anal intraepithelial neoplasia II–III, high-grade anal intraepithelial neoplasia)
T1	Tumor <2 cm
T2	Tumor >2 cm but <5 cm
T3	Tumor >5 cm
T4	Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Stage	TNM classification
0	Tis N0 M0
I	T1 N0 M0
IIA	T2 N0 M0
IIB	T3 N0 M0
IIIA	T1-2 N1 M0
IIIB	T4 N0 M0
IIIC	T3-4 N1 M0
IV	Any T Any N M1

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(PET) of the chest, abdomen, and pelvis can assist with metastatic workup and evaluation of the inguinal-femoral nodes, which are involved in approximately 15–25% of cases [7]. Lymph node metastasis is related to size and differentiation of the primary tumor, and lymph node metastasis in T1 disease is extremely rare [8]. For this reason, well or moderately differentiated T1 lesions are amenable to radiation therapy (RT) alone or wide local excision (WLE) alone with negative margins (Table 9.2). Inguinal lymph node dissection is not recommended unless the nodes are clinically positive or a patient presents with recurrent or residual disease. In the setting of positive margins after initial WLE, re-excision should be considered if

Table 9.2 Treatment of perianal squamous cell carcinoma

Tumor stage	Description	Treatment
T1N0, well-moderately differentiated	<2 cm	Local excision to negative margins OR radiotherapy
T2N0, well-moderately differentiated	>2 cm, <5 cm	Radiotherapy + concurrent chemotherapy, consider inguinal radiation
T3-4, N+, or poorly differentiated	>5 cm, invading adjacent organs	Radiotherapy + concurrent chemotherapy, inguinal and pelvic radiation

feasible. If re-excision is not feasible (i.e., proximity to the external sphincter muscles), local RT ± 5-fluorouracil (FU)-based chemotherapy is recommended. RT is indicated in poorly differentiated T1, T2-T4, or N+ disease. RT is most often offered with concurrent chemotherapy based on data extrapolated from large clinical trials examining SCC of the anal canal [9, 10]. Focused irradiation fields along with elective irradiation to the inguinal lymph nodes are offered in T2 disease, while inclusion of inguinal and pelvic lymph nodes is standard in T3-4, N+, or poorly differentiated disease [11]. Concurrent chemotherapy regimens consist of 5-FU/mitomycin, capecitabine/mitomycin, or 5-FU/cisplatin [12–14]. For metastatic disease, platinum-based chemotherapies are offered with consideration of palliative RT for bulky primary disease. After treatment, surveillance is similar to that of anal canal SCC with clinical exam and anoscopy 8–12 weeks after chemoradiation and every 3–6 months for 5 years. Suspicion of recurrent or persistent disease should be confirmed with biopsy, and if persistent disease is present, reevaluation in 4 weeks followed by every 3 months if regression is present versus restaging and consideration of salvage abdominoperineal resection (APR) if not. Cause-specific survival in patients who are candidates for local excision alone ranges from 69 to 88% at 5 years, with locoregional control rates of 54–70% [15, 16]. In patients who undergo RT with or without chemoradiation, 5–10-year locoregional control rates range from 58 to 88%, with cause-specific survival at 10 years reported up to 92% [8, 11, 17–20].

Paget's Disease

Extramammary Paget's disease (carcinoma in situ) was first described in the scrotal area in 1889 [21]. Since then, it has been noted in other anogenital sites including the perianal skin. Perianal Paget's disease accounts for <1% of anal diseases and 6.5% of all cases of Paget's disease [4, 22]. Paget's disease can be classified as either primary or secondary based on the presence or absence of synchronous or metachronous internal malignancy. Primary Paget's disease of the perianal skin arises in the epidermis or squamous epithelium and may be associated with a malignant invasive component. Meanwhile, secondary Paget's disease is defined by its association with a synchronous or metachronous internal malignancy that may be tubo-ovarian or gastrointestinal (GI) in origin [23]. Rates of associated malignancy

with perianal Paget's disease range from 33% to 86% and are often the result of direct intraepithelial tumor extension [24].

Paget's disease typically presents as pruritic, crusted, verrucous, or exudative patches that may be hypopigmented or red [25]. They are more common in men and typically present in the fifth decade [26]. Diagnosis is obtained via punch skin biopsy, but diagnosis is often delayed as patients are usually initially treated with topical agents. Histology reveals Paget cells which are characterized by abundant cytoplasm with vesicular nuclei and prominent nucleoli (class A cells) or signet ring-like with eccentrically displaced nuclei due to large cytoplasmic mucin droplets (type B cells) [27]. Immunohistochemical stains may aid in the differentiation between primary and secondary Paget diseases. Secondary Paget cells arising from colorectal adenocarcinoma often demonstrate a CK20+/CK7-/CDX2+ profile, while primary Paget cells are typically CK20-/CK7+/GCDFP15+, but this is not always the case [4].

Once a diagnosis of Paget's disease is confirmed on biopsy, investigations should be undertaken to rule out a concurrent internal malignancy, including colonoscopy and CT of the abdomen and pelvis. Pelvic magnetic resonance imaging may be useful to evaluate the extent and depth of invasion of the perianal lesion. PET may also be useful in aiding in the identification of an FDG-avid internal malignancy and ruling out distant metastases [28]. Optimal treatment is unclear based on the rarity of the disease, but the general recommendation is wide local excision with 1–2 cm margins to achieve clear margins when there is no concurrent invasive cancer present. Diverting colostomy may be considered if a large area is to be resected and flap coverage may be needed. Patients with underlying anorectal cancers may require an APR.

The role of radiation therapy in extramammary Paget disease has been described in multiple small studies with considerable heterogeneity in dose and technique. For example, a systematic review of 19 retrospective studies evaluating radiation therapy in extramammary Paget disease (genital and perianal) demonstrated a range in treatment regimen dosing from 30 to 80.2 Gray (Gy) delivered in 3–43 fractions [29]. Patients were treated in a variety of settings and intents including neoadjuvant, adjuvant, definitive, and palliative. Based on the results of this review, the authors suggested definitive radiation therapy in patients with recurrent disease or those refusing or unfit for surgery to a total dose of 60 Gy or greater directed to the primary disease and a 2–5 cm margin, with consideration of prophylactic radiation to the inguinal lymph nodes (45–50 Gy). They also suggest radiation treatment in the adjuvant setting for positive margins (>60 Gy) or close margins (45–60 Gy), again with consideration of prophylactic inguinal lymph node radiation if invasion into the dermis is present.

Basal Cell Carcinoma

Basal cell carcinomas (BCC) represent the most common cutaneous neoplasm; however, its presence in the perianal region is rare, comprising only 0.2% of all anorectal neoplasms [4]. It is unusual for BCC to develop in areas devoid of sun

exposure; however, chronic irritation or prior radiotherapy has been proposed to contribute to their development in the perianal area [30]. Perianal BCC may appear as smooth or ulcerated nodular lesions. Histological analysis reveals BCCs in the perianal region to most frequently be of nodular type, and BCL2 and BerEp4 positivity helps distinguish it from other neoplasms such as the more aggressive basaloid SCC, which otherwise may appear histologically similar [4]. Up to one-third of patients with perianal BCC additionally have BCCs at other sites; thus a full body cutaneous exam should be performed [31]. Metastasis is a very unusual occurrence, and BCC in the perianal region does not appear to be any more aggressive than cutaneous BCC [32]. A review of patients with perianal BCC at Mayo Clinic in Rochester ($n = 19$) reveals that all but two patients underwent local excision to clear margins, including one patient with a very large BCC measuring 8.5 cm who required subsequent skin grafting [31]. The remaining two patients underwent electrodesiccation and Mohs microsurgery. At a mean follow-up of 72 months, there were no recurrences, and on histological review all lesions were superficial without invasion of deep structures, suggesting that these lesions are nonaggressive and adequately treated with local excision. Radiotherapy is not well described in perianal BCC but does have a role in cutaneous BCC of sun-exposed areas, including as definitive therapy in certain patients based on preference or high operative risk. RT in perianal SCC disease is described only in single patients, with one case report describing a favorable response in a patient deemed too-high risk for surgery after administration of a total 51 Gy of focused radiation over 17 fractions [33]. Local excision with negative margins is the recommended treatment for perianal BCC and is associated with excellent cure rates.

Rhabdomyosarcoma

Rhabdomyosarcoma is the most common sarcoma in children. Only 2% are located in the perineal or perianal regions, with prognosis in this area being uncharacteristically poor [34]. Perianal rhabdomyosarcoma often presents in children as an anal polypoid mass. Diagnosis is confirmed with excisional biopsy. Four main histopathologic subtypes of rhabdomyosarcoma are described: (1) embryonal, (2) alveolar, (3) pleomorphic, and (4) undifferentiated [35]. Up to 50% of patients present with nodal disease [36]. On clinical presentation, patients may be initially misdiagnosed with an infectious etiology, and those with inguinal involvement have been initially misdiagnosed with inguinal/femoral hernias or lymphoma [36].

Prognosis is poor, with 5-year overall survival (OS) ranging from 20 to 49% [37]. Age represents a significant prognostic factor, with 5-year OS in patients >10 years old reported between 13% and 20%, in contrast to 71–75% in patients <10 years. Younger patients tend to present with more favorable prognostic factors, such as node-negative disease and embryonal histology, whereas older patients are

more likely to have alveolar histology, tumors >5 cm, and nodal disease, all of which also represent poor prognostic indicators [36, 37].

Excision of the primary lesion should be performed to histologically negative margins. A complete non-mutilating resection is usually not possible at the time of diagnosis, thus preoperative radiation therapy should be given to patients older than 1 year. The gross tumor volume with a 1 cm margin is used as the clinical target volume, and regional lymph nodes included in all patients with suspicious or proven nodal involvement. A typical regimen has been described as 50.4 Gy to the gross tumor in patients older than 3 years old [37]. Efforts should be undertaken to protect growth plates and preserve fertility. In patients without evident nodal disease, CT scan underestimates the number of patients with positive nodes, and these should be evaluated surgically with inguinal sentinel lymph node biopsy. Clinically evident lymph nodes should be confirmed with biopsy as well. Patients with lymph node involvement require additional radiation therapy, which should be prescribed at full dose [36]. In patients >10 years old without evident nodal disease, prophylactic irradiation to a lower dose of 36 Gy to the ilioinguinal nodes has been recommended due to the high rate of nodal recurrence in this population [37]. Systemic chemotherapy is also indicated in the adjuvant or neoadjuvant setting for this disease.

Metastases

Metastases to the perianal region from distant malignancies are extremely rare. Of these, metastatic spread from colorectal cancers is most common. However, there have been case reports of metastasis to the perianal region of non-small-cell lung cancer mimicking hemorrhoids and perianal abscess [38–40]. Life expectancy is predictably short in this scenario, as this is a manifestation of aggressive distant metastatic spread.

Conclusion

Squamous cell neoplasms are the most commonly encountered perianal malignancy. However, this chapter highlights a number of other malignancies that can present in the perianal region, which, although varied, share a common theme of rarity and thus frequent misdiagnosis for benign pathology. This results in diagnostic and treatment delays that can alter prognosis. Workup of these perianal lesions is similar, consisting of histologic tissue diagnosis followed by clinical and radiographic staging evaluation. Treatment almost invariably involves surgical resection, ranging from local excision to radical resection with APR, and frequently utilizes a multimodal approach combining chemo- and radiation therapy.

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