Anal Cancer

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Introduction

Anal cancer is uncommon, representing 2.5% of all gastrointestinal tract malignancies, with an annual incidence rate of 1.8 per 100,000 in the USA and approximately 500 incident cases yearly in Canada [1–3]. Nearly two-thirds of incident cases are in women [2, 3]. Over the past decade, incidence has risen by 2% per year [2, 4]. Squamous cell carcinomas account for most anal cancers and are the focus of this chapter, but other histologic types including adenocarcinoma (mostly from anal glands), melanoma, neuroendocrine, and sarcoma occur in the anus rarely [5]. Annual incidence is higher in those with immunodeficiency: 6–12 per 100,000 after solid organ transplantation, and 50 to 145 per 100,000 in those with HIV infection [6–9].

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Terminology

- *Anal canal* The anal canal extends from the anorectal ring (the palpable upper border of the anal sphincter at the puborectalis muscles) to the lowermost edge of the sphincter complex corresponding to the anal verge or introitus of the anal orifice (Fig. 3.1) [10]. Anal cancer is classified as anal canal cancer if the lesion cannot be fully visualized with gentle traction of the buttocks [11, 12]. Proximal to distal, the anal canal contains several types of mucosa: glandular/columnar, transitional (anal transition zone), nonkeratinizing squamous (anoderm), keratinizing squamous (the dentate line divides keratinizing and nonkeratinizing), and merges with the hair-bearing perianal skin (true epidermis with epidermal appendages) at the mucocutaneous junction (anal verge). The treatment of anal canal

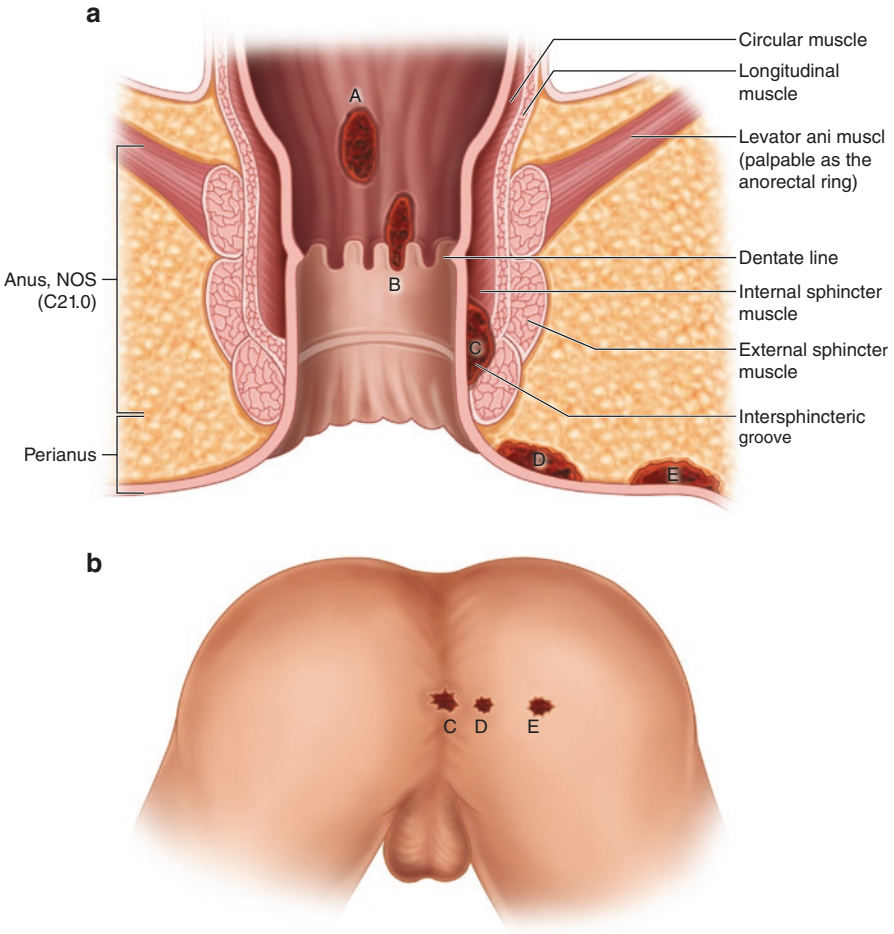

Fig. 3.1 Anal cancer (A–C), perianal cancer (D), and skin cancer (E). (**a**) coronal cross-section (**b**) perineal view

tumors has been standardized for all squamous cell carcinomas irrespective of histological subtype (keratinizing or non-keratinizing, epidermoid, transitional, basaloid, or cloacogenic) due to similar prognosis and response to treatment [13].

- *Perianal* The perianal skin (previously anal margin) begins at the anal verge and extends over a 5 cm radius (Fig. 3.1). It is further defined by the presence of epidermal appendages, and contains the pigmented skin. Perianal cancers are those that can be fully visualized with gentle traction of the buttocks [11, 12]. Those further than 5 cm from the anal orifice are classified as skin cancers.
- *Regional lymph nodes* The proximal anal canal (above the dentate line) has lymphatic drainage to the mesorectal, superior rectal, and internal iliac nodes. Distal to the dentate line, drainage is to the inguinal nodes and external iliac nodes.
- *Precursor lesions (anal squamous intraepithelial lesions)* The Lower Anogenital Squamous Terminology (LAST) should be used [14, 15]. HPV-related squamous anogenital precursor lesions are divided into low-grade squamous intraepithelial lesions (LSILs) and high-grade squamous intraepithelial lesions (HSILs) based on mitotic activity, depth of dermal involvement, and abnormalities in squamous cell differentiation. LSIL can then be subclassified into condyloma (raised papillary proliferation with low-grade viral cytopathologic changes), and flat lesions labelled anal intraepithelial neoplasia 1 (AIN1). HSIL can be subclassified into AIN2 and AIN3 based on depth of abnormal cells. Generally, LSIL is observed, and HSIL is treated. Older terms such as high-grade anal intraepithelial neoplasia (HGAIN) and low-grade anal intraepithelial neoplasia (LGAIN), Bowen disease, and carcinoma in situ should not be used. Similarly, these squamous lesions are differentiated from extramammary Paget disease which is an apocrine neoplasm from sweat glands; pagetoid spread, known as secondary extramammary Paget disease, can occur from adjacent colorectal adenocarcinoma, urothelial carcinoma, or melanoma [15].
- *Superficially invasive squamous cell carcinoma (SISCCA)* Invasive squamous carcinoma that invades ≤3 mm from the basement membrane has a horizontal spread ≤7 mm, and must have been completely excised to confirm limited extent of the tumor [14]. These are classified as T1 anal carcinomas by AJCC [11]. SISCCA are typically identified by high-resolution anoscopy (HRA) and ongoing studies are investigating the role of excision alone as treatment for these lesions [16].

Risk Factors and Precursor Lesions

Anal cancer is an human papillomavirus (HPV)-associated cancer, like cervical, vaginal, penile, and oropharyngeal cancers, with 80–90% attributable to HPV [4, 17–19]. High-risk HPV types include HPV 16 and HPV 18 in 80–90% of cases, as well as HPV 31, 33, 45, 52, and 58 in a lesser proportion [17, 18, 20]. Oncogenesis is associated with persistent infection with high-risk HPV producing oncoproteins E6 and E7 which bind cellular proteins, including p53 and pRb from the tumor suppressor genes TP53 and retinoblastoma, deregulating DNA repair and apoptosis, and stimulating cell-cycle progression [21].

Table 3.1 Risk factors for anal cancer

HPV exposure [26–29]	Immunodeficiency	Other
Lifetime number of sexual partners	HIV infection [6, 9, 30]	Female sex [33]
Prior sexually transmitted infection	Autoimmune disorder [31]	Smoking [34]
Prior anogenital warts (condyloma)	Solid organ transplantation [6, 7]	Age
Anoreceptive intercourse	Immunosuppressive medications [32]	
Prior HPV-associated squamous anogenital cancers (cervical, vulvar, vaginal, penile)		

Risk factors for anal cancer largely relate to HPV exposure and immunodeficiency enabling persistence of HPV infection (Table 3.1) [22, 23]. Benign anal conditions such as hemorrhoids and fissures, and inflammatory bowel diseases, are not associated with an increased risk of anal cancer [24, 25].

HPV-related precursor lesions can be (1) clinically apparent raised condylomata, (2) incidentally found in anorectal surgical specimens, or (3) subclinical flat lesions seen on HRA or as subtle plaques, erythema, pigmentation, or pruritis. Histologically they are classified as LSIL or HSIL. LSIL represents morphologic features of HPV infection, while HSIL is a non-obligate precancerous lesion [14]. Typically, condylomata are LSIL, and flat lesions can be LSIL or HSIL.

Anal condyloma acuminata (anal warts) are the most common HPV-related anogenital lesions, and present as exophytic, soft, cauliflower-like masses [15]. Typically associated with low-risk HPV types 6 and 11, condylomata are low-risk lesions that may recur but have little, if any, risk of progression to carcinoma [12]. A small proportion of condylomata, more so anal canal lesions, may be associated with high-risk HPV and may progress to HSIL and invasive carcinoma, but this association is not fully clear [15]. A condyloma is distinguished from skin stags and hemorrhoids clinically. Flat LSIL (AIN1) are typically within the anal canal. They should be differentiated from seborrheic keratosis and psoriasiform dermatitis, and can be histologically similar to reactive changes [14, 15]. HSIL can arise in a condyloma, but typically are a flat lesion. Because the morphologic features of AIN2 fall between HPV infection (LSIL) and precancer (HSIL), immunohistochemical staining for p16, a biomarker for HPV-related cell proliferation is used to confirm HSIL when morphological features of AIN2 are present [14]. AIN2 that is p16 negative is classified as LSIL. Use of the LAST criteria limits inter-rater discordance in pathology interpretation [14, 15].

LSIL may spontaneously regress or progress to HSIL. HSIL is less likely to regress, and may progress to anal cancer. Population-based estimates of the rate of progression from HSIL to anal cancer may be as high as 2% per year (10% at 5 years), and may be higher in those with HIV [16, 35–40]. Spontaneous regression of HSIL may occur in some [36, 41]. There is no conclusive evidence that treatment of HSIL effectively prevents incident anal cancer; retrospective studies show variable results comparing treatment of HSIL to watchful waiting [16, 42–45]. Two ongoing randomized clinical trials (ANCHOR and HPV-SAVE) aim to investigate this question [46, 47]. The management of anal squamous intraepithelial lesions is detailed in Table 3.2

Table 3.2 Management of anal squamous intraepithelial lesions (precursor lesions)

	Work-up	Treatment		Follow-up
		Primary	Recurrence	
LSIL (condyloma, AIN 1)	Comprehensive history Digital anorectal examination. High-resolution anoscopy (HRA) with acetic acid 3% and Lugol's iodine [48]	Biopsy to rule out HSIL Watchful waiting recommended, may regress and low risk of progression Condylomata may regress, or can be treated with the same modalities as HSIL or other treatments (cryotherapy, sinecatechins [49], podophyllotoxin [50])	Same as primary	No clear evidence to guide method or frequency. History, DRE, conventional anoscopy or HRA, and/or anal cytology, are all available options [43, 51]
HSIL (AIN 2, AIN 3)	Gynecological examination in female patients, with cervical cancer screening as appropriate Genital examination in male patients to exclude HPV-related disease HIV testing Consider pathology review to confirm diagnosis by LAST criteria [14].	Watchful waiting with history, DRE, conventional anoscopy or HRA every 4–6 months Patient-applied topical/ intra-anal treatment 5% imiquimod cream 3/ week for 16 weeks [52–54] 5% fluorouracil for 9–16 weeks [53, 55] Cidofovir 1% gel for 6 weeks [56, 57] Local/ablative treatments with HRA Trichloroacetic acid (TCA) [58, 59] Electrocautery ablation [53, 60–62] Radiofrequency ablation provides circumferential treatment [63] Infrared coagulation [64, 65] Cryotherapy	High rate of recurrence with all treatment options available Retreatment and surveillance possible	If watchful waiting, history, DRE, simple anoscopy or HRA every 4–6 months After complete treatment, no clear evidence to guide method or frequency. History, DRE, conventional anoscopy or HRA, and/or anal cytology, are all available options. At least yearly, and some recommend every 6 months particularly in those with HIV [43, 51]

Thorough clinical assessment should be done to exclude concomitant anal cancer.
Treatment choice based on location (canal or perianal), extent (>30–50% circumference in canal), availability, preference (patient- or physician-applied). A topical/intra-anal can be used for greater extent or patient preference for self-application; local/ablative treatment for smaller or remaining lesions [16, 43, 51].
Ablation requires destructive ablation of only the epidermal layer; margins are not required. for ablative techniques within the anal canal, avoid potential stenosis by ablating <30–50% of circumference at one treatment.
If access to HRA is not available, clinical assessment, ablative treatments, and follow-up can be done with conventional anoscopy with or without acetic acid 3%, but recurrence may be increased due to decreased sensitivity [51]
Recurrence of HSIL is common (20–50% at 1 year), but can be retreated; recurrence may decrease with HRA-directed therapy allowing adequate lesion recognition and eradication [16, 60, 61, 66]
With improved topical and ablative techniques as well as HRA, mapping procedures and wide local excision are no longer needed even for diffuse disease. Wide excision causes extensive tissue destruction, wound complications, and does not have lower recurrence risk [67]. If HRA is not available, can consider mapping procedure under general anesthesia in high-risk patients to determine extent of HSIL and assist with surveillance intensity. If considering wide local excision (>1 cm margins), this should be done only if the lesion is <30% of the anal circumference with no sphincter involvement. With wide local excision, recurrence rates are up to 63% in 1 year

AIN anal intraepithelial lesion, *HRA* high-resolution anoscopy, *HSIL* high-grade squamous intraepithelial lesion, *LSIL* low-grade squamous intraepithelial lesion

Anal Cancer

Almost half of patients present with bleeding; a third with mass sensation; some may have pain, irritation, or pruritis; and a fifth are asymptomatic [51, 68]. Diagnostic delay may occur if nonspecific anorectal symptoms are attributed to benign anorectal pathology such as hemorrhoids [51]. Pain and itching should be treated seriously even if invasion cannot be confirmed on biopsy. The onset of pain and symptoms is a key indicator of possible recurrence.

The Union for International Cancer Control's (UICC)/American Joint Committee on Cancer (AJCC) eighth edition is the recommended anal cancer staging system [11]. This is based on tumor size, invasion of adjacent structures, regional nodal involvement, and distant metastases. Notable changes from UICC/AJCC seventh edition include staging perianal cancers such as anal canal cancers rather than squamous cell skin cancers as previously done; removal of N2 and N3 categories and defining N1a, N1b, and N1c; and revision of stage groupings including subclassification of stage II into IIA and IIB with differing prognosis [69]. Tumor size determines T-category: ≤2 cm (T1), >2 to ≤5 cm (T2), >5 cm (T3), and T4 can be any size but invades adjacent organ (e.g., vagina, urethra, bladder) [11]. Any regional nodal involvement is staged N1; this is subclassified into N1a (mesorectal, internal iliac, or inguinal), N1b (external iliac only), N1c (any N1a with external iliac) [11]. Regarding stage classifications, any distant metastasis is stage IV, any regional nodal metastasis or T4 category are stage III, larger tumors (>2 cm) without nodal involvement is stage II, and small tumors without nodal involvement (≤2 cm) are stage I.

At presentation, 50% are localized, 30% regional, and 15% distant, with population-based overall survival at 5 years of 82%, 64%, and 30%, respectively [2]. Tumor size >5 cm, regional nodal and extrapelvic metastases are the most important prognostic features influencing overall survival [69, 70]. Tumor >5 cm and tumor invasion to other organs are frequently identified as risk factors for colostomy [70–72]. Currently, there are no other prognostic or predictive biomarkers established for routine clinical use [73].

Historically, anal cancers were treated with radical surgery by abdominoperineal resection; however, in a few centers radical radiation without chemotherapy was used to facilitate sphincter preservation. In 1974, Nigro et al. first described preoperative combined chemoradiotherapy in an attempt to reduce recurrence rates after abdominoperineal resection and observed complete clinical response in the first three patients and complete pathological response in the two that underwent surgery [74]. This led to the investigation of what has now become the standard treatment – concurrent radiation and chemotherapy without surgery as primary treatment, reserving surgery for treatment salvage of persistent or recurrent disease. Concurrent radiation and chemotherapy results in sphincter preservation in the majority of cases and allows prophylactic treatment to uninvolved nodes reducing of nodal recurrence [75, 76]. The management of anal cancer is detailed in Tables 3.3, and 3.4. Table 3.5 summarizes landmark studies in anal cancer treatment.

Table 3.3 Management of anal cancer: local/regional disease (any T, any N, M0)

		Treatment		
	Work-up	Primary	Recurrence	Follow-up

Anal canal cancer, any local or regional (T1–T4, N0, or N+)
Perianal cancer, 2 cm or more or regional disease (T2–T4, N0, or any T, N+)
	• Comprehensive history
	• Digital anorectal examination
	• Clinical assessment of inguinal lymph nodes (FNAB if suspicious)
	• Conventional anoscopy, biopsy primary tumor for histologic confirmation
	• Gynecological examination in female patients, with cervical cancer screening as appropriate
	• Genital examination in male patients to exclude HPV-related disease
	• HIV testing
	• Fertility preservation considerations
	• Imaging
	  • CT thorax
	  • CT abdomen and pelvis
	  • Pelvic MRI for locoregional staging and assessing sphincter involvement.
	  • PET for tumors >T1N0, may alter radiation planning [13, 51, 77, 78]
		• Primary curative-intent treatment is concurrent radiation and chemotherapy (CRT) with 5FU + MMC to the primary lesion and regional nodal basins (for N+ disease or elective node irradiation if N-) [13, 51, 78–83]
		• CRT with 5FU + MMC better DFS and OS than CRT with 5FU + Cis [84, 85]
		• Induction chemotherapy prior to CRT or maintenance chemotherapy after CRT has no added benefit [80, 85, 86]
		• CRT with 5FU + MMC better local recurrence, colostomy-free, and DFS than CRT with 5FU alone [82]
		• Primary surgical management should be reserved for select cases based on patient factors such as prior pelvic radiation, incontinence, fistula, and should follow a discussion at a MCC
		• Surgery for defunctioning stoma if fistula or fecal incontinence that will lead to greater skin toxicity during CRT
			Local persistence (>6 months or progression) or recurrence after cCR
			• Salvage surgery with abdominoperineal resection and multivisceral resection of adherent structures
			• 20–30% will have persistent or recurrent disease [51]
			• R0 resection achieved in 60–90% [87–94]
			• Locoregional recurrence after salvage surgery 30–75% [87–94]
			• 5-year OS 25–85% [87–94]
			Regional recurrence
			• Recurrence rates <5% in those who receive elective radiation to inguinal regions
			• Formal groin dissection and/or consideration of inguinal irradiation (if the inguinal region has not received prior radiation therapy) +/− chemotherapy; limited data to guide this treatment choice [75, 95–97]
				Assess for cCR after CRT starting 8–12 weeks after CRT [13, 51, 78, 85]
				• History, DRE, inguinal lymph nodes, anoscopy as indicated
				• Persistent disease after CRT, reassess every 4 weeks up to 6 months. 30% may take 6 months for cCR [85, 98]
				• Progression or persistence after 6 months, biopsy to confirm, restage, discussion for salvage surgery
				• No biopsy to confirm cCR
				• Radiation proctitis is meaningful long-term toxicity
				Surveillance after cCR or curative surgery [13, 51, 78]
				• History, physical examination including DRE, anoscopy if indicated every 3 months for 2 years, then every 6 months for 1 year, then annually until 5 years
				• CT chest, abdomen, pelvis if T3–4 or N+ (MRI if recommended by radiologist), every 6 months for 3 years, starting 3 months after treatment

Table 3.3 (continued)

	Work-up	Treatment		Follow-up
		Primary	Recurrence	
Perianal cancer, <2 cm, well-differentiated (T1, N0)		• Wide local excision provided that sphincter function is not compromised [13, 51, 99] • There is no agreement on what margin of resection constitutes an "adequate" margin, particularly with respect to the deep margin. In surgical planning, 1 cm radial margins are recommended [23, 47]		Perianal cancer treated with wide local excision • For residual HSIL, observation or 5% imiquimod cream 3/week for 16 weeks [52–54] • Consider referral for HRA surveillance of recurrence or incident HSIL • Consider anal cytology or HPV-DNA testing in surveillance

- Ensure that the lesion is biopsy-proven squamous cell carcinoma prior to proceeding with comprehensive staging investigations.
- Patients presenting with clinical or radiographic evidence of inguinal lymph node metastases should undergo pretreatment FNA biopsy to confirm the diagnosis if the result may alter radiation treatment planning.
- Consider HIV testing if the patient has a known risk factor. Patients with HIV should receive concomitant management of HIV infection by their primary care physician or infectious disease specialist. otherwise, patients with HIV should be treated similarly to those without HIV [13, 51, 78].
- If invasive SCC found incidentally on surgical specimen, discuss at MCC regarding re-excision vs CRT
- Superficially invasive squamous cell carcinoma (SISCCA), which invades ≤3 mm and is ≤7 mm wide, usually seen on HRA, if completely excised with margins ≥1 mm, some consider omission of CRT even if within the anal canal [16]
- Due to the need for wide lateral margins and prior pelvic RT, patients undergoing salvage surgery experience a high rate of postoperative complications (35–75%) particularly perineal infections and delayed wound healing [87–91]. Use of a myocutaneous flap for perineal reconstruction should be part of surgical planning [87–91, 100].
- Monitor for, counsel, and treat anorectal, urinary, and sexual function, fertility, and lymphedema [13, 68, 78]

5FU 5-fluorouracil, *cCR* complete clinical response, *Cis* cisplatin, *CRT* chemoradiotherapy, *DRE* digital rectal examination, *FNAB* fine-needle aspiration biopsy, *MCC* multidisciplinary cancer conference, *MMC* mitomycin C, *OS* overall survival

Table 3.4 Management of anal canal and perianal cancer: metastatic (any T, any N, M+)

Work-up	Treatment
Comprehensive history Digital anorectal examination Clinical assessment of inguinal lymph nodes (FNAB if suspicious) Conventional anoscopy, biopsy primary tumor for histologic confirmation Gynecological examination in female patients, with cervical cancer screening as appropriate Genital examination in male patients to exclude HPV-related disease HIV testing Hepatitis serology in preparation for systemic therapy Fertility preservation considerations Imaging CT thorax CT abdomen and pelvis Pelvic MRI	Most common sites are liver, lung, and extrapelvic lymph nodes; 10–20% of patients [85, 101, 102] Limited data to guide treatment choices [78] Systemic treatments are the main treatment options. 5FU + Cis has been most published and supported by guidelines as first-line albeit results are modest and treatment is associated with substantial toxicity [13, 78] Other combinations are being actively studied including docetaxel+5FU + Cis and immunotherapy [78, 103–105] There are very little data to support local treatments of metastatic disease including surgery or radiotherapy [106] If the primary cancer and/or symptomatic regional node metastases are present, consider the addition of chemoradiation or surgical excision for local control (as described for M0 disease)

5FU 5-fluorouracil, *Cis* cisplatin, *DRE* digital rectal examination, *FNAB* fine-needle aspiration biopsy

Prevention and Screening

Vaccination should be routinely administered to everyone between ages 9–13 to prevent initial HPV infection, and later if not previously immunized including MSM and those with immunodeficiency [13, 20, 114, 115]. HPV-9 nonvalent vaccine targets high-risk HPV types 16, 18, 31, 33, 45, 52, and 58, as well as low-risk HPV 6 and 11, accounting for nearly all causes of HPV-associated cancers and condyloma [20, 116]. Efficacy for preventing persistent infection is over 90% [117–119]. The prior quadrivalent vaccine targeted HPV 16, 18, 6, 11 [117]. Safer sex practices including routine condom use, as well as smoking cessation should also be advocated [8].

Screening is proposed for well-established high-risk groups including persons living with HIV, men who have sex with men (MSM), and MSM with HIV infection who have even greater risk [9, 28, 30, 40, 51, 120, 121]. Screening may allow early detection of HPV-related precursor lesions which can be treated to prevent anal cancer. However, evidence is not yet available to demonstrate reduced anal cancer incidence, mortality benefit, cost-effectiveness, or optimal screening approach and follow-up [43, 120, 122]. Ongoing studies will inform screening strategies [46, 47, 123]. At least, for those in high-risk populations, discussion of the risk of anal cancer and symptoms that should prompt clinical assessment and routine digital anorectal examination is appropriate [124]. Screening methods include anal cytology, HPV testing, high-resolution anoscopy, and directed biopsies [120–122, 125, 126]. A strategy analogous to cervical cancer screening includes anal cytology or HPV testing to triage use of HRA and directed biopsy. Anal cytology is categorized using

Table 3.5 Landmark studies

Topic	Study	Methods	Results
First use of CRT (preoperative)	Nigro et al. (1974) [74]	Case reports, $n = 3$ Concurrent 30 Gy RT + 5FU + MMC APR after 6 weeks	CRT can induce CR Two patients had a complete pathologic response at time of APR One patient declined surgery, but had a complete clinical response which was sustained at 1-year follow-up
Radical CRT (surgery only if persistent or recurrent disease)	Cummings et al. (1980) [107]	Single-arm cohort, $n = 6$ Concurrent 45 Gy RT + 5FU + MMC	CRT without surgery is a possible treatment option All patients had cCR with retained continence No local recurrence with 6–20-month-follow-up
CRT protocols (surgery only if persistent or recurrent disease)	UKCCCR ACT I (1996) [79] 13-year update (2010) [102]	RCT, $n = 585$ RT alone vs. CRT (RT + 5FU + MMC)	CRT is superior to RT alone (reporting at 12 years) cCR (30% vs. 39%) Locoregional recurrence (59% vs. 34%; HR 0.46, 95% CI 0.35–0.60, $p < 0.001$) Colostomy-free survival (20% vs 30%; HR 0.76, 95% CI 0.63–0.91, $p = 0.004$) Anal cancer-specific survival (51% vs. 64%; HR 0.67, 95% CI 0.51–0.88, $p = 0.004$) OS not statistically different (at 12 years, 28% vs. 33%; HR 0.86, 95% CI 0.70–1.04), $p = 0.12$)
	EORTC 22861 (1997) [81]	Multicenter RCT, $n = 110$ RT alone vs. CRT (RT + MMC-5FU)	CRT is superior to RT alone (reporting at 5 years) cCR (54% RT vs. 80% CRT) Locoregional recurrence (18% higher, $p = 0.02$) Colostomy-free rate (32% higher, $p = 0.002$) Event-free survival (absolute difference not reported, $p = 0.03$) OS not statistically different (54% vs. 58%, $p = 0.17$)
	RTOG 87–04 (1996) [82]	RCT, $n = 310$ RT + 5FU vs. RT + MMC-5FU.	CRT with MMC + 5FU is superior to CRT with 5FU alone, but increased toxicity (at 4 years) Locoregional recurrence (16% vs. 34%, $p < 0.001$) Colostomy-free rate (78% vs. 91%; $p = 0.002$ DFS (51% vs. 73%; $p < 0.001$) Toxicity in MMC group higher (7% vs. 23% grade 4 and 5 toxicity, $p < 0.001$) OS not different at 4 years

Table 3.5 (continued)

Topic	Study	Methods	Results
CRT intensification (surgery only if persistent or recurrent disease)	RTOG 98–11 (2008) [80] 5-year update (2012) [84]	RCT, $n = 682$ RT + 5FU+MMC vs. induction Cis-5FU then RT + Cis-5FU	CRT with MMC-5FU is superior to induction chemotherapy (Cis-5FU) followed by CRT with Cis-5FU (reporting at 5 years) DFS (68% vs. 58%; HR 1.39, 95% CI, 1.10–1.76, $p = 0.006$) OS (78% vs. 70%; HR 1.37, 95% CI 1.04–1.81, $p = 0.026$) Colostomy-free survival (72% vs 65%, HR 1.29, 95% CI, 0.99–1.67, $p = 0.05$). MMC arm higher acute toxicity (62% vs 42% grade 3–4 toxicity, $p < 0.001$)
	ACCORD 03 (2012) [86]	RCT, $n = 307$ 2x2 factorial trial (4 arms) Induction Cis-5FU then RT + Cis-5FU then standard dose RT boost. Induction Cis-5FU then RT+ Cis-5FU then high- dose RT boost RT + Cis-5FU then standard dose RT boost RT + Cis-5FU then high- dose RT boost	The addition of induction chemotherapy or high-dose RT boost did not demonstrate improved colostomy-free survival Induction Cis-5FU vs. no induction; 68% vs 58%, $p = 0.37$. Standard-dose RT boost vs. high-dose RT boost; 73.7% vs. 77.8%, $p = 0.067$.
	ACT II (2013) [85]	RCT, $n = 940$ 2x2 factorial trial (4 arms) RT + 5FU + MMC + maintenance 5FU + Cis (2 doses) RT + 5FU + MMC + no maintenance RT + 5FU + Cis + maintenance 5FU + Cis (2 doses) RT + 5FU + Cis + no maintenance	CRT with MMC- 5FU vs Cis-5FU is similar (reporting at 5 years) cCR similar (90% vs 90%; absolute difference − 0.9%, 95% CI -4.9–3.1, 30% without cCR at 11 weeks had cCR by 26 weeks Colostomy-free survival (68% vs 67%) DFS similar (69% vs. 69%; HR 0.95, 95% CI 0.75–1.19) OS similar (79% vs. 77%; HR 1.05, 95% CI 0.80–1.38) Maintenance chemotherapy did not offer improvement over CRT alone Colostomy-free survival (69% vs 66%) DFS (70% vs. 69%; HR 0.95, 95% CI 0.75–1.21). OS (76% vs. 79%, HR 1.07 CI 0.81–1.41).

(continued)

Table 3.5 (continued)

Topic	Study	Methods	Results
Intensity modulated radiation therapy (IMRT) to reduce toxicity	RTOG 0529 (2013) [108]	Phase 2 trial, $n = 63$ IMRT+MMC-5FU	Outcomes in this prospective single-arm study were compared to conventional RT + MMC-5FU in RTOG98–11 Grade 2+ gastrointestinal/ genitourinary adverse events similar (77% in both trials) IMRT had improved acute grade 2+ hematologic, 73% (98–11 85%, $p = 0.032$), grade 3+ gastrointestinal, 21% (98–11 36%, $p = 0.008$), and grade 3+ dermatologic adverse events 23% (98–11 49%, $P < 0.0001$)
	Hosni et al. 2018 [109]	Prospective single-arm cohort, $n = 101$ IMRT+MMC-5FU	Most common acute grade ≥ 3 toxicities were skin (42%) and hematological (31%). 5-year OS 83% 5-year DFS 76% 5-year CFS 75%
Surgery	Correa et al. 2013 [110]	Retrospective single-arm cohort, $n = 111$ Salvage surgery for persistence or recurrence after CRT	83% required APR with en bloc resection of local structures (mostly vagina and uterus) 77% R0 resection margin 5-year OS 25% (95% CI 16–17%)
	Lefèvre et al. 2012 [111]	Retrospective single-arm cohort, $n = 105$ Salvage surgery for persistence or recurrence after CRT (7% primary surgery for contraindication to radiation)	All received APR (no report of en bloc resection) 82% R0 resection margin 5-year OS 61%
	Eeson et al. 2011 [96]	Retrospective single-arm cohort, $n = 51$ Salvage surgery for persistence or recurrence after CRT	All APR 63% Ro resection margin 5-year OS 29%
	ACT II 2016 (abstract) [112]	RCT, $n = 940$ Reporting on 291 patients with persistent or recurrent disease	107 (31%) underwent attempted salvage surgery with abdominoperineal resection 2-year OS 54% (95%CI 43–63%)
	Penderson et al. 2018 [113]	Retrospective single-arm cohort, $n = 47$ Salvage surgery for persistence or recurrence after CRT	33% required APR with en bloc resection (almost all hysterectomy) 85% R0 resection margin 5-year OS 50%

Table 3.5 (continued)

Topic	Study	Methods	Results
Systemic treatment for metastatic or unresectable disease	KEYNOTE-028 [105]	Phase Ib trial, *n* = 25 Pembrolizumab (anti-PD-1 immunotherapy)	Overall response rate 17% (95%CI 5–37%). Disease control rate 58% Adverse events 64%, most common diarrhea, fatigue, and nausea
	NCI9673 [104]	Phase 2 trial, *n* = 37 Nivolumab (anti-PD-1 immunotherapy)	Overall response rate 24% (95% CI 15–33%); 5% complete response. Grade 3 adverse event 14% (anemia, fatigue, rash, and hypothyroidism)
	Epitopes-HPV02 [103]	Phase 2 trial, *n* = 69 Docetaxel+5FU + Cis	Progression-free survival at 1 year 48%. Grade 3–4 adverse event 70%, most common neutropenia, diarrhea

5FU 5-fluorouracil, *APR* abdominoperineal resection, *cCR* complete clinical response, *Cis* cisplatin, *CRT* chemoradiotherapy, *DFS* disease-free survival, *MMC* mitomycin C, *OS* overall survival

the Bethesda system into negative, atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL); atypical squamous cells, cannot exclude HSIL (ASC-H); or HSIL [127]. Those with any abnormal cytology (ACS-US or more) are then screened with HRA and directed biopsies [51, 120, 128]. Anal cytology testing and interpretation, HRA, and follow-up strategies require expertise, and use of screening strategies should not be done without local expertise [48, 51, 129–131].

Referring to Medical Oncology

1. All patients with a biopsy-proven diagnosis of anal canal carcinoma should be referred to a medical oncologist for consideration of primary combined-modality chemoradiotherapy.
2. All patients with a biopsy-proven diagnosis of perianal carcinoma not suitable for local excision should be referred to a medical oncologist for consideration of primary combined-modality chemoradiotherapy.

Referring to Radiation Oncology

1. All patients with a biopsy-proven diagnosis of anal canal carcinoma should be referred to a radiation oncologist for consideration of primary combined-modality chemoradiotherapy.
2. All patients with a biopsy-proven diagnosis of perianal carcinoma not suitable for local excision should be referred to radiation oncologist for consideration of primary combined-modality chemoradiotherapy.

Referring to Multidisciplinary Cancer Conference

1. All patients with clinically suspected or biopsy-proven persistent or recurrent anal carcinoma following primary combined-modality or surgical treatment should be discussed at a Multidisciplinary Cancer Conference (MCC).
2. Patients not suitable for combined-modality chemoradiotherapy as the primary treatment of an anal carcinoma (due to patient comorbidities or tumor-related factors such as prior pelvic radiation, incontinence, fistula) should be discussed at an MCC, and considered for radical radiation alone or radical surgery (possibly with adjuvant preoperative or postoperative radiation with/without chemotherapy).
3. Patients presenting with metastatic disease should be discussed at MCC.
4. All patients with a biopsy-proven diagnosis of *adenocarcinoma* of the anal canal or perianal area should be discussed at MCC. Standard of care remains multimodality treatment including surgery as well as chemotherapy and radiation, like that in rectal adenocarcinoma. Several small series (including the Toronto experience) have found that local control can be achieved in about 50% of cases with adenocarcinomas, less than about 3 cm in size using combination chemoradiation alone. Treatment plans should be individualized on a case-by-case basis.

Toronto Pearls

- For patients undergoing chemoradiotherapy, the use of intensity modulated radiation therapy is associated with less treatment toxicity and better quality of life [132, 133].
- For patients undergoing radical salvage surgery, the use of a myocutaneous flap for perineal reconstruction is recommended.
- In order to achieve an R0 resection in locally advanced or recurrent disease, a multidisciplinary surgical team (including uro-oncology, plastic surgery, and/or orthopedic surgery) should be used in the context of multivisceral pelvic resections.
- HIV-positive patients should be managed similarly to non-HIV-infected patients. The risk of excessive reaction to radiation and/or chemotherapy is low. Treatment should be adjusted on an individual basis based on toxicity and side-effect profile.
- Previous pelvic radiation is a relative, but not an absolute, contraindication to radiation and chemotherapy for anal cancer. Such patients should be referred to a radiation oncologist for assessment and discussed at an MCC.

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