Chapter 23
Anal Cancer

Serah Choi, Hans T. Chung, and Mekhail Anwar

VI

PEARLS

- 8,080 estimated new cases and 1,080 estimated deaths in the United States in 2016.
- 75–80% are squamous cell carcinoma (SCC); others are adenocarcinoma or melanoma.
- HPV: found in 85–95% and strongly associated with SCC and may be requisite for disease formation. High-grade anal intraepithelial lesions (HSIL) are precursors. In particular HPV-16, 18 as in cervical cancer.
- HPV vaccines in the United States: quadrivalent vaccine (HPV 6, 11, 16, and 18); 9-valent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58); and bivalent vaccine (HPV 16 and 18).
- 11% of untreated HSIL progress to SCC; 50% progress with extensive disease of immunosuppression; with treatment, progression is reduced to 0.4%.
  - HIV positivity increases risk, likely through an association with immunodeficiency in the setting of HPV coinfection. Increased risk if CD4 < 200.
- Additional risk factors: >10 sexual partners, history of genital warts, receptive anal intercourse, chronic immunosuppression, and cigarette smoking.
- Anatomy: anal canal is 3–5 cm long. Extends from anal verge to the anorectal ring. The dentate line lies within the

Eric K. Hansen and M. Roach III (eds.), *Handbook of Evidence-Based Radiation Oncology*, https://doi.org/10.1007/978-3-319-62642-0_23

anal canal and divides it by histology. Proximal to the dentate line is colorectal mucosa, distal to it is nonkeratinizing squamous epithelium. The dentate line contains transitional mucosa. Anal margin is a 5 cm ring of skin around the anus. Use CT to measure depth of inguinal nodes using the femoral vessels as a surrogate due to large variations.

- Anal margin tumors: may behave like skin cancers, and can be treated as skin cancers as long as there is no involvement of the anal sphincter, tumor is <2 cm, and moderately or well-differentiated, and resected with adequate margins
- Adenocarcinoma: higher local and distant recurrence rates with chemo-RT compared to SCC. Treatment similar to that of rectal cancer. Use 5-FU chemo-RT pre-op followed by APR.
- Lymph node drainage: superiorly (above dentate line) along hemorrhoidal vessels to perirectal and internal iliac nodes; inferior canal (below dentate line) and anal verge to inguinal nodes.
- Presentation: bleeding, anorectal pain/sensation of mass, altered bowel movements/rectal urgency, genital warts/condyloma, pruritus, asymptomatic.

WORKUP

- H&P. Include inguinal LN evaluation. Note anal sphincter tone, pain, bleeding, HIV risk factors, inflammatory bowel disease, prior RT. For women, a comprehensive gynecological exam should be performed. On DRE, note anal sphincter tone and tumor location (clock location prone or supine position, distance from verge, circumferential involvement, size, and superior extent).
- Labs: CBC, HIV test if any risk factors. CD4 count if HIV-positive.
- Proctoscopy with biopsy.
- May biopsy inguinal nodes if clinically suspicious. Only FNA, avoid open biopsy.

- CT chest/abdomen and pelvic CT or MRI.
- PET/CT is recommended as it is better than CT at detecting the primary tumor and is more sensitive at staging nodal disease (Winton, Br J Cancer 2009; Mistrangelo, IJROBP 2012; Cotter, IJROBP 2006; Schwarz, IJROBP 2008; Trautmann, Mol Imaging Biol 2005).

Table 23.1 STAGING (AJCC 7TH ED., 2010): ANAL CANAL

Primary tumor (T)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ (Bowen's disease, high-grade squamous intraepithelial lesion (HSIL), anal intraepithelial neoplasia II–III (AIN II–III))
T1: Tumor 2 cm or less in greatest dimension
T2: Tumor more than 2 cm, but not more than 5 cm in greatest dimension
T3: Tumor more than 5 cm in greatest dimension
T4: Tumor of any size invades adjacent organ(s), e.g., vagina, urethra, and bladder[a]
[a]*Note*: Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4

Regional lymph nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in perirectal lymph node(s)
N2: Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3: Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

Distant metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

Anatomical stage/prognostic groups

0:	Tis N0 M0
I:	T1 N0 M0
II:	T2 N0 M0
	T3 N0 M0
IIIA:	T1–T3 N1 M0
	T4 N0 M0
IIIB:	T4 N1 M0
	Any T N2 M0
	Any T N3 M0
IV:	Any T Any N M1

TABLE 23.2 (AJCC 8TH ED., 2017) DEFINITION OF PRIMARY TUMOR (T)

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 neoplasias 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

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

Definition of Regional Lymph Node (N)	
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 Nla nodes

DEFINITION OF DISTANT METASTASIS (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC PROGNOSTIC STAGE GROUPS

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T1	N1	M0	IIIA
T2	N0	M0	IIA
T2	N1	M0	IIIA
T3	N0	M0	IIB

T3	N1	M0	IIIC
T4	N0	M0	IIIB
T4	N1	M0	IIIC
Any T	Any N	M1	IV

TREATMENT RECOMMENDATIONS

Table 23.3 TREATMENT RECOMMENDATIONS

Situations	Recommended treatments
Anal canal, stage I–III with intact sphincter	Concurrent chemo-RT with 5-FU/mitomycin C
Anal canal, recurrence	Abdominoperineal resection. Salvage rate ~50% after chemo-RT Inguinal node recurrence: groin dissection
Distant metastasis	5FU/cisplatin chemo. Consider local RT for palliation, in particular for pts with good PS and limited metastatic disease
Anal margin tumors	Wide local excision with ≥1 cm margin. Well-differentiated T1N0 can be observed with close follow-up. All others get definitive chemo-RT to primary with elective inguinal LN RT for T2-4 and poorly differentiated tumors. Include pelvic LN if involvement of anal canal above dentate line or node positive. Alternative is post-op RT or chemo-RT with inguinal management as above. Dose 45 Gy elective, 60 Gy to gross disease

TRIALS

CHEMO-RT VS. RT

- *UKCCCR ACT I* (Lancet 1996; Northover, Br J Cancer 2010): 585 pts with epidermoid cancer of anal canal or margin. RT: 45 Gy + boost (15 Gy EBRT or 25 Gy brachy) ± 5-FU + mitomycin C (MMC). 6-wk break in RT. Chemo-RT improved 3-yr LC (59% vs. 36%), but no significant change in 3-yr OS (65% vs. 58%). Poorer results with RT alone may be due to mandatory 6-wk

break. 13-yr median follow-up: for every 100 pts treated with chemo-RT, 25.3 fewer pts with LRR and 12.5 fewer anal cancer deaths vs. 100 pts treated with RT alone. There was a 9.1% increase in nonanal cancer deaths in the first 5 yrs of chemo-RT, which disappeared by 10 yrs.

- *EORTC* (Bartelink, JCO 1997): 110 pts. T3-4N0-3 or T1-2N1-3. RT (45 Gy + 15–20 Gy boost) + concurrent chemo (bolus 5-FU + MMC) vs. RT alone. 6-wk break in RT, prior to boost. Chemo-RT improved CR rate (80% vs. 54%), 5-yr LC (68% vs. 50%), colostomy-free survival (72% vs. 40%), and PFS (61% vs. 43%). No difference in OS (57% vs. 52%). Poorer results with RT alone may again be due to mandatory 6-wk break.
- For pts ineligible for concurrent chemo, good results are achievable with RT alone:
  - Deniaud-Alexandre (IJROBP 2003). 305 pts treated with 45 Gy EBRT, 4–6 wk break, then boost of 20 Gy EBRT (279 pts) or brachy (17 pts). Only 19 pts received concurrent chemo. Complete response rate: T1 96%, T2 87%, T3 79%, and T4 44%. Salvage APR was used successfully for 44% of locally progressive tumors and 54% of local recurrences.

ROLE OF MITOMYCIN (MMC)

- *RTOG 87-04* (Flam, JCO 1996): 291 pts treated with 45 Gy + 5FU ± MMC. Median follow-up of 36 mos. If no CR at 6 wks, gave 9 Gy boost +5-FU/cisplatin. 5-FU given as bolus × 4 day starting d1, d29 (1000 mg/m^2/day). MMC given as 10 mg/m^2 bolus d1, d29. MMC improved CR rate (92% vs. 85%) and decreased 4-yr colostomy rate (9% vs. 22%). No difference in 4-yr OS (75 vs. 70%).

ROLE OF CISPLATIN

- *ACT II* (James, Lancet Oncol 2013): 940 pts with anal cancer [stage T1–T2 (50%), T3–T4 (43%); LN-(62%), LN+ (30%)] treated with 5-FU (1,000 mg/m^2/day on d1-4 and 29–32) and RT (50.4 Gy in 28 fx), randomized to either concurrent MMC (12 mg/m^2, d1) or cisplatin (60 mg/m^2 on d1 and 29), and also randomized to maintenance therapy (2c of cisplatin/5-FU weeks 11 and 14) 4 wks after

chemo-RT or no maintenance therapy. No significant difference in complete response at 26 wks between MMC (90.5%) and cisplatin (89.6%) groups. Similar toxicity between the MMC (71%) and cisplatin (72%) groups. No significant difference in PFS between maintenance (74%) vs. nonmaintenance (73%) groups.

- Based on the above results and RTOG 98-11 (see below), 5-FU/MMC chemotherapy remains the standard of care.
- It remains unclear whether the 2nd dose of MMC improves efficacy or merely increases toxicity. Some phase III trials have used 2 cycles, while others have used 1 cycle. Retrospective series suggests similar outcomes with less toxicity with only 1 cycle (Yeung, Curr Oncol 2014; White, Radiother Oncol 2015).

ROLE OF INDUCTION CHEMO

- No proven advantage to induction chemo exists; Results to 98-11 may indicate a disadvantage with neoadjuvant chemo.
- *RTOG 98-11* (Ajani, JAMA 2008; Gunderson, JCO 2012; Gunderson, IJROBP 2013): 644 pts, T2–T4, any N. Neoadjuvant cisplatin + 5-FU × 2 followed by concurrent cisplatin +5-FU × 2 and 45–59 Gy vs. concurrent 5-FU + mitomycin and 45–59 Gy. Worse colostomy rate in cisplatin arm (19%) vs. mitomycin arm (10%). At long-term FU, upfront RT + 5FU/MCC improved 5-yr DFS (68% vs. 58%) and OS (78% vs. 71%) vs. induction/concurrent 5FU/cisplatin + RT. T- and N-stage impacted outcomes. In 5FU/MMC arm:
  - 3-yr colostomy: T2N0 9%, T3N0 12%, T4N0 20%, T2N+ 4%, T3N+ 19%, T4N+ 28%.
  - 3-yr LRF: T2N0 10%, T3N0 22%, T4N0 27%, T2N+ 18%, T3N+ 38%, T4N+ 61%.
  - 5-yr DFS: T2N0 80%, T3N0 60%, T4N0 65%, T2N+ 68%, T3N+ 43%, T4N+ 27%.
- *ACCORD 03 Trial* (Peiffert, JCO 2012): 283 pts with locally advanced anal cancer randomized to: (1) two induction chemo cycles (5-FU 800 mg/m^2/d IV infusion, days 1–4 and 29–32; and cisplatin 80 mg/m^2 IV, on days 1 and 29), concomitant chemo-RT (45 Gy in 25 fxs/5 wks, 5-FU and cisplatin during wks 1–5), and standard-dose boost (15 Gy); (2) two induction chemo cycles, concomitant

chemo-RT and high-dose boost (20–25 Gy); (3) concomitant chemo-RT and standard dose boost; and (4) concomitant chemo-RT and high-dose boost. Induction chemo or high-dose radiation boost did not improve 5-yr colostomy-free survival rates.

INFUSIONAL 5-FU VS. CAPECITABINE

- Capecitabine is a promising alternative to 5FU for anal cancer, but phase III data are needed.
- Phase II data with oral capecitabine concurrently with mitomycin and RT in anal cancer report overall low toxicity (Glynne-Jones, IJROBP 2008).
- BC Cancer Agency (Peixoto, J Gastrointest Oncol 2016): retrospective single institution study of 300 pts who received either 5-FU/MMC (64.6%) vs. capecitabine/MMC (35.3%) in combination with RT for locally advanced anal cancer. No difference in disease-free survival or anal cancer-specific survival.

HIV

- Oehler-Jänne (J Clin Oncol 2008): retrospective, multicentric cohort comparison of 40 HIV+ pts with HAART and 81 HIV- pts treated with RT or CRT. 55% of HIV+ pts had AIDS-defining clinical conditions. CR was 92% of HIV+ and 96% of HIV- cases. 5-yr OS was 61% in HIV+ and 65% in HIV- pts at a median follow-up of 36 mos. 5-yr LC worse in HIV+ pts (38%) vs. HIV- pts (87%), compromising cancer-specific survival and sphincter preservation. Increased grade 3/4 acute skin and hematological in HIV+ pts.
- White (Am J Clin Oncol 2017): single institution retrospective cohort study of 53 consecutive HIV+ pts treated between 1987 and 2013 vs. 205 consecutive HIV- pts treated between 2003 and 2013. Median RT dose was 54 Gy (28–60 Gy), concurrent chemo was 2 cycles of 5-FU/MMC on day 1 ± day 29. 70% of the HIV+ pts were on HAART at the time of treatment, 65% of pts had an undetectable HIV viral load, and the mean CD4 count was 455. At 3 yrs, no significant difference in PFS (75% vs. 76%),

colostomy-free survival (85% vs. 85%), or cancer-specific survival (79% vs. 88%, $P = 0.36$), respectively.

BRACHYTHERAPY

- Not frequently used in North America due to higher complication rates, including risk of necrosis. Rates of necrosis in the range of 7–15% (Sandhu, IJROBP 1998; Gerard, Radiother Oncol 1998), 6% complication requiring surgery (Ng, IJROBP 1988).

IMRT

- Multiple studies have reported similar LRC, DFS, colostomy rates, but comparable or lower toxicity with IMRT vs. traditional planning techniques.
- RTOG 0529 (Kachnic, IJROBP 2013): phase II multi-institutional trial. 52 pts, 54% with stage II, 25% IIIA, and 21% IIIB. 77% experienced grade 2+ GI/GU acute AEs (vs. RTOG 9811 77%). There were significant reductions in acute adverse events (AEs): grade 2+ hematologic (73% vs. 85% in RTOG 9811), grade 3+ GI (21% vs. 36% in RTOG 9811), and grade 3+ dermatological (23% vs. 49% in RTOG 9811).
- Call (Am J Clin Oncol 2016). Multi-institutional retrospective review of 152 pts treated with IMRT. 3-yr OS 87%, CFS T1-2 96% vs. T3-4 84%, LC T1-2 90% vs. T3-3 79%. Severe acute toxicity: skin 20%, GI 11%, and hematological 41%.

RT DOSE

- Optimal dose of RT continues to be explored.
- Multi-institutional and retrospective analyses report improved LC for doses >54–55 Gy (e.g., Huang, World J Gastroenterol 2007; Widder, Radiother Oncol 2008).
- ACCORD 03 trial (above) reported nonsignificant trend for improved colostomy-free survival with increased RT boost dose 20–25 Gy vs. 15 Gy (78% vs. 74%, $p = 0.067$).
- Elevated dose with a treatment break does not appear to improve disease outcomes. For example, RTOG 92-08

(John, Cancer J Sci Am 1996) treated pts with 5-FU/MMC + 59.6 Gy with 2 wk planned break included and colostomy rate at 2 yrs was 30%.

POST-TREATMENT BIOPSY

- Cummings (IJROBP 1991): no benefit to routine rebiopsy at 6 weeks post chemo-RT. Continued regression of tumor for up to 12 months, mean time to regression 3 months. ACT II trial reported optimal time point for evaluation of disease response is at 26 weeks because 72% of pts who did not show a CR at 11 weeks had achieved a CR by 26 weeks (Glynne-Jones, Lancet Oncol 2017).
- Follow pts clinically. Biopsy for clinically suspicious lesions.

SALVAGE APR

- Several studies report that salvage APR can achieve 30–77% LC after chemo-RT.
- Ellenhorn (Ann Surg Oncol 1994): retrospective review of 38 pts treated with RT + 5-FU/MMC. 5-yr OS was 44% when salvage APR used for chemo-RT failure.

RADIATION TECHNIQUES

GENERAL POINTS

- IMRT is favored over 3D conformal RT to reduce toxicity. It is critical to follow detailed target volumes as used in RTOG 0529.
- Minimize treatment breaks (try to keep under 2 weeks). Overall treatment time, but not duration of RT, has a detrimental effect on local failure and colostomy rate (Ben-Josef, JCO 2010).
- HIV+ pts with CD4 < 50–150.
  - Consider weekly 5FU/Cisplatin.
  - Consider RT alone 4.
  - (Re)institute HAART.
- HIV+ pts with CD4 < 150–200.

- Personalize treatment, but consider standard of care treatment with 5FU/MMC/RT.
- Consider cycle 2 dose reduction or omission of 2nd cycle MMC.

- HIV+ pts: post-therapy, rigorous HIV management is needed.

SIMULATION AND PLANNING

- Simulate patient supine, frog leg in vac lock bag immobilization.
- Anal marker to mark anal verge.
- Consider bolus on superficial large palpable groin nodes and any exposed tumor
- Treat with full bladder to minimize small bowel toxicity and use oral contrast 1–1.5 h before simulation. For patients who have trouble keeping a consistent full bladder, an empty bladder should be considered for reproducibility.
- Use PET-CT findings in treatment planning.

CONVENTIONAL PLANNING (RTOG 98-11 TECHNIQUE)

- Targets: primary tumor, grossly enlarged LN, internal/external iliac LN, inguinal LN.
- Initial large field (all patients) treated AP/PA, energy 18 MV AP, 6 MV PA, dose 30.6 Gy at 1.8 Gy/fx.
  - Borders: superior = L5/S1. Inferior = 2.5 cm margin on anus and tumor. AP field includes lateral inguinal nodes. PA field = 2 cm lateral to greater sciatic notch (not including lateral inguinal LN).
  - Supplementary RT delivered to inguinal nodes with anterior electron fields matched with exit of PA field. Alternatively, may use modified segmental boost photon technique (Moran, IJROBP 2004).
- Reduced field #1 (all patients) drops AP/PA superior border to inferior border of sacroiliac joints and is treated 14.4 Gy at 1.8 Gy/fx (total 45 Gy). If N0, field is also reduced off inguinal nodes after 36 Gy.
- Reduced field #2 (for T3–T4, LN+, and T2 lesions with residual disease after 45 Gy).

- Boost original tumor plus 2–2.5 cm margin 9–14 Gy at 1.8–2 Gy/fx (total 54–59 Gy) using either a multifield technique or laterals or a direct photon or electron perineal field.
- Involved inguinal and/or pelvic LN should be included if small bowel can be avoided, boost 9–14 Gy (total 54–59 Gy) with electrons.

RTOG 0529 IMRT TECHNIQUE

- Follow RTOG anorectal contouring atlas (Myerson, IJROBP 2008).
- Uses dose painting (all PTVs treated simultaneously).
- GTVA = gross primary tumor.
- GTVN50 = all involved nodal regions with macroscopic disease <3 cm greatest dimension.
- GTVN54 = all nodal regions containing macroscopic disease >3 cm greatest dimension.
- CTVA: 2.5 cm expansion around gross primary disease and anal canal.
- CTV45, CTV50, CTV54 includes the nodal regions (respectively, uninvolved, involved with nodes <3 cm, and involved with nodes >3 cm) and a 1.0 cm expansion (except into uninvolved bone, genitourinary structures, muscles, or bowel).
- For T2N0:
  - PTVA (primary tumor): 50.4 Gy in 28 fx of 1.8 Gy.
  - PTV42 (all nodal regions receives): 42 Gy in 28 fx of 1.5 Gy.
- For T3-4N0:
  - PTVA: 54 Gy in 30 fx of 1.8 Gy (but for large T3 or T4 tumors, we recommend a subsequent cone-down to 55.8 to 59.4 Gy at 1.8 Gy/fx).
  - PTV45: 45 Gy in 30 fx of 1.5 Gy.
- For N+:
  - PTVA: 54 Gy in 30 fx of 1.8 Gy.
  - PTV45 (uninvolved LN): 45 Gy in 30 fx of 1.5 Gy.
  - PTV50 (LN $\leq$ 3 cm): 50.4 Gy in 30 fx of 1.68 Gy.
  - PTV54 (LN > 3 cm): 54 Gy in 30 fx of 1.8 Gy.
- For further details, see http://www.rtog.org/members/protocols/0529/0529.pdf

UCSF IMRT DOSES

- We use dose-painting (all PTVs treated simultaneously).
- Primary tumor doses:
  - T1: 50.4–53.2 Gy/28 fx.
  - T2: 53.2 Gy/28 fx.
  - T3: 56–58.8 Gy/28 fx.
  - T4: 58.8 Gy/28 fx.
- Involved lymph nodes:
  - 50.4 Gy/28 fx if ≤2 cm.
  - 54–58.8 Gy if >2 cm.
- High-risk lymph nodes (perirectal, presacral, internal iliacs):
  - 47.6 Gy/28 fx.
- Low-risk lymph nodes (external iliacs and inguinals):
  - 44.8 Gy/28 fx.

DOSE LIMITATIONS

- See RTOG 0529 constraints. UCSF constraints:
- Small bowel: Dmax < 54 Gy, ≤ 30% volume > 45 Gy
- Bladder: Dmax < 54 Gy; ≤ 30% volume > 45 Gy
- Femoral Neck: Dmax < 45 Gy
- Gluteal folds: minimize dose, < 36 Gy if possible
- Skin (0.5 cm rind): minimize dose, < 20 Gy

COMPLICATIONS

- Acute complications: skin reaction/desquamation, leukopenia, thrombocytopenia, proctitis, diarrhea, and cystitis.
- Subacute and late complications include chronic diarrhea, rectal urgency, sterility, impotence, vaginal dryness, and vaginal fibrosis/stenosis (use vaginal dilator status post-XRT to help avoid), and possibly decreased testosterone.
- Increased risk of late pelvic fracture, particularly among older women.

FOLLOW-UP

- H&P with anal & inguinal LN exam q8–12 wks until CR, then every 3–6 mos × 5 yrs. Examine more frequently if persistent disease (e.g., monthly).

- On exam if mass increases in size, or new clinical symptoms develop (pain, bleeding, incontinence) → biopsy. If locally recurrent → salvage APR. If metastatic disease → 5-FU/cisplatin. If tumor decreasing in size, continue to follow. Median time to regression ~3 months, but tumor response can still be observed up to 6 months.
- Anoscopy q6–12 mos × 3 yrs.
- For T3–T4 or inguinal LN+: annual CT chest/abdomen/pelvis for 3 yrs.
- Most recurrences occur within 2 yrs.
- Anal pap, if available, is useful for follow-up.
- Recommend vaginal dilator and pelvic floor physical therapy in women to help reduce stenosis/narrowing, starting at 4 weeks post-therapy.
- Male pts may notice decrease in ejaculate; testosterone levels may be checked for sexual difficulties.

Acknowledgment The authors thank Amy Gillis MD and Gautam Prasad MD, PhD for their work on the prior edition of this chapter.

REFERENCES

Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA. 2008;299(16):1914–21.

Bartelink H, Roelofsen F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol. 1997;15:2040–9.

Ben-Josef E, Moughan J, Ajani JA, et al. Impact of overall treatment time on survival and local control in patients with anal cancer: a pooled data analysis of Radiation Therapy Oncology Group trials 87-04 and 98-11. J Clin Oncol. 2010;28(34):5061–6.

Boman BM, Moertel CG, et al. Carcinoma of the anal canal. A clinical and pathological study of 188 cases. Cancer. 1984;54:114–25.

Call JA, Prendergast BM, Jensen LG, et al. Intensity-modulated radiation therapy for anal cancer: results from a multi-institutional retrospective cohort study. Am J Clin Oncol. 2016;39(1):8–12.

Cotter SE, Grigsby PW, Siegel BA, et al. FDG-PET/CT in the evaluation of anal carcinoma. Int J Radiat Oncol Biol Phys. 2006;65:720–5.

Cummings BJ, Keane TJ, O'Sullivan B, et al. Epidermoid anal cancer: treatment by radiation alone or by radiation and 5-fluorouracil with and without mitomycin-c. Int J Radiat Oncol Biol Phys. 1991;21(5):1115–25.

Deniaud-Alexandre E, Touboul E, Tiret E, et al. Results of definitive irradiation in a series of 305 epidermoid carcinomas of the anal canal. Int J Radiat Oncol Biol Phys. 2003;56(5):1259–73.

Ellenhorn JD, Enker WE, Quan SH. Salvage abdominoperineal resection following combined chemotherapy and radiotherapy for epidermoid carcinoma of the anus. Ann Surg Oncol. 1994;1:105–10.

Flam M, Madhu J, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a Phase III Randomized Intergroup Study. J Clin Oncol. 1996;14:2527–39.

Gerard JP, Ayzac L, et al. Treatment of anal canal carcinoma with high dose radiation therapy and concomitant fluorouracil-cisplatinum. Long-term results in 95 patients. Radiother Oncol. 1998;46(3):249–56.

Glynne-Jones R, Meadows H, Wan S, et al. Extra – a multicenter phase ii study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin c in anal cancer. Int J Radiat Oncol Biol Phys. 2008;72(1):119–26.

Glynne-Jones R, Sebag-Montefiore D, Meadows HM, et al. Best time to assess complete clinical response after chemoradiotherapy in squamous cell carcinoma of the anus (ACT II): a post-hoc analysis of randomised controlled phase 3 trial. Lancet Oncol. 2017;S1470-2045(17):30071–2.

Greenall MJ, Quan HQ, Decosse JJ. Epidermoid cancer of the anus. Br J Surg. 1985;72:S97.

Gunderson LL, Winter KA, Ajani JA, et al. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol. 2012;30(35):4344–51.

Gunderson LL, Moughan J, Ajani JA, et al. Anal carcinoma: impact of TN category of disease on survival, disease relapse, and colostomy failure in US Gastrointestinal Intergroup RTOG 98-11 phase 3 trial. Int J Radiat Oncol Biol Phys. 2013;87(4):638–45.

Hatfield P, Cooper R, Sebag-Montefiore D. Involved-field, low-dose chemoradiotherapy for early-stage anal carcinoma. Int J Radiat Oncol Biol Phys. 2008;70(2):419–24.

Hoffman R, Welton ML, et al. The significance of pretreatment CD4 count on the outcome and treatment tolerance of HIV-positive pts with anal cancer. Int J Radiat Oncol Biol Phys. 1999;44:127–31.

Huang K, Haas-Kogan D, Weinberg V, et al. Higher radiation dose with a shorter treatment duration improves outcome for locally advanced carcinoma of anal canal. World J Gastroenterol. 2007;13(6):895–900.

James R, Glynne-Jones D, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial. Lancet Oncol. 2013;14:516–24.

John M, Pajak T, et al. Dose escalation in chemoradiation for anal cancer: preliminary results of RTOG 92-08. Cancer J Sci Am. 1996;2(4):205.

Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys. 2013;86:27–33.

Koh WJ, Chiu M, Stelzer KJ, et al. Femoral vessel depth and the implications for groin node radiation. Int J Radiat Oncol Biol Phys. 1993;27:969–74.

Martenson JA, Gunderson LL. External radiation therapy without chemotherapy in the management of anal cancer. Cancer. 1993;71(5):1736–40.

Meropol NJ, Niedzwiecki D, Shank B, et al. Induction therapy for poor-prognosis anal canal carcinoma: a phase II study of the Cancer and Leukemia Group B (CALGB 9281). J Clin Oncol. 2008;26(19):3229–34.

Milano MT, Jani AB, Farrey KJ, et al. Intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys. 2005;63:354–61.

Mistrangelo M, Pelosi E, Bellò M, et al. Role of positron emission tomography-computed tomography in the management of anal cancer. Int J RadiatOncolBiol Phys. 2012;84(1):66–72.

Moran M, Lund MW, Ahmad M, et al. Improved treatment of pelvis and inguinal nodes using modified segmental boost technique: dosimetric evaluation. Int J Radiat Oncol Biol Phys. 2004;59(5):1523–30.

Myerson RJ, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: an Radiation Therapy Oncology Group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys. 2008;74:824–30.

National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER). https://www.seer.cancer.gov/statfacts/html/anus.html. Accessed 5 Dec 2016.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Anal Carcinoma (Version 1.2017). https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf. Accessed 5 Dec 2016.

Ng Y, Ying Kin NY, Pigneux J, et al. Our experience of conservative treatment of anal cancal carcinoma combining external irradiation and interstitial implants. Int J Radiat Oncol Biol Phys. 1988;14:253–9.

Northover J, Glynne-Jones R, Sebag-Montefiore D, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). Br J Cancer. 2010;102:1123–8.

Oehler-Jänne C, Huguet F, Provencher S, et al. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. J Clin Oncol. 2008;26:2550–7.

Papagikos M, Crane CH, et al. Chemoradiation for adenocarcinoma of the anus. Int J Radiat Oncol Biol Phys. 2003;55:669–78.

Papillon J, Montbarbon JF. Epidermoid carcinoma of the anal canal. A series of 276 cases. Dis Colon Rectum. 1987;30:324–33.

Peiffert D, Bey P, Pernot M, et al. Conservative treatment by irradiation of epidermoid carcinomas of the anal margin. Int J Radiat Oncol Biol Phys. 1997;39:57–66.

Peiffert D, Tournier-Rangeard L, Gérard JP, et al. Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. J Clin Oncol. 2012;30:1941–8.

Peixoto RD, Wan DD, Schellenberg D, et al. A comparison between 5-fluorouracil/mitomycin and capecitabine/mitomycin in combination with radiation for anal cancer. J Gastrointest Oncol. 2016;7:665–72.

Salama JK, Mell LK, Schomas DA, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: a multicenter experience. J Clin Oncol. 2007;29:4851–6.

Sandhu APS, Symonds RP, et al. Interstitial Iridium-192 implantation combined with external radiotherapy in anal cancer: ten yrs experience. Int J Radiat Oncol Biol Phys. 1998;40:575–81.

Schwarz JK, Siegel BA, Dehdashti F, et al. Tumor response and survival predicted by post-therapy FDG-PET/CT in anal cancer. Int J Radiat Oncol Biol Phys. 2008;71(1):180–6.

Trautmann TG, Zuger JH. Positron emission tomography for pretreatment staging and post-treatment evaluation in cancer of the anal canal. Mol Imaging Biol. 2005;7:309–13.

UKCCCR Anal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomized trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. Lancet. 1996;348:1049–54.

Widder J, Kastenberger R, Fercher E, et al. Radiation dose associated with local control in advanced anal cancer: retrospective analysis of 129 patients. Radiother Oncol. 2008;87(3):367–75.

Winton Ed, Heriot AG, Ng M, et al.The impact of 18-fluorodeoxyglucose positron emission tomography on the staging, management and outcome of anal cancer. Br J Cancer. 2009;100(5):693–700.

White EC, Goldman K, Aleshin A, et al. Chemoradiotherapy for squamous cell carcinoma of the anal canal: comparison of one versus two cyclesmitomycin-C. Radiother Oncol. 2015;117(2):240–5.

White EC, Khodayari B, Erickson KT, et al. Comparison of toxicity and treatment outcomes in HIV-positive versus HIV-negative patients with squamous cell carcinoma of the anal canal. Am J Clin Oncol. 2017;40(4):386–92.

Wo JY, Hong TS, Callister MD, et al. Anal carcinoma. In: Gunderson LL, Tepper JE, editors. Clinical radiation oncology. 4th ed. Philadelphia: Churchill Livingstone; 2015. p. 1019–34.e4.

Yeung R, McConnell Y, Roxin G, et al. One compared with two cycles of mitomycin C in chemoradiotherapy for anal cancer: analysis of outcomes and toxicity. Curr Oncol. 2014;21(3):e449–56. https://doi.org/10.3747/co.21.1903.