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Anal Cancer

Tushar Samdani and Garrett M. Nash

Key Concepts

- Chemoradiotherapy (CRT) is the primary treatment for patient with anal squamous cell carcinoma (mitomycin+5-FU+radiotherapy). The dosage of radiotherapy varies based on the size of the tumor and presence of lymph node involvement.
- **Surgery** (local excision) can be used to remove some small squamous cell carcinomas (usually measuring <1 cm or ½ in.) that do not involve the anal sphincter musculature.
- Following primary treatment with chemoradiotherapy, patients are evaluated with repeat physical examination of the anal area at approximately 8–12 weeks after completion of treatment, and then at 6- to 8-week intervals until resolution of any suspicious findings. Patients with persistent but nonprogressive disease may be followed up to 6 months after chemoradiotherapy for assessment of complete remission.
- Patients with progressive disease or recurrence after chemoradiotherapy are considered for salvage abdominoperineal resection (APR).
- Dosage of radiotherapy and chemotherapy may be modified based on CD4 count and blood count in immunocompromised patients.
- Anal melanoma is very aggressive, and is generally treated with local excision (LE).
- Anal adenocarcinoma is treated with APR and usually with neoadjuvant chemoradiotherapy, as in treatment for distal rectal adenocarcinoma.

Introduction

Anal cancer accounts for only a small percentage (4 %) of all cancers of the lower alimentary tract [1]. Approximately 0.2 % of men and women will be diagnosed with anal cancer at some point during their lifetime, based on 2009–2011

data. As per the American Cancer Society: Cancer Facts and Figures 2015, estimated new cases of anal cancer in the USA will be approximately 7270 in 2015; the estimated deaths from anal cancer in 2015 will be approximately 1010 (Tables 21-1 and 21-2) [2].

Risk Factors

The incidence of anal cancer appears to have risen over the last few years. This may be due to a higher incidence in persons engaging in receptive anal intercourse, or having multiple sexual partners. These practices increase the likelihood of infection with human papillomavirus (HPV), which is strongly associated with premalignant anal squamous intraepithelial lesions and the development of anal squamous cell cancer [3].

Risk factors associated with anal cancer:

- Sexually transmitted disease.
- Anal receptive intercourse.
- More than ten sexual partners.
- The presence of precancerous anal lesions such as condylomas or high-grade anal intraepithelial neoplasia, and cervical, vulvar, or vaginal cancers.
- Immunosuppression secondary to solid organ transplantation or chronic glucocorticoid therapy.
- HIV seropositivity, low CD4 count.
- Smoking.

Anatomy of the Anal Canal

Complete knowledge of anatomical landmarks and histological features of the anal canal is crucial in order to understand the origins of different types of anal neoplasms and determine their management (see Chap. 1). The surgical anal canal extends from the puborectal sling to the intersphincteric groove (the white line of Hilton). It is histologically divided into two unequal

sections (the upper two-thirds and lower one-third) by the dentate line (pectinate line), which is the site of fusion of the proctodeum below and the post-allantoic gut above (Fig. 21-1).

TABLE 21-1. WHO histological classification of malignant tumors of the anal canal

<ul style="list-style-type: none"> • Carcinoma <ul style="list-style-type: none"> – Squamous cell carcinoma – Adenocarcinoma <ul style="list-style-type: none"> Rectal type Of anal glands Within anorectal fistula – Mucinous adenocarcinoma – Small-cell carcinoma – Undifferentiated carcinoma – Others 	<ul style="list-style-type: none"> • Carcinoid tumor • Malignant melanoma • Nonepithelial tumors • Secondary tumors
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WHO World Health Organization
Source: AJCC Cancer Staging Manual plus EZTNM, 6th edition

- The anal canal just above the dentate line (for about 1–2 cm) is known as the anal transition zone (ATZ). Beyond this transition zone, the [surgical] anal canal is lined with columnar epithelium. Its lower ends are joined together by folds of mucus membranes known as anal valves. The upper two-thirds of the anal canal are supplied by the **superior rectal artery**, which is a branch of the **inferior mesenteric artery**.
- The lower one-third of the anal canal is lined by **stratified squamous epithelium** that blends with the skin. The lower one-third is supplied by the **inferior rectal artery**, which is a branch of the **internal pudendal artery**.

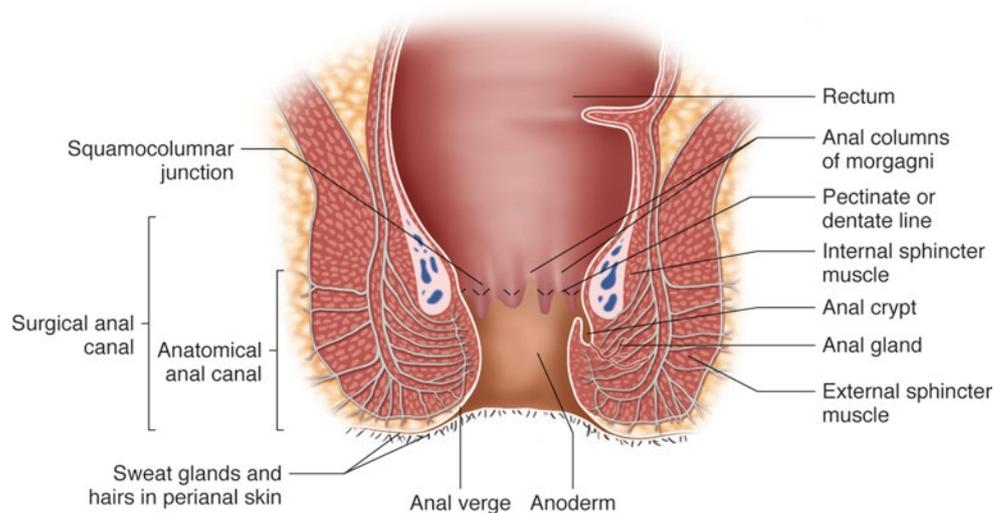
The anal margin extends laterally from the intersphincteric groove to a radius of approximately 5 cm, and is characterized by keratinized stratified squamous epithelium. The intersphincteric groove indicates the junction between keratinized

TABLE 21-2. TNM classification for anal cancer

	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 HISL), 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, bladder (direct invasion of rectal wall, perirectal skin, subcutaneous tissue, or sphincter muscle is not classified as T4)
	Regional lymph node (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 unilateral inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes
	Distant metastases (M)
M0	No distant metastasis
M1	Distant metastasis

Source: AJCC Cancer Staging Manual plus EZTNM, 6th edition

FIGURE 21-1. Anal canal anatomy.



stratified squamous epithelium and the non-keratinized stratified squamous epithelium [4, 5]. Anal squamous cell carcinoma commonly arises from either squamous epithelium of the lower part of the anal canal. Rarely does it arise from the ATZ. On the other hand, histological variants of SCC, such as transitional, basaloid, and cloacogenic variants, arise from ATZ. Adenocarcinoma of the anal canal originates from the colorectal zone in the upper portion of the anal canal or from the glandular cells of the ATZ mucosa whereas anal margin squamous cell carcinoma arises lateral to intersphincteric groove. Of note, histological features of anal melanoma are similar to cutaneous melanoma arising from basal cell layer of stratified squamous epithelium.

Some authors have simplified classification of the anal region, dividing it into three easily identifiable regions based on visual examination [6].

Intra-anal lesions are lesions that cannot be visualized on perianal examination until gentle traction is applied on the buttocks.

Perianal lesions are completely visible, without traction on the buttocks, extending within 5 cm of the anal margin.

Skin lesions fall outside the 5 cm radius from the anal opening. Hence, some have classified this into three distinct regions: intra-anal (visualized with gentle traction on the buttocks), perianal, and skin tumors (beyond a 5 cm radius from the anal opening).

Squamous Cell Carcinoma of the Anal Canal

In the USA, the median age at diagnosis of squamous cell carcinoma of the anal canal (SCAC) is 60–65 years, and there is slightly higher incidence in women [3, 7].

Symptoms

Approximately one-third of patients with SCAC are asymptomatic, or have nonspecific symptoms on presentation. Clinical manifestations of anal canal tumors are mainly related to tumor size and extent of infiltration. The most common symptom is rectal bleeding, which is seen in approximately 45 % of cases, followed by anal pain or sensation of anal mass, seen in 30 % [8, 9]. Other symptoms include anal pruritus, discomfort in sitting, a change in bowel habits, incontinence (due to tumor infiltration into the sphincter), discharge, bleeding, fissure, or fistula. Diagnosis may be delayed because initial symptoms are nonspecific, and the anal canal is often a difficult location for examination. Moreover, because anal cancer is rare, many primary care practitioners have little experience in diagnosing it.

The clinical diagnosis of an anal tumor should be confirmed by histologic examination. A forceps or needle biopsy may be done to establish the diagnosis. It is very important to

document an exact description of location and appearance of the biopsy site, as this will help in planning radiation fields and posttreatment surveillance. If the lesion is large or involves the sphincter, an excisional biopsy is inadvisable because the subsequent wound healing may delay optimal chemoradiation treatment (CRT). Enlarged lymph nodes may be excised or biopsied with needle aspiration, under radiological guidance [3, 10].

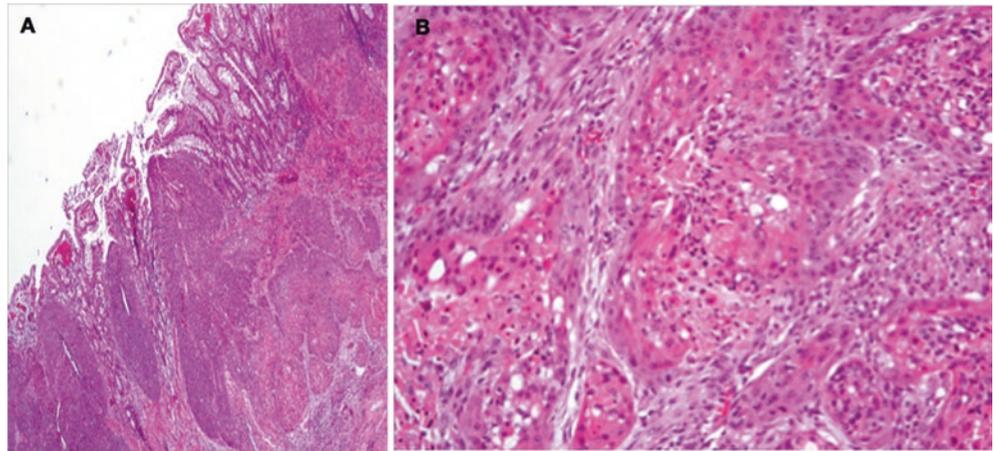
Examination

Detailed physical examination is very important, as a lesion in the anal canal may be easily missed on cursory exam. Physical examination includes inspection to assess for tumor location, size, and extent, and direct visualization of the mass via anoscopy, rigid proctoscopy, or flexible sigmoidoscopy, which may be retroflexed in the rectum. Digital rectal exam should be done to assess sphincter function, and relation of tumor to the sphincter (Figs. 21-2 and 21-3a, b). The tumor may present as a small ulcer or fissure with slightly exophytic and indurated margins, and irregular thickening of the anal canal. If a thorough anal canal examination is not possible due to significant perianal pain or spasm, examination under anesthesia may be done to assess the tumor. Along with local examination of the anal canal, groin lymph nodes (LNs) should be examined to rule out involvement. It has been traditionally recommended that patients with an anal cancer should undergo colonoscopy to evaluate for synchronous colorectal lesions [3, 10]; however, it should be noted that there are no definitive data demonstrating an association between SCAC and adenomatous neoplasia of the colon or rectum. In women



FIGURE 21-2. Anal cancer.

FIGURE 21-3. Anal squamous cell carcinoma invading rectal mucosa. (a) Low power view; (b) higher power view.



with anal cancer, a pelvic examination may be performed to determine the extent of invasion of an anterior lesion into the posterior vagina. Female patients should have routine gynecologic evaluations, given the risk of other HPV-associated diseases such as cervical dysplasia (Fig. 21-4) [11].

Investigation

Treatment of anal cancer is based on the stage of the tumor. Therefore, a comprehensive physical exam should be complemented with imaging, to determine the possibility of locoregional or systemic spread.

Investigation of Choice

- Locoregional staging: MRI of the rectum/pelvis, with or without endoscopic ultrasound.
- Distant metastasis: CT scan of the chest, abdomen, or pelvis; or FDG PET/CT.

MRI of the Rectum/Pelvis

MRI provides high-resolution, multiplanar information regarding the location, size, circumferential and craniocaudal extent of the primary tumor, and involvement of adjacent structures, including the sphincter (Fig. 21-5). The sensitivity of MRI in identifying SCAC has been reported to approach 90–100 % [12]. Along with evaluation of the primary tumor, MRI can be used to assess involvement of the pelvis and inguinal LNs. MRI determines LN involvement based on various criteria such as LN size, loss of the normal bean-shaped morphology and fatty hilum, internal T1 and T2 signal heterogeneity with central necrosis, and inhomogeneous enhancement. Short-axis threshold values of 8 mm, 5 mm, and 10 mm have been suggested for pelvic, perirectal, and inguinal LNs, respectively [13, 14].

Transanal Endoscopic Ultrasound

Transanal endoscopic ultrasound may be used to assess local staging of anal cancer (Fig. 21-6). This modality may be

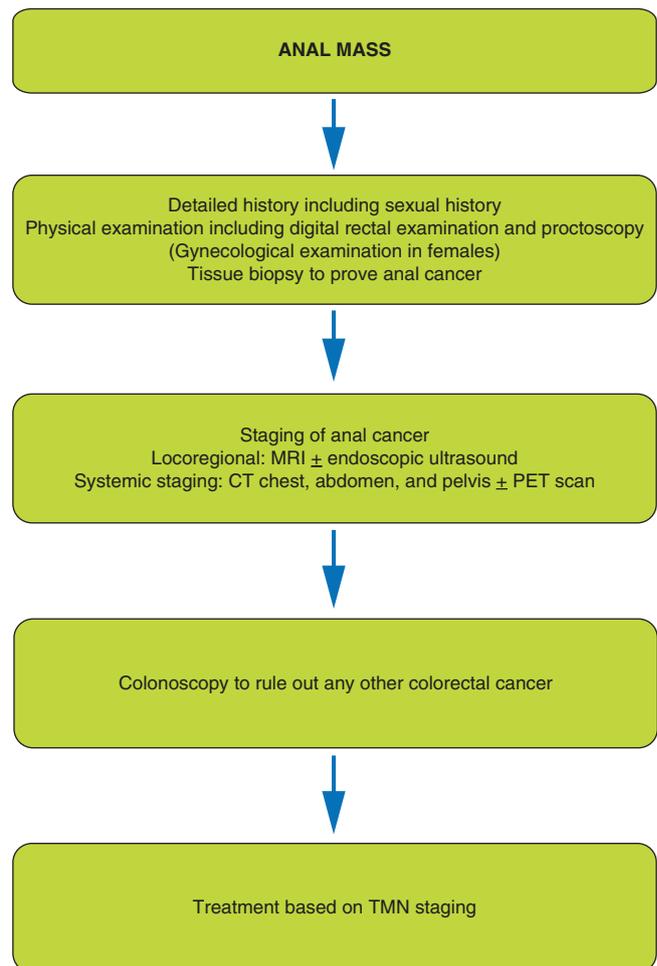


FIGURE 21-4. Algorithm for anal mass evaluation and work-up.

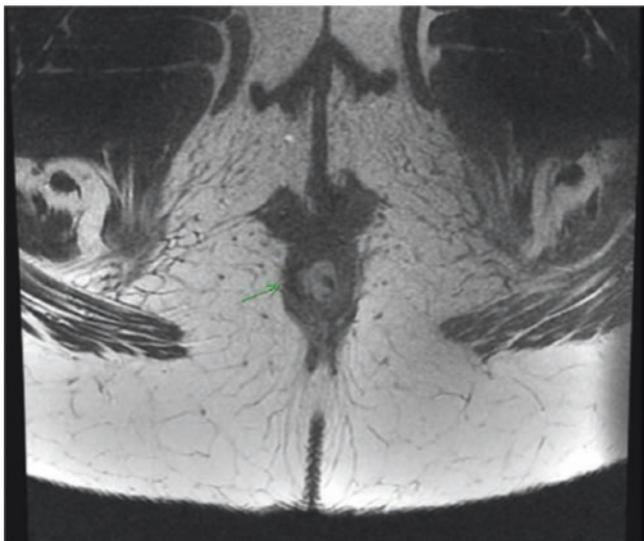


FIGURE 21-5. Anal cancer: pretreatment MRI T2 oblique, suspicion for focal tumor invasion into the right lateral internal anal sphincter (green arrow).

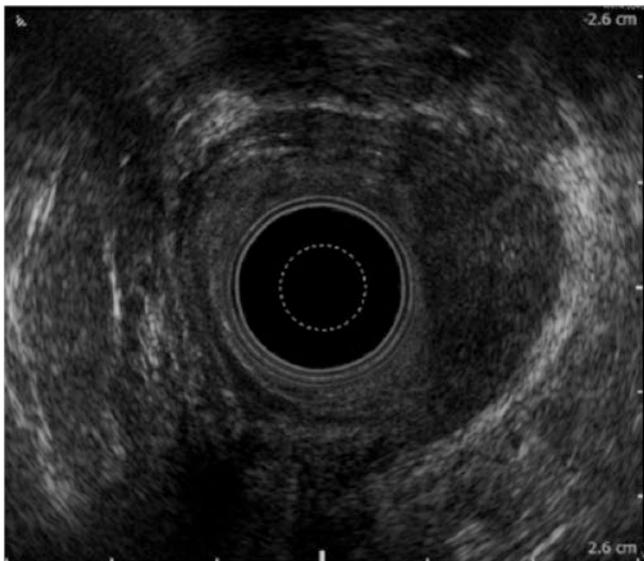


FIGURE 21-6. Transanal endoscopic ultrasound can be used to assess local staging of anal cancer.

superior to MRI in evaluating small superficial tumors [15]. However, the limitations of transanal endoscopic ultrasound include an inability to ascertain involvement of the proximal pelvis or groin LNs, and it may be difficult to use in assessing a stenotic or painful anal lesion. Lastly, its accuracy is highly operator dependent.

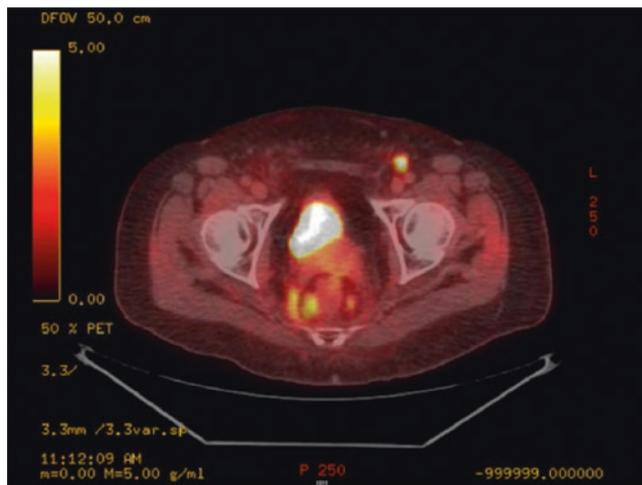


FIGURE 21-7. Anal cancer: left inguinal adenopathy and mesorectal adenopathy seen on PET/CT.

CT Scan of Chest, Abdomen, and Pelvis with IV Contrast

CT scanning of the chest, abdomen, and pelvis is used to identify possible metastatic disease [16].

FDG PET/CT

Approximately 98 % of anal tumors are FDG avid. Hence, FDG PET/CT has assumed an increasing role in the staging and assessment of treatment response [17]. PET/CT may be used to evaluate primary tumor size, LN status, and distant metastasis, and may help in planning radiation therapy by clearly defining the site of metabolically active tumor. It may also be useful in posttreatment surveillance (Fig. 21-7). PET/CT is indicated for node-positive and T2–T4 anal canal and anal margin cancer to verify staging before treatment. PET/CT has become part of the standard work-up, particularly for evaluating LNs that appear ambiguous on CT, to aid in management, and to serve as a pretreatment baseline. PET/CT has demonstrated a sensitivity of >90 % and a specificity of 80 %. PET/CT has been shown to alter the staging of anal carcinoma in approximately 20 % of cases, and treatment intent in approximately 3–5 %. The main impact of PET/CT on therapy stems from its superiority in detecting involved pelvic or inguinal nodes, prompting the radiation oncologist to include these in the RT field [18, 19, 20]. PET/CT has also impacted posttreatment management in 18 % of anal cancer patients (Fig. 21-8). It may confirm persistence of disease or local recurrence, and influence decision making regarding the use of chemotherapy in patients with metastatic disease [3, 21]. The high negative predictive value of PET-CT may dictate avoidance of unnecessary biopsy after chemoradiotherapy.

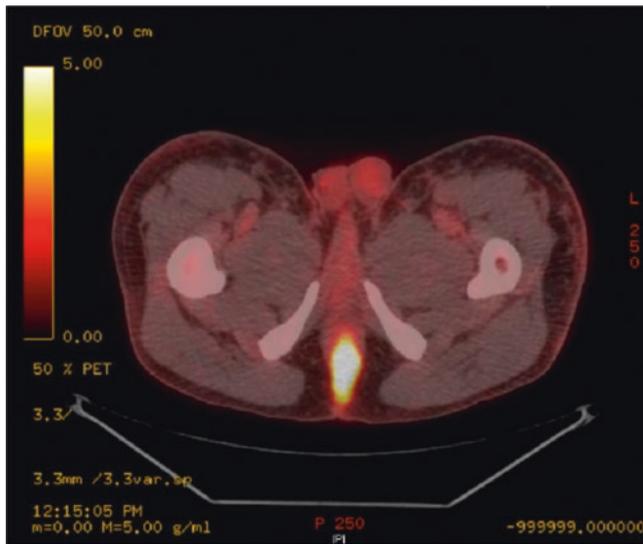


FIGURE 21-8. Anal cancer: pretreatment SUV = 18.1.

Summary of the Initial Work-Up of Anal Cancer

1. In the setting of a T1 tumor, after a thorough physical exam, MRI of the rectum/pelvis or transanal endoscopic ultrasound may be used for additional local staging. In the absence of nodal disease, a CT scan of the chest and abdomen may be used for distant staging.
2. In the setting of a T2–T4 tumor or node-positive anal cancer, PET/CT may be used in addition to MRI or transanal endoscopic ultrasound to screen for distant metastases, to assess response to CRT, and as a tool in subsequent cancer surveillance.

Treatment of Anal Cancer

Until three decades ago, abdominoperineal resection (APR) of the rectosigmoid and anus was the preferred surgical procedure for most cancers of the anal canal. This radical operation was performed in order to achieve adequate margins of resection [8]. Local resection was done for smaller lesions. Surgical treatment alone was associated with local failure in 27–47 % of cases [22]. Early tumors could be cured by APR, with 5-year survival rates of 50–70 %. However, APR entails a permanent intestinal stoma and is associated with substantial morbidity. Over the last three decades, there has been significant change in the management of epidermoid anal carcinomas, with more patients undergoing nonsurgical treatment.

Evolution in the Management of Anal Cancer (Fig. 21-9)

Radiotherapy

Dosage

Dosage of RT varies based on the size of the tumor and presence of suspected LN involvement. In general, larger can-

cers require higher doses of radiation. The database of the RTOG 9811 trial suggests that size >5 cm is a poor prognostic factor [29]. Doses in the range of 30 Gy, with concurrent mitomycin C and 5-FU, have been shown to control small tumors (CCR rate of 86 %) and subclinical disease effectively. The preliminary results of the ACCORD-03 trial compared 45 Gy in 25 patients plus a 15 Gy boost with a higher dose, but found no benefit in CFS, and higher toxicity, at >59 Gy [30]. Similar results were reported in the RTOG 92-08 trial [31].

Patients with SCAC receive a minimum RT dose of 45 Gy to the primary cancer. The recommended initial dose is 30.6 Gy to the pelvis, anus, perineum, and inguinal nodes. Following initial dose of 30.6 Gy, field of radiation should be reduced from L5–S1 junction to bottom of sacroiliac joints. In patients without nodal metastasis, inguinal nodes are not included in radiation field after 36 Gy. Patients with disease clinically staged as node positive or T3–T4 or with T2 residual disease after 45 Gy should receive an additional boost of 9–14 Gy [28].

Field of Radiotherapy

Multi-field techniques with supervoltage radiation (photon energy >6 mV) are used to deliver a minimum dose of 45 Gy in 1.8 Gy fractions (25 fractions over 5 weeks) to the primary cancer. The RTOG panel established three elective clinical target volume (CTV) areas: CTVa targets the perirectal, presacral, and internal iliac regions; CTVb targets the iliac LNs; and CTVc targets the inguinal LNs; inclusion of all is recommended in RT for anal cancer. The superior field border includes the rectosigmoid junction (L5–S1 junction); the inferior border includes the anus, with a minimum 2.5 cm margin around the anus and tumor; the lateral border includes the lateral inguinal nodes, based on imaging or body landmarks. An attempt should be made to reduce the dose to the femoral heads [32, 33] (Fig. 21-10).

Side Effects [34–36]

The short-term side effects of RT include:

- Dermatitis.
- Temporary anal swelling and pain.
- Frequency and urgency in defecation.
- Nausea, weakness.
- Vaginal discomfort and discharge.

These side effects often improve after radiation stops.

Long-term side effects include:

- Anal stenosis.
- Pelvic fracture.
- Chronic radiation proctitis.
- Vaginal stenosis (female patients should be encouraged to use a vaginal dilator).

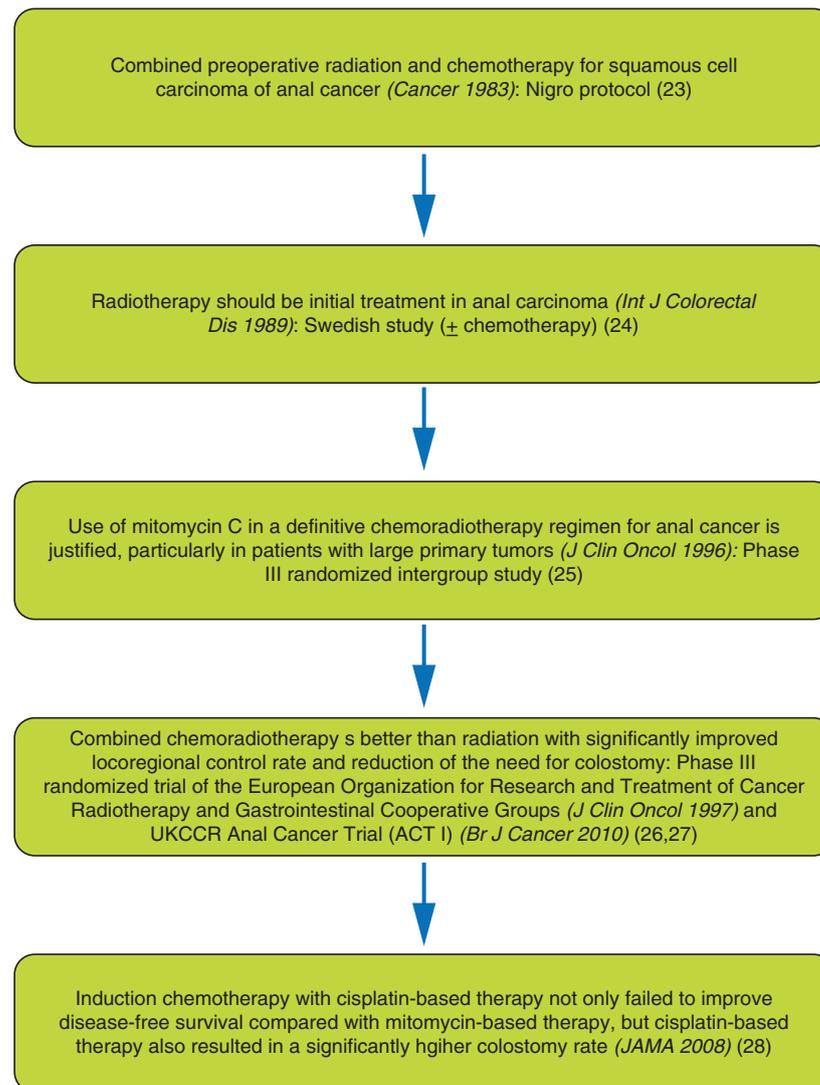


FIGURE 21-9. Evolution of management of anal cancer (algorithm).

- Radiation may affect fertility in both women and men (patients should be informed about sperm and ovarian tissue banking).
- Dyspareunia.
- Lymphedema.

Special Considerations

Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) utilizes detailed beam shaping, enabling precision in targeting tumor and sparing normal tissue. Compared with conventional

three-dimensional (3D) CRT (Figs. 21-11 and 21-12), IMRT may spare the perineal skin, external genitalia, and bladder, reducing toxicity to surrounding anatomic structures, and preventing toxicity-related delay in completion of treatment—thereby improving treatment outcomes [3, 72, 73]. In a retrospective study from Memorial Sloan Kettering Cancer Center of 221 patients with anal SCC treated with CRT between 1991 and 2007, 44 patients received IMRT and 177 received 3DCRT. The 2-year local recurrence-free survival, distant metastasis-free survival, colostomy-free survival, and overall survival were 88 %, 83 %, 96 %, and 92 %, respectively, in the IMRT group, and 81 %, 88 %, 91 %, and 89 %, respectively, in the 3DCRT group, demonstrating no significant difference between the groups [74].

FIGURE 21-10. External beam radiotherapy.

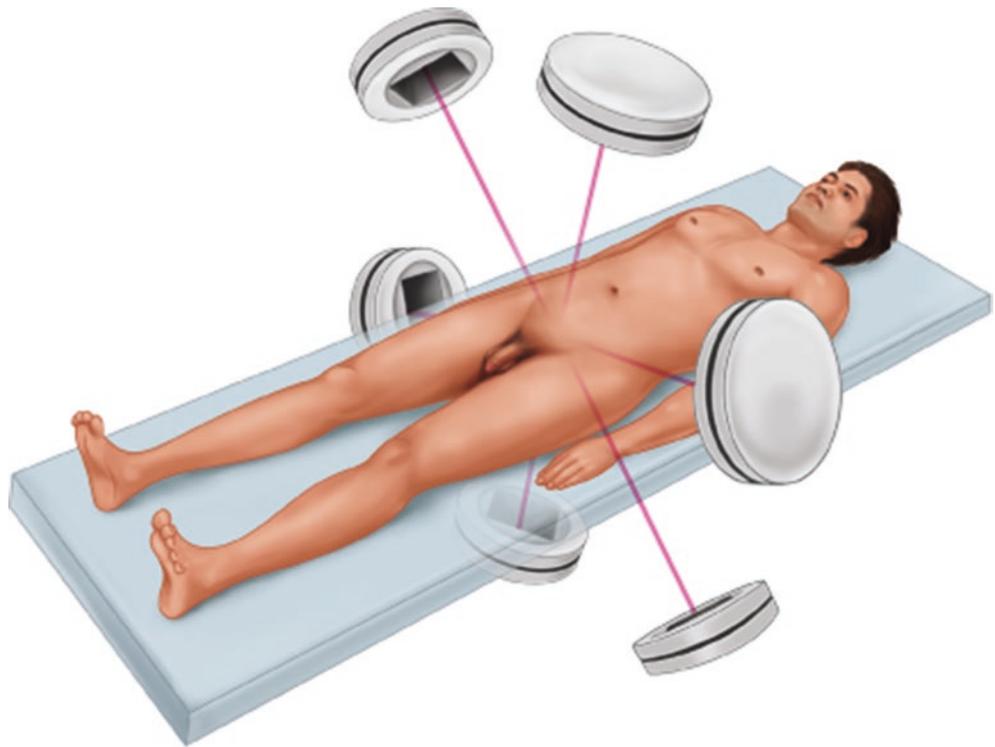


FIGURE 21-11. T1N0 anal SCC—IMRT: 4500cGy in 180cGy fractions to pelvic nodes (orange); 5000cGy in 200cGy fractions to primary tumor (red).

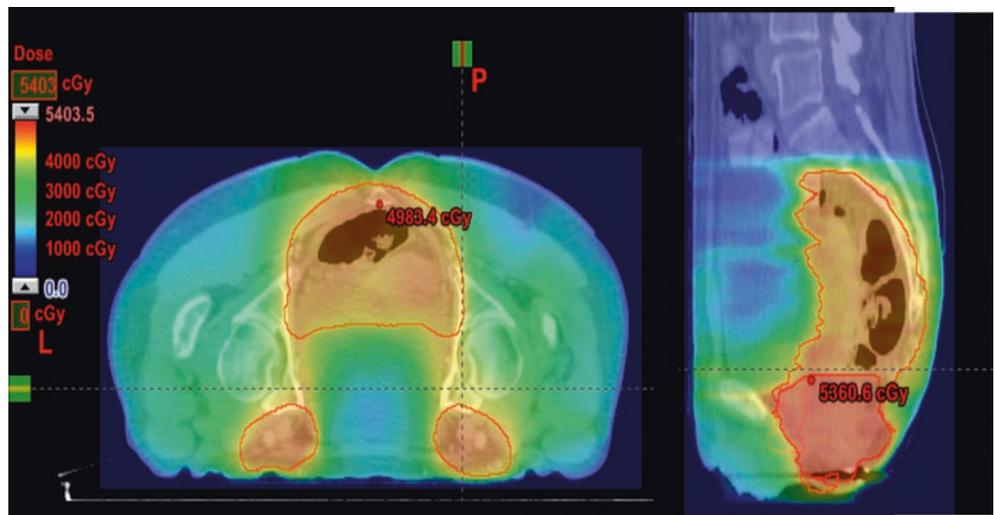
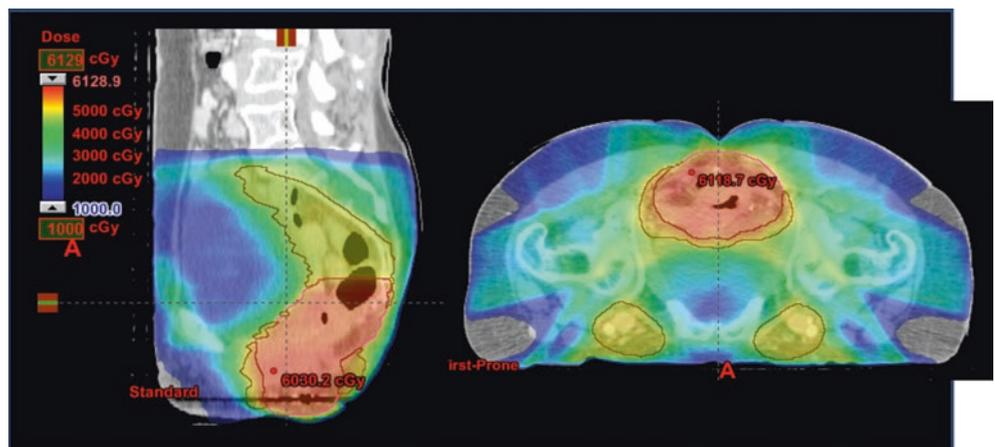


FIGURE 21-12. T3N1 anal SCC—IMRT: 4500cGy in 180cGy fractions to pelvic nodes (brown); 5000cGy in 200cGy fractions to primary tumor (red); additional boost of 600cGy in 200cGy fractions to the primary tumor (red).



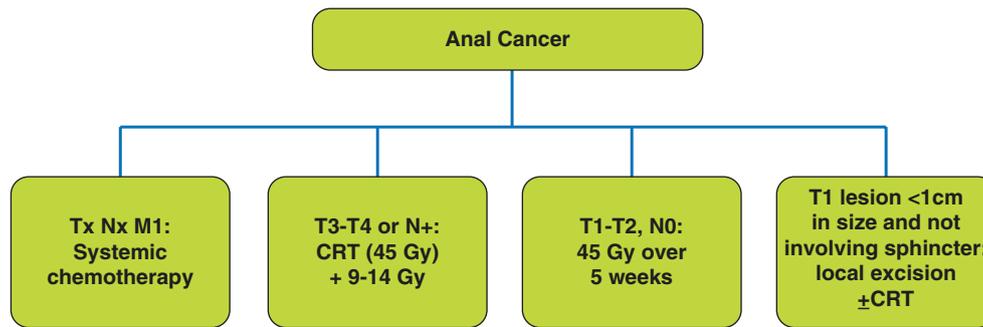


FIGURE 21-13. Anal cancer treatment.

Current Management Protocol (Fig. 21-13)

Limited Localized Disease: Stages I–III (Any T, Any N, M0)

LE can be used to remove some small tumors (usually measuring <1 cm or ½ in.) that do not involve the sphincter. In some cases, this may be followed with chemotherapy and RT, which is especially recommended in the setting of a positive margin. The standard treatment for anal cancers that cannot be removed without harming the anal sphincter is RT combined with chemotherapy (CRT).

Current primary recommendations for the treatment of non-metastatic anal cancer include CRT; commonly used therapeutic drugs include 5-FU and mitomycin.

Mitomycin + 5-FU + RT

This regimen consists of 5-FU 1000 mg/m²/day delivered via IV continuous infusion on days 1–4 and 29–32 (maximum daily dose of 5-FU=2000 mg/day), plus mitomycin 10 mg/m² via IV bolus on days 1 and 29 (maximum=20 mg per dose) [28]. RT may be included in all stages of disease, with a minimum 45 Gy delivered over 5 weeks. Additional RT of 9–14 Gy may be considered for patients with T3, T4, or node-positive disease, or those with residual disease after an initial dose of 45 Gy [37, 38].

Metastatic Disease (Stage IV): Any T, Any N, M1

Metastatic disease is commonly treated with cisplatin-based (5-FU + cisplatin) chemotherapy.

Cisplatin + 5-FU

The regimen consists of 5-FU 1000 mg/m²/day via IV continuous infusion on days 1–5, plus cisplatin 100 mg/m² via IV on day 2, repeated every 28 days [39]. Patients with meta-

static disease receiving systemic chemotherapy have approximate survival rates of 60 % at 1 year and 32 % at 5 years, respectively [8, 39].

In some patients with metastatic disease, surgical intervention may be required for relief of symptoms such as pain, bleeding, or fecal incontinence.

Prognostic Factors

The size of the primary tumor and the presence of nodal or distant metastases are the principal determinates of outcome. Patients with de novo tumors >5 cm are at significantly increased risk of requiring an APR with permanent colostomy, and such tumors are associated with inferior disease-free and overall survival. Male gender and HIV-positive status may portend an unfavorable long-term outcome [8, 40, 41].

Evaluation of Treatment Response

The mainstay in assessment of tumor response is clinical follow-up. Patients are evaluated by repeat physical examination of the anal area at approximately 8–12 weeks after completion of chemoradiotherapy, and at 6- to 8-week intervals until resolution of any suspicious findings. Based on evaluation, patients are classified with respect to remission, as follows:

- *Persistent disease:* Patients with persistent disease but no progression are followed closely to see if further regression occurs. Based on the ACT II study, patients with persistent but nonprogressive disease may be followed up to 6 months after chemoradiotherapy, until determination of complete remission.
- *Complete remission:* Patients with complete remission should undergo evaluation every 3–6 months for 5 years. This should include digital rectal examination, endoscopic examination, and examination of the groin. CT

scan of the chest, abdomen, and pelvis, or PET/CT, is performed annually for 3 years in patients with slow disease regression, and those who initially had locally advanced disease (T3/T4) or node-positive cancer.

- *Progressive or persistent disease at 6 months:* If the patient has persistent disease at 6 months, or progressive disease develops in the meantime, biopsy may be done to confirm cancer. Biopsy is recommended earlier in the setting of tumor mass progression or unsatisfactory response to treatment [3, 8, 10, 36]. However, unnecessary biopsy should be avoided to minimize the risk of soft tissue infections, tissue necrosis, or impairment of anal function.

Salvage Treatment

Approximately 10–30 % of patients have persistent or recurrent disease after initial CRT. Risk factors associated with failure of initial treatment include:

- HIV-positive status.
- High T and N stage at original presentation.
- Interruption of treatment during CRT.

Progressive disease is biopsied and restaged before salvage treatment [42–44]. Some studies recommend an additional RT of 9 Gy, rather than resorting to APR immediately. However, salvage surgery is generally recommended for persistent anal cancer. Surgical treatment is based on the extent of the persisting tumor. Patients with very limited residual tumor may be able to undergo LE. Others with larger residual disease should undergo salvage APR. Salvage APR is associated with 5-year locoregional control in 30–77 % of patients [43, 45, 46]; overall survival at 5 years ranges from 30 to 60 %. Wound complications are common, and may be seen in as many as 80 % of patients who undergo salvage APR after CRT. In order to reduce wound complications, muscle flap reconstruction of the perineum may be considered [47].

Treatment of Recurrent Anal Cancer

If anal cancer recurs locally after initial treatment, restaging is performed to rule out systemic metastasis; this includes CT chest, abdomen, and pelvis or PET/CT based on institutional preference. Local recurrence after CRT is commonly managed with salvage APR. Isolated recurrence in an inguinal node may be treated with RT to the groin, with or without chemotherapy, if there is no history of previous RT to the groin. If isolated recurrence develops in an inguinal node despite previous RT, inguinal node dissection may be performed without an APR [25, 48] (Table 21-3).

Treatment of HIV-Positive Patients

HIV is associated with a markedly increased incidence of anal cancer, most likely due to immunosuppression, and

HPV infection secondary to anal-receptive intercourse [49, 50]. Initial treatment of anal cancer is CRT; however, certain factors such as a patient's CD4 count play a role in modifying the dose of RT; doses range from 32 to 63 Gy; chemotherapy may be delivered in conventional dose regimens, including 5-FU combined with mitomycin or cisplatin. Studies have shown that patients with CD4 >200 have acceptable treatment-related toxicity and may achieve very good disease control. On the other hand, patients with CD4 <200 have a markedly higher incidence of treatment-related morbidities. However, this is not associated with decreased overall survival. The chemotherapy dose may need to be altered, based on the patient's blood counts.

Mitomycin+5-FU: If nadir WBC count is <2400 but >1000, or if nadir platelet count is >50,000 but <85,000, the second dose of mitomycin is reduced to 7.5 mg/m², from 10 mg/m².

If nadir WBC count is <1000 or if platelet count is <50,000, the second dose of mitomycin is reduced to 5 mg/m², from 10 mg/m².

On day 28, if the WBC count is <2400 or the platelet count is <85,000, chemotherapy is delayed for 1 week [25].

There is a higher incidence of in situ anal cancer among homosexual and bisexual men, irrespective of their HIV status. Data suggest that anal cytology screening in these men every 2–3 years may be cost effective and yield benefits in life expectancy [51].

Anal Melanoma

Anal melanoma represents 1–4 % of all anorectal malignancies. It is the third most common site of melanoma, after the skin and retina, accounting for less than 1 % of all melanomas [52, 53]. It is most commonly seen in females, and the mean age of presentation is 60 years [54]. These tumors arise from the transitional epithelium of the anal canal, the anoderm, or the mucocutaneous junction.

Symptoms

The most common symptom of anal melanoma is bleeding per rectum. However, as in the setting of any other anal lesion the patient may present with pain, change in bowel habits, or tenesmus. Early lesions may be mistaken as thrombosed hemorrhoids [53].

Physical Examination

A thorough physical exam, including assessment of the groin, should be done. Anal melanoma may be pigmented, and either polypoid or ulcerated, with raised edges. Satellite lesions may also be present.

Histopathological Diagnosis

The features of anal melanoma resemble those of cutaneous melanomas. The majority shows a junctional component adjacent to the invasive tumor, which proves that the lesion is primary in nature. The tumor cell expresses S-100, HMB-45, and Melan A. Perineural invasion is an important prognostic factor (Figs. 21-14 and 21-15) [5, 55].

Treatment

The overall prognosis of anal melanoma is dismal, with a 10- to 19-month survival after diagnosis [56, 57]. Melanoma does not respond well to chemotherapy or RT; thus, **surgery** is the principal treatment when disease is localized. The extent of surgical resection is a matter of debate. Anal melanoma is very aggressive, and up to 35 % of patients initially pres-

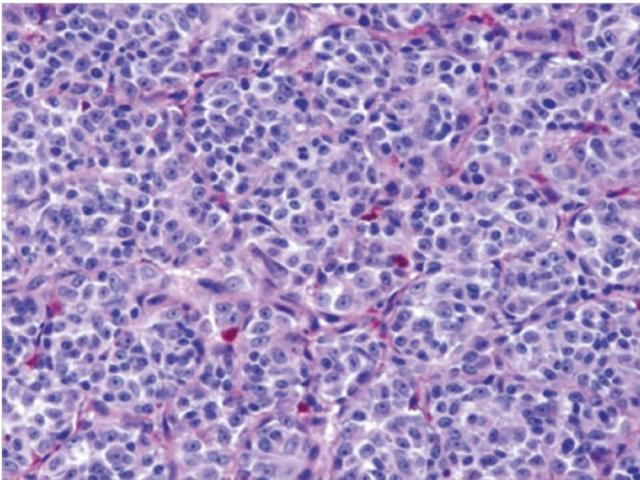


FIGURE 21-14. Anal melanoma with epithelioid morphology.

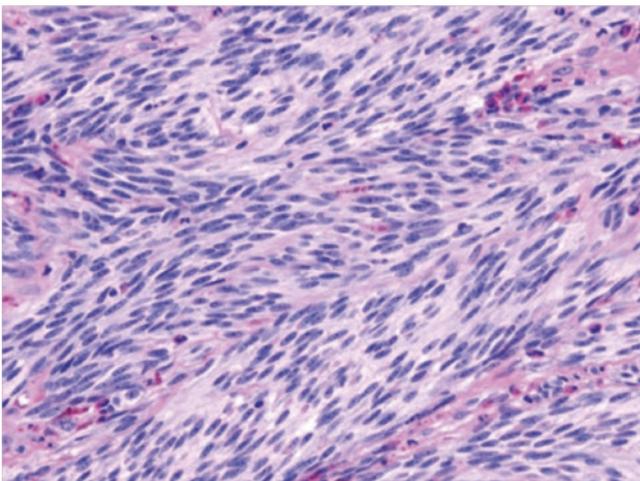


FIGURE 21-15. Anal melanoma with spindle cell morphology.

ent with metastatic disease. Patients with tumor >1 cm are unlikely to be cured by any type of treatment. Some authors claim that APR is the first choice of treatment, particularly for patients with small tumors and no evidence of nodal metastasis. However, as most patients with anal melanoma die of distant metastasis, major operative intervention like abdominoperineal resection may not offer a survival advantage; hence some author prefer local excision as initial treatment for melanoma. Melanoma of anal canal is sometimes detected as an incidental tumor when local excision is done for hemorrhoids. If R0 resection is achieved during local excision for hemorrhoids, patients do not need further intervention and have shown acceptable cure rates. Palliative local excision should be considered for patients with local symptoms due to anal melanoma (Table 21-3) [53, 54, 58–62].

Anal Margin Squamous Cell Carcinoma

(Fig. 21-16)

The anal margin begins at the margin of hair-bearing perianal skin, extending onto the perianal skin for a 5 cm radius. SCC at the anal margin behaves like any other SCC of the skin, and drains into regional LNs such as the inguinal nodes. Anal margin SCC accounts for one-fourth to one-third of all anal SCC [63–65].

Epidemiology

SCC of the anal margin generally presents in patients between 65 and 75 years of age. There is no gender predilection [63, 64].

Symptoms

Like other anal canal tumors, diagnosis of SCC of the anal margin is delayed because of nonspecific symptoms, and difficult location. The most common presentation is a symptomatic mass in the perianal region, or persistent pruritus. Any person with persistent pruritus in the perianal region should be thoroughly examined for a perianal mass; suspicious lesions should be biopsied.

Examination

A thorough exam including assessment of the groins should be performed in patients with anal canal tumors. The relationship of tumor to the anal sphincter must be ascertained [68].

Staging

A CT of the chest, abdomen, and pelvis should be performed to rule out distant metastasis.

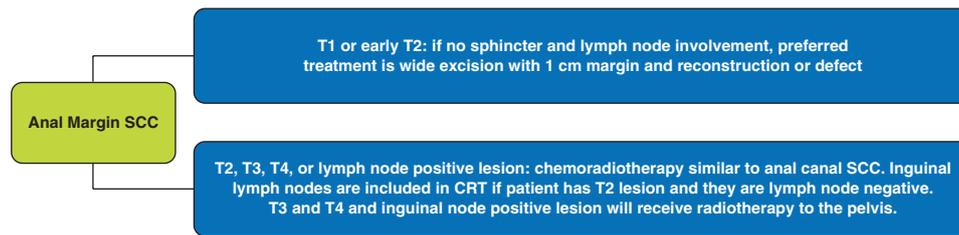


FIGURE 21-16. Algorithm for management of anal margin cancer.

Lymph node involvement: Studies have shown that the chance of LN involvement in a T1 lesion is extremely low. However, the chance of LN involvement in a T2 lesion is 24 %, and as high as 67 % in a T3 lesion [63].

Management (Fig. 21-6)

Management depends upon:

- Size of tumor.
- LN involvement.
- Sphincter involvement.

T1 N0 lesions: If there is no sphincter or LN involvement, the preferred treatment is wide excision with a 1 cm margin, when possible. The defect may be closed primarily; however, a large defect may require a V-Y advancement flap or skin graft. If the defect cannot be closed with an advancement flap, a pedicle flap may be necessary.

T2 N0 lesions: Early T2 lesions may be treated with surgery if no LN involvement is present; however, advanced lesions may be treated with CRT, as the chance of occult LN involvement is higher. Surgery to achieve a clear margin may result in an unacceptably large defect.

T3, T4, or LN-positive lesions: CRT protocols similar to those given for anal canal SCC are used. Inguinal LNs are included in CRT. T3 and T4 and inguinal node-positive lesions should receive radiotherapy (RT) to the pelvis [63–69].

Anal Adenocarcinoma

Primary mucinous adenocarcinoma of the anus is a rare malignancy, accounting for approximately 3 % of anal cancers. Most anal adenocarcinomas originate from the colorectal zone in the upper portion of the anal canal, or from the glandular cells of the ATZ mucosa.

Adenocarcinoma of the anal canal can be categorized based on origin (Fig. 21-17).

- **Colorectal-type adenocarcinoma:** Macroscopically and histologically, these lesions are indistinguishable from ordinary colorectal adenocarcinoma. However, they carry

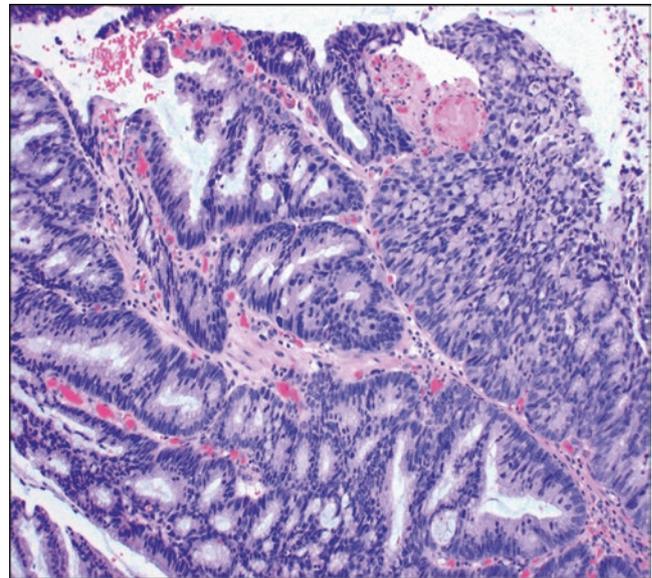


FIGURE 21-17 Superficial portion of an anal adenocarcinoma showing a low-grade gland forming component and a high-grade component with more solid growth.

a higher risk of nodal disease along the inguinal and femoral nodal chains. Immunohistology shows positivity for cytokeratin (CK) 20 and CDX2, and negativity for CK7, which is compatible with colorectal subtype anal adenocarcinoma.

- **Adenocarcinoma within an anorectal fistula:** Anorectal fistulae can be developmental or acquired due to inflammatory conditions such as Crohn's disease.
- **Adenocarcinoma of the anal glands:** This diagnosis is given if the tumor is primary to the anal canal and centered within the wall of the anorectal area, without a pre-existing fistula and without surface mucosa dysplasia, irrespective of the extent of mucin production. Anal gland adenocarcinoma is CK7 positive [5].

Clinical Features and Diagnosis

Anal adenocarcinoma presents with symptoms similar to those of any other anal mass. Thorough physical examination and biopsy are required to confirm the diagnosis.

TABLE 21-3. Types of anal cancer and preferred treatment

Type of anal cancer	Preferred treatment
Recurrent SCC	Local recurrences after treatment with radiation therapy and chemotherapy are treated with salvage APR
Anal melanoma	Local excision
Anal adenocarcinoma	Combined modality treatment including APR with adjuvant CRT to be optimal treatment

Staging

Staging is similar to that done for anal canal SCC.

Prognostic Factors

Prognostic factors in anal adenocarcinoma are [70]:

- T stage.
- N stage.
- Histologic grade.
- Treatment modality.

Management (Table 21-3)

Due to the rarity of this disease, very few studies have been published reporting on management of anal adenocarcinoma. Management options include LE, radical surgery (APR) with or without chemotherapy, or CRT. Historically, APR was the preferred treatment; however, with recent advances in CRT, a combined modality treatment including APR plus adjuvant CRT is considered optimal [70–77].

Biologicals

SCC of the anus commonly overexpresses EGFR. EGFR and KRAS mutations appear rare (76, 77). In a study by Lukan et al. the potential role of EGFR inhibition was supported by partial remission, minor remission, or no progression in five patients with wild-type KRAS anal cancer treated with either cetuximab as a single agent or cetuximab with irinotecan. Two patients with KRAS mutation did not respond to cetuximab, and had progression of disease. The authors concluded that cetuximab-based treatment can be used in patients with metastatic KRAS wild-type anal cancer after failure of, or as an alternative to, cisplatin/5-fluorouracil (FU)-based therapy [77].

Conclusions

Anal cancer is an uncommon gastrointestinal cancer. A thorough clinical examination and high index of suspicion are needed for diagnosis. Chemoradiotherapy, using 5-FU/mitomycin C with RT, is the mainstay of treatment for patients with anal SCC; early T1 tumors may be treated surgically, if

excision does not compromise sphincter function. Patients with metastatic anal SCC are most commonly treated with cisplatin-based chemotherapy. Improvements in current treatment modalities including IMRT, and biologics such as cetuximab, may provide more refined and successful treatments for patients with anal cancer.

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