So Now My Patient Has Squamous Cell Cancer: Diagnosis, Staging, and Treatment of Squamous Cell Carcinoma of the Anal Canal and Anal Margin

Cindy Kin, MD, MS, FACS¹

¹ Department of Surgery, Stanford University School of Medicine, Stanford, California

Address for correspondence Cindy Kin, MD, MS, FACS, Department of Surgery, Stanford University School of Medicine, 300 Pasteur Drive, H3680K, Stanford, CA 94305 (e-mail: cindykin@stanford.edu).

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Abstract

Keywords

- ▶ anal squamous cell carcinoma
- ▶ chemoradiation
- ▶ abdominoperineal resection
- ▶ wide local excision

Squamous cell carcinomas of the anal canal and the anal margin are rare malignancies that are increasing in incidence. Patients with these tumors often experience delayed treatment due to delay in diagnosis or misdiagnosis of the condition. Distinguishing between anal canal and anal margin tumors has implications for staging and treatment. Chemoradiation therapy is the mainstay of treatment for anal canal squamous cell, with abdominoperineal resection reserved for salvage treatment in cases of persistent or recurrent disease. Early anal margin squamous cell carcinoma can be treated with wide local excision, but more advanced tumors require a combination of chemoradiation therapy and surgical excision.

Squamous cell carcinoma of the anal canal and margin is a rare but growing problem. The Surveillance, Epidemiology, and End Results (SEER) Program data demonstrate that incidence rates of anal squamous cell cancer have increased over the last two decades by 2.2% per year among men and 2.3% per year among women. Between 2000 and 2011, the incidence rate for invasive anal squamous cell carcinoma among women is greater than that for men (15.5 vs. 10.7 per 1,000,000), with an overall relative risk of 1.29. This likely reflects the higher prevalence of anal infection with carcinogenic HPV among women. Overall, the non-Hispanic white population has the highest incidence ratio (15.4 per 1,000,000) followed by the black population (12.6 per 1,000,000). However, black men have higher rates of invasive anal cancer with a relative risk of 1.19. The incidence rate for invasive anal squamous cell carcinoma increases with increasing age.¹

This review will discuss the diagnosis, staging, and treatment of squamous cell carcinoma of the anal canal and margin.

Diagnosis

Delayed diagnosis of anal canal and anal margin squamous cell carcinomas often occurs due to initial misdiagnosis as hemorrhoids or other benign anorectal conditions (▶ Fig. 1).

Other patient factors such as embarrassment or denial may also cause a delay in diagnosis and treatment until the disease has progressed to an advanced stage (▶ Fig. 2). A thorough history of anal and bowel symptoms should be elicited, although it is important to remember that 20% of patients with anal cancer are asymptomatic. The most common presenting symptoms of patients with anal cancer include rectal pain (61%), rectal bleeding (59%), sensation of a rectal mass (30%), complaint of hemorrhoids (28%), weight loss (26%), change in stool caliber (17%), constipation (17%), and fecal incontinence (11%).² Other symptoms include pruritus or anal discharge. Tenesmus and fecal incontinence may indicate anal sphincter involvement. Patients may also present with inguinal lymphadenopathy.

Risk factors for anal cancer should be identified, including high-risk sexual behaviors, known human papillomavirus (HPV) infection, history of infection with sexually transmitted diseases that may predispose the patient to HPV, cervical dysplasia or cancer, genital warts, high-grade anal dysplasia, HIV infection, smoking, and chronic immunosuppression.^{3–12} The incidence of anal cancer among HIV-positive patients is 42 times that of the general population.^{4,13,14} Highly active antiretroviral therapy (HAART) has not affected the incidence of anal cancer in this population. The incidence has actually increased in the HAART era, which may indicate that the risk of

Fig. 1 Anal canal squamous cell carcinoma extending to the anal margin. As there is an anal canal component, this should be treated as an anal canal carcinoma. The patient's diagnosis was delayed by several months, as she was initially thought to have hemorrhoids on evaluation by her primary care physician and gastroenterologist.

anal cancer increases over the time period that a patient is infected with HIV.¹⁵ Long-term immunosuppression after organ transplantation is associated with a 10-fold increased risk for anal cancer.¹⁶ Patients with end-stage renal disease

Fig. 2 Squamous cell carcinoma involving the anal canal, anal margin, perineum, scrotum, and perianal skin. Delayed diagnosis and management may occur due to patient factors such as embarrassment or denial. (Photo courtesy of Mark Welton, MD.)

have over a fourfold increased risk for developing anal cancer.¹⁷ Tobacco smoking is also associated with anal cancer, conferring a two- to fivefold increased risk depending on the number of years of smoking.^{18,19}

The physical examination should include external examination of the anal margin and perianal skin, digital rectal exam and anoscopy of the anal canal, and palpation of the groin for enlarged inguinal nodes. Firmness, friability, and bleeding are suspicious characteristics that warrant tissue biopsy for definitive diagnosis. Performing a pelvic examination to assess for vaginal wall involvement is also important. Anorectal examination under anesthesia may be necessary to obtain a tissue diagnosis, depending on how uncomfortable the patient is.

Distinguishing between anal canal squamous cell carcinoma and anal margin squamous cell carcinoma is important for deciding on the right treatment regimen, and for determining prognosis. The anal canal is defined as the mucosa extending from the rectum, inclusive of the anal transition zone and dentate line, to its junction with skin.²⁰ The anal margin is defined as the region extending from the anal verge to a 5-cm-radius around the anal verge (►Fig. 3). Outside of that 5-cm radius is the perianal skin. Lesions that are completely visible upon effacement of the buttocks are considered anal margin lesions. Lesions that are at least partially within the anal canal—that is, not completely visible upon effacement of the buttocks—are considered anal canal lesions (►Fig. 1).

Staging

The staging systems for squamous cell carcinoma of the anal canal and anal margin determined by the AJCC are detailed in ►Tables 1 and 2.²¹ Perianal squamous cell carcinomas (those occurring outside of the 5-cm radius of the anal verge) will not be discussed in this review.²² CTs of the chest, abdomen, and pelvis are required to assess for locoregional spread and distant metastasis. Head CT may be performed if

Fig. 3 Very large condyloma with a focus of invasive squamous cell carcinoma on final pathology. As this lesion is completely visible upon effacement of the buttocks, it is considered an anal margin lesion.

Table 1 AJCC TNM staging of anal canal squamous cell carcinoma

Primary tumor (T)			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ (high-grade squamous intraepithelial lesion, anal intraepithelial neoplasia IIIII)		
T1	Tumor ≤2 cm in greatest dimension		
T2	Tumor >2 cm and ≤5 cm in greatest dimension		
T3	Tumor >5 cm in greatest dimension		
T4	Tumor of any size invading into adjacent organ(s) such as vagina, urethra, bladder. (Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or sphincter muscle 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		
Staging	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2–3	N0	M0
IIIA	T1–3	N1	M0
	T4	N0	M0
IIIB	T4	N1	M0
	Any T	N2–3	M0
IV	Any T	Any N	M1

there is a clinical indication, as squamous cell carcinoma has been known to metastasize to the brain.

MRI of the pelvis is frequently used for staging the primary tumor and regional nodes. Anal endosonography is another imaging modality that can be helpful for staging anal canal squamous cell carcinomas. It has a high concordance with MRI, and may be superior in its detection of small superficial tumors. However, cross-sectional imaging is still necessary for nodal staging in the inguinal and internal iliac regions.²³ Three-dimensional anal endosonography may offer superior staging accuracy and improved interobserver and intraobserver consistency compared with two-dimensional anal endosonography.^{24,25}

Table 2 AJCC TNM staging of anal margin squamous cell carcinoma

Primary tumor (T)			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ (high-grade squamous intraepithelial lesion, anal intraepithelial neoplasia II–III)		
T1	Tumor ≤2 cm in greatest dimension		
T2	Tumor >2 cm and ≤5 cm in greatest dimension		
T3	Tumor >5 cm in greatest dimension		
T4	Tumor of any size invades deep extradermal structures		
Regional lymph nodes (N)			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node(s)		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Staging	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2–4	N0	M0
III	T4	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1

If suspicious lymph nodes are detected, fine needle aspiration (FNA) may be performed under ultrasound guidance if it will affect treatment. For example, the nodal status of the inguinal nodes may determine whether they are included in the radiation field. Sentinel lymph node biopsy has been used to determine the status of the inguinal nodes to direct subsequent treatment.^{26–29} Sentinel lymph node biopsy appears to be more accurate than PET-CT in determining the status of the inguinal nodes due to the higher rate of false-positive nodes on PET-CT.³⁰ However, sentinel lymph node biopsy is not considered standard of care.

FDG-PET/CT is not part of the routine staging workup, but it should be performed if there are any suspicious lesions noted. Screening colonoscopy should also be performed. Patients who are at high risk for HIV infection should be tested. Those who are HIV positive need to have their CD4 cell counts tested before starting therapy.

Treatment of Anal Canal Squamous Cell Carcinoma

Anal canal squamous cell carcinoma is five times more common than anal margin squamous cell carcinoma. Less

than 20% of patients develop distant metastasis, and over 90% present with locoregional disease. A substantial proportion of patients present with locally advanced disease: 10% present with T1 tumors, 50% with T2 tumors, 30% with T3 tumors, and 10% with T4 tumors.³¹ The higher the T stage, the higher the risk for lymph node spread and distant metastases. Patients with T1 tumors have a 0 to 5% risk of positive lymph nodes, T2 tumors have an 8.5% risk, T3 tumors have a 18 to 28% risk, and T4 tumors have a 27 to 35% risk. Distant metastases occur most frequently to liver, lung, and bone.³²

Nonsurgical

The first-line treatment for anal canal squamous cell carcinoma is now chemoradiation therapy. The landmark publication by Norman Nigro in 1974 demonstrated its effectiveness in treatment of this malignancy over radical surgical resection with abdominoperineal resection.^{33–36} The original Nigro protocol is detailed in ►Table 3. Since then, multiple studies have corroborated his findings and chemoradiation has become the standard of care for the definitive treatment of anal canal squamous cell carcinoma.^{37,38} In multiple prospective multi-institutional randomized controlled trials, mitomycin C with 5-fluorouracil (5-FU) was proven to be an integral part of the chemotherapeutic regimen in a randomized controlled trial, despite greater toxicity compared with 5-FU with radiation therapy or radiation therapy alone. The addition of mitomycin C resulted in higher rates of sphincter preservation and disease-free survival.^{39–43} The modified Nigro protocol is detailed in ►Table 4. Patients who cannot tolerate the toxicity of combined chemotherapy and radiation may

undergo radiation therapy alone, especially if they have early-stage tumors.^{31,32,44,45}

The GI Intergroup Radiation Therapy Oncology Group (RTOG) 98–11 Phase III trial was performed to determine whether cisplatin could replace mitomycin C during radiation therapy with infusional 5-FU. The group that received concurrent mitomycin C with radiation therapy and infusional 5-FU had statistically better 5-year disease-free survival (67.8 vs. 57.8%, *p* = 0.006) and 5-year overall survival (78.3 vs. 70.7%, *p* = 0.026) compared with those who received cisplatin with radiation therapy and infusional 5-FU. There was also a trend toward better colostomy-free survival and lower locoregional failure in the mitomycin arm.^{46,47} Maintenance chemotherapy has also not been shown to improve oncologic outcomes.⁴⁸

Inclusion of the bilateral groins in the radiation field for patients with clinically negative inguinal nodes is done in some centers, but there is no consensus on this. While some centers avoid radiating clinically negative groin fields to avoid the potential morbidity, other centers radiate the groins routinely due to the risk for inguinal lymph node metastases even with a negative sentinel lymph node biopsy.⁴⁹

Intensity-modulated radiation therapy (IMRT) allows for delivery of total radiation doses of up to 60 Gy to the primary tumor while reducing the radiation dose to surrounding tissues, thus reducing the radiation-induced toxicity seen with conventional radiation therapy. These toxicities cause skin complications, pain, hematological symptoms, and diarrhea and lead to treatment breaks in 40 to 60% of patients.⁴⁸ IMRT has been shown to reduce acute hematologic and gastrointestinal toxicities without compromising oncologic outcomes.^{50–54}

The majority of patients will demonstrate a complete clinical response within 6 to 8 weeks after completing treatment. Patients who are partial regression noted at 6 to 8 weeks after treatment completion should continue to undergo close follow-up to determine if complete regression occurs over the next several months. If there appears to be residual tumor at 6 months that is not continuing to regress, or progression of disease, then biopsy should be considered to confirm the diagnosis.

For patients who experience a complete remission, post-treatment surveillance includes at least visual inspection, digital rectal examination, anoscopy, and palpation of inguinal nodes every 3 to 6 months in the first 2 years, every 6 to 12 months until 5 years, and annually thereafter.⁵⁵ CT, MRI, or PET scans may be used for assessing distant recurrence, but there are no clear guidelines on how often these are needed. While endoscopic ultrasound may be helpful for initial staging of anal canal cancers, there is debate over whether it offers any advantage over digital rectal examination for detection of recurrent anal cancer, and therefore is not recommended for routine surveillance.^{56–59}

Surgical

Patients with persistent, progressive, or recurrent disease after chemoradiation therapy should undergo salvage surgery with abdominoperineal resection. Up to 30% of patients

Table 3 Original Nigro regimen for the treatment of anal canal squamous cell carcinoma

External beam radiotherapy	30 Gy delivered to the pelvis in 15 fractions beginning on day 1
Chemotherapy	<ul style="list-style-type: none">• 5-FU as continuous infusion on days 1–4• Mitomycin C given as intravenous bolus on day 1• 5-FU as continuous infusion on days 28–31

Table 4 Modified Nigro regimen for the treatment of anal canal squamous cell carcinoma

External beam radiotherapy	45–55 Gy delivered to the pelvis in 20–28 fractions over 4–5 wk
Chemotherapy	<ul style="list-style-type: none">• 5-FU as continuous infusion over 4–5 d during the first and final weeks of radiation therapy• Mitomycin C on day 1

with anal canal carcinoma will undergo radical salvage surgery. Preoperative workup for salvage surgery includes tissue confirmation of disease, local staging with MRI, and CT of the chest, abdomen, and pelvis or PET/CT to rule out distant metastatic disease. A wide resection on the perineum often results in a large perineal defect. Female patients often require en bloc posterior vaginectomy to obtain clear margins. Because of the size of the perineal defect and the history of high-dose radiation to the area, perineal reconstruction with myocutaneous flaps is usually necessary and can decrease the risk of perineal wound complications^{60,61} (► **Figs. 4–7**). The vertical rectus abdominis myocutaneous flap is preferred over gracilis flaps due to its greater bulk.

Inguinal lymph node disease should be treated primarily with chemoradiation therapy. However, persistent, progressive, or recurrent disease in the inguinal lymph nodes may require radical groin dissection. Flap reconstruction may be required given the high risk of wound healing complications in an irradiated field.

Salvage surgery outcomes are 5-year survival of 30 to 60%.⁶² Outcomes after salvage surgery are worse in patients who initially present with node-positive disease or who receive a total radiation dose of less than 55 Gy.⁶³ Favorable prognostic factors include recurrence (rather than persistence) of disease, late recurrence rather than early recurrence, and negative margins.^{64,65} Surgical outcomes include high postoperative complication rates (72%).⁶⁶ Salvage surgery should not be undertaken unless R0 resection is expected to be achieved.

Fig. 4 Salvage abdominoperineal resection for persistent or recurrent anal canal squamous cell carcinoma after primary chemoradiation therapy often requires perineal reconstruction, preferably with a vertical rectus abdominis myocutaneous flap, due to the resulting large perineal defect and history of high-dose irradiation. (Photo courtesy of Gordon Lee, MD.)

Fig. 5 Female patients with persistent or recurrent anal canal squamous cell carcinoma often require en bloc posterior vaginectomy to obtain clear margins. Using the skin paddle of the vertical rectus abdominis myocutaneous flap to reconstruct the posterior vaginal wall and the rest of the perineal defect can offer excellent outcomes. (Photo courtesy of Gordon Lee, MD.)

Fig. 6 Perineal defect after salvage abdominoperineal resection for persistent anal canal squamous cell carcinoma. (Photo courtesy of Arash Momeni, MD.)

Fig. 7 Reconstruction of the perineal defect with a vertical rectus abdominis myocutaneous flap. (Photo courtesy of Arash Momeni, MD.)

Treatment of Anal Margin Squamous Cell Carcinoma

Due to the high rates of delayed diagnosis of anal margin cancers, 50 to 70% of patients have locally advanced T3 or T4 disease at the time of diagnosis.² Lymph node spread occurs via the inguinal and femoral nodes and is more likely to occur with larger primary tumors. Positive nodal status, cell differentiation, and tumor size correlate with cancer-specific survival.⁶⁷

Treatment of anal margin squamous cell carcinoma depends on the size, location, and sphincter involvement. There are no definitive guidelines for making the decision between wide local excision and definitive chemoradiation therapy, and treatment strategies vary by institution. T1 and early T2 lesions may be treated with wide local excision with 1-cm margins. Given that rates of locoregional recurrence after local excision range from 40 to 67%, adjuvant chemoradiation therapy should be considered.^{67–69} For larger tumors, particularly those that invade the sphincter complex, primary chemoradiation therapy should be performed, with abdominoperineal resection reserved for salvage treatment. For smaller tumors, primary chemoradiation therapy alone is associated with high locoregional failure rates compared with surgical excision plus radiation; so, for tumors that can be successfully excised with adequate margins, wide local excision as a primary therapy followed by adjuvant chemoradiation is the preferred strategy.^{69–73}

The management of the inguinal lymph nodes in cases of anal margin carcinoma is controversial and recommendations vary as to which patients should undergo prophylactic radiation to clinically negative inguinal nodes. Some institutions recommend prophylactic inguinal radiation for all T stages, while others recommend it for tumors over a certain T stage. The argument for prophylactic radiation to the inguinal nodes regardless of tumor size is that up to 25% of patients with clinically negative inguinal nodes will have occult metastases.^{70,72}

Posttreatment surveillance should be conducted with visual inspection, digital rectal exam, anoscopy, and bilateral inguinal node palpation every 3 months for the first 2 years, every 6 months until the fifth year, and every 1 to 2 years thereafter.

New Developments in Treatment of Anal Cancer

Addition of brachytherapy to standard chemoradiation regimens has been studied and has had some promising oncologic results with 5-year disease-specific survival of 91%, stoma-free survival of 97%, and overall survival of 75% in patients with anal canal squamous cell carcinoma. The results were not as promising in patients with anal margin squamous cell cancers who received an electron boost after chemoradiation therapy, who were found to have a 5-year disease-specific survival of 78%, stoma-free survival of 80%, and overall survival of 68%.⁷⁴

Special Populations

Patients who are immunosuppressed due to organ transplantation or HIV infection appear to have similar oncologic outcomes after chemoradiation for anal squamous cell carcinoma compared with those who are immunocompetent.^{75,76}

In patients with HIV infection undergoing chemoradiation therapy, CD4 counts should be followed and patients should be monitored closely for the development of opportunistic infections. Those with CD4 counts greater than 200 cells/mL can undergo standard combined chemoradiation therapy.⁷⁷ Patients with lower CD4 counts are more likely to experience toxicity and require breaks in therapy and dose reductions.⁷⁸ Poorer overall survival is associated with high viral load and low CD4 count.⁷⁹

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