Clinical features and staging of anal cancer

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INTRODUCTION

The incidence of anal cancer is low in the United States, with less than 1000 new cases diagnosed annually [1]. Information on worldwide incidence is available from the GLOBOCAN database.

However, the incidence of anal cancer in the general population has increased over the last 30 years. A higher incidence has been associated with female sex, infection with human papillomavirus (HPV), lifetime number of sexual partners, genital warts, cigarette smoking, receptive anal intercourse, and infection with HIV. (See "Classification and epidemiology of anal cancer".)

The term "anal cancer" usually refers to squamous cell cancer (SCC), which represents the majority of cancers arising in the anal canal. Anal adenocarcinomas are less common, and they are staged as anal SCC but treated in a manner similar to rectal adenocarcinoma. On the other hand, SCCs that arise in the rectum are treated as anal canal SCCs.

This topic review will cover the clinical features and staging of anal cancers. The classification, histology, and epidemiology of anal cancer, the principles of treatment for anal and rectal SCCs as well as adenocarcinomas of the anus, the diagnosis and management of anal intraepithelial neoplasia, and an overview of the link between HPV infection and cancer are presented separately. (See "Classification and epidemiology of anal cancer" and "Treatment of anal cancer" and "Anal squamous intraepithelial lesions: Epidemiology, clinical presentation, diagnosis,

screening, prevention, and treatment" and "Virology of human papillomavirus infections and the link to cancer".)

ANAL CANAL VERSUS PERIANAL SKIN CANCERS

The anal canal begins where the rectum enters the puborectalis sling at the apex of the anal sphincter complex (palpable as the anorectal ring on digital rectal examination and approximately 1 to 2 cm proximal to the dentate line) and ends where the squamous mucosa blends with the perianal skin, which roughly coincides with the palpable intersphincteric groove or the outermost boundary of the internal sphincter muscle (figure 1).

The anus consists of a glandular mucosa-lined anal canal and the epidermis-lined perianal "margin." The anus encompasses mucosa of three different histologic types (proximal to distal, respectively): glandular (mucosa lined), transitional, and squamous. Distally, the squamous mucosa (which is devoid of epidermal appendages, hair follicles, apocrine glands, and sweat glands) merges with the hair-bearing perianal skin (true epidermis). This mucocutaneous junction has been referred to as the anal "verge" or margin. (See "Classification and epidemiology of anal cancer".)

Four distinct categories of tumors arise in the anal region:

- Tumors that develop from any of the three types of mucosa and that cannot be visualized in their entirety while gentle traction is placed on the buttocks are termed anal canal cancers [2]:
  - Tumors arising in the transitional or squamous mucosa are squamous cell cancers (SCCs) and appear to behave similarly, despite their sometimes variable morphologic appearance. By convention, most series that report outcomes of "anal cancer" refer exclusively to these tumors. By common definition, the term "anal cancer" refers to SCCs arising within the mucosa of the anus, and the two terms will be used interchangeably throughout this review.
  - Basaloid (also termed junctional or cloacogenic) carcinoma is a variant of SCC that arises from the epithelial transitional zone. However, these terms have largely been abandoned because these tumors are now recognized as nonkeratinizing types of SCC. Tumors arising within the anal canal above the dentate line are termed nonkeratinizing SCCs, while those arising within the anal canal distal to the pectinate (dentate) line are termed keratinizing SCCs.

- Adenocarcinomas arising from glandular elements within the anal canal are rare, but they appear to share a similar natural history with rectal adenocarcinomas and are treated similarly. (See "Treatment of anal cancer", section on 'Anal adenocarcinoma'.)

- Tumors arising within the hair-bearing skin at or distal to the squamous mucocutaneous junction have been referred to as anal margin cancers. However, the most recent (eighth) edition of the American Joint Committee on Cancer (AJCC) cancer staging manual and the fifth edition of the World Health Organization (WHO) classification of tumors of the digestive tract define tumors that arise within the skin at or distal to the squamous mucocutaneous junction, that can be seen in their entirety with gentle traction placed on the buttocks, and that are within 5 cm of the anus as perianal cancers [2,3]. Like most clinicians, we treat SCC lesions of the perianal skin the same as anal canal cancers, using radiation therapy (RT) and concurrent chemotherapy. Local treatment, surgery, or local RT (electrons) is used only when the lesion is very separate from the anal verge and is a discrete skin lesion.

- Primary rectal SCCs, which are very rare, can be difficult to distinguish from anal cancers, but they are treated according to the same approach as anal cancers. (See "Treatment of anal cancer", section on 'Rectal squamous cell cancers'.)

CLINICAL FEATURES

Rectal bleeding is the most common initial symptom of anal cancer, occurring in approximately 45 percent of patients. Anorectal pain or the sensation of a rectal mass is present in 30 percent, while 20 percent have no tumor-related symptoms [4-6]. Bleeding from a mass at or just above the anal sphincter (figure 1) may be falsely attributed to hemorrhoids, and this may delay the diagnosis.

Among patients with anal squamous cell cancer (SCC), a history of anorectal condyloma is present in approximately 50 percent of gay men and in fewer than 30 percent of women and straight men; these values are much greater than in normal controls (1 to 2 percent) [7]. Tumors of the perianal skin, especially Bowen's disease or Paget disease, may present with pruritus ani or a bleeding erythematous eczematoid plaque. (See "Classification and epidemiology of anal cancer".)

STAGING

TNM staging criteria — All carcinomas (squamous cell, adenocarcinoma) that arise within any of the mucosal surfaces of the anal canal or the perianal skin are staged and treated similarly. The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) have jointly established a Tumor, Node, Metastasis (TNM) staging system for anal canal cancers that is based on tumor size/invasion of adjacent structures and the presence or absence of nodal or distant metastases.

The newest version (eighth edition, 2017) is outlined in the table (table 1) [2]. There are some major changes compared with 2010: perianal skin cancers are staged and treated like anal canal cancers (rather than squamous cell skin cancers); the N2 and N3 categories are removed; new categories of N1a, N1b, and N1c are defined; and the stage groups are revised to reflect the new N categories.

At initial presentation, most patients have a T1 or T2 lesion, and fewer than 20 percent are node positive [6,8-12]. The probability of nodal spread is directly related to the tumor size and location. It is far more common in cancers that originate in the anal canal than on the perianal skin.

Tumor size (T stage) and nodal status (N stage) are the most significant prognostic factors for patients with anal squamous cell cancer (SCC) [9,10,12,13]. In the above series of 270 patients, the five-year survival by stage was as follows [10] (see "Treatment of anal cancer", section on 'Prognosis'):

- T1 – 86 percent
- T2 – 86 percent
- T3 – 60 percent
- T4 – 45 percent
- N0 – 76 percent
- Node positive – 54 percent

Nodal assessment and pathways of lymphatic drainage — Lymphatic drainage of anal canal and perianal skin cancers is dependent on the anatomic site of origin (figure 1) [8,9,14]. Tumors originating above the dentate line, similar to rectal cancers, drain to the mesorectal and internal iliac nodes. In contrast, tumors arising below the dentate line may also spread to the superficial inguinal and external iliac (deep inguinal) nodes. In contrast to earlier editions, in the eighth edition of the AJCC/UICC staging system, metastases in the inguinal, mesorectal, internal, or external iliac are all considered N1 (table 1) [2].

Staging evaluation — Pretreatment clinical staging consists of physical examination and biopsy of the primary tumor, palpation of the groin, computed tomography (CT) of the chest, CT

or magnetic resonance imaging (MRI) of the abdomen and pelvis, and an integrated positron emission tomography (PET)/CT scan.

Historically, both the staging and treatment of anal cancer were surgical and consisted of abdominoperineal resection and inguinal lymph node dissection. However, combined chemoradiotherapy has emerged as the preferred method of treatment, with radiation therapy (RT) administered to the sites of primary disease and lymphatic spread, usually with prophylactic irradiation of clinically negative groins. This strategy has significantly reduced the rate of locoregional recurrence and led to markedly improved control of gross nodal disease. (See "Treatment of anal cancer", section on 'Radiation therapy dose and schedule'.)

Surgical staging is no longer performed routinely. Clinical staging for anal canal cancers consists of physical examination and biopsy of the primary tumor, palpation of the groin, CT of the chest, CT or MRI of the abdomen and pelvis, and PET scan. For women, a gynecologic examination should be done, including screening for cervical cancer.

The same staging evaluation is recommended for SCCs of the perianal skin, although guidelines from the National Comprehensive Cancer Network (NCCN) do not include a PET scan in this situation [15].

Positron emission tomography scan — We perform an integrated PET/CT in the pretreatment staging workup for most patients with anal canal cancers. If there is clearly positive fluorodeoxyglucose (FDG) uptake in the inguinal nodes, these nodes are included in the RT field. Questionable nodes should be biopsied if the finding will change the RT portal. Others disagree. Guidelines from the NCCN suggest consideration of an integrated PET/CT scan as a component of the pretreatment staging evaluation for anal canal cancers (but not perianal skin cancers) and emphasize that it does not replace a diagnostic CT [15]. European Society for Medical Oncology (ESMO) guidelines consider PET/CT to be an optional component of the staging evaluation [16].

The sensitivity of physical examination and CT/MRI is suboptimal to detect inguinal nodal metastases, many of which are ≤5 mm and below the limit of detection [17]. Adding an integrated FDG-PET/CT scan to the staging workup has a significant impact on therapy planning, particularly in identifying patients who need higher dose RT to the groin and those with otherwise occult metastatic disease [18-22]. A meta-analysis of 12 studies concluded that, compared with conventional imaging, an additional staging PET scan changed nodal staging in 28 percent of patients [22].

Tumor markers — We do not routinely assay for any tumor marker, including carcinoembryonic antigen (CEA), prior to treatment in patients with localized anal SCC, and this

is consistent with guidelines from the NCCN and ESMO [15,16].

There are no tumor markers that are consistently elevated in anal SCC. Elevations in serum CEA can be found in between 20 and 39 percent of cases [23-25]. If initially elevated, a further rise in serum CEA following treatment may provide an early signal to suggest disease persistence or recurrence.

PRETREATMENT ASSESSMENT FOR HIV INFECTION

The pretreatment assessment for a patient with known HIV/AIDS should include a thorough history, including infectious diseases and use of antiretroviral therapy (ART); review of HIV serology; cluster of differentiation 4 (CD4) count and percentage; viral load; and screening for coinfections, including viral hepatitis. (See "Initial evaluation of adults with HIV".)

If HIV status is unknown, we recommend HIV testing for all individuals with newly diagnosed anal squamous cell cancer (SCC) or basal cell cancer. This recommendation is consistent with guidelines from the National Comprehensive Cancer Network (NCCN) [15]. We do not routinely test for HIV status in patients with anal adenocarcinoma, unless the individual patient's history suggests that screening may be warranted. (See "Screening and diagnostic testing for HIV infection".)

As noted above, infection with HIV is a risk factor for anal cancer, although anal cancer is not a disease-defining condition for progression to AIDS. (See 'Introduction' above and "The natural history and clinical features of HIV infection in adults and adolescents", section on 'AIDS-defining conditions'.)

HIV-associated anal SCC is potentially curable with combined modality therapy, and most data suggest that response to therapy, local control, and survival are as good as in non-HIV-infected patients, particularly in the era of potent ART (previously called highly active ART). In general, HIV positive patients are treated similarly to non-HIV positive individuals. A low CD4 count does not necessarily predict greater treatment-related toxicity. However, patients with active HIV/AIDS-related complications or a history of complications (eg, opportunistic infections, other malignancies) may not tolerate full-dose therapy or may require dose adjustment or treatment without mitomycin. (See "Treatment of anal cancer", section on 'Patients living with HIV'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Anal cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Anal cancer (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Four distinct categories of tumors arise in the anal region:
  - Tumors that develop from any of the three types of lining mucosa (glandular, transitional, and squamous) and that cannot be visualized in their entirety while gentle traction is placed on the buttocks are termed anal canal cancers and are staged and treated similarly. The vast majority are squamous cell cancers (SCCs). (See 'Introduction' above.)
  - Tumors arising within the hair-bearing skin at or distal to the squamous mucocutaneous junction have been referred to as anal margin cancers. However, the most recent (eighth) edition of the American Joint Committee on Cancer (AJCC) cancer staging manual defines tumors that arise within the skin at or distal to the squamous mucocutaneous junction, that can be seen in their entirety with gentle traction placed on the buttocks, and that are within 5 cm of the anus as perianal skin cancers. (See 'Anal canal versus perianal skin cancers' above.)

- Adenocarcinomas arising from glandular elements within the anal canal are rare, but they appear to share a similar natural history with rectal adenocarcinomas and are treated similarly. (See "Treatment of anal cancer", section on 'Anal adenocarcinoma'.)

- Primary rectal SCCs, which are very rare, can be difficult to distinguish from anal cancers, but they are treated according to the same approach as anal cancers. (See "Treatment of anal cancer", section on 'Rectal squamous cell cancers'.)

- All carcinomas (squamous cell, adenocarcinoma) that arise within any of the mucosal surfaces of the anal canal or the perianal skin are staged and treated as anal canal cancers. The AJCC and the Union for International Cancer Control (UICC) have jointly established a Tumor, Node, Metastasis (TNM) staging system for anal canal cancers that is based on tumor size/invasion of adjacent structures and the presence or absence of nodal or distant metastases. The newest version (eighth edition, 2017) is outlined in the table (table 1). (See 'TNM staging criteria' above.)

- Pretreatment clinical staging consists of physical examination and biopsy of the primary tumor, palpation of the groin, computed tomography (CT) of the chest, CT or magnetic resonance imaging (MRI) of the abdomen and pelvis, and an integrated positron emission tomography (PET)/CT scan. (See 'Staging evaluation' above.)

- We do not routinely assay for any tumor marker, including carcinoembryonic antigen (CEA), prior to treatment in patients with localized anal SCC. (See 'Tumor markers' above.)

- The pretreatment assessment for a patient with known HIV/AIDS should include a thorough history, including infectious diseases and use of antiretroviral therapy (ART); review of HIV serology; cluster of differentiation 4 (CD4) count and percentage; viral load; and screening for coinfections, including viral hepatitis. If HIV status is unknown, we recommend HIV testing for all individuals with newly diagnosed anal cancer. This recommendation is consistent with guidelines from the National Comprehensive Cancer Network (NCCN). (See 'Pretreatment assessment for HIV infection' above.)

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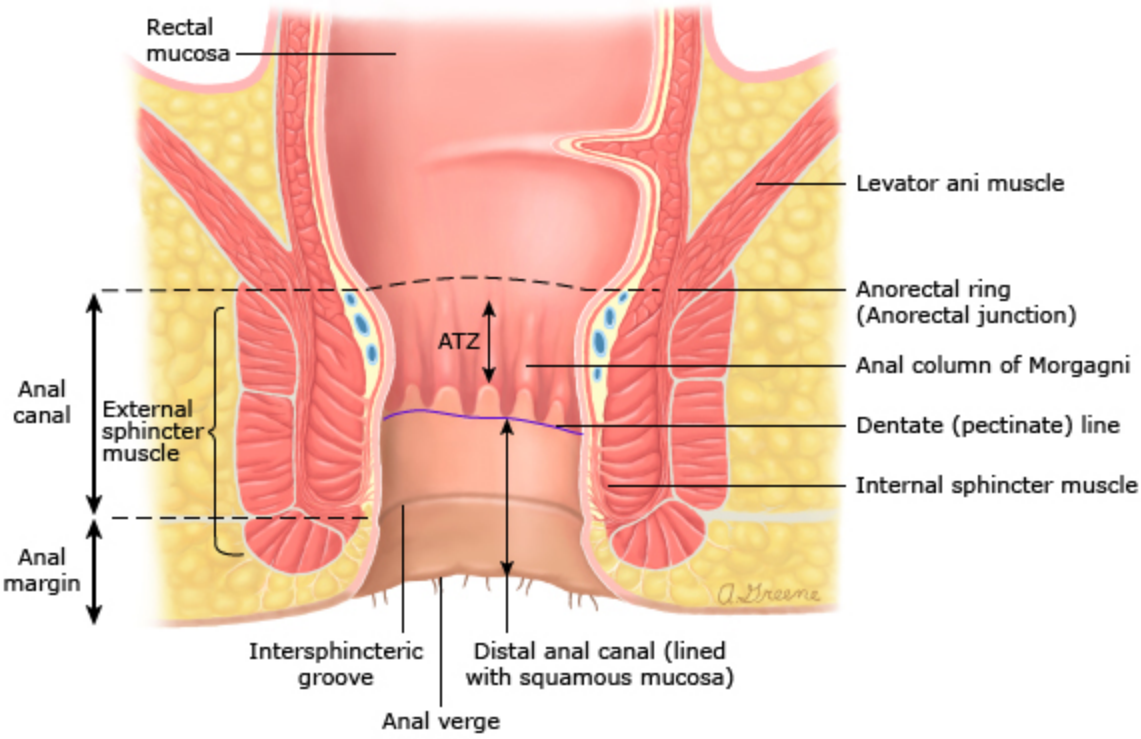
GRAPHICS

Anatomy of the anus and rectum



The anal canal is 2.5 to 4.0 cm long and begins superiorly where the rectal ampulla is narrowed by the anorectal ring. This palpable muscular ring is formed by fusion of the puborectalis muscle (part of the levator ani muscle complex) with the more inferior internal and external anal canal sphincters.

The external anal canal sphincter ends just distally to the internal anal canal sphincter; the intersphincteric groove is the palpable plane that can be palpated between the termination of the two sphincters. The presence of the intersphincteric groove coincides roughly with the anal verge, which marks the distal portion of the anal canal. The perianus or anal margin extends 5 cm laterally from the anal verge and is characterized by the presence of hair follicles and glands.

The interior of the anal canal can be divided into proximal and distal portions by an irregular line formed by the anal valves called the dentate (or pectinate) line (colored purple in the diagram). The portions of the anal canal proximal and distal to the dentate line have different origins of arterial supply, nerve innervation, and venous lymphatic drainage. The squamo-columnar junction (SCJ) lies within the proximal portion of the anal canal and marks the transition between rectal columnar epithelium to anal squamous epithelium. The exact position of the SCJ changes with time due to replacement of columnar epithelium with squamous epithelium in a process known as squamous metaplasia. The anal transformation zone (ATZ) is the zone where all aspects of squamous

metaplasia are currently found and/or have occurred. The ATZ is marked by the SCJ proximally and extends distally to approximately the level of the dentate line.

Graphic 62539 Version 16.0

Anal cancer TNM staging AJCC UICC 8th edition

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 neoplasia II-III, high-grade anal intraepithelial neoplasia)
T1	Tumor ≤2 cm
T2	Tumor >2 cm but ≤5 cm
T3	Tumor >5 cm
T4	Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder
Regional lymph nodes (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 N1a nodes
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

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

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Graphic 110681 Version 7.0

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