An Update on Tumors of the Anal Canal

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- **Context.**—The anal canal possesses complex anatomy and histology and gives rise to a variety of tumor types. Challenging issues remain with regard to both the pathologic diagnosis and the clinical management of these tumors.

- **Objectives.**—To provide an updated overview of the histogenesis, clinical and pathologic characteristics, diagnostic terminology, and relevant clinical management of the various types of anal canal tumors.

As stated in *Pathology and Genetics of Tumours of the Digestive System: The World Health Organization (WHO) Classification of Tumours,* “despite its short length, the anal canal produces a variety of tumor types reflecting its complex anatomic and histological structure.” These tumor types can be categorized as follows: (1) squamous cell tumors including condyloma acuminatum, flat squamous dysplasia, and invasive squamous cell carcinoma and its variants; (2) adenocarcinoma including rectal type adenocarcinoma, the so-called anal gland adenocarcinoma, fistula-related mucinous adenocarcinoma, and intraepithelial adenocarcinoma (ie, Paget disease); (3) neuroendocrine neoplasms including carcinoid tumor, small cell carcinoma, and non–small cell high-grade neuroendocrine carcinoma; (4) malignant melanoma; (5) mesenchymal tumors; and (6) malignant lymphoma. Although these anal canal tumors as a group account for only about 1.5% of all gastrointestinal tract neoplasms, their pathologic diagnosis and clinical management can be challenging to both pathologists and clinicians. This review aims at providing an updated overview of the histogenesis, clinical and pathologic characteristics, diagnostic terminology, and clinical management of anal canal tumors. Attention will also be directed to the differential diagnosis of poorly differentiated anal canal tumors and the utility of immunohistochemical stains in difficult diagnostic scenarios.

**NORMAL ANATOMY AND HISTOLOGY**

The anal canal can be defined either surgically or histologically. As illustrated in Figure 1, the “surgical anal canal” extends cephalocaudally from the level of the pelvic floor (the anorectal ring or the junction of the puborectalis portion of the levator ani muscle with the external anal sphincter) to the proximal margin of the anal verge. Thus defined, the anal canal corresponds to the segment that is invested by the internal anal sphincter, and is about 4.0 cm in length. The dentate (pectinate) line is located roughly at the midpoint.

Histologically, the anal canal is divided into 3 parts on the basis of its lining epithelium: colorectal zone lined by colorectal-type glandular mucosa proximally, anal transition zone (ATZ) often lined by an epithelium that has varying appearances in the middle, and the squamous mucosa–lined distal portion (Figure 1). The delineation of the lower border of the anal canal, that is, the junction between squamous mucosa and anal margin epidermis, is often evident grossly by the different consistency and appearance of the 2 lining epithelia and microscopically by the lack of skin adnexal structures in squamous mucosa and their presence in anal margin. The upper border, however, is difficult to delineate because of the lack of any discernible landmarks either grossly or microscopically. Most pathologists therefore tend to ignore the colorectal zone and rely only on the grossly visible dentate line as the superior border of the anal canal (which indeed is the definition of the “anatomic anal canal”).

The lining epithelium of the ATZ is a subject of interest. Embryologically, this epithelium represents the fusion point of 2 epithelial derivatives from different germ layers, one from the endodermal hindgut lining the superior part of the primitive anal canal, and the other from the ectodermal protoderm lining the inferior part. Histologically, it is often composed of multiple cell layers, extending from the small basal cells at the bottom to the...
surface cells (which can be columnar, cuboidal or polygonal, or flattened)\(^5\) (Figure 2). Here small areas can show umbrella-shaped surface cells and more distinct cell borders. In the literature, this epithelium has been variously designated as transitional, intermediate, or cloacogenic. Scattered foci of colorectal crypts or small areas of mature squamous epithelium may also be seen in the ATZ. In some individuals, this histologic transitional zone interposed between colorectal type glandular mucosa and squamous mucosa may be absent altogether.

The epithelium in the ATZ may also contain mucin, endocrine cells,\(^6\) and melanocytes.\(^7\) In addition, the anal ducts that drain anal glands open in the ATZ (Figure 3). The anal ducts may penetrate the internal anal sphincter and may extend into perianal fat. The duct epithelium shares morphologic and immunohistochemical characteristics with the overlying ATZ mucosa. Both tend to be positive for CK7 and negative for CK20.\(^8\) It is believed that the anal glands and ducts may take part in the formation of anal fistulae. These various epithelial elements account for the different types of neoplasms that may occur in the anal canal.

**SQUAMOUS NEOPLASIA**

**Overview**

Anal squamous cell carcinoma originates from either the squamous epithelium of the lower part of the anal canal (most common) or the ATZ mucosa. The occurrence of histologic variants of squamous cell carcinoma, such as transitional, basaloid, and cloacogenic types, has been attributed to the varied nature of the ATZ epithelium. Squamous cell carcinoma and its variants account for about 70% of all anal cancers in the United States.\(^9\) Various etiologies have been implicated in cancer development, the most significant being human papillomavirus (HPV) infection. An anal squamous cell carcinoma may or may not be preceded by squamous dysplasia. Subtyping of anal squamous cell carcinomas was once advocated by the WHO but is now believed to be of no clinical significance. Staging of anal canal cancer is based on the tumor size and the unique lymphatic drainage system in this region. Cancer prevention and treatment have evolved over time. Issues remain regarding optimizing diagnostic and therapeutic approaches and determining the potential for prophylactic HPV vaccines to prevent anal HPV infection and anal cancer in at-risk groups.

**Risk Factors**

Epidemiologic studies have shown that most anal cancers are associated with HPV infection, predominately oncogenic types 16 (HPV-16) and 18 (HPV-18).\(^9,10\) A recent meta-analysis reported an HPV prevalence of 91.5%, 93.9%, and 84.3% among 671 anal intraepithelial neoplasia (AIN)1 cases, 609 AIN 2/3 cases, and 955 anal carcinomas, respectively.\(^11\) Anal intercourse is among the presumed mechanisms by which HPV is introduced into the anal canal. Men with human immunodeficiency virus (HIV) are also at increased risk for anal cancer.

Other risk factors include an increasing number of sexual partners, a history of anogenital warts, previous lower genital tract dysplasia or carcinoma, and a history of smoking. In addition to HIV infection, immunosuppression in solid organ transplant and immune disorders has also been shown to be a risk factor.\(^10\)

**Preinvasive Lesions**

1) **Anal Condyloma Acuminatum (Anal Wart).—** Although the natural history of progression to squamous dysplasia...
and squamous cell carcinoma is still to be defined, anal condyloma acuminatum (anal wart) is in general regarded as a lesion with the potential to develop cancer, the reported incidence of squamous cell carcinoma of the anus in patients with anal condyloma being 3% to 4% and likely increasing.12,13

The histologic hallmark of a typical condyloma acuminatum is the presence of koilocytic changes (vacuolated cytoplasm and enlarged, hyperchromatic nuclei with irregular nuclear membranes, with or without binucleation) in a cauliflower-like growth that is composed of papillary excrescences lined by hyperkeratotic squamous epithelium. Koilocytic changes may be absent, however, presumably because the viral infection has subsided.14

While many anal condylomata, particularly those of anal skin (perineum), harbor low-risk HPV (types 6 or 11) and may therefore be regarded as having a minimal risk of progression to cancer, those of anal canal may be associated with high-risk types (such as HPV-16) or a mixture of low- and high-risk types and may go on to develop malignancy. This is particularly true in immunocompromised patients. Therefore, condylomata without high-grade dysplasia do not necessarily always equate to low-risk HPV infection, a misconception not uncommon among both clinicians and pathologists.

For pathologic diagnosis, those lesions with typical condylomatous features as described above may be diagnosed as “condyloma acuminatum,” whereas those that also have conventional histologic evidence of low-grade dysplasia (ie, atypia and mitoses in the lower third of the epithelium) as “condyloma acuminatum with mild dysplasia (low-grade squamous intraepithelial lesion/anal intraepithelial neoplasia 1 [LSIL/AIN I]).” Others may classify all condylomata without high-grade dysplasia under the term condyloma acuminatum (LSIL/AIN I), or...
alternatively, *condyloma acuminatum*; there is no evidence of high-grade dysplasia.\textsuperscript{35}

2) **Flat Dysplasia.**—Compared to condyloma, flat squamous lesions are more frequently associated with high-risk HPV infection. Grading of dysplasia again follows what has been established for cervical lesions. In the 2-tiered system, mild dysplasia constitutes LSIL. High-grade SIL (HSIL) then encompasses lesions that have mitotic activity higher than the lower third of the mucosa and that often have full thickness atypia and loss of polarity (moderate and severe dysplasia).

Terminology for noncondylomatous squamous dysplasia involving the anal canal mucosa (ATZ and the squamous zone) versus that involving the hair-bearing anal/perianal skin can be confusing. Conventionally, lesions involving the former have been termed *dysplasia, in situ carcinoma,* or *anal intraepithelial neoplasia,* whereas lesions involving the skin, *Bowen disease.* Bowen disease conventionally carries with it the implication of having a strong tendency to recur after local treatment but with only a small percentage progressing to invasive squamous cell carcinoma.\textsuperscript{16,17} However, given that such squamous lesions are not always restricted to 1 region, distinct separation of terminology does not always seem logical.

Indeed, the more recent recommendation states that all squamous lesions occurring both in the anal canal and the perianal skin or skin of perineum be termed either low-grade squamous intraepithelial lesion or high-grade squamous intraepithelial lesion.\textsuperscript{18} Bowen disease would then fall into the HSIL category. Such recommendations, however, have yet to be fully adopted. At the current time, some pathologists still prefer to use Bowen disease for anal skin, while others are using dysplasia or squamous intraepithelial lesion for all sites.

The utility of p16 and Ki-67 immunohistochemical staining for diagnosing anal squamous dysplasia has been studied less intensely than it has for gynecologic cases. A recent study of anal intraepithelial neoplasia indicated that, like in the uterine cervix, both markers offer utility to distinguish low-grade SIL from high-grade SIL. In general, high-grade SIL tends to have diffuse p16 staining and an increased number of Ki-67–positive cells in the middle or upper third of the epithelium (positive p16 staining refers to the presence of nuclear or cytoplasmic reactivity and for Ki-67, the presence of nuclear reactivity).\textsuperscript{19} It is to be noted, however, that p16 positive staining has also been observed in LSIL associated with high-risk HPV types. Thus, these markers may be more valuable in the distinction of reactive squamous epithelium from dysplastic squamous epithelium than in separating low-grade from high-grade dysplasia.\textsuperscript{35}

**Giant Condyloma of Buschke and Lowenstein/ Verrucous Carcinoma**

First described by Buschke in 1886 and later by Buschke and Lowenstein in 1925,\textsuperscript{20} the “giant condyloma of Buschke and Lowenstein” refers to a slow-growing neoplasm that has a tendency to recur and to form abscesses and fistulae. Verrucous carcinoma was first described by Ackerman\textsuperscript{21} in 1948 for a low-grade carcinoma of oral mucosal viral warts. Subsequently, this term has been expanded to lesions of other sites. It is believed that the giant condyloma of Buschke and Lowenstein represents the anogenital version of verrucous carcinoma and is an intermediate state between condyloma acuminatum and squamous cell carcinoma.\textsuperscript{15,22} It appears that this tumor does not arise from malignant transformation of a condyloma but represents a low-grade form of squamous cell carcinoma. Like conventional condylomata, these lesions are more likely to be associated with low-risk HPV. It remains to be elucidated which viral or host risk factors play a role in promoting the oncogenic potential of HPV-6 and HPV-11 to result in a giant condyloma of Buschke and Lowenstein that can be locally invasive.\textsuperscript{23–26}

The histologic appearance on a biopsy specimen may be identical to that seen in common condyloma acuminatum (surface hyperkeratosis, prominent acanthosis and papillomatosis, with orderly arrangement of the epithelial layers). However, excision specimens will often demonstrate an endophytic component that is not present in ordinary condylomata. The endophytic growth is composed of an intact but often irregular base with blunt downward projections and keratin-filled cysts and is associated with destruction of the underlying tissue.

The biology of such lesions is typically that of local invasion without metastasis. It is to be noted that the presence of severe cytologic atypia or stromal invasion in an infiltrative fashion (different from the pushing downward growth as described above) should lead to the diagnosis of squamous cell carcinoma, with appropriately aggressive therapy (see below).

**Squamous Cell Carcinoma**

Anal squamous cell carcinoma occurs more frequently in women than in men (1.5 versus 1.0 per 100,000).\textsuperscript{30} The clinical presentation is nonspecific. Anal bleeding appears to be the most common presenting symptom.

Histologic subtyping of anal squamous cell carcinomas was once recommended by the WHO,\textsuperscript{27} and the categories included large-cell keratinizing squamous carcinoma, large-cell nonkeratinizing squamous carcinoma, and basaloid carcinoma. Others\textsuperscript{28,29} have advocated dividing these tumors into (1) squamous cell carcinoma, analogous to its counterpart elsewhere in the skin, and (2) cloacogenic (transitional, basaloid) carcinoma, supposedly originating from the ATZ mucosa.

The morphologic patterns that are commonly associated with basaloid or cloacogenic carcinoma include nested and trabecular growth of small cells without the intercellular bridges typical of conventional squamous cell carcinoma (Figure 4), although foci of more conventional squamous differentiation can usually be found. Peripheral palisading similar to that of cutaneous basal cell carcinoma may be present. Sometimes, these tumors can have small cystic foci lined by mucin-producing cells, the reason for the former designation of mucoepidermoid carcinoma (Figure 5). Others may grow in lobules and contain prominent eosinophilic, hyaline, paucicellular basement membrane–like material around and within tumor nests, resulting in an appearance simulating that of an adenoid cystic carcinoma\textsuperscript{30} (Figure 6, A through D). Central necrosis and mitotic figures may be prominent, but cellular pleomorphism is not typical.

However, histologic subtyping of anal squamous cell carcinomas is difficult in practice and has little clinical value. Very commonly, a single tumor can show mixtures of histologic subtypes, including foci of conventional squamous cell carcinoma. Thus, the WHO now suggests...
that the generic term "squamous cell carcinoma" be used for all these variants. However, the following histologic subtypes seem to have a less favorable prognosis: (1) squamous cell carcinoma with mucinous microcysts (areas with well-formed acinar or cystic spaces containing mucin that are positive for Alcian blue and periodic acid–Schiff with diastase), and (2) small cell (anaplastic) carcinoma (not small cell neuroendocrine carcinoma). Moreover, poor keratinization, prominent basaloid features, and small tumor cell size are related to infection with high-risk HPV. Thus, in the pathologic diagnosis, a comment may be made about these histologic variations that may affect prognosis or reflect different etiology.

Grading of squamous cell carcinoma should be based on the degree of cellular differentiation, which is reflected mainly by the extent of keratin production and cell cohesiveness. Poor differentiation based on the degree of dissociation of tumor cells has been related to poor prognosis by univariate analysis. Grading based on biopsy material may be misleading, as it may not be representative of the tumor as a whole.

As defined by the AJCC, pathologic tumor staging of anal squamous cell carcinoma is based on tumor size, and pathologic lymph node staging is based on the lymphatic drainage system in this region. Tumors proximal to the pectinate line drain into the pelvis along the middle rectal vessels to the pelvic side walls and internal iliac chains and superiorly via the superior rectal vessels to the periaortic nodes. Tumors distal to the dentate line drain along cutaneous pathways to the inguinal and the femoral nodal chains.

Prevention and Management of Squamous Cell Lesions

Although many independent as well as interrelated etiologies have been implicated in anal squamous cell lesions, HPV remains the most significant. Thus, much attention has been given to the role of HPV typing in triaging patients with anal lesions, particularly in high-risk patient populations. However, as yet, whether the presence of specific HPV subtypes as detected by either HPV in situ hybridization or polymerase chain reaction will allow more accurate and cost-effective prediction of precancerous lesions remains an unanswered question. Currently, intense screening with high-resolution anoscopy and cytology, and HPV testing with polymerase chain reaction or fluorescence in situ hybridization are mainly limited to
investigations in high-risk subpopulations such as HIV-positive homosexual men. The efficacy of HPV prophylactic vaccines in preventing anal squamous neoplasia is also still at an investigational stage, although its clinical use in the near future may be anticipated.

Management of precursor lesions remains a challenge. Squamous intraepithelial lesion is often a multifocal process; thus, complete local excision is often inadequate or not possible because of the morbidity of the procedure. Newer strategies include topical immunomodulation, photodynamic therapy, and therapeutic vaccines. However, long-term follow-up to determine the efficacy of these treatments is not available. Office-based or operating room procedures directed by high-resolution anoscopy and cytology are believed to result in clearance of HSIL in up to 80% of patients, malignant progression in 1%, and less morbidity than wide local excision.

Typical giant condyloma of Buschke-Lowenstein/verrucous carcinoma is often managed surgically with complete excision being the preferred initial treatment. Resection, chemotherapy, and focused radiation have all been used; however, the response has been generally unpredictable.

Management of invasive anal squamous cell carcinoma has shifted during the past 3 to 4 decades from surgery (ie, abdominoperineal resection) to a combined therapy incorporating pelvic radiation and chemotherapy (5-fluorouracil and mitomycin C), with surgery reserved for persistent or recurrent disease. This combined modality therapy has resulted in an estimated 5-year disease-free survival of 60% and 5-year overall survival of 75%. Significant predictors for treatment failure include high T stage and completion of radiotherapy. In the era of highly active antiretroviral therapy, the outcome after chemoradiotherapy for HIV-related cancers is comparable to that for patients without HIV, although there may be significant toxicity; earlier diagnosis and risk-adapted therapy are key to success for such patients.

**ADENOCARCINOMA**

**Overview**

Adenocarcinoma of the anal canal accounts for about 10% (5%–19%) of all anal canal cancers. Most such tumors have a colorectal phenotype and represent tumors originating from the colorectal zone in the upper portion of the anal canal or from the glandular cells of the ATZ mucosa. Distinction of these tumors from lower rectal adenocarcinomas directly extending into the anal canal can be very difficult or impossible. “Anal gland adenocarcinoma” and “fistula associated adenocarcinoma” constitute the 2 other major types of adenocarcinoma; both are categorized by the WHO under the term *extramucosal (perianal) adenocarcinoma*. Finally, Paget disease represents a form of intraepithelial adenocarcinoma and will be discussed in this section as well. As a whole, adenocarcinoma of the anal canal represents a unique challenge both for pathologic diagnosis and for clinical management. Its rarity makes it difficult to perform controlled clinical studies or large retrospective reviews.

**Risk Factors**

Little is known about risk factors. High-risk HPV types may play a role, as their presence has been documented in at least some cases of anal adenocarcinoma. Crohn disease or other inflammatory conditions that result in chronic anal fistula may predispose to development of fistula-associated adenocarcinomas.

**Colorectal-Type Adenocarcinoma**

The most significant clinical implication of distinguishing the anal canal origin of these tumors relates to its pattern of local spread, which reflects the dual lymphatic drainage as mentioned under staging of squamous cell carcinomas. Thus, a colorectal type adenocarcinoma occurring within the anal canal carries a higher risk of nodal disease along the inguinal and femoral nodal chains than a rectum-based adenocarcinoma.

Histologic diagnosis rarely poses a significant challenge. However, it is worth mentioning that colorectal type adenocarcinoma of this site (as is also true for the distal rectum) may have unexpected CK7 expression, although it is usually accompanied by coexpression of CK20 (as opposed to anal gland carcinomas that usually do not have CK20 positivity, see below).

**Anal Gland Adenocarcinoma**

Although the original WHO classification listed this tumor under the category “adenocarcinoma of anal glands,” these tumors may actually arise from or be related to anal ducts that drain the anal glands, and may therefore be more appropriately termed *anal duct adenocarcinoma*. In reality, the association or connection with normal anal gland/ducts is often hard to demonstrate histologically, and the reported cases under this category vary widely in microscopic appearance.

Hobbs et al in 2001 studied 14 cases of anal canal adenocarcinoma and identified 7 cases that fit a set of criteria that the authors defined for carcinoma of anal gland type: haphazardly dispersed, small glands with scant mucin production that invade the wall of the anorectal area without an intraluminal component; the tumor glands are positive for CK7. Others reported clinically and grossly typical anal gland–type cancers with a histologic appearance inseparable from that of conventional mucinous-type colorectal adenocarcinoma. Moreover, carcinomas associated with anal fistulae are often mucinous, and it remains to be determined if at least some of these fistula-associated tumors are actually of anal gland or anal duct origin.

Thus, the histologic pattern of anal gland adenocarcinoma remains to be sharply defined. In practice, it would seem reasonable to render this diagnosis when the tumor is primary to the anal canal, centered within the wall of the anorectal area without a preexisting fistula and without surface mucosa dysplasia, irrespective of the extent of mucin production (Figure 7).

**Adenocarcinoma Within Anorectal Fistula**

Anorectal fistulae may be developmental or acquired. The latter are often secondary to inflammatory conditions such as Crohn disease. Adenocarcinomas arising in anorectal fistulae have been documented and histologic appearance of such tumors is often that of a well-differentiated mucinous adenocarcinoma. The exact cell of origin is difficult to determine. Some may possibly be related to rectal-type glandular mucosa, while others are related to anal glands or ducts. As mentioned above,
distinction of anal gland adenocarcinoma from adenocarcinoma within anorectal fistula can be difficult, as some fistulae may result from dilated anal glands or ducts. Indeed, histochemical studies seem to suggest that at least some fistula-associated adenocarcinomas have mucin characteristics that are similar to those of anal glands.46

Figure 7. This mucin-producing adenocarcinoma is centered in the wall of the anorectal transition zone, not associated with surface mucosa dysplasia or fistula disease. It is tempting to assume that this tumor is of anal gland or anal duct origin (hematoxylin-eosin, original magnification ×400).

Figure 8. Anal Paget disease associated with nonneoplastic proliferation of background squamous mucosa (hematoxylin-eosin, original magnification ×400).

Paget Disease

Extramammary Paget disease was first described in 1889 in an article by Crocker46 entitled “Paget’s Disease Affecting the Scrotum and Penis,” 15 years after James Paget’s initial description of mammary Paget disease.45 Subsequently, the lesion was also seen in other anogenital sites, including vulvar skin (most common), perineum, anal margin skin, and anal canal.

Clinically, the disease often presents in elderly patients as a pruritic, red or white, crusted patch in anal skin. Conventionally, anal Paget disease, similar to its counterpart in other extramammary sites, has been divided into “primary” and “secondary” diseases. Primary Paget disease encompasses those cases that originate from the epidermis or squamous epithelium and may or may not evolve into an invasive lesion during its course. The histogenesis of primary Paget disease remains elusive, with the proposed cells of origin including pluripotent epidermal stem cells,47 adnexal stem cells,48 intraepidermal Toker cells,28,49 or apocrine glands.54 “Secondary” Paget disease in the anal region is often associated with an underlying visceral malignancy, most commonly a colorectal type adenocarcinoma. The visceral malignancy may be synchronous or metachronous. Given that the literature reports are largely limited to case reports or small series, it is difficult to accurately determine the prevalence of primary versus secondary Paget disease. Some55 estimate that in patients who have perianal Paget disease, the incidence of a synchronous visceral carcinoma is more than 50%. Others56,57 suggest that perianal Paget disease may be associated with tubo-ovarian adenocarcinoma in 7% to 24% of cases and gastrointestinal carcinoma in 12% to 14%.

Sometimes, a distal rectal or anal canal adenocarcinoma may be associated with very limited pagetoid extension of cancer cells in the overlying or immediately adjacent squamous epithelium that does not result in a gross appearance of Paget disease. Strictly speaking, this is a form of secondary Paget disease as well, although its clinical significance in this setting seems trivial.

Diagnostic issues arise when a primary anal Paget disease is associated with an invasive component, or when a secondary Paget disease is associated with a metachronous internal malignancy that is not apparent at the time the Paget disease manifests clinically. Consequently, there have been research efforts that aim at distinguishing primary from secondary conditions by immunohistochemical phenotyping. The rarity of the disease, however, has been a significant limiting factor to such efforts. Thus, although promising patterns have emerged, issues remain. Goldblum and Hart48 reported that 4 of 4 cases of anal Paget disease that were associated with rectal adenocarcinoma showed a CK7+/CK20+/GCDFP15+ phenotype in both the Paget disease and the rectal adenocarcinoma, whereas 4 of 6 cases of anal Paget disease without a documented rectal adenocarcinoma had a CK7+/CK20−/GCDFP15+ phenotype. Similar results also have been reported by others in both anal and vulvar Paget disease. Thus, CK7 appears to be a universal marker of Paget cells, regardless of their site or the presence of an associated internal malignancy. CK20 positivity seems to be a uniform finding in cases that are associated with rectal adenocarcinoma. However, CK20 expression has been observed in occasional cases of primary anal and vulvar Paget disease; thus, its specificity is less than perfect. In such cases, GCDFP15 expression may be helpful.

It is intriguing to note that a more recent study4 reported a CK7+/CK20+ phenotype in only 13% (4 of 30) of rectal adenocarcinomas unassociated with Paget disease, a rate comparable to that reported for nonrectal large bowel adenocarcinomas. The question then is what promotes certain CK7-positive rectal adenocarcinomas to develop secondary Paget disease.

Interestingly, anal Paget disease is typically associated with hyperplastic changes in the involved squamous mucosa (Figure 8). Awareness of such changes may help point to the diagnosis of Paget disease (particularly at the time of frozen section procedure) or avoid the misdiagnosis of squamous dysplasia.
Prevention and Management

Little is known about cancer prevention that is specific for anal adenocarcinoma. Treatment options vary widely from primary surgical resection to definitive chemoradiation or neoadjuvant chemoradiation and surgical resection. The management of Paget disease is primarily surgical. Local recurrence is common because of the common presence of multifocal disease, and the difficulty in delineating the lesion grossly. Survival outcome in these patients is often dictated by the presence or absence and stage of an invasive component.

NEUROENDOCRINE NEOPLASMS

Neuroendocrine neoplasms may occasionally occur in the anal canal. Most such tumors probably originate from neuroendocrine cells residing in colorectal type mucosa, although neuroendocrine cells are known to exist in ATZ mucosa as well.

Studies dedicated solely to anal canal neuroendocrine neoplasms are essentially limited to case reports. As a group, well-differentiated neuroendocrine tumors, that is, carcinoid tumors, of the anorectum are believed to have an indolent clinical course. In a recent study of 70 carcinoid tumors of the rectum (including those of anal canal), we observed the following features as indicators for poor prognosis: large size, deep invasion, lymphovascular invasion, and an elevated mitotic rate (>2 per 50 high-power fields [HPFs]).

High-grade neuroendocrine carcinomas, small cell or non–small cell type, may occur in the anal canal as well, constituting 5% (3 of 65) of all high-grade neuroendocrine carcinomas of the entire tubular gastrointestinal tract in our series.

From a diagnostic point of view, anorectal carcinoid tumors with a tubular pattern (a pattern not uncommonly seen in this location) may be confused with conventional adenocarcinoma; and high-grade neuroendocrine carcinomas may be confused with poorly differentiated adenocarcinoma, basaloid squamous cell carcinoma, or melanoma. This may be particularly problematic in biopsy samples. In this scenario, immunohistochemical stains are helpful. Expression of neuroendocrine markers is common but not universal, and labeling may be focal. Small cell carcinomas of the anus may show immunoreactivity for thyroid transcription factor–1 (TTF-1), a phenomenon reported in a variety of other extrapulmonary sites as well. Stains for squamous differentiation (34βE12 and p63/4A4) yield negative

Figure 9. Virtually all malignant tumors occurring in the anal canal can become poorly differentiated and difficult to recognize. Shown here are a large cell–type, high-grade neuroendocrine carcinoma (A), a poorly differentiated squamous cell carcinoma (B), a poorly differentiated adenocarcinoma (C), and a malignant melanoma (D) (hematoxylin-eosin, original magnifications ×200 [A, B, and C] and ×400 [D]).
results in anal small cell carcinomas. However, similar to its counterpart in other sites, anal small cell carcinoma may contain scattered nests of cells with squamous differentiation, usually constituting less than 5% of the entire tumor volume. Awareness of such a phenomenon will help avoid misdiagnosing such tumors as true squamous cell carcinomas.

**MALIGNANT MELANOMA**

Anal melanomas account for about 4% of anal canal tumors and less than 1% of all melanomas. The histologic features of anal melanoma resemble those of cutaneous melanomas. Most show a junctional component adjacent to the invasive tumor, and this finding is evidence that the lesion is primary. The desmoplastic variant may occasionally occur at this site as well, and diagnosis may be challenging and requires immunohistochemical support.

Management of anal melanoma remains a major challenge. Despite the fact that most patients present with localized and apparently curable primary tumors, the mean survival is only 2 years. The extent of surgical resection (abdominoperineal resection versus local excision) does not seem to significantly impact outcome, as patients often die of distant metastases. In a study of 46 patients, perineural invasion was an important prognostic factor.

Recent studies have shed light on the pathogenetic molecular pathways in melanoma of various sites. In a study of 20 anal melanomas, Antonescu et al. identified 3 KIT mutation-carrying tumors, and by in vitro drug testing, showed that the KIT (L576P) mutant was responsive to specific kinase inhibitors.

**MESENCHYMAAL TUMORS**

Although a variety of mesenchymal tumors may occur in the anal canal, such as smooth muscle tumors, gastrointestinal stromal tumors (GISTs), schwannomas, sarcomas related to endometriosis or the müllerian system, and lymphangiomas, the most commonly seen are smooth muscle tumors and GISTs. An accurate estimation of their relative frequency is difficult because many tumors previously designated as smooth muscle or neural tumors may now be classified as GISTs.

Leiomyomas often originate from muscularis mucosae, appear as intraluminal polyps, and are cured by complete removal. Leiomyosarcomas, on the other hand, are histologically high-grade sarcomas with at least focal pleomorphism and high mitotic activity. Most leiomyosarcomas also present as intraluminal polyloid tumors, although origin specifically from the muscularis mucosae could not be documented in any of the 8 leiomyosarcomas of the rectum and anus studied by Miettinen et al. Anorectal leiomyosarcomas may have a better prognosis when compared to GISTs with comparable mitotic counts.

Gastrointestinal stromal tumors only infrequently arise in the large bowel. Within the large bowel, however, the rectum is the most common site. Gastrointestinal stromal tumors of the anal canal are on record as well, estimated to account for about 2% to 8% of anorectal GISTs. In the anorectum, GISTs may be of spindle cell (65%), epithelioid, or mixed types. Immunohistochemically, 84% of c-kit–positive GISTs stain positively for CD34, 29% for smooth muscle actin, and 4% for S100 protein. As with GISTs of other sites, tumor size and mitotic count are significant prognostic factors. Miettinen et al have shown that in the rectum and anus, GISTs larger than 5 cm or with more than 5 mitoses per 50 HPFs are likely to behave in a malignant fashion, whereas those smaller than 2 cm and with less than 5 mitoses per 50 HPFs only rarely recur or cause death, and those with a size between 2 cm and 5 cm and a mitotic count of less than 5 mitoses per 50 HPFs have a low frequency of malignant behavior, intermediate between the above 2 categories.

**MALIGNANT LYMPHOMA**

Primary lymphoma of the anal canal is rare. However, cases of both Hodgkin disease and non-Hodgkin lymphomas are on record. Immunocompromised patients infected with HIV are particularly at risk. In this

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**Table 1. Morphologic and Immunophenotypic Features of Anal Canal Malignancies**

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<tr>
<th>Tumor Type</th>
<th>Morphology</th>
<th>Immunohistochemical Staining</th>
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<tr>
<td>Squamous cell carcinoma</td>
<td>Squamous differentiation</td>
<td>HMW Keratin</td>
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<tr>
<td>Adenocarcinoma</td>
<td>Mucin, gland formation</td>
<td>++</td>
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<tr>
<td>NE tumor</td>
<td>Trabecular, organoid, or nested. No or low mitotic activity.</td>
<td>–</td>
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<tr>
<td>Carcinoid</td>
<td>Can have foci of squamous differentiation</td>
<td>–</td>
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<tr>
<td>Small cell carcinoma</td>
<td>(Squamous foci +)</td>
<td>–</td>
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<tr>
<td>High-grade NE carcinoma</td>
<td>May simulate carcinoma, but with high mitotic activity and often foci of necrosis</td>
<td>–</td>
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<tr>
<td>Melanoma</td>
<td>In situ component, melanin pigment</td>
<td>–</td>
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<td>Sarcoma</td>
<td>Lacks cohesiveness</td>
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<td>Lymphoma</td>
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Abbreviations: HMW, high molecular weight; NE, neuroendocrine.

* No entry indicates data not relevant.
population, the lymphomas are mainly B-cell type and high grade. In contrast, in the non-HIV–infected population, anal lymphomas tend to occur in older patients, are also B-cell type, but are often lower grade.

**TUMORLIKE CONDITIONS**

A variety of lesions may mimic anal neoplasms. For example, ectopic prostatic tissue, endometriosis, inflammatory cloacogenic polyp, and prolapse-related lesions can all form a mass lesion.

**DIFFERENTIAL DIAGNOSIS OF POORLY DIFFERENTIATED ANAL CANAL NEOPLASMS**

Essentially all malignant tumor entities occurring in the anal canal may be poorly differentiated, such that the distinction among the various histologic types becomes a challenge. Commonly, these tumors assume the appearance of a cellular neoplasm with a solid growth pattern (Figure 9, A through D). A typical challenging scenario is distinguishing a poorly differentiated squamous cell carcinoma with basaloid features from a small cell (neuroendocrine) carcinoma. Also typically challenging is the distinction of a malignant melanoma from literally every other cellular tumor with a solid growth pattern, including GIST. Table 1 provides some key morphologic and immunohistochemical features that are useful in resolving these diagnostic dilemmas. Morphologically, a number of points deserve special attention. First, small cell carcinoma may have foci of abrupt squamous differentiation, as described above, and as such, can be mistaken for squamous cell carcinoma. Second, carcinoïd tumors and small cell carcinomas (or non-small cell–type high-grade neuroendocrine carcinomas) can be superficially similar, particularly in a small and crushed biopsy specimen. In this scenario, the presence of increased mitotic activity and high Ki-67 labeling index favor a diagnosis of high-grade neuroendocrine carcinoma or small cell carcinoma. Lastly, in situ growth and pigment production can be very helpful in diagnosing melanoma. From an immunohistochemical point of view, additional worthwhile points are listed in Table 2. Ultimately, however, the key to achieving a correct diagnosis is the integration of morphologic and immunohistochemical findings.

**References**


