Uncommon Anal Neoplasms

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KEYWORDS

- Unusual cancers • Anal neuroendocrine tumor • Anal melanoma • Anal lymphoma

KEY POINTS

- Unusual cases of anal cancer comprise histologies of anal gland and canal adenocarcinoma, anal lymphoma, anal neuroendocrine tumors, and anal melanomas.
- Incidence is likely to rise with the greater use of colonoscopy and better imaging techniques, such as MRI.
- Management is based on usual treatment of underlying tumor type rather than that of anal epithelioid cancer.
- Improvements in outcome may result from an effort to collect rare cases of anal cancer on an international database.

Anal cancer is a rare disease with epidermoid cancers accounting for 1% to 2% of all digestive tract malignancies.[1] Less common anal neoplasms comprise approximately 20% to 25% of these,[2] including anal canal adenocarcinoma, anorectal melanoma, mesenchymal and neurogenic tumors of the anal canal (in particular gastrointestinal

stromal tumors [GIST], schwannomas, and sarcomas), neuroendocrine tumors (NETs), lymphoma, and basal cell carcinoma (BCC). The anal canal is also a rare site for metastasis from other primary malignancies. As imaging technology improves, particularly MRI, and colonoscopy becomes routine, many rarer tumors are detected incidentally. Diligent linkage of clinical features with expert histopathology assessment identifies uncommon anal neoplasms to ensure that appropriate management is instituted.

ADENOCARCINOMA OF THE ANAL CANAL

Adenocarcinoma of the anal canal (ACA) accounts for 5% to 19% of all anal canal cancers.[3,4] These are subclassified under the World Health Organization Classification of Tumors into three main subtypes: (1) colorectal-type adenocarcinoma, (2) anal gland adenocarcinoma, and (3) fistula-associated adenocarcinoma.[5] In addition, a form of intraepithelial adenocarcinoma, also known as Paget disease, is a distinct entity and affects areas with a high density of apocrine glands around the anogenital region.

The clinical signs of adenocarcinoma, such as anal squamous cell anal cancer (SCC), are often nonspecific and the diagnosis is commonly made serendipitously in patients undergoing excision of presumed benign conditions. Management of ACA is challenging because of its rarity, difficulty in confirming diagnosis, and lack of direct evidence for particular clinical management strategies.[6] There is little information regarding risk factors; however, there is some linkage to high-risk subtypes of human papilloma virus, mainly subtype 18.[7]

Colorectal-Type Adenocarcinoma

These tumors represent either downward spread of a primary rectal adenocarcinoma (RA) or de novo carcinoma arising in residual glandular cells of the anal transition zone just above the dentate line. In contrast to a rectal-based adenocarcinoma, there is a higher risk of inguinal and femoral nodal involvement because of the dual lymphatic drainage of the anus.[8] Histologically and clinically these cancers are indistinguishable from usual rectal tumors and apart from their anatomic location do not represent a special entity. In most cases the histologic diagnosis is straightforward. However, on immunohistochemistry, colorectal-type ACA may have unexpected cytokeratin (CK) 7 expression, although this is usually accompanied by coexpression of CK20.[6] This is different from anal gland carcinomas, which usually are CK20 negative.

In practice, tumors used to be classified as rectal cancers on digital examination if their epicenter was located greater than 2 cm proximal to the dentate line or the anorectal ring, and as anal canal cancers if their epicenter was less than 2 cm below the dentate line.[9] Newer imaging techniques, such as MRI, assist with delineating site of origin more accurately, particularly if there is a polypoid stalk (**Figs. 1** and **2**).

Anal Gland Adenocarcinoma

Anal gland tumors usually originate from the anal ducts and demonstrate continuity with the anal gland epithelium. There are only a few case reports demonstrating convincing evidence of the origin of the tumor from an anal gland.[10–13] These tumors are sometimes termed as "anal duct adenocarcinoma" because of their putative origin and are characterized histologically by the combination of ductal and mucinous areas. Hobbs and colleagues[14] defined the following criteria: cells haphazardly dispersed, invading the wall of the anorectal area, containing small glands with little mucin production and without an intraluminal component; and immune-histochemical positivity for CK7. Kuroda and colleagues[15] have demonstrated that CK7, CK19, and MUC5AC immune-histochemical reactivity is a marker for adenocarcinoma of anal gland origin.

Fig. 1. MRI coronal T2-weighted: polypoidal adenocarcinoma (*arrow*) from low rectum.

In clinical practice, if tumor is present within the anal canal wall, without a pre-existing fistula or dysplasia of the surface mucosa, then irrespective of the extent of mucin production it is more likely to be anal gland adenocarcinoma.

Adenocarcinoma Within Anorectal Fistula

Anorectal fistulae may be developmental or acquired secondary to underlying inflammatory bowel disease, such as Crohn disease.[16–18] Adenocarcinomas arising in anorectal fistulae usually have the histologic appearance of a well-differentiated mucinous adenocarcinoma; however, tubular adenocarcinomas and squamous cell neoplasia can also be present[17,19,20] (**Fig. 3**). The cell of origin could be related to either rectal-type glandular mucosa or anal glands or ducts. Occasionally there is evidence of epithelioid granulomas secondary to inflammation or extravasated mucin, in the absence of other signs of underlying inflammatory bowel disease. Rarely, adenocarcinomas can arise in congenital duplications of the lower part of the hindgut, which can be lined by rectal mucosa that has a tendency to become malignant.[17]
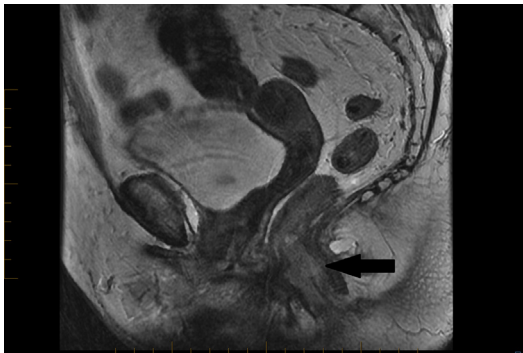

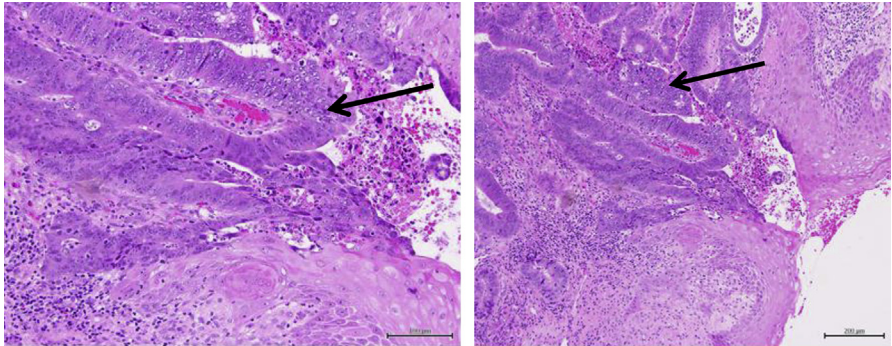**Fig. 2.** MRI sagittal T2-weighted: anal canal adenocarcinoma (*arrow*).

Fig. 3. Adenocarcinoma of the anal canal. Malignant glands (*arrows*) are seen extending from the luminal surface, underrunning the adjacent squamous epithelium and infiltrating the surrounding soft tissues.

Management of Anal Adenocarcinoma

Locoregional disease

Importantly, the management of adenocarcinomas arising in the anal canal follows the same principles as rectal cancer, rather than SCC anus. The primary treatment is surgical resection, typically abdominoperineal resection (APR) because sphincter preservation is not achievable. The literature supports surgical resection as providing the lowest rates of local relapse, recognizing that with historical data sets there is inevitable selection bias. Based on limited data, survival rates seem to be improved with multimodality management with chemotherapy and radiotherapy given before or after surgery, with improvement in local and systemic control.[2,3,8,10,21] For anal adenocarcinoma, data exist for benefit from radiation therapy given either neoadjuvantly or adjuvantly for T3-4 and N1-2 stage, as per rectal cancer.[22,23] Intensity modulated radiation therapy (IMRT) and Volumetric modulated arc therapy (VMAT) techniques are recommended and treatment volume should reflect the lymphatic drainage of the anus, including inguinal lymph nodes.[23]

Prognosis

Only limited case series have been reported. The most recent data from a Surveillance, Epidemiology and End Results database review from 1990 to 2011 compared survival of patients diagnosed with ACA, anal SCC, and RA. Median overall survival (OS) of patients with ACA was 33 months, compared with SCC of 118 months and RA of 68 months (*P*<.01). Multivariate analysis demonstrated that ACA had worse prognosis than SCC (hazard ratio, 0.66; 95% confidence interval, 0.59–0.75; *P*<.01) and RA (hazard ratio, 0.68; 95% confidence interval, 0.61–0.77; *P*<.01). Improved survival was observed in patients who underwent radical surgery (hazard ratio, 0.71; 95% confidence interval, 0.51–1.00; *P* = .05).[4]

The importance of resection of adenocarcinomas arising in the anal canal was demonstrated in a retrospective series from MD Anderson Cancer Center in which 16 patients were treated between 1976 and 1998 with either primary radiotherapy or definitive chemoradiation (no surgery).[22] When compared stage for stage with 92 patients with SCC treated with definitive chemoradiation, patients with ACA had a higher 5-year local recurrence rate (18% for SCC vs 54% for ACA) and worse disease-free survival (DFS) (77% vs 19%, respectively) and 5-year OS (85% vs 64%).

A multicenter retrospective study (1974–2000) from the Rare Cancer Network compared 82 patients treated with different modalities. The 5-year actuarial local

relapse rate was 20% for APR (n = 6), 37% for radiotherapy plus surgery (n = 45), and 36% for definitive chemoradiation (n = 31). The 5-year OS was 21%, 29%, and 58%, respectively; 5-year DFS was 22%, 25%, and 54%.[23] Such data support the role of radiotherapy and raise the potential of definitive chemoradiation allowing sphincter preservation.

Metastatic disease

As with local therapy, management of metastatic disease follows the protocols used for colorectal cancer. Combination or single-agent palliative chemotherapy is used to prolong survival and improve local control and quality of life (QoL). There is paucity of data informing the choice of chemotherapy regimens or the role of newer targeted drugs. Overall outcome seems to be worse than patients with metastatic colorectal cancer.[24]

PAGET DISEASE OF THE ANAL CANAL

Paget disease of anal canal falls under the extramammary Paget disease group and was first described by Crocker[25] in 1889. It most commonly occurs in elderly patients and manifests as red or white-crusted patches of skin with associated pruritus in the anal region. Paget disease can also occur in other anogenital sites, most commonly in vulval skin, perineum, and anal margin skin. Primary Paget disease of the anus takes its origin from the epidermis or squamous epithelium and may not always evolve into an invasive lesion. In contrast, secondary Paget disease is often linked to an underlying visceral malignancy (eg, colorectal or ovarian carcinoma) and can either present synchronously or metachronously to the primary. Based on limited data, the incidence of synchronous visceral malignancy could be greater than 50% and should be excluded at diagnosis.[21] Occasionally histologically pagetoid extension of cancer cells from an underlying anal or RA is seen in the overlying or immediately adjacent squamous epithelium.

Histologically, Paget disease is classically associated with hyperplastic changes in the involved squamous mucosal surface. Knowledge of such changes assists in making the diagnosis of Paget disease especially during frozen section procedures, to avoid the misdiagnosis of simple squamous dysplasia. There have been efforts to distinguish primary from secondary disease based on immunohistochemical phenotyping; however, data are limited to small case series.[26] It seems that CK7 is a marker of Paget cells, irrespective of their site or an associated visceral malignancy. If it is associated with RA then cells are uniformly immunoreactive to CK20. CK20 expression is seen also in vulvar Paget disease. In those cases, GCDFP15 expression may be helpful; if positive it can lend support toward a nonrectal origin.

The management of Paget disease is usually surgical. The extent of treatment of noninvasive lesions is determined by preoperative mapping of the lesion and intraoperative confirmation by frozen sections to ascertain clear surgical margins. The prognosis of noninvasive Paget disease is good; however, local recurrence is often seen because of the presence of multifocal disease.

Locally invasive perianal Paget disease usually requires a radical surgical approach, although definitive chemoradiotherapy has also been used.[21] Management of secondary Paget disease is directed toward the treatment of the underlying malignancy and these patients have a guarded prognosis.[27,28]

ANORECTAL MELANOMA

Anorectal mucosal melanoma accounts for approximately 0.05% of all colorectal malignancies and 1% of all anal canal cancers.[29,30] It originates in the rectum in 42% and

anal canal in 33%, respectively, whereas the primary site cannot be determined in about 25%. Risk factors are not clearly defined apart from the association with human immunodeficiency virus infection.[31–33] Unlike other mucosal melanomas, anorectal site is more common in whites and females with median age of diagnosis at 60 years. Patients typically present with bleeding or a mass, anorectal pain, or change in bowel habit.[34] Occasionally, melanoma is an incidental pathologic finding after hemorrhoidectomy or anal polyp resection. Anorectal mucosal melanoma is pigmented in approximately one-third of cases and at presentation most lesions are greater than 2 mm thick. Regional lymph node involvement is seen in 60% of cases and distant metastases are present at diagnoses in about 30%.[35–38]

Pathology and Staging

Overall 20% of mucosal melanomas are multifocal, compared with less than 5% of cutaneous melanomas and 40% are amelanotic.[39,40] Histologic features are similar to cutaneous melanomas showing a junctional component adjacent to the invasive tumor, which also serves as evidence that the lesion is primary rather than metastatic (Fig. 4). The desmoplastic variant may occasionally occur at this site. Diagnosis may be challenging and requires immunohistochemical confirmation with tumor cells expressing S-100, HMB-45, and melan A (see Fig. 4). Factors associated with poor prognosis are tumor size and thickness, regional lymph node involvement, presence of perineural invasion, and amelanotic subtype.[37,41,42]

Anorectal melanoma is not addressed by the current American Joint Committee on Cancer staging system. Based on retrospective series, it is categorized as localized disease only, regional lymph node involvement, or distant metastases.[43,44] Survival outcomes from the Surveillance, Epidemiology and End Results database review of 183 patients treated for anorectal mucosal melanoma over a historic period (1973–2003) are presented in Table 1.[36]

Management

Locoregional disease
The primary aim of surgery is for curative resection (wide excision) to achieve negative margins. If possible a sphincter-sparing excision is performed; occasionally APR is

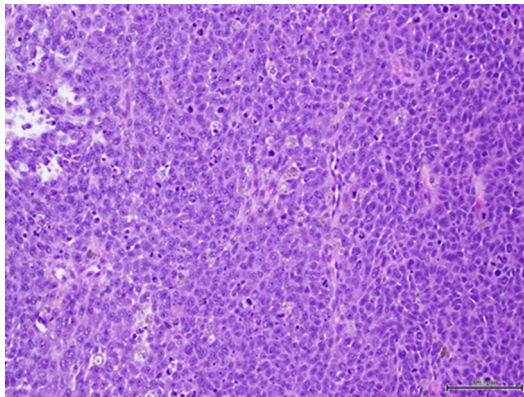**Fig. 4.** Melanoma, with hematoxylin and eosin (original magnification ×200) and with S100 immunohistochemical staining. Discohesive sheets of markedly atypical, epithelioid cells with prominent nucleoli and scattered mitoses and apoptotic cells are present in the soft tissue beneath the squamous epithelium. The tumor also showed focal but subtle melanin pigment.

Table 1
Surveillance, Epidemiology and End Results database review for the period 1973–2003 for survival outcomes in patients with anorectal mucosal melanoma

Stage[a]	Median Overall Survival, mo	Survival Rate, %
I (localized disease)	24	26.7
II (regional lymph node involved)	17	9.8
III (distant metastases)	8	0

[a] Defined as per data collection.

necessary for bulky disease or as salvage for patients with local but not systemic recurrence.[45] The impact of the extent of resection on long-term outcome has been reported in a few retrospective case series only. Although there is some evidence lending support to upfront APR providing improved local control at the expense of higher morbidity and detriment to QoL and functional capacity,[42,43] there is no evidence that more extensive surgery is associated with a better OS.[37,46–48] There is no proven role for sentinel lymph node biopsy or elective bilateral inguinal lymph node dissection in the absence of clinical nodal disease.[46,49,50]

Factors associated with a better outcome are R0 resection and tumor stage, based on the Swedish National Cancer Registry dataset. In a published series of 251 patients, the 5-year survival rates following an R0 resection were 19% compared with 6% where local excision was incomplete.[46,47]

Adjuvant therapy

Adjuvant treatment to improve locoregional relapse rate or OS has not been prospectively studied; however, adjuvant radiotherapy is often added to improve local control. The MD Anderson Cancer Center has reported on a series of 54 patients treated during 1989 to 2008 with hypofractionated radiotherapy (25–30 Gy in 5–6 fractions over a 2- to 3-week period) following sphincter-sparing local excision. The radiation was added as an alternative to APR. This approach was associated with local control in 82% of patients with sphincter preservation in 92% but there was no demonstrable impact on OS, with only 30% alive at 5 years.[51] The development of IMRT and VMAT techniques significantly reduces toxicity, which may increase its utility.

Systemic adjuvant therapy is not established in patients with mucosal melanoma. The only randomized evidence comes from a phase II study from China that enrolled 189 patients with resected mucosal melanoma. A total of 56 patients had anorectal melanoma and patients were randomized to observation (n = 21), 1 year of interferon alfa-2b (n = 17), or chemotherapy (n = 18; temozolomide plus cisplatin).[52] The median DFS was significantly prolonged in the chemotherapy arm compared with interferon and observation (20.8 vs 9.4 vs 5.4 months, respectively) as was median OS (49 vs 40 vs 21 months). However, no data have been reported in Western populations.

Metastatic disease

Treatment is based on extrapolation from trials of metastatic cutaneous melanoma. Few patients with melanoma of mucosal origin were enrolled in the clinical trials of modern antimelanoma therapies, with specific exclusion criteria for primaries of mucosal origin.

Approximately 10% of mucosal melanomas harbor the *BRAF* v600E driver mutation and a further 25% have somatic mutations including 9% with *KIT* mutations in exon 11 or 13.[53,54] Among all patients with mucosal melanoma with *BRAF* mutation, anorectal mucosal origin is the most common (20%) primary site.[55,56]

Results from three small phase II trials evaluating the role of imatinib in advanced mucosal melanoma (no breakdown of site of origin stated) harboring somatic alterations of *KIT* demonstrate significant activity[53,57,58] (**Table 2**).

Retrospective analysis from three major US centers demonstrated encouraging activity of the anti-CTLA4 immunotherapy agent ipilimumab in 33 patients with metastatic mucosal melanoma (eight of anorectal origin).[59] Data from 71 patients with metastatic mucosal melanoma (eight of anal origin) from a European extended access program for ipilimumab documented a disease control rate of 36% at median follow-up of 22 months.[60]

A pooled analysis of 121 patients with advanced mucosal melanoma from six trials using the human IgG4 anti-PD-1 monoclonal antibody nivolumab alone or combined with ipilimumab was presented at the 2015 Society of Melanoma Research Conference. A clinically meaningful improvement with monotherapy and combination was demonstrated in the whole group (primary site unstated) with overall response rate for dual therapy of 37%.[61]

PRIMARY LYMPHOMA OF THE ANORECTAL REGION

Anorectal lymphomas are rare comprising only 0.2% of anorectal tumors. Most are non-Hodgkin lymphoma; lymphoma at this site represents 9% of all non-Hodgkin lymphoma.[62,63] Cases of anorectal Hodgkin disease are extremely rare.[64] Anorectal lymphoma is reported to mainly affect young males but this is biased by data relating to the common association with AIDS (mean age, 34 vs 65 in HIV-negative group), particularly when the CD4 count is less than 100 per mm^3. The usage of highly active anti-retroviral therapy has impacted significantly on the incidence of AIDS-associated lymphoma.[65] AIDS-related lymphoma usually presents as extranodal disease and in one-quarter of patients the anorectal region is involved. Patients usually present with a mass or chronic ulceration with or without local lymphadenopathy; however, many patients are normal at examination and have normal initial investigations. In most AIDS-related cases the pathology demonstrates a high-grade large cell immunoblastic or pleomorphic B-cell lymphoma.[66,67] In patients without HIV, anal lymphoma is more commonly found at older age, is more prevalent in men, and is associated with risk factors including ulcerative colitis or other immunodeficiency conditions. Histologically these are most commonly lower grade B cell histology including mucosal-associated lymphatic tissue.[68]

Management

Patients are treated in line with standard lymphoma management protocols and surgery is restricted to biopsy, although some studies have suggested surgery for

Table 2			
Phase II trials evaluating the role of imatinib in advanced mucosal melanoma			
Trial	Carvajal et al,[53] 2011 N = 25	Hodi et al,[57] 2013 N = 25	Guo et al,[58] 2011 N = 43
Overall response rate	16%	29%[a]	—
Median progression-free survival	12 wk	—	3.5 mo
Median overall survival	46.3 wk	77%	53.5%
Disease control rates	—	—	—

[a] Best objective response rate.

resectable lesions.[63,69,70] Treatment of localized anal lymphoma may involve external beam radiotherapy in addition to chemotherapy. In comparison with the pre–highly active antiretroviral therapy era where OS was 8 months in AIDS-related Diffuse Large Bcell Lymphoma, the current 5-year OS approximates 60% to 80%.[71]

ANAL NEUROENDOCRINE TUMORS

Neuroendocrine cancer can arise anywhere in the body, but neuroendocrine neoplasms of the anorectal region are extremely rare and probably arise from the neuroendocrine cells in colorectal type mucosa, although neuroendocrine cells can be present in anal transitional zone mucosa. Incidental discovery at colonoscopy is increasingly common, as is the case with rectal NETs.[72] A recent analysis of NETs incidence in Ontario, Canada (population 13.6 million) between Jan 1994 and March 2012 documented less than 15 cases of anal origin of a total of 5619 NETs; in comparison there were 690 cases of rectal origin (12.3%) (S. Singh, personal communication, 2016, with permission and disclosure: parts of this material are based on data and information provided by Cancer Care Ontario. The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of Cancer Care Ontario. No endorsement by Cancer Care Ontario is intended or should be inferred).[73]

The classification of gastroenteropancreatic neuroendocrine neoplasms has evolved and the World Health Organization endorses the European Neuroendocrine Tumor Society's grading system for neuroendocrine neoplasms of any site within the digestive tract. This is based on the proliferative rate to stratify grade and requires a mitotic count and the Ki-67 labeling index. This system classifies well-differentiated tumors into low-grade (G1) and intermediate-grade (G2) categories; and all poorly differentiated NETs are classified as high-grade (G3) neuroendocrine carcinomas.[74,75] Low-to-intermediate grade NETs can be indolent in their clinical course; however, large tumor size, invasion depth, lymphovascular invasion, and an elevated mitotic rate are associated with poor prognosis.[74,75] Anal NETs seem to behave more aggressively and the rare anal NET portends a poor prognosis.[76–78]

Pathology

Morphologically, well-differentiated NETs display an organoid arrangement of the tumor cells with nesting, trabecular, or gyriform patterns. The cells have round-to-oval nuclei with coarsely stippled chromatin and granular cytoplasm. They display strong and diffuse immunohistochemical reactivity to neuroendocrine markers, such as chromogranin and synaptophysin. Poorly differentiated high-grade neuroendocrine carcinomas have a more sheet-like or diffuse architecture, irregular nuclei, and less cytoplasmic granularity, with patchy or even negligent expression of neuroendocrine markers.[79] Immunohistochemical stains are particularly helpful on biopsy samples when differentiating between usual adenocarcinoma; however, high-grade neuroendocrine carcinomas may be confused with poorly differentiated adenocarcinoma, SCC, or melanoma. Small cell carcinomas of the anal canal may show immune-reactivity for thyroid transcription factor–1 and CK and usually lack staining with synaptophysin and chromogranin and markers of squamous differentiation (34bE12 and p63/4A4). Occasionally a mixed differentiation is present with small cell carcinoma containing dispersed foci of cells with squamous differentiation, usually consisting of less than 5% of the entire tumor specimen, or a mixed differentiation with the presence of adenocarcinoma and neuroendocrine carcinoma cells.[80]

Management

Treatment of anorectal NET is usually determined by size of primary lesion, with surgical excision as the only definitive cure. Tumors that are low grade and are of small size (<1 cm) and depth (confined to the mucosa or submucosa, T1) carry a low risk of metastases and are managed with skilled endoscopic resection. This is preferred for superficial or polypoid lesions; however, there is a risk of positive resection margin.[81] Surgery is usually reserved for lesions 1 to 2 cm with features of invasion or where endoscopic resection is technically difficult. Larger tumors have higher metastatic potential and should undergo complete resection including regional lymph nodes, which could be either APR or anterior resection.[82] 68Ga-DOTATATE PET/computed tomography is used in staging and has high accuracy in detecting bone and soft tissue metastatic disease.[83] Transanal endoscopic microsurgery is an emerging modality where accurate local full-thickness excision of lesions is performed with minimal morbidity.[84] Transanal endoscopic microsurgery in a series of 24 patients resulted in negative resection margins with no local recurrences for patients with either primary lesions or residual disease after endoscopic resection.[85] In selective advanced cases palliative resection can also be considered particularly to debulk the tumor to alleviate symptoms and improve QoL.

Treatment recommendations for management of advanced disease are based on extrapolation from trials of mid-gut NETs because there is a paucity of published data for patients with metastatic colorectal NETs.[86] Somatostatin analogues, peptide-receptor targeted therapy, liver-directed therapies (eg, hepatic bland embolization), radiofrequency ablation and selective internal radiotherapy, interferon alpha, and cytotoxic chemotherapy are used and angiogenesis inhibitors and mTOR inhibitors have recently been added to the therapeutic armamentarium.[82] Treatment in the metastatic setting is usually dictated by the bulk of disease, symptoms, and patient's overall performance status. Aggressive treatment should be considered given the ultimately poor prognosis.

MESENCHYMAL NEOPLASMS

The most common mesenchymal tumors arising in the anal canal are smooth muscle tumors and GIST. Schwannomas, sarcomas related to endometriosis or the mullerian system, and lymphagiomas have also been reported.[6,87,88]

Gastrointestinal Stromal Tumors

Approximately 2% to 8% of anorectal GISTs arise in the anal canal and account for 5% to 10% of all GISTs.[88,89] Morphologically GISTs are spindle cell (65%), epithelioid, or mixed types. A total of 84% of c-kit-positive GISTs stain positively for CD34, with 29% positive for SMA and 4% for S100 protein.[88] In a series of 133 anorectal GISTs including three cases of anal origin, the tumors were histologically similar to gastric and small intestinal GIST with CD117 positive in 96%. Exons 9, 11, and 13 of the c-kit gene were amplified in 29 cases and exon 11 mutations were seen in 17 tumors.[88] DOG-1 is another useful immunohistochemical stain expressed in most GISTs; however, in a report of 12 cases, the single anorectal GIST was not positive.[90–92]

There are no data specifically for anal GIST to suggest a difference from the significant prognostic factors of all GISTs being tumor size and mitotic index. GISTs greater than 5 cm or with greater than 5 mitoses/50 HPFs behave aggressively, whereas size 2 to 5 cm with mitotic count less than 5/HPF have an intermediate risk profile.[68,93]

Surgical resection is the definitive curative treatment. Sphincter preservation must be weighed against recurrence risk because anorectal GISTs could have a variable anatomic relapse pattern. Size and location dictate the extent of resection, with small lesions amenable to mucosal resection; APR is required for more advanced disease.[93–95] MRI is particularly useful for local tumor assessment (**Figs. 5** and **6**). Multiple large studies with long-term follow-up have established the role of adjuvant imatinib therapy in patients with resected GIST, although there is differential efficacy according to subtype of mutation present; no specific profiling of anal GIST mutations have been reported. Data for the anal subset from prospective trials are scant because two of the largest trials of adjuvant imatinib for completely resected GIST by the American College of Surgeons Oncology Group (ACOSOG Z9000 and Z9001) enrolled only 35 anorectal GIST of a total of 751 patients.

BASAL CELL CARCINOMA

BCC of the anus is extremely rare, comprising approximately 0.2% of all anorectal malignancies.[96] Lesions arise at the anal margin and are usually 1 to 2 cm in diameter. BCCs are commonly ulcerated with a raised margin and are often misdiagnosed as anal fissures or hemorrhoids. Histopathologic confirmation is required to distinguish from the basaloid SCC, because this has management implications.[97,98] Wide local excision is the treatment of choice and is curative in most cases; however, APR may be required where the lesion is invading the anal canal and into deeper surrounding tissue. BCCs seldom metastasize and in the two largest series published (Paterson and colleagues,[99] n = 21; Gibson and Ahmed,[100] n = 51), the recurrence rate post wide local excision ranges from 0% to 29% of patients but the cancer-specific survival at 5-year was 100%.

METASTASES TO ANAL CANAL

The anal canal could be a rare site for metastases for any kind of malignancy. In the literature only a few cases have been reported of metastases from breast, lung, colon,
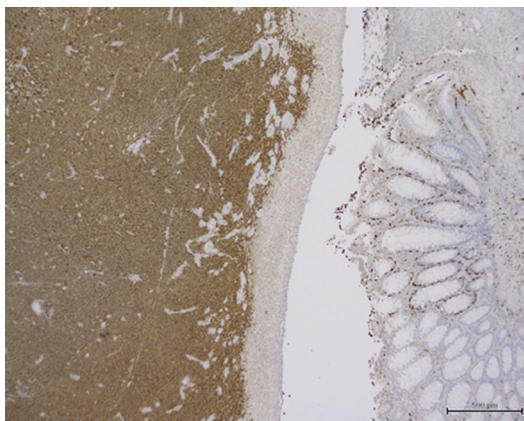
Fig. 5. The malignant cells show strong diffuse staining for S100 (original magnification ×40). Positivity was also demonstrated using a cocktail of antibodies that included HMB-45, Melan-A, and tyrosinase.
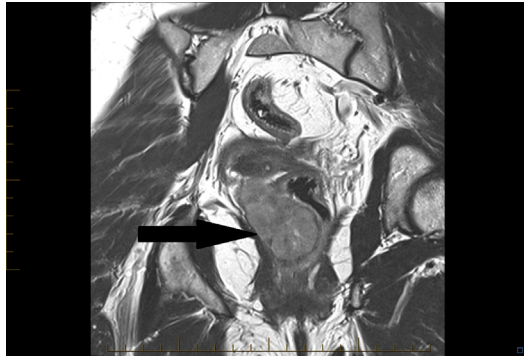
Fig. 6. MRI coronal T2-weighted: primary anorectal GIST (*arrow*).

and pancreatic cancer (**Table 3**).[101–107] Thorough histologic and immunohistochemical analysis is warranted where there is a suspicion of metastases.

SUMMARY

Uncommon neoplasms of the anal canal are associated with significant diagnostic dilemma in clinical practice and a high index of suspicion and particularly pathologic expertise is needed. **Table 4** illustrates some essential morphologic and immunohistochemical properties of uncommon anal canal neoplasms that could be used as a guide. The incidence as with all anal cancers is likely to increase over time, particularly of small, incidental lesions found because of use of more frequent colonoscopy and high-definition MRI. Generally treatment follows that of the same histologic subtype in other anatomic locations rather than usual anal SCC. Surgical intervention is considered as the cornerstone for cure in early and localized disease; however, removal of the anal canal is associated with significant morbidities and QoL issues. Clinical trials in rare anal cancer subtypes are unlikely to be performed but a strong case is made for a centralized global registry/database that could be established under the auspices of the International Rare Care Initiative collaboration.

Table 3
Published case reports of metastasis to anal canal

Author/Year	Demographic Information	Site of Primary	Histologic and Immunohistochemistry Features
Takahashi et al,[107] 2011	Case series of 6	Colorectal	Not available
Bochicchio et al,[102] 2012	72 F	Breast	Adenocarcinoma of mammary origin, ER/PR/Her2-ve
Puglisi et al,[103] 2009	88 F	Breast	Invasive lobular carcinoma
Haberstich et al,[104] 2005	78 F	Breast	Ductal carcinoma
Dawson et al,[105] 1985	70 F	Breast	Invasive lobular carcinoma
Kawahara et al,[106] 1994	75 M	Lung	Squamous cell carcinoma
Ejtehadi et al,[101] 2014	79 F	Ampullary	Adenocarcinoma, pancreatobilliary type. CK7/CK17/MUC1 +, (−ve K20/CDX2/MUC2)

Table 4
Histologic identification of rare anal cancer subtypes using morphologic features and immunophenotypic profiles

Tumor	Morphology	Immunohistochemistry Reactivity						
		Keratin	P63	Ki-67	Neuroendocrine Markers[a]	Melanoma Markers[b]	Lymphoma Markers[c]	Other
Adenocarcinoma	Gland forming, mucin producing	−/+	−	−	−	−	−	…
NET								
Carcinoid	Trabecular/organoid No or low proliferative index	−	−	<10%	++	−	−	…
Small cell	Can have squamous differentiation	− (squamous foci+)	− (squamous foci+)	>50%	+/−	−	−	…
High-grade neuroendocrine carcinoma	Can mimic carcinoid but high mitoses ± necrosis	−	−	>30%–50%	+/−	−	−	…
Melanoma	Lesions resemble cutaneous melanoma, pigmentation +/−	−	−	−	−	++	−	…
Non-Hodgkin lymphoma	Large cell immunoblastic or pleomorphic	−	−	−	−	−	++	…
GIST	Cellular tumor with solid growth pattern	−	−	−	−	−	−	CD117 +/− DOG1 CD34, SMA
Sarcoma	Variable depending on type	+/−	−	Variable	−	…	−	Variable

^a Synaptophysin, chromogranin.
^b Melan, S100, HMB 45.
^c CD45, LCA.

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