Malignant Conditions Including Squamous Cell Carcinoma and Rare Cancers

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Cancers of the anus, anal canal and anorectum are rare conditions comprising less than 2.5 % of gastrointestinal malignancies. However, the incidence has increased over the past several decades. In the United States there will be an estimated 5,820 new cases diagnosed in 2011, up from 4,660 new case in 2006 [1].

Anatomy

There are several important anatomic landmarks in the perianal region. The *anal verge* is the lowest portion of the anal canal or the external anal orifice. It overlies the intersphincteric groove and can be distinguished as the border between hair-bearing anal margin skin and non hair-bearing anoderm. The *anal margin* includes the skin 5 cm external, in a radial direction, to the anal verge that can be visualised by applying gentle traction to the buttocks. The *surgical anal canal* extends cephalad from the anal verge to the anorectal ring. The distal anal canal is lined by stratified squamous epithelium, while the proximal anal canal is lined by columnar epithelium similar to that of the rectum. In between is the *anal transition zone* demarcated distally by the *dentate line* and extends proximally 6–12 mm. This area is lined by basal, columnar and cuboidal cells, and the epithelium is cloacogenic, transitional or squamous.

Lymphatic drainage of the anal canal depends on the location in relation to the dentate line. The areas below the dentate line drain into the inguinal and femoral lymph nodes, whereas lesions above the dentate line are likely to drain to the perirectal and paravertebral lymph nodes, similar to rectal cancers.

Squamous Cell Carcinoma (SCC) of the Anal Margin

Anal margin is defined as the skin extending 5 cm external to the anal verge. Cancers in this area are less common that those within the anal canal. There are no large or prospective studies of anal margin tumours, and these lesions are often combined with anal canal cancers in larger series and trials. Anal margin tumours are uncommon. For example, they only comprise 7 % of anal tumours treated by the United Kingdom's Christie Hospital NHS Trust, reported in their large series of 254 anal cancer patients [2]. Wide local excision is the mainstay of treatment for small (≤2 cm), superficial well-differentiated tumours that can be removed with clear surgical margins, as continence can typically be maintained. With negative resection margins, outcomes are good.

Adjuncts such as chemotherapy and radiation have been used in more advanced disease

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or those that have recurred. Abdominoperineal resection should be reserved for those with locally recurrent disease after radiotherapy and/or chemotherapy. Patients with anal margin cancers that are not amenable to primary resection are thought to have less favourable outcomes [3]. However, in the few randomised trials on anal cancer that include anal margin tumours and report stratified results, anal margin cancers had similar outcomes to anal canal cancers [4, 5].

Several retrospective studies with small numbers of patients have been published looking at anal margin cancer specifically. Khanfir et al. report a 5-year locoregional control rate of 78 %, 5-year disease-free survival of 51 % and 5-year overall survival of 55 %. Only 35 % of these patients had chemotherapy [6]. Grabenbauer et al. describe patients with anal margin cancers, highlighting worse outcomes compared with anal canal cancers. These patients had a 50 % complete remission rate at 6 weeks after chemoradiation (compared with 92 % in anal canal tumours), 21 % local recurrence (compared with 8 % in anal canal tumours) and 5-year overall survival of 54 % (compared with 75 % for anal canal tumours). All patients in this series had chemoradiation (CRT) with 5-FU and mitomycin C [3]. Anal conservation rates are reported as 65 [7], 69 [3] and 80 % [6]. Chapet et al. report local control rates of 58 % in patients who had a local excision followed by irradiation and 64 % in patients with irradiation alone. 5-year overall survival in all 26 patients was 71 %. Half of these patients received chemotherapy [7].

Squamous Cell Carcinoma (SCC) of the Anal Canal

According to the United States' Surveillance Epidemiology and End Results (SEER) database, 50 % of patients with anal cancer have disease confined to the anus, 29 % have regional lymph node involvement or direct spread beyond the primary, and 12 % have metastatic disease, while 9 % have an unknown stage [8].

Risk Factors

Evidence indicates that the incidence of anal cancer is rising [9] possibly due to more prevalent human papillomavirus (HPV) infection, immunosuppression, anoreceptive intercourse and smoking [10]. In addition, history of other HPV-related gynaecologic neoplasms, particularly vulvar cancer, has been associated with increased incidence of anal SCC. Women with history of in situ of invasive gynaecological neoplasm have a 13-fold increase in anal cancer compared with expected rates [11].

Staging

Staging of anal cancer is done in accordance with the American Joint Committee on Cancer (AJCC); TMN staging system includes assessment of the size of the primary lesion, lymph node status and distant metastasis (Table 7.1). The primary tumour is evaluated by inspection and palpation to determine the size and location in relation to the anal verge and to determine if it involves the anal margin or anal canal. Presently, this staging classification does not take into account sphincter involvement, which may have functional and prognostic significance. Additional studies to further define the tumour anatomy and distribution are often necessary when the lesion is large or deeply invasive.

The extent of disease, including the presence or absence of metastatic lymph nodes, guides planning of radiation fields. Therefore, accuracy of pretreatment staging is important. Lymph node status is determined primarily by palpation of the groins with the addition of cross-sectional imaging to evaluate for deeper inguinal and pelvic nodes. There are no reliable size criteria for abnormal nodes. Enlarged groin nodes may be reactive and without malignant cells. Accuracy of clinical exam alone is disappointing since 44 % of lymph node metastases are less than 5 mm in diameter [12].

A chest x-ray or chest computed tomography (CT) and an abdominopelvic CT are often

Table 7.1 AJCC 7th edition staging system for anal cancer

T1	Tumour 2 cm or less		
T2	Tumour more than 2 cm but not more than 5 cm in greatest dimension		
T3	Tumour more than 5 cm in greatest dimension		
T4	Tumour of any size invades adjacent organ(s), e.g. vagina, urethra or bladder (invasion of the sphincter muscle(s) is not classified as T4)		
N0	No regional lymph node metastasis		
N1	Metastasis to perirectal lymph node(s)		
N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)		
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes		
M0	No distant metastasis		
M1	Distant metastasis		
Stage	**T**	**N**	**M**
I	T1	N0	M0
II	T2	N0	M0
	T3	N0	M0
IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
IIIB	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
IV	Any T	Any N	M1

included to evaluate for distant metastasis. Involved common iliac and periaortic lymph nodes are important to detect because while they are categorised as distant disease, it is possible to include them in the radiation fields.

Ultrasound

Endoanal ultrasound (EAUS) is a relatively inexpensive, safe and well-tolerated examination, which can be useful to evaluate the extent of local disease. There are limitations in patients with stenosis. In addition, the field of view is limited with an inability to assess distant mesorectal, inguinal or iliac nodes. In certain centres, EAUS is used to obtain two- or three-dimensional images to assess tumour location and spread within the anal canal and surrounding lymph nodes. The difficulty in assessing test characteristics such as sensitivity and specificity is that the majority of patients treated with chemoradiotherapy do not undergo pathological confirmation of node status. Some studies use a cut-off of 1 cm or larger for presumed positive lymph nodes [13]. Metastatic lymph nodes are typically round hypoechoic structures. Using size criteria alone, as mentioned above, may under-stage a significant percentage of patients.

MRI

Initial staging with magnetic resonance imaging may provide more useful information about local extent of pelvic disease, but it is more expensive and labour-intensive and may be contraindicated in certain patients (e.g. those with pacemakers). Anal canal tumours, when compared to the gluteus muscles, tend to have an intermediate signal intensity (SI) on T2-weighted images and isointense SI on T1-weighted images. Tumour involvement of the sphincter complex or urogenital structures can best be seen on T2-weighted MRI, as ill-defined intermediate SI infiltration or encasement [14]. Metastatic lymph nodes demonstrate similar signal intensity to the primary tumour. Perirectal lymph nodes with a maximum short-axis diameter of more than 5 mm and inguinal and pelvic sidewall nodes with a maximum short-axis diameter of more than 10 mm are often considered to contain carcinoma. Parikh et al. note similar limitations in both ultrasound and MRI with over-staging reactive lymph nodes and under-staging microscopic involvement. The European Society for Medical Oncology guidelines have recommended both EAUS and MRI in the primary staging of anal carcinoma. Ultrasound is felt to be more accurate for T stage, particularly early T stage, whereas MRI may identify more lymph nodes [13].

Several studies have evaluated the role of MRI in assessing the tumour before and after

CRT. It has been found to be useful in assessing the primary tumour size, signal intensity and infiltration of adjacent structures [15]. Tumour response was assessed by recording change in tumour size and signal intensity. After treatment, a decrease in tumour size accompanied by reduction and stability of the MR T2 signal characteristics at 1 year after CRT was associated with favourable outcomes. There are clear limitations to MRI including posttreatment oedema and scarring, but this tends to stabilise in T2-weighted SI and scar size after 1 year. Other studies have failed to identify predictive MRI features in the early posttreatment period for outcomes such as locoregional recurrence [16].

PET/CT

At diagnosis, ^{18}fluorodeoxyglucose uptake on positron emission tomography/computed tomography (FDG-PET/CT) is also used to evaluate lymph node status and distant metastases. FDG-PET/CT can be used for radiation therapy treatment planning by clearly defining sites of metabolically active tumour [17]. With FDG-PET/CT, the detection rate of non-excised tumours on initial examination was 93 % [18].

PET scan may provide additional information as a biomarker with higher maximum standardised uptake value (SUV) associated with an increased risk of nodal metastasis at diagnosis and worse disease-free survival. Patients with high anal tumour SUV (max) at diagnosis were at an increased risk of persistent or recurrent disease on post-therapy FDG-PET at 4 months. An SUV (max) $\geq$5.6 was associated with poorer disease-free survival [19]. In addition, PET/CT can upstage anal cancers and influence further management. In one study, 12.5 % of patients had a change in management based on PET/CT results, including 7.5 % ($n=3$) who were found to have FDG-avid inguinal lymph nodes that led to broader radiation fields. One patient had a FDG-avid periaortic node which was included in the radiation field, and one patient had a lung metastasis treated with metastasectomy [20].

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SLNB) has been studied as an adjunct to physical exam for evaluating for node-positive disease. 99mTc colloid is injected into the peri-tumoral tissue and lymphoscintigraphy performed. During the surgery, blue dye can also be used. The sentinel inguinal node is identified by a handheld gamma probe and dye visualisation. Multidirectional lymphatic drainage (mesenteric, iliac, inguinal) can occur in up to 56 % patients [21]. As many as 27 % of patients were found to have metastases in a lymph node that was not evident on clinical exam [22]. Other authors voice concerns over the use of sentinel lymph node biopsies to make decisions to omit inguinal radiation, particularly in patients with high-risk primary lesion. Several small series have reported 7–14 % rate of subsequent inguinal lymph node metastases within 2 years, despite negative SLNB on histopathology. Many of these patients did not have the inguinal lymph nodes included in the initial radiation fields. These were considered false-negative SLNB [21, 23]. De Jong's review of the literature included eight studies with a total of 143 patients. There was a 96.5 % detection rate of the sentinel lymph node, but the authors were unable to calculate a false-negative SLN detection rate. Further studies are needed before this can be broadly applied.

Prognostic Factors

The most important prognostic factors in anal cancer are thought to be T, N and M stages [24]. Locoregional control rates vary from 50 % at 3 years seen in the large (585 patients) UKCCCR randomised trial to 71.5 % at 5 years (88 % for stage I, 69 % for stage II, 77 % for stage IIIA and 60 % for stage IIIB) as reported in a group of 286 patients from France [25].

As the tumour size increases, there is a clear increase in local recurrence. Wright et al. in their series of 180 patients from Memorial Sloan-Kettering Cancer Center describe a 3-year locoregional failure rate of 15 % in T1/T2 patients compared with 42 % in T3/T4 patients

($p=0.0009$) [26]. Larger tumour size (higher T stage) is also associated with a decrease in survival (T1, 94 %; T2, 79 %; T3, 53 %; and T4, 19 %) [27].

The impact of nodal involvement on outcomes is weaker. The Radiation Therapy Oncology Group trial (RTOG 87-04) found those with node-positive disease had a higher colostomy rate (an indirect marker for local failure). Similarly, the European Organization for the Research and Treatment of Cancer (EORTC) trial comparing radiation alone to CRT showed significantly higher local failure rates ($p=0.0017$) and lower survival ($p=0.045$) in those with positive nodes, regardless of treatment arm, compared to node negative patients, but the extent or size of nodal spread did not influence prognosis [4]. In a 12-year review of 167 anal cancer patients, both increasing T stage (HR 1.7) and N stage (HR 1.47) were significantly associated with locoregional failure [28].

Certain pathological subtypes, such as basaloid subtype, and patients with human immunodeficiency virus have been shown to have a lower overall survival rate [28]. Additional factors found to be significant for worse prognosis on multivariate analysis included older age [3, 29] failure to complete radiation therapy [24], HIV-positive status [30] and dose intensity of chemotherapy less than or equal to 75 % [3]. Tobacco smoking has also been identified as a risk factor. Those who smoke tend to have the diagnosis of SCC at a younger age and have more frequent recurrence (32 % of smokers vs. 20 % of non-smokers) at a shorter interval. In addition, smokers had a significantly worse overall 5-year survival (45 % in smokers and 20 % in non-smokers; $p=0.05$) [31].

Surgical Therapy

Historically, surgical excision was the first-line treatment prior to the development of combined modality therapy championed by Nigro in the 1970s [32]. Before this sentinel publication, local excision was acceptable for lesions smaller than 2 cm with favourable pathological feature, confined to the mucosa or submucosa. The data on these small lesions is often skewed by the inclusion of those with anal margin cancer. Greenall et al. reported that 10 % of the anal canal lesions were amenable to local excision [33]. There was a 41 % rate of local recurrence and a 64 % overall 5-year survival. Those treated with abdominoperineal resection had a 38–71 % 5-year survival rate. With surgery alone, local pelvic or perineal recurrence accounted for 50–70 % of failures, and only 10–20 % died from distant metastases.

Current strategies favour combined modality therapy (CMT) first, with radical resection of anal squamous cell cancer reserved for those with persistent or recurrent disease after CMT, those who are unable to tolerate CMT and those who are not candidates for CMT.

Radiation Alone Versus Combined Modality Therapy

Radiation therapy results in an antitumour response in the majority of patients. Most protocols since Nigro's publications in 1974 have included chemotherapy with the radiation. However, external beam radiation therapy alone or in conjunction with brachytherapy was used in the 1980s and 1990s. With radiation alone, local control rates range from 61 to 100 % with overall 5-year survival rates of 50–94 % [34].

Two randomised controlled trials compare concomitant radiotherapy and chemotherapy to radiotherapy alone as definitive treatment for anal SCC.

The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) randomised 585 patients with anal cancer to receive either 45 Gy in 20 or 25 fractions alone or with concurrent 5-fluorouracil during the first and last weeks of radiation and mitomycin on the first day of radiation [35]. They assessed for response at 6 weeks, and if there was >50 % tumour response, an additional boost of 25 Gy was given. Assessment of tumour response was done 2 months after completion of the boost. There was a higher incidence of early toxicity (within the first 2 months) with CMT, but the rates of late toxicity were similar. Early morbidities included leucopenia,

thrombocytopenia, skin reactions and gastrointestinal and genitourinary symptoms. There were no significant differences in perineal wound complications. There were similar rates of treatment-related morbidities necessitating surgery in both groups; these were included in the local failure analysis.

In both groups the majority of local failures occurred within the first 18 months. There was a significant reduction in the local failure rate in the CMT group (39 %) compared with the XRT-only group (61 %) at 3 years. The 3-year overall survival rate between the two arms was not statistically different (XRT only = 58 %, CMT = 65 %). The mortality rate from anal cancer at 3 years was significantly higher in the XRT group at 39 % versus 28 % in the CMT group ($p = 0.02$). Long-term follow-up at 12 years shows that these significant differences persist [36].

Similarly, the European Organization for the Research and Treatment of Cancer (EORTC) radiotherapy and gastrointestinal cooperative group demonstrated that the addition of chemotherapy to radiotherapy in patients with greater than 5 cm (≥T3) primary tumours or positive lymph nodes resulted in a significant increase in the complete remission rate from 54 % for radiotherapy alone to 80 % for CMT [4]. The locoregional control rate improved by 18 % at 5 years, and the colostomy-free rate increased by 32 % in those who received CMT. There was no significant difference in late side effects, although anal ulcers were more frequently observed in the combined-treatment arm. Despite better locoregional control and better progression-free survival in the CMT group, the survival rate remained similar in both treatment arms. Several significant prognostic factors were identified; nodal involvement, skin ulceration and male sex showed worse local control, and nodal involvement and skin ulceration showed worse overall survival. The size of the primary and percent circumference did not show any prognostic value nor did the location of the primary (canal vs. margin). Both UKCCCR and EORTC studies showed improved local control and decreased stoma rates with CMT compared to radiation alone without increased toxicity.

There have been several studies to evaluate the use of other cytotoxic chemotherapy agents in conjunction with radiation therapy. The most prominent has been cisplatin (CP). The RTOG 98-11 multicenter trial published in 2008 showed that the mitomycin C (MMC) group compared to the CP group had similar 5-year disease-free survival rates (60 % vs. 54 %; $p = 0.17$), overall survival rates (75 % vs. 70 %; $p = 0.10$), locoregional recurrence (25 % vs. 33 %) and distant metastasis (15 % vs. 19 %). The rate of colostomy was significantly lower for the MMC group (10 % vs. 19 % $p = 0.02$). There was, however, more haematological toxicity in the MMC arm [5].

Similarly, the Anal Cancer Trial (ACT) II failed to confirm any advantage of CP in the CRT regimen or 5-FU- and CP-based maintenance chemotherapy [37]. Other long-term studies show equivalent results in overall survival with MMC and CP. A study from Brazil showed that the overall colostomy rate was not significantly different with MMC versus CP. The 10-year overall survival and disease-free survival rates for the MMC group were 52 and 53 % and for the CP group 54 and 49 %, respectively ($p = 0.32$ and $p = 0.92$) [38].

Modifications of the radiation therapy include intensity-modulated radiation therapy (IMRT), which involves using PET/CT to defining high-, intermediate- and low-risk planning target volumes (PTV). Using treatment-planning software, the dose of radiation is tailored to provide graded doses of radiation to these different risk PTV areas. The high-risk PTV typically includes primary tumour and grossly positive nodal disease. Intermediate-risk PTV includes the internal iliac region inferior to the SI joint, the perirectal nodes as well as the high-risk PTV. The low-risk PTV area includes the inguinal nodes, external iliac nodes and the internal iliac nodes superior to the inferior edge of the SI joint. A recent small retrospective study has shown the benefits of IMRT with chemotherapy. With IMRT the duration of treatment is significantly shorter, requiring less frequent treatment breaks. In addition, when comparing IMRT to conventional RT, IMRT showed significantly better 3-year overall survival (88 % vs. 52 %), locoregional control (92 %

vs. 57 %) and progression-free survival (84 % vs. 57 %) [39]. The results of a prospective study, RTOG 0529, are awaited. A recent analysis of sites of locoregional failure from Memorial Sloan-Kettering Cancer Center concludes that inguinal and all pelvic nodal regions should be included in the PTV for IMRT, including the external iliac, internal iliac and presacral regions. The authors also recommend that common iliac nodes should be included in the radiation fields of patients with advanced T and N stage disease, based on 4 of 58 (7 %) common iliac node recurrences, three of which were not "in-field" in this subset of patients [26].

Management of Lymph Nodes

If the inguinal lymph nodes are found to be positive on physical exam or imaging and FNA confirms the finding, these nodes are then included in the radiation field. Many have advocated for routine prophylactic inguinal irradiation regardless of T stage, citing a 2 % 5-year inguinal lymph node recurrence rate for the prophylactic group compared to 16 % in those who did not get upfront inguinal radiation [40]. In patients who did not receive inguinal radiation, there was a 12 % rate of inguinal lymph node recurrence in those with T1 or T2 lesions and 30 % rate for T3 or T4 lesions. Many of the radiation treatment protocols used in the randomised trials include the inguinal nodes in all patients [5, 35, 38, 41].

Surveillance

The current guidelines for follow-up of patients with anal cancer after definitive CRT include serial digital rectal examination, with biopsy of suspicious lesions every 3 months beginning 8–12 weeks after completing CRT [42]. Cell death may continue up to 12 weeks after completion of CRT [43]. In addition, treatment-related ulcers may persist for 3–6 months [44]. Differentiation of treatment effect versus residual tumour can be challenging, and liberal use of biopsies is recommended. The Tru-Cut core biopsy needle can be used for sampling of deeper tissues in the ischiorectal fossa [3]. Most local recurrences, however, are apparent on physical exam, and a biopsy is obtained to confirm the diagnosis [35].

Follow-Up Imaging

The role of ultrasound in the follow-up of treated anal cancer is controversial. It is difficult to distinguish oedema and scar from persistent tumour on EAUS. In addition, this can be painful for patients with a relative anal stenosis. Some authors have recommended that waiting 16–20 weeks after radiation is sufficient to allow for resolution of oedema and improves the accuracy of the ultrasound imaging [45]. Serial exams can monitor for changes in the size of the scar, and this modality may add to routine clinical follow-up [46].

FDG-PET/CT, a non-invasive technique, has been studied to both determine residual disease and predict recurrence and survival. During post-treatment follow-up, FDG-PET/CT had, on a per examination basis, sensitivity for the detection of persistent or recurrent disease of 93 % and specificity of 81 % [18]. The 2-year cancer-specific survival was 94 % for those with a complete metabolic response (CMR) and 39 % for those with persistent FDG uptake post-CRT on PET/CT scan at a median of 2 months after completion of CRT, ($p = 0.0008$) [42]. CMR was associated with significantly improved progression-free and cause-specific survival compared with partial metabolic response. In fact, the results of the posttreatment FDG-PET/CT were more predictive of survival outcome than the pretreatment T stage. A similar predictive power of the PET response to radiation therapy has also been shown in a prospective study on 92 women with cervical cancer by the same researchers from Washington University in St. Louis, Missouri [47]. Another retrospective study of 48 patients with anal cancer showed a 5-year overall survival difference of 88 % in those with a CMR, 69 % for those with a partial metabolic response and 0 % in those with no metabolic response ($p < 0.0001$)

[48]. This study noted that 20 % of patients had coincident FDG-avid abnormalities that were not related to anal carcinoma—in three patients, separate primary malignancies were diagnosed. Studies on post-therapy PET/CT show that this modality is promising as a surveillance technique, but further confirmatory prospective data is needed to justify its routine use. Additionally, the timing of post-CRT PET/CT is thought to impact the specificity of this test, but at this point there is no data to clarify when PET/CT should be performed.

MRI has also been a part of follow-up but is reported in only a few studies. Stabilisation of the T2-weighted SI and scar size more than 1 year after CRT is associated with good outcomes in one small study of 15 patients [15]. With this modality it is important to establish a base line and look for stability of the images [14].

Outcomes

With varying CRT protocols using 5-FU/MMC and XRT, the complete response rates range from 72 to 95 %, with local failure of 25–39 % and overall 5-year survival of 58–84 % (Table 7.2). In multivariate analysis in the RTOG 98-11 trial, male sex ($p=0.02$), clinically positive nodes ($p<0.001$) and tumour size greater than 5 cm ($p=0.004$) were independent prognostic factors for worse survival. With the mitomycin-based treatment, local failure occurred in 13 %, regional failure rate was 7, and 25 % had distant metastasis at 5 years. Overall survival rates were less than 50 % at 4 years in those with tumour >5 cm and clinically positive lymph nodes [5].

Colostomy rate has been used as an end point for trials. Few studies distinguish the indication for the colostomy—whether it is created for tumour or treatment-related factors. Cumulative colostomy rates range from 4 to 23 % with standard CRT [5, 35, 37]. As many as 20 % of colostomies are created to deal with treatment-related effects [5, 35], and up to 10 % are created to deal with the presenting symptoms [37].

Complications

As mentioned above, radiation is associated with haematological toxicity in 60 % of patients that may interrupt treatment. Non-haematological toxicity rates may be reduced with the intensity-modulated radiotherapy technique [39]. Irradiation of the inguinofemoral region can lead to serious complications with acute and late toxicity. Acute toxicity includes epidermolysis with ulceration and superinfection of the skin, while late toxicity includes inguinal fibrosis, external genitalia oedema, neurogenic bladder, lower limb lymphedema, osteonecrosis of the femoral head, artery stenosis and soft tissue sarcomas. There was no difference in late toxicity rates observed

Table 7.2 Anal cancer outcomes after chemoradiation in randomised clinical trials

Study	*N*	Study comparison	Complete response (%)	Local/regional failure	Disease-free survival	Overall survival
UKCCCR [35]	283	XRT alone versus CMT	95	39 % at 3 years	–	65 % at 3 years
EORTC [4]	51	XRT alone versus CMT	80	33 % at 3 years*	–	58 % at 5 years*
ECOG/RTOG 87-04 [41]	146	XRT and 5-FU ± mitomycin C	92	–	73 % at 4 years	78 % at 4 years*
RTOG 98-11 [5]	324	CMT with mitomycin C versus cisplatin	–	25 % at 5 years	67 % at 3 years	84 % at 3 years
Brazil [38]	93	CMT with mitomycin C versus cisplatin	72	31 % at 5 years		61 % at 5 years

*Results from the mitomycin C groups displayed

between those receiving radiation alone and with the addition of 5-FU and MMC in both the EORTC and the UKCCR trials.

Quality of Life

Overall quality of life has been found to be good at a median of 51 months after CRT using the EORTC QLQ-CR29 and the global QLQ-C30 questionnaires in those who had a complete response [49]. Increased urinary frequency in 40 % of patients and some degree of faecal incontinence in 47 % of patients has been reported. More than half maintained an interest in having sexual relations, but 100 % of male patients had difficulty maintaining an erection. For women who maintained an interest in having sexual relations, 50 % reported having pain or discomfort during intercourse, and 100 % of men had difficulty maintaining an erection [49]. Another study that used EORTC questionnaires found that fatigue was the strongest predictor of impaired function-related quality of life [50].

Salvage Surgery

Salvage surgery is a curative approach to recurrent anal cancer after radiotherapy or chemoradiation. Almost always, an abdominoperineal resection (APR) is required, although scattered reports of local excision or low anterior resection can be found in the literature [51]. Between 17 % and 39 % of patients diagnosed with curable anal cancer will eventually require consideration of salvage APR for local control [2, 52, 53]. Not all patients with isolated local recurrence can be salvaged, as some will be unresectable when the recurrence is detected. In a large comprehensive series of anal cancer patients from a tertiary referral centre, Christie NHS hospital in Manchester, England, the surgical salvage rate for local recurrence was 82.7 % in those who had undergone chemoradiation and 71.4 % in those who had undergone radiation alone. Upon occasion, APR is performed because of the toxicity of radiation therapy [7]. In some cases recurrent or persistent disease cannot be ruled out, and these patients undergo APR [54].

Early detection of local recurrence can improve the chance for offering salvage surgery to the patient. Patients are examined carefully 3–6 months after chemoradiation or radiotherapy. Liberal use of examination under anaesthesia with biopsy is helpful as recurrences in the anal canal may be difficult to detect in patients who are often tender from treatment and whose examination findings can be confounded by radiation injury. Reported time to local recurrence after chemoradiation ranges from 12 to 21 months [55–58]. The recurrence is usually detected as a mass in 45–95 % of cases, and patients may complain of new anal pain or bleeding. The UKCCCR study found that recurrences were nearly always digitally palpable. In reported series of salvage APR for anal cancer, persistent disease comprises one-third to half of patients in nearly all series.

Preoperative planning is poorly described in published case series but is essential in planning an R0 resection. Renehan indicates that CT imaging, and more recently MRI, is used for preoperative planning. Preoperative planning is critical because many patients require a multivisceral resection (MVR) as part of salvage surgery. Most series report that 40–60 % of salvage patients require MVR [51–53, 56]. In one of the largest series ($n=95$) from France, Lefevre et al. report that 86 % of APRs for anal cancer included MVR, with the majority (70 %) comprising posterior colpectomy.

Salvage APR for anal cancer can be difficult and laborious due to bulky disease and fibrosis resulting from chemoradiation. The median blood loss ranges from 400 cc [57] to 1,000 cc [56], and operative duration has been reported as a mean of 4.6 [59] to 6 h [56]. In one series of 62 patients, three (8.5 %) patients developed profound bleeding during the resection that resulted in closing the abdomen with packs and reoperation the subsequent day [52].

Given the size of the soft tissue defect after APR and the difficulties with wound healing in an intensely radiated field, many authors describe myocutaneous flap closures of the perineal wound. The flap commonly used is the vertical rectus abdominis flap (VRAM). In many series,

nearly half of patients had a flap closure of the perineal wound [53, 56, 59]. Renehan et al. reported that nearly all cases are closed with a flap. Flaps do not completely prevent perineal wound complications, and in one series, all patients who had myocutaneous flap procedures developed perineal wound breakdown [58]. Lefevre et al. report no differences in perineal complications in the flap versus no flap groups, with a reoperation rate of 17 % in the VRAM group and 26 % in the group without VRAM. The benefit of VRAM was the decrease in time to perineal wound healing with a median time to healing of 19 days compared to 95 days in the group without a VRAM. There was a statistically significant difference in perineal hernia rates between groups, with no perineal hernias in patients with VRAM reconstruction.

Post-operative complication rates vary substantially. High rates (~70 %) are reported by Schiller et al. from Canada, Ferenschild et al. from the Netherlands and Lefevre et al. from France. Stewart et al. from the United States report an 18 % rate of late (>30 days) complications. These are predominantly perineal wound complications with rates of infection or dehiscence between 35 and 80 %. Renehan et al. describe that 66 % of perineal wound problems require over 3 months to heal, and Stewart et al. report a median time to perineal wound healing in all patients of 7 months.

Obtaining an R0 resection poses some challenges when performing salvage resection of recurrent or persistent anal cancer. Renehan et al. found that a positive resection margin was a risk factor for decreased overall survival in their report of 73 patients. R1 or R2 resections are reported in 8.5 [53] to 32 % [57] of cases, with many authors reporting rates close to 20 % [54, 56, 60]. Lefevre et al. argue that liberal use of the VRAM flap allows the surgeon to obtain wider margins on the tumour. The location of positive margins is not described in any of the literature.

Reported survival rates after salvage surgery range from around 30 [51, 60] to 64 % [53]. Survival rates are not improved with more recently published series suggesting that modern surgical practices are not improving outcomes. Predictors of survival are not consistent amongst reports, likely reflecting the small size of series—all include fewer than 100 patients and most include 40 or fewer patients (Table 7.3). Nilsson et al. found T3 or T4 tumours, persistent cancer, node-positive disease and older age associated with worse overall survival. Patients with persistent cancer had a 5-year overall survival of 33 % compared with 82 % in patients with recurrent cancer.

Table 7.3 Predictors of survival after salvage surgery for anal cancer

Study	Univariate analysis	Multivariable analysis
Akbari et al. [52]	Tumour size >5 cm	Persistent disease at salvage
	Adjacent organ involvement	Node-positive disease at salvage
Nilsson et al. [53]	Older age	None significant
	T3 or T4	
	Persistent disease at salvage	
	Node-positive disease	
Schiller et al. [57]	Charlson comorbidity	Charlson comorbidity
	Male sex	Male sex
	Lymphovascular invasion	Tumour size
	Histologic grade	
Stewart et al. [58]	Tumour size >5 cm	Node-positive disease
	Persistent disease at salvage	Positive margins
	Adjacent organ involvement	
	Node-positive disease	
	Positive margins	

Secondary failures after APR, unfortunately, are reported commonly. Reports range from 39 to 60 %. Most recurrences occur within 2 years [51], and many are locoregional diseases only. Eeson et al. also found that patients with HIV trended toward higher rates of recurrence (odds ratio 3.0; $p=0.08$) [60]. There is little information on the use of adjuvant therapy after salvage APR.

With high complication rates, modest survival benefits and high rates of recurrence after salvage APR, some authors question the utility

of salvage APR [60]; however, the procedure remains the only effective therapeutic option in these patients.

Metastasis

The role of hepatic resection for SCC remains poorly defined. In general, the development of distant metastasis portends a poor prognosis and there are no good therapeutic options. Salvage systemic chemotherapy has been used in SCC of the head and neck and is largely unhelpful with low response rates and short duration of response [61]. Despite being the most common site of distant metastasis in anal cancer, resection of hepatic SCC metastasis is uncommon [62]. Pawlik et al. published a multicenter study of 52 patients with SCC and liver metastasis that went on to liver-directed treatment [63]. In 27 of these, anal SCC was the primary. With a median follow-up of 18 months, nearly two-thirds developed recurrence. The median disease-free survival was 9.6 months. The liver was the most common site of tumour recurrence, with the majority also having extrahepatic disease as a component of failure. Those patients with hepatic metastases ≥5 cm in size and those with positive pathological resection margins tended to have increased risk of recurrence. Other factors, including presentation with synchronous distant disease, lack of response to chemotherapy, multifocal hepatic disease or bilateral liver disease, were not associated with risk of recurrence in this small study. Overall 5-year survival was 23 % after the hepatic metastasectomy. Overall survival was negatively impacted by synchronous disease, liver tumour size ≥5 cm and positive surgical resection margin. Longer disease-free interval may act as a marker of tumour biology. The authors of this study note that selection of appropriate patients for hepatic resection of metastatic SCC must be individualised and include an extensive evaluation of other sites of disease. Although the majority of patients recur, there is a subset of patients, as many as 25 %, that can achieve long-term survival. Since many recurrences occur systemically, improvements in survival will likely depend on the development of novel, more efficacious systemic chemotherapeutic agents.

Special Patient Subgroups: HIV, Transplant, and Systemic Lupus Erythematosus

HIV patients tend to be younger than non-HIV patients, male and present with early-stage disease. Most are on HAART therapy [30, 64]. Some studies have shown HIV+ patients tend to have lower complete response and overall survival rates [65], whereas others have shown the survival is not significantly worse in those with HIV [30]. Several studies agree that there are higher rates of treatment-related toxicity in those with HIV. These toxicities represent major clinical challenges and limit overall CRT dose and therefore can impact survival [65].

Solid organ transplant patients have an elevated risk of anal cancer compared to the general population (standardised incidence ratio 5.84; $p<0.001$), with an excess absolute risk of 9.6/100,000 person-years [66]. Patients with systemic lupus erythematosus are at increased risk for HPV-associated malignancies. A Danish cohort study noted a standardised incidence ratio (SIR) of 26.9 (95 % CI 8.7–83.4) with over 13 years of follow-up. There was also increased SIRs for vulvar, cervical and non-melanoma skin cancer [67].

Anal Adenocarcinoma

Anal canal adenocarcinomas are thought to arise from the ductal epithelium of anal glands at the level of the dentate line. These rare neoplasms are usually diagnosed after they have grown to a size that obliterates a definitive determination of the site of origin, and associated dysplasia in neighbouring epithelial cells is almost never described. It is estimated that adenocarcinomas comprise 16 % of anal canal neoplasms [68].

Information on the behaviour and possible treatment options can only be gleaned through several small case series. Beal et al. from

Memorial Sloan-Kettering Cancer Center in New York City report on 13 patients over a 12-year time period [69]. Basik et al. from Roswell Park Cancer Institute in Buffalo, New York, report ten patients over a 27-year time period [70]. Chang et al. report on 28 curatively treated patients over a 20-year time period from the MD Anderson Cancer Center in Houston, Texas [71]. Jensen et al. review 21 patients reported in a Danish national database over a 40-year time period [72]. Belkacemi et al. report on 82 patients collected over 25 years in a European Rare Cancer Network database [73]. In a less detailed analysis, the SEER database of the United States is used by Kounalakis et al. to describe the treatment and outcome of 165 patients over 16 years [74], and similarly Myerson et al. use the National Cancer Data Base (NCDB) of the American College of Surgeons to report on 213 patients over 1 year. While offering larger numbers, the disadvantage of the latter two databases is that distal rectal adenocarcinomas may not be reliably excluded from the analysis.

Treatment

The treatment approaches for anal adenocarcinoma are so variable that they are not consistent even within the same series. Radiation therapy is commonly used with or without surgery. Either local excision or abdominoperineal resection is chosen as the surgical approach, and criteria for choosing between these two options are not described. Some, but not all, reports include chemotherapy, and typically 5-FU-based chemotherapy is administered with scattered patients additionally receiving mitomycin C or less commonly cisplatin. Radiation therapy is usually administered via external beam in widely varying doses, up to 59 Gy. Seven (16 %) patients were treated with brachytherapy alone in the series by Belkacemi et al.

The overall impression of authors of recent series is that preoperative chemoradiation followed by radical resection of the anus is most likely to provide local control and possibly improved survival in patients with anal adenocarcinoma [69, 71, 75]. Chang et al. found radical resection to be the only predictor of overall survival in their multivariable analysis.

Prognosis

The most dismal survival data comes from Denmark where the 5-year survival was 4.8 %. Patients were older (median age 70 years) and most tumours were quite large (median 10 cm) at diagnosis. 62 % had distant metastases at presentation. Surgical treatment was utilised, but no mention of chemotherapy or radiation was made in this series. The best reported 5-year overall survival of 63 % was reported by Chang et al. amongst patients who underwent radical resection (APR). The associated median disease-free survival was 32 months. Nearly half (43 %) of curatively treated patients in this series underwent preoperative chemoradiation followed by APR. Patients who underwent local excision followed by external beam radiation had a 43 % 5-year overall survival and median disease-free survival of 13 months. Beal et al. report a 26-month median survival. Using SEER data from the United States, Kounalakis et al. found a 58 % 5-year survival in patients who underwent APR alone and 50 % 5-year survival in patients who underwent APR followed by XRT. Due to the nature of the database, the use of chemotherapy in these patients was unknown. Myerson et al. found a 5-year survival of 41 % in all patients. Basik et al. found a median survival of 29 months overall, and Belkacemi et al. found a 5-year overall survival of 39 %, which was improved amongst patients who had chemotherapy and radiation without surgery.

Recurrence

Local recurrence after various treatment approaches is common in most series. Local recurrence occurred in 35 % of patients over 5 years in the series from the Rare Cancer Network, a series in which only a minority of patients had an APR as part of treatment. The small series from Basik et al., Beal et al. and

Papagikos et al. found locally failure rates of 20, 38 and 54 %, respectively. Median time to recurrence was reported as 20 months in one series [75]. A few patients with local recurrences after local excision and radiotherapy underwent salvage APR with good results [69, 75].

Distant metastases are just as common as, if not more common than, local recurrence in most reported series. Chang et al. reported 43 % of patients developed distant metastasis. Fifty percent of patients in the series from Basik et al. recurred with distant metastases, and all of these recurrences were also associated with inguinal disease.

Prognostic Factors

As would be expected, earlier stage at diagnosis is associated with a better overall survival. In the report by Myerson et al., stages 0 through 2 had a 60.4 % 5-year overall survival, compared to stage 3 tumours with a 30 % 5-year survival. Belkacemi et al. found that T1 tumours were associated with a 72 % 5-year overall survival, compared to T2/T3 tumours, which had a 37 % 5-year overall survival. In their series, N2/N3 disease had a 13 % 5-year overall survival, compared to N0/N1 which had 46 % 5-year overall survival. Local recurrence was also statistically associated with higher T and N stage. Tumour size ≥4 cm was associated with worse 5-year overall survival in univariate, but not multivariable, analysis. Higher tumour grade was independently associated with overall (OR 3.65) and disease-free survival (RR 2.44). Tumour grade was also a predictor of disease-free survival in a multivariable analysis reported by Chang et al. Using SEER data, Kounalikis et al. found worse survival in older patients (OR 1.05), patients with node-positive disease (OR 3.77) and patients who had radiation alone compared to patients who had surgical treatment (OR 2.78).

Anal Melanoma

Anal melanoma is a rare tumour. The anorectum is the third most common site for a primary melanoma, and these melanomas represent 5 % or less of anal neoplasms [76, 77]. The incidence of anal melanoma is estimated at 1/1,000,000 for women and 0.7/1,000,000 for men [78]. In most series, women represent a higher proportion of patients than men. No increase in the incidence of anorectal melanoma has been detected over the past decades. Because of the rare nature of this tumour, information on its behaviour arises from small case series gathered over decades, which describe heterogeneous treatment approaches.

Most patients present with rectal bleeding and/or anal pain, and diagnostic delays are a common occurrence. In up to 50 % of patients reported in retrospective series, the lesion is initially diagnosed as a haemorrhoid [79, 80] and some are only diagnosed in pathological review of haemorrhoid specimens [81].

Anal melanomas vary in size at presentation. The majority of tumours are reported in the anal canal as opposed to the anal margin. Anorectal melanoma is thought to arise from melanocytic cells in the anal mucosa which can invade the lamina propria proximally into the rectal submucosa [82]. Many authors suspect that melanomas cannot arise from cells proximal to the transitional epithelium of the anal canal [78, 82]. A small proportion of melanomas grow in the rectum with some series specifying that intervening normal rectum is seen between the lesion and the dentate line. Occasionally authors describe patients with satellite tumour nodules in the distal rectum that has similarities to in-transit metastases in cutaneous melanoma [83, 84]. Histologic descriptions consistently show that 20–30 % of tumours are amelanotic [85–87]. Some tumours show ulceration and junctional activity. Spindled histology can be seen and explains why some tumours can be mistaken for sarcoma on histology [85, 86].

Anorectal melanoma can spread to the mesorectal, inguinal and pelvic lymph nodes. Spread to mesorectal lymph nodes is seen frequently, with a rate of 42–69 % in APR specimens [81, 83]. There is no AJCC staging system for anal melanoma. Authors typically classify patients as stage I for localised disease, stage II for locoregional disease (including inguinal and pelvic lymph nodes) and stage III for metastatic disease.

Details of diagnostic testing on presentation are not well described in the literature. A substantial proportion of patients present with metastatic disease from 20 to 60 % [83, 88, 89]. Case series show no obvious or consistent predictors of metastasis based on primary tumour characteristics. After diagnosis of anal melanoma, all patients should all have a metastatic work-up with cross-sectional imaging. Metastases are most commonly identified in the liver and by the lung. There are no reports on the utility of PET/CT for this disease. Tumour markers are not described except in the series by Ishizone et al. In this series of five case reports, serum 5-S-cysteinyldopa (5-S-CD) was reported in one patient; however, the results and utility of this test was not discussed.

Treatment

Surgery

Anal melanomas are curatively treated with either wide local excision or abdominoperineal resection (APR). Nearly all series show no survival differences between these two surgical approaches [90, 91] and therefore conclude that APR is appropriate only for tumours which cannot be merely excised due to sphincter invasion. This has been the conclusion of several authors of reviews on this disease [92, 93]. Even early-stage anal melanoma does not benefit from aggressive surgical resection. In a separate analysis of stage I patients from the nationwide registry of the Netherlands, patients who had an APR patients had the same rate survival as patients who had a local excision [94]. A few series show a survival advantage in the APR group. A small series of 19 patients from Korea showed an unusually prolonged median survival of 66 months in the 12 patients who had abdominoperineal resection and 11.2 months in the seven patients of the local excision group [87].

In terms of local control, APR is consistently found to be superior to a local excision. Many series report high local recurrence rates after wide local excision. Pessaux et al., in their series of 40 patients, found a 48 % LR rate after local excision compared to a 22.2 % local recurrence rate after APR. Ross et al. reported 32 patients from MD Anderson Cancer Center, finding local recurrence in 58 % of local excision patients compared with 29 % of APR patients; however, concomitant distant metastases were seen in 82 % of these patients [95]. Haitao reported a series of 57 cases from Beijing and found a 65 % rate of local recurrence in patients with a wide local excision statistically significantly higher than 15.6 % after APR. Belli found 45.8 % local recurrence rate after local excision versus no local recurrence after extended resection, but frequent distant metastases, seen in 69 % of patients after rectal resection. It must be emphasised that the impact of local recurrence on these groups of patients is outweighed by the frequent occurrence of metastatic disease. All patients with locoregional recurrence in the series reported from Antoniuk et al. showed metastatic disease within 6 months. Few case series comment on whether any patients die of anal melanoma without metastatic disease. Since case series are small, there are few tumour characteristics on physical examination, histology or imaging to allow the surgeon to determine whether a subset of patients could benefit from the decrease risk of local recurrence seen after an APR. Negative microscopic margins are advised whether the procedure is a local excision or an APR, but no studies have looked at this as a risk factor for recurrence. One study reported worse survival for R2 versus R0 resections, but no difference in 5-year survival between R1 and R0 resections [86].

Chemotherapy

Chemotherapy is used for treatment of patients with metastatic disease. Agents used typically include dacarbazine, nimustine, vinblastine and cisplatin. Response rates have not been favourable, except in case reports. The response rate to dacarbazine is reported to be 20 % at most. Adjuvant chemotherapy has also been reported [81, 87]. In 79 patients summarised over multiple case series from Japan, there was no significant difference in survival between 18 patients who received adjuvant chemotherapy and 15 patients who did not receive chemotherapy [85]. Biologic

therapy with interferon and interleukin-2 is also reported in limited series and with no clear success apart from isolated cases. One report from Memorial Sloan-Kettering documents complete regression of the primary and metastasis after cisplatin, temozolomide, doxorubicin and external beam radiotherapy, with 12 months of follow-up [96].

Radiation Therapy

Radiation therapy is occasionally reported in some patients from many series, typically used for local control of advanced tumours in patients with metastatic disease. One series from MD Anderson shows that local excision followed by 30 Gy of external beam radiation was adequate treatment and afforded a 31 % 5-year overall survival for patients with stage I and II disease [89]. Some authors report that a fraction of their patients underwent adjuvant radiotherapy, but selection criteria are not described [81].

Patterns of Recurrence

Most patients experience disease recurrence after curative procedures, and the majority of these (40–65 %) are distant metastases [81, 95]. Isolated local recurrence is infrequently reported and when present is seen in a small proportion of patients [81]. Inguinal node relapse is common, seen after treatment in up to 39 % of curatively treated patients [95]. In the report by Brady et al., 27 % of patients had an isolated inguinal recurrence [81].

Prognosis

The overall survival (OS) for patients with anal melanoma is poor. SEER reports a 5-year OS of 32 % for patients who present with local disease, 17 % for patients who present with regional disease and no survival in patients with metastatic disease. Median survivals are reported to be 12–18 months in most institutional series [79, 89, 95, 97] with some studies showing slightly more prolonged survivals of 22 months [85, 98]. Most reports comment upon a few patients who had long-term survival [76, 80, 82, 98].

Not surprisingly, advanced stage at presentation predicts worse prognosis [85, 90, 91, 94]. Brady et al. reported that amongst patients with resectable disease who underwent APR, those found to have uninvolved mesenteric nodes had significantly improved disease-free survival than those with positive mesenteric nodes (40 % vs. 11 %; $p<0.01$). For unclear reasons, patients have been found to have better survival in more recent series. Other markers that have been investigated show no consistent prognostic significance; however, it is difficult to draw firm conclusions due to a limited sample size in case series. Tumour thickness was associated with survival in the series of 36 patients from Memorial Sloan-Kettering by Wanebo, with patients who have lesions <2 mm experiencing long-term survival and poor prognosis (mean survival of 8 months) in patients with lesions 3–5 mm thick. Tumour thickness was also found to be associated with worse prognosis by Ballo et al. Tumour size <2 cm was associated with better survival in the series reported from the Swedish National Cancer Registry [78]. Ballo et al. also found that tumour size matters, reporting a disease-free survival of 66 % in tumours ≤4 cm versus 19 % in larger tumours ($p=0.04$). However, Pessaux et al. in an institutional review of 40 cases found no association between overall survival and tumour size or thickness. Depth of invasion is not reported consistently as a risk factor. The presence of melanin in the tumour is not predictive of better prognosis. Histologic factors such as mitotic rate or ulceration have not been investigated for prognostic significance.

Leiomyoma, Leiomyosarcoma and Gastrointestinal Stromal Tumour (GIST) of the Anus

Stromal tumours of the anus are extraordinarily rare. The collective literature on these tumours predominantly describes leiomyomas and leiomyosarcoma. Investigators in collaboration with John E. Skandalakis and Stephen W. Gray have

compiled and updated the case reports of these tumours from the worldwide literature extending back as far as 1881 [99, 100]. However, this literature combines tumours of the rectum and the anus. Leiomyomas and leiomyosarcomas are reported with similar frequency. The distinction between the malignant and benign smooth muscle tumours at any site of the body is dependent on histologic evaluation. Both tumours have a spindle cell appearance, with leiomyosarcomas showing pleomorphic cells, hyperchromatic nuclei and increased mitotic activity. Leiomyosarcomas and GISTs spread beyond the local site of origin to distant metastatic sites or the abdominopelvic cavity. Regional lymph node spread is uncommon.

In the most recent inventory of case reports, which tracks reports up until 1996, 432 leiomyomas and 480 leiomyosarcomas of the anus and rectum were identified [101]. Amongst cases where tumour site of origin was described precisely, 8.1 % of leiomyomas and 6.4 % of leiomyosarcomas were in the anus. Only 19 anal leiomyosarcomas have been reported in the world literature [102, 103]. Outcomes described for anorectal smooth muscle tumours are therefore heavily skewed by patients with rectal tumours. Anal tumours have been described at the internal anal sphincter, the anorectal junction and the anal verge. Over half of anorectal cases were larger than 5 cm at presentation. The peak age at diagnosis for anorectal leiomyomas was 40–59 years and for leiomyosarcoma was 50–69 years [101].

Overall, 20 % of anorectal leiomyosarcomas show metastatic behaviour. The liver is the most common site of spread, but metastases to the lung, bone and adrenals have also been described. Local disease recurrence is also common, occurring in 87 % of patients in the most recent evaluation of case series [101]. Some of these recurrences occur after a long (>5 years) disease-free interval. Based on small numbers over accumulated case series, the estimated 5-year survival rate is 37.5 %.

Authors recommend a complete excision, which in many cases amounts to an abdominoperineal resection [102, 104, 105]. Typically tumours >5 cm are bulky enough to require an APR, but there are no retrospective comparisons to support this. Leiomyomas should be widely excised, and a 2 cm margin has been recommended [100]. Careful attention to the margins may be important in preventing recurrence. Some leiomyomas are reported to recur as leiomyosarcomas [100, 101].

Anal GISTs are less common than smooth muscle tumours. Accurate reporting of GIST in the literature, which hinges on immunohistochemical staining for the tyrosine kinase receptor, *kit*, is reliable only in the past two decades. It is therefore possible that prior reports of anorectal leiomyosarcomas may in reality include unrecognised GISTs [106]. The largest series of anorectal GISTs by Miettenen et al., which combines the Armed Forces Institute of Pathology and University of Helsinki databases, includes only three anal tumours, comprising 2 % of the reported patients [107]. Two other recent reports can be identified in the literature [108, 109]. It is reasonable to suppose that the behaviour of this tumour likely follows the risk stratification criteria using tumour size and mitotic activity [110], though there is no evidence as of yet that substantiates this assumption. There is no retrospective data that can tease out whether a local excision may be adequate compared to an APR, though, as seen with the discussion on anal melanoma and anal adenocarcinoma, common sense dictates that an APR would be indicated when a local excision with negative margins is not possible.

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