Guidelines

doi:10.1111/codi.13709

Association of Coloproctology of Great Britain & Ireland (ACPGBI): Guidelines for the Management of Cancer of the Colon, Rectum and Anus (2017) – Anal Cancer

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8 Anal Cancer

8.1 Background

In these guidelines, anal cancer refers specifically to squamous cell carcinoma (SCC) of the anus. The key recommendations from the ACPGBI position statement for the management of anal cancer (Lindsey, 2011) are referenced here.

Although anal cancer remains an uncommon tumour, its incidence has increased significantly in the past 20 years (Wilkinson *et al.*, 2014) and is now ~1.2 per 100 000 population, with 1233 new cases diagnosed in the UK in 2013 (Cancer Research UK). There is a female preponderance, with a female to male ratio of 1.8:1. Human papillomavirus (HPV) infection is the main predisposing factor in 90% (Frisch *et al.*, 1997), with subtype 16 and 18 found in 81% and 4% of tumours (Alemany *et al.*, 2015). The presence of HIV or other causes of immunosuppression may accelerate anal cancer development.

Anal cancers are sub-divided into anal canal and anal margin tumours (within 5 cm radius of anal orifice). Anal canal SCCs have different patterns of locoregional spread to low rectal adenocarcinomas and are staged and treated differently. Anal margin SCCs arise from the hair-bearing skin, distal to the anal verge. However, the distinction between anal canal and anal margin may not be possible when a patient presents with a locally advanced tumour involving both sites.

8.2 Anal Cancer Multidisciplinary Team (MDT)

Anal cancer requires a specialist MDT approach to deliver appropriate treatment and optimize outcomes (Renehan & O'Dwyer, 2011a). In 2004 regional Anal Cancer MDTs were established within each cancer network (NICE, 2004). The underlying principles have been maintained for NHS Commissioning from 2013 onwards (NHS England, 2013). The agreed Anal Cancer MDT

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service includes a core team of colorectal surgeons, oncologists, radiologists and pathologists, supported by a dedicated MDT coordinator, clinical nurse specialist (CNS) and data manager. The extended team includes a plastic surgeon and a gynaecological oncologist, with a surgical practice in the treatment of vulval and vaginal cancers.

All patients with suspected or newly (histologically) diagnosed anal cancer should be referred to the Anal Cancer MDT, for primary management. As the primary treatment modality for most anal cancers is by synchronous chemoradiotherapy (CRT), the MDT should comprise of one or at most two oncologists. The MDT should have two designated surgeons specializing in the surgery of anal cancer. All surgery (including local excision and salvage surgery) should be undertaken by these surgeons. Histopathology specimens should be reviewed by the Anal Cancer MDT pathologist. The MDT may need to seek advice and assistance from other surgical specialties, including urologists, vascular surgeons.

Colorectal MDTs should have defined pathways to refer all patients with a new anal cancer diagnosis or recurrence to a specialist Anal Cancer MDT.

Recommendation grade D

8.3 Investigations

8.3.1 Presentation and diagnosis

Anal cancer may present with pain, bleeding, discharge, mass and occasionally tenesmus or sepsis. These symptoms may be mistaken for other benign conditions, resulting in delayed referral. Pelvic or perineal sepsis with, or without, fistula formation is sometimes seen with advanced tumours.

Among men who have sex with men (MSM), and who are HIV positive, the incidence is approximately 80 per 100 000 population in the modern highly active antiretroviral therapy (HAART) era. Amongst MSM who are HIV negative, risk remains increased compared with the general population (approximately 5 per 100 000 population) (Machalek *et al.*, 2012). Despite these increased risks, HIV positive patients account for <10% of all anal cancer patients.

The role of routine testing of all patients with newly diagnosed anal cancer for HIV infection remains debated. In the practice of most Anal Cancer MDTs, HIV positive patients account for a small proportion of anal cancers and most will already have been diagnosed prior to developing cancer. However, identifying a patient to be HIV positive prior to commencing CRT may enable optimal management of both conditions. The NCRI PLATO trial mandates routine HIV testing of all potentially eligible patients.

Female patients should have up to date cervical cancer screening PAP smears prior to commencement of treatment if possible, due to the strong association with HPV infection.

A history of cigarette smoking is also relevant and patients should be encouraged to stop prior to commencement of treatment, as continued smoking is associated with poorer treatment outcomes (Linam *et al.*, 2012; Ramamoorthy *et al.*, 2008).

The median age of patients diagnosed with anal cancer is 60 years and 20% are 75 years or older. Therefore it is important to assess performance status and co-morbidities, particularly renal and cardiac conditions. Some patients will be unfit to tolerate the full standard treatment options and appropriate modification of treatment protocols will be required.

All patients with newly diagnosed anal cancer should have detailed assessment of co-morbidity and performance status to plan treatment.

Recommendation grade D

HIV testing should be routinely considered. For known HIV-positive patients, up to date assessment of immune status (viral load and CD4 count) should be obtained.

Recommendation grade C

Female patients should have up to date cervical cancer screening PAP smears.

Recommendation grade D

8.3.2 Pre-treatment assessment and staging

The current AJCC-UICC TNM 7th edition staging system should be used (Brierley *et al.*, 2010). The T stage is based on size (T1: ≤2 cm, T2: >2 to 5.0 cm, T3 >5 cm) and in T4 tumours, invasion of adjacent organs such as vagina, urethra and bladder. Sphincter involvement does not constitute T4 disease. The N stage reflects the pattern of lymphatic spread (N1: mesorectal nodes, N2: unilateral internal iliac or/and inguinal nodes, N3: mesorectal and inguinal, or bilateral internal iliac or bilateral inguinal nodes). Less than 15% of patients have distant metastases at diagnosis. The TNM 8th edition was published in December 2016 (Brierley *et al.*, 2016), but will only be implemented on 1st January 2018. The main change is that tumours of the anal margin and perianal skin, defined as within 5 cm of the anal margin will be classified with carcinomas of the anal canal.

Anal cancers should be routinely staged by detailed clinical assessment, magnetic resonance imaging (MRI) of the pelvis, computed tomography (CT) of the chest, abdomen and pelvis. The additional use of 18-

fluorodeoxyglucose positron emission tomography (18F-FDG PET/CT) can improve locoregional lymph node and metastatic staging, as well as aid radiotherapy planning (Jones *et al.*, 2015). Endoscopic ultrasound (EUS) may provide better delineation of small T1 tumours (Otto *et al.*, 2009) compared with MRI.

8.3.2.1 Detailed clinical assessment

A detailed clinical evaluation is mandatory to establish the size and exact location in relation to the anal verge and rectum, the degree of anal canal circumference involvement and its effect on sphincter and bowel function. Vaginal examination should be performed in females. Approximately 30% of patients will have palpable inguinal lymph nodes at presentation but up to half may be reactive to an inflammatory or infectious process. Patients who are unable to tolerate digital rectal examination should have examination under anaesthetic (EUA) for local disease assessment and biopsy.

8.3.2.2 Imaging

- *MRI pelvis:* For locoregional staging. Similar MRI sequences to those used for low rectal cancers should be utilized with pelvic phased array coils centred for the anal canal and including the anorectal junction/lower rectum. Recommendations for cross-sectional imaging in colon, rectum and anal cancer (second edition) have been published by the Royal College of Radiologists (The Royal College of Radiologists, 2014).
- *CT chest, abdomen and pelvis with intravenous iodinated contrast agent:* For detection of distant metastases. Both CT and MRI will detect enlarged pelvic side-wall and inguinal lymph nodes with similar accuracy, but MRI is better at characterizing mesorectal lymph nodes.
- *18F-FDG PET/CT:* For tumours at higher risk for lymph node and distant metastases (≥T2). FDG PET/CT detects sites of lymph node involvement and distant metastases, which were not obvious on MRI or CT (Saboo *et al.*, 2013) and can influence management in up to 29% of cases (Wells & Fox, 2012), particularly for defining gross tumour volume for radiotherapy planning. A recent systematic review and meta-analysis reported that whilst FDG PET/CT is highly specific (pooled estimate 90%) for detecting involved lymph nodes, the major concern it that it lacks sensitivity (pooled estimate 56%) (Caldarella *et al.*, 2014). The NCCN Anal Carcinoma Guidelines 2016 (National Comprehensive Cancer Network, 2016) state that although routine use of 18F-FDG PET/CT has not yet been validated, it should be considered for all tumours in addition to diagnostic CT.
- *Endoscopic ultrasound (EUS):* EUS can assess the depth of invasion and relation to the anal sphincter muscles, particularly in small tumours. However this additional information is unlikely to aid the management of most anal cancers.
- *Inguinal lymph nodes:* Enlarged inguinal lymph nodes may be metastatic or reactive. Involved inguinal lymph nodes can be detected by clinical and radiological features, and in equivocal cases, fine needle aspiration (FNA) may be beneficial if it demonstrates SCC. These develop in 16–36% of patients (Gerard *et al.*, 2001). Involved lymph nodes tend to be hard, irregular and can become fixed to underlying muscle or skin when extracapsular spread occurs. However, over 40% of involved lymph nodes measure <5 mm in diameter (Wade *et al.*, 1989) and are clinically undetectable, even on 18F-FDG PET/CT. Conversely, enlarged (>1 cm short axis) lymph nodes may be reactive or metastatic.

Ultrasound assessment with or without fine needle aspiration (FNA) should be performed when management is dependent on knowing the nature of an enlarged lymph node (Esen, 2006). However, this may not be necessary if the lymph node is avid on 18-FDG PET/CT or there is high clinical suspicion of involvement, based on MRI characteristics. The staging and management of inguinal lymph nodes was reviewed in the ACPGBI Position Statement for Anal Cancer (Branagan, 2011). Sentinel node biopsy is not an established staging tool in patients with anal cancer.

Routine staging should consist of a detailed clinical assessment, MRI pelvis and CT chest, abdomen and pelvis. The use of 18F-FDG PET/CT in addition, should be considered, if available, for all patients with ≥T2 tumours and are suitable for radical chemoradiotherapy (CRT).

Recommendation grade C

The AJCC/UICC TNM staging system should be used. The current version is the 7th edition, but will this be replaced by the 8th edition on 1 January 2018.

Recommendation grade D

8.4 Treatment

The presentation of anal cancer can range from small, superficial tumours to large, extensively infiltrative tumours, involving multiple groups of pelvic lymph nodes. The aim of treatment is to achieve best oncological outcomes, in terms of locoregional disease control and overall survival at minimal cost, in terms of acute and late morbidity and treatment-related mortality.

Standard treatment for most patients with anal cancer is definitive chemoradiotherapy (CRT). The main purpose of using CRT in patients with smaller tumours, not

amenable to local excision, is to avoid major resection with stoma and to preserve anal sphincter function. At the opposite end of the spectrum, CRT offers potential cure to patients with surgically unresectable tumours, whilst retaining satisfactory sphincter function in most cases.

8.4.1 Surgery

8.4.1.1 Wide local excision

Local excision alone may adequately treat small (T1) tumours at the anal margin and can achieve good local control (Namiq *et al.*, 2016; Wietfeldt & Thiele, 2009). The tumour should be excised with a margin of normal perianal skin and deeper tissue. On the deeper aspect a small portion of the distal internal anal sphincter may be removed to achieve an adequate margin. Where sphincter resection is considered necessary, patients should be warned of a risk of impaired continence. Small wounds may be left open whereas larger defects may require some form of advancement or rotational flap to cover. This should ideally be performed by an anal cancer MDT surgeon, following agreement within the MDT to attempt a complete excision.

In locally excised anal margin tumours, the minimum safe margin of excision is unknown, as there have been no published studies on this topic. To address this uncertainty, recruitment to ACT 3 (incorporated in the over-arching PLATO trial) is encouraged. This is a non-randomized phase II trial designed to determine if patients with ≤1 mm margins following local excision of anal margin tumours, who receive additional low-dose CRT, have acceptably low rates of locoregional failure.

On the other hand, anal canal SCCs are technically more difficult to excise due to their site, it is especially difficult to obtain adequate deep margin clearance without compromising continence (Namiq *et al.*, 2016). Therefore, any attempt at local excision of an anal canal cancer should be regarded as more likely to represent a generous diagnostic biopsy rather than being a curative procedure. If the histology is reported as invasive SCC with a margin ≤1 mm, adjuvant CRT should be considered. Polypoid anal canal lesions can often be macroscopically locally excised for histological assessment, which may sometimes contain a focus of invasive SCC. Providing the excision margin appears adequate (>1 mm), careful surveillance may be performed.

There is an emerging entity known as SISCCA (superficially invasive squamous cell carcinoma of the anus) defined by an invasive lesion completely excised with ≤3 mm stromal invasion and ≤7 mm superficial spread (Arana *et al.*, 2015). In carefully considered cases, with a clear surveillance plan, there may be a role for watch and wait in these patients.

8.4.1.2 Abdominoperineal excision

Abdominoperineal excision (APE) is no longer the primary treatment of choice for most anal cancers, not amenable to local excision (Northover, 1991). There are a small number of indications for APE as primary treatment: (i) when radiotherapy is contraindicated (for example, previous prostate or cervical radiotherapy), (ii) when the patient is unfit for CRT but deemed fit for a 'once-only' operation, or (iii) the patient declines CRT.

8.4.1.3 Formation of pre-treatment stomas

Patients with advanced tumours may need a defunctioning stoma prior to commencing treatment. Definite indications include bowel obstruction, significant incontinence, fistulation and peri-anal sepsis. Relative indications, such as vaginal invasion, severe tenesmus or severe defaecating pain are to improve the probability of the patient completing CRT with no unplanned treatment interruptions. Pre-treatment stomas are rarely required in patients with tumours ≤5 cm (Cooper *et al.*, 2012) but above 5 cm, the necessity increases exponentially with size (Beaumont *et al.*, 2012).

Despite achieving complete tumour response following completion of CRT the reversal rate of pre-treatment stomas is generally low (Cooper *et al.*, 2012; Glynne-Jones *et al.*, 2014a). These patients often have extensive destruction of the normal sphincter anatomy, as well as fibrosis and stenosis of the anal canal. Therefore, the type of stoma that is formed should be made with the knowledge that it is likely to be permanent and an end-colostomy is generally the most appropriate. Where stoma closure is contemplated, patients need to be counseled about the unpredictable and often poor functional outcomes in terms of evacuation and continence.

The presence of a perianal fistula should be managed by a long-term Seton prior to commencement of CRT. Interruption of CRT due to peri-anal sepsis is invariably associated with a poor outcome and is avoidable.

8.4.1.4 Inguinal lymph node dissection

Involved inguinal lymph nodes are usually treated with the primary tumour using CRT. If radiotherapy to the pelvis is contraindicated, therapeutic block dissection of involved lymph nodes or prophylactic dissection of non-involved lymph nodes may be considered, as part of the APE (section 8.4.1.2).

T1 anal margin cancers (≤2 cm) may be locally excised, as long as this can be achieved without compromising sphincter function. This should ideally be performed by an anal cancer MDT surgeon,

following agreement within the MDT to attempt a complete excision.

Recommendation grade C

T1 anal canal cancers are unlikely to be adequately locally excised without compromising sphincter function. This should ideally be performed by an anal cancer MDT surgeon, following agreement within the MDT to attempt excision. However any attempt at local excision should be regarded as more likely to represent a generous diagnostic biopsy, unless it can be demonstrated that margins are clear.

Recommendation grade D

When a pre-treatment stoma is indicated, patients should be warned that such stomas are often permanent, even in the presence of local disease control.

Recommendation grade C

8.4.2 Chemoradiotherapy (CRT)

Chemoradiotherapy (CRT) using synchronous mitomycin and 5FU with low dose radiotherapy (30 Gy) was first trialed in the preoperative setting by Norman Nigro (Nigro *et al.*, 1974). This resulted in high clinical and pathological complete response rates, enabling most patients to avoid surgery (Nigro, 1984). Subsequent non-randomized studies reported good outcomes with CRT alone (Cummings *et al.*, 1980; Gerard *et al.*, 1998).

8.4.2.1 Randomized controlled trials

The UKCCCR ACT I (585 patients) and EORTC 22861 (110 patients) trials reported improved local control and fewer colostomies with CRT using mitomycin/5FU, compared with radiotherapy alone (Bartelink *et al.*, 1997; Northover *et al.*, 2010; UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research, 1996). The RTOG 87-04 trial (310 patients) reported improved disease-free survival (DFS) and fewer colostomies in patients receiving CRT with mitomycin/5FU, compared to 5FU alone (Flam *et al.*, 1996).

The RTOG 98-11 trial (682 patients) compared 2 cycles of induction cisplatin/5FU followed by CRT using 2 further cycles of cisplatin/5FU *vs* standard CRT with mitomycin/5FU. Intensification of treatment resulted in significantly worse outcomes, in terms of toxicity, tumour control, colostomies and overall survival (Ajani *et al.*, 2009; Gunderson *et al.*, 2012). The UK ACT II trial (940 patients) was a 2×2 design comparing CRT using cisplatin/5FU *vs* mitomycin/5FU, with or without 2 cycles of adjuvant cisplatin/5FU. There was no difference in PFS between cisplatin and mitomycin, and no benefit from maintenance chemotherapy (James *et al.*, 2013). The ACCORD-03 trial (307 patients) was also a 2×2 design, comparing 2 cycles of induction cisplatin/5FU *vs* no induction chemotherapy and a standard dose (15 Gy) *vs* a high dose boost (20–15 Gy). Colostomy-free survival was not improved by either induction chemotherapy or a higher dose of radiotherapy (Peiffert *et al.*, 2012).

8.4.2.2 Radiation dose, fractionation and delivery

Early trials (ACT I, EORTC 22861) using large parallel opposed phase I radiotherapy fields incorporated a 6 week gap before phase II, to allow improvement of the severe associated skin reaction. It is now recognized that prolongation of the overall treatment time by inclusion of a gap, or use of induction chemotherapy is detrimental to local control (Ben-Josef *et al.*, 2010; Glynne-Jones *et al.*, 2015; Glynne-Jones *et al.*, 2011). The subsequent ACT II trial was designed to deliver 50.4 Gy in 28 fractions continuously over 5.5 weeks, with phase II commencing after 30.6 Gy instead of 45 Gy. Despite receiving a lower total dose in both phases compared to other trials, 90% of patients achieved complete clinical response.

Locally advanced (T3-4) tumours have worse outcomes (Ajani *et al.*, 2009; James *et al.*, 2013; Sunesen *et al.*, 2011) than less advanced (T1-2) tumours. Present trial data do not support radiation dose escalation above 54 Gy or use of induction chemotherapy, and further trials are needed to establish optimum treatment strategy, particularly for more advanced tumours (Glynne-Jones & Lim, 2011). On the other hand, many patients with anal cancer will not tolerate standard CRT due to co-morbidities or poor performance status. Using low dose CRT (30–40 Gy) can be a safer and yet effective compromise, especially for smaller tumours but longer follow-up data are needed (Charnley *et al.*, 2005; Glynne-Jones *et al.*, 2014b; Smith *et al.*, 1994).

Capecitabine, which is an orally administered fluoropyrimidine, has been demonstrated to be as effective as infusional 5FU for adjuvant and palliative treatment in colorectal cancer (Twelves *et al.*, 2005), as well as combined with radiotherapy in rectal cancer (O'Connell *et al.*, 2014), but with a slightly differing toxicity profile. Although capecitabine has not been formally evaluated in a phase III anal cancer trial, its use instead of 5FU is supported by single centre series (Thind *et al.*, 2014) and within NCCN and ESMO guidelines (Glynne-Jones *et al.*, 2014b; National Comprehensive Cancer Network, 2016).

Prophylactic low dose radiotherapy to clinically uninvolved inguinal lymph nodes is very effective in preventing recurrence and should be routinely given to all T2-4 tumours of the anal canal and margin. When omitted,

recurrence rates around 30% have been reported (Ortholan *et al.*, 2012). The UK ACT II and RTOG 98-11 trials reduced the radiation dose to uninvolved pelvic lymph nodes to 30.6 and 36 Gy respectively, significantly reducing the severity of acute skin toxicity. Smaller tumours have a lower risk of inguinal lymph node recurrence without prophylactic inguinal radiotherapy, which may be safely omitted in most T1 tumours (Tomaszewski *et al.*, 2012). However, as the acute and late toxicity associated with prophylactic inguinal radiotherapy when using modern radiotherapy techniques is low, along with studies indicating relative high rates of recurrence in non-irradiated patients (Matthews *et al.*, 2011), the default position is to include the inguinal lymph nodes in the prophylactic low dose volume.

Recent modernization of radiotherapy facilities throughout the UK has enabled all units to routinely deliver highly conformal intensity-modulated radiotherapy (IMRT), using a range of delivery methods such as multiple fixed fields, volumetric modulated arc therapy (VMAT) and tomotherapy. The use of IMRT reduces the volume of normal tissue receiving high-dose radiation (Brooks *et al.*, 2013), to reduce severity of acute and late toxicities. In addition, IMRT allows for variation of radiation dose to multiple planning target volumes (PTV) according to clinical requirement, including dose escalation given over the same number of radiotherapy fractions, known as simultaneous integrated boost (SIB). Although there have been multiple reported single centre series of IMRT for anal cancer, the only prospective trial completed was RTOG 0529 phase II (Kachnic *et al.*, 2013). The early oncological outcomes appear comparable to conventionally treated patients but mature data on late toxicity are yet to be published.

The process for IMRT volume outlining, planning and delivery are highly complex and subject to very significant variations between oncologists and their centres. Therefore standardization of treatment is essential, particularly to avoid geographical miss of disease, which compromises cancer outcomes (Myerson *et al.*, 2009; Ng *et al.*, 2012). A UK consensus document for outlining, planning, dose objectives and constraints and dose delivery is available on-line at www.analimrtguidance.co.uk. This consensus has taken into account the excellent results achieved in the ACT II trial, together with a review of radiotherapy planning and dose delivered to patients in the trial and has resulted in an adaptation of the recommended dose prescription (Muirhead *et al.*, 2014). These changes have been integrated into the UK PLATO phase III trial protocol, which will also oversee a quality assurance program for delivery of high quality radiotherapy for this population. A brief summary of the UK recommendations is as follows;

T1N0 tumours: planning target volume of the anal tumour (PTV_Anal) treated to 50.4 Gy in 28 fractions (1.8 Gy per fraction) over 5.5 weeks. The decision to use an additional elective (prophylactic) volume (PTV_Elec) to treat clinically uninvolved pelvic and inguinal lymph nodes is left to the oncologist.

T2N0 (and T3N0 at oncologist's discretion) tumours: PTV_Anal treated to 50.4 Gy in 28 fractions over 5.5 weeks. In addition, all patients are to receive 40 Gy in 28 fractions (1.43 Gy per fraction) over 5.5 weeks to PTV_Elec.

T4N0 or any N+ (and T3N0 at oncologist's discretion) tumours: PTV_Anal treated to 53.2 Gy in 28 fractions (1.9 Gy per fraction) over 5.5 weeks. The PTV to involved lymph nodes (PTV_Nodes) to 50.4 Gy in 28 fractions over 5.5 weeks. All other uninvolved lymph node regions (PTV_Elec) treated to 40 Gy in 28 fractions over 5.5 weeks.

Close adherence to the step-by-step directions within the UK guidance on how to outline and generate the various PTVs is recommended, ideally with mentoring by experienced departments for the first few cases. The AGITG guidelines and atlas for IMRT in anal cancer provides additional learning information (Ng *et al.*, 2012).

8.4.2.3 Late toxicity of CRT

Pre-menopausal women should be counseled about premature radiation-induced menopause. Embryo cryopreservation prior to commencing CRT may enable female patients to have children, but will require a surrogate in addition and will delay commencement of treatment. Referral to the fertility team for discussion of options may be appropriate. Vaginal stenosis can occur and referral to a gynaecology CNS for advice and provision of vaginal dilators should be considered in all women after completion of treatment.

Male patients should be counseled about permanent azoospermia and offered the opportunity for sperm storage. Testosterone levels may be reduced with impaired physical, psychological and sexual function after treatment (Buchli *et al.*, 2011). Erectile dysfunction may be due to low testosterone levels or nerve damage by radiation. Testosterone hormone replacement may be beneficial.

Patients treated for locally advanced tumours commonly experience incontinence from sphincter dysfunction or evacuatory problems secondary to fibrotic stenosis. Assessment and management by the pelvic floor specialists can be offered. In severe cases, a defunctioning stoma may be the only available option.

Radiation-induced small bowel strictures can present with obstructive symptoms and weight loss (Andreyev

et al., 2012) but are uncommon, due to the relatively low standard radiation doses used for anal cancer. Pelvic insufficiency fractures occur in up to 5% of patients, more commonly in women, causing lower back or pelvic pain (Herman *et al.*, 2009). The radiological appearance may be misinterpreted for bone metastasis.

Definitive CRT (radiotherapy with synchronous mitomycin and either, infusional 5FU or oral capecitabine) is the standard treatment for all anal cancers that are not amenable to local excision, unless radiotherapy is contraindicated.

Recommendation grade A

Mitomycin is an important component of the CRT schedule but cisplatin can be used instead, if mitomycin is contraindicated. The routine use of induction or adjuvant chemotherapy is not recommended.

Recommendation grade A

Intensity modulated radiotherapy (IMRT) should be considered for all patients in whom definitive CRT is intended, in order to reduce acute toxicity and possibly late toxicity. Standardization of radiotherapy volume outlining, planning and delivery should be based on published consensus guidelines.

Recommendation grade B

The minimum radiation dose for microscopic disease should be 40 Gy in 28 fractions over 5.5 weeks using IMRT or 30.6 Gy in 17 fractions over 3.5 weeks using the original ACT II protocol. Uninvolved inguinal lymph nodes should be routinely treated in all T2-4 tumours, but may be selectively omitted in small T1 tumours.

Recommendation grade B

Treatment gaps (planned or unplanned) are detrimental to local control. Radiotherapy should be delivered continuously with no treatment gap. Formation of a pre-treatment stoma prior to commencing CRT should be considered in patients with severe symptoms to enable better treatment compliance.

Recommendation grade B

8.4.3 Anal intraepithelial neoplasia (AIN)

Anal intraepithelial neoplasia (AIN) is often asymptomatic but may be associated with pruritus, bleeding, discharge and pain. AIN is caused by HPV infection and its clinical behaviour has strong parallels with cervical (CIN) and vulval/vaginal (VIN/VAIN) intraepithelial neoplasia. All three can occur together in the same individual. The clinical relevance of AIN is that it is precursor lesion for anal SCC.

A recent overview of guidelines on the management of AIN have pointed to three key problems, which in turn are a source of much confusion. First, there are inconsistencies with terminology. AIN is traditionally graded as AIN I, II and III. To aid management algorithms, the terminology of LSIL and HSIL (low- and high-grade squamous cell intra-epithelial lesions) was introduced over a decade ago. LSIL corresponded to AIN I; HSIL to AIN II and III. More recently, the terms LGAIN and HGAIN, respectively low-grade and high-grade AIN, were introduced. Alam *et al.* (Alam *et al.*, 2016) point out that some guidelines have confusingly restricted HGAIN to AIN III.

Second, of the three guidelines reviewed, Alam *et al.* (2016) showed that often the cited evidence is historic. Third, although HIV status (positive *vs* negative) and MSM status are hugely important in terms of transformation rates, this classification does not feature predominantly in clinical treatment and surveillance algorithms.

In a historic single institute series of 35 patients with AIN, the transformation to invasive SCC was estimated to be 50% in six immune-compromised patients (Scholefield *et al.*, 2005). They estimated that AIN transformation rates to anal SCC in the general population were very low. More systematic evidence is now available through systematic review and advanced meta-analytic methods to estimate progression rates 'from high-grade AIN to anal cancer of one in 633 patients (one in 377 in the HAART era) per year in HIV-positive MSM, and one in 4196 patients per year in HIV-negative MSM' (Machalek *et al.*, 2012). These categorizations should form the basis for stratification in management. Thus, a clinical algorithm based on the nomenclature of high-risk (HIV-positive MSM, and other immune-compromised such as transplant patients); high-moderate risk (HIV-negative MSM; HIV negative gay lesbian); and low-moderate (the 'rest') should be considered.

The central tenet of management of AIN (analogous to CIN) is that if one can induce regression or eradicate AIN, then malignant transformation can be prevented. However, to-date, there is no direct evidence to support this pathway to prevention of anal SCC (as there is for CIN to invasive cervical carcinoma). Targeted biopsies using high-resolution anoscopy and 3% acetic acid to the anal canal mucosa (similar to colposcopy) can help identify areas of AIN. Anoscopy is mandated in trials, but its role in clinical practice is not yet established.

The diagnosis of AIN can be suspected clinically or with the aid of magnification, but can only be confirmed and graded histologically. To avoid the risk of misdiagnosis of invasive disease and potential for over-

treatment, the diagnosis of AIN III should be confirmed by the specialist histopathologist within the Anal Cancer MDT.

There are several therapeutic options. Topical therapies include trichloroacetic acid, 5FU and immunomodulator creams (such as imquimod). Ablative therapies including infrared coagulation, electrocautery, carbon dioxide laser and photodynamic therapy have also been used (Scholefield *et al.*, 2011; Weis, 2013). Recent evidence from a Dutch randomized trial in 156 HIV positive MSM showed that electrocautery is better than imiquimod and fluorouracil in the treatment of AIN (where the endpoint was AIN regression/disappearance), but recognized that recurrence rates were substantial (Richel *et al.*, 2013).

The surveillance of patients with AIN II and III is predominantly aimed at the identification of early invasive carcinoma that can be treated by local excision or localized CRT with reduced treatment-related morbidity. High-risk patients should be followed up at six monthly intervals for at least 5 years, ideally with periodic photographic documentation of the perianal region. There should be a low threshold to repeat biopsies of any changing or bleeding lesion. Small, discrete lesions should be excised.

During surveillance, historically multiple biopsies by mapping has been advocated, often repeatedly. This is increasingly less favoured because of risk of perianal scarring and pain, with little impact on management.

Through AIN surveillance, new histological entities are emerging. Superficially invasive squamous-cell carcinoma of the anus (SISCCA) is defined by three criteria: an invasive squamous carcinoma that (i) has an invasive depth of ≤3 mm from the basement membrane of the point of origin, and (ii) has a horizontal spread of ≤7 mm in maximal extent, and (iii) has been completely excised (Darragh *et al.*, 2012). Currently, reported series are small but it may be that many of these can be managed by watchful waiting (Arana *et al.*, 2015). This needs be considered through a specialist Anal Cancer MDT. Older terminology such as perianal Bowen's disease have been abandoned.

All suspicious anal lesions should be excised or biopsied. Targeted biopsy of anal lesions suspicious for AIN is mandatory in high-risk groups to exclude invasive disease.

Recommendation grade D

All cases of AIN II and III should be reviewed and subsequently managed by the specialist Anal Cancer MDT.

Recommendation grade D

Female patients with AIN should be screened for synchronous CIN, VIN and VAIN.

Recommendation grade D

Consider HIV testing in patients with recurrent or multifocal AIN.

Recommendation grade C

In HIV-positive MSM, the use of electrocautery may have better results compared with imiquimod and fluorouracil.

Recommendation grade B

8.4.4 Anal cancer in HIV positive patients

The British HIV Association has published guidelines for HIV-associated malignancies 2014 (Bower *et al.*, 2014). The key messages on the management of HIV patients with anal cancer are summarized in this section.

Although anal cancer is not an AIDS-defining malignancy, its incidence is 30–40 times higher in people living with HIV (PLWH) and occurs at a younger age (Chiao *et al.*, 2008; Clark *et al.*, 2004; Kim *et al.*, 2001; Shiels *et al.*, 2009). It is highest in HIV positive MSM (Machalek *et al.*, 2012). Most anal cancers are attributable to HPV infection and the prevalence is higher in PLWH (Palefsky *et al.*, 2001). Despite the advent of combined anti-retroviral therapy (cART) the risk of developing anal cancer has remained unchanged (van Leeuwen *et al.*, 2009), probably due to significantly prolonged survival in PLWH allowing time for the progression from HPV infection through the phases of anal dysplasia to invasive anal cancer.

Tumour stage at diagnosis appears similar between HIV-positive and HIV-negative individuals (Hammad *et al.*, 2011; Hogg *et al.*, 2009; Kim *et al.*, 2001; Linam *et al.*, 2012). As late presentation may occur if anal symptoms are erroneously attributed to warts and haemorrhoids, which are common in this population, there should be a low threshold for referring all suspected cases for EUA and biopsy of the anal canal and rectum. Although there is scant evidence that screening for anal cancer by identifying and ablating pre-invasive AIN influences the risk of developing anal cancer (Wells *et al.*, 2014), the prevalence of AIN in PLWH is high, with reports of up to 25% in MSM (Melo *et al.*, 2014). Centres caring for these patients should have access to high-resolution anoscopy services.

There is consensus that HIV patients can be safely treated with CRT and that the outcomes achieved are similar to those in the general population (Alfa-Wali *et al.*, 2012; Fraunholz *et al.*, 2011; Hammad *et al.*, 2011; Hogg *et al.*, 2009; Linam *et al.*, 2012; Oehler-Janne *et al.*, 2008). Although some studies reported higher, grade 3–4

toxicities in patients with low CD4 cell counts, this is not a consistent finding. The use of cART seems to have reduced the toxicity of CRT (Alfa-Wali *et al.*, 2012; Blazy *et al.*, 2005; Fraunholz *et al.*, 2011; Fraunholz *et al.*, 2010; Hogg *et al.*, 2009; Oehler-Janne *et al.*, 2008; Wexler *et al.*, 2008), but a significant and prolonged decline in CD4 cell count can still occur despite continued use of concomitant cART (Alfa-Wali *et al.*, 2012; Wexler *et al.*, 2008). Therefore patients with anal cancer should be considered for opportunistic infection prophylaxis prior to commencing CRT, in partnership with their HIV team. The British HIV Association has published guidelines for the treatment and prevention of opportunistic infections (Nelson *et al.*, 2011). Combined ART should be started in patients newly diagnosed with HIV and continued during CRT in those known to be HIV positive.

Salvage surgery may be appropriate for PLWH with locoregional disease failure following CRT, although experience in this population is limited (Cunin *et al.*, 2014). Patients with metastatic disease or further relapse following salvage surgery may be considered for palliative chemotherapy or best supportive care.

In summary, survival of PLWH has improved significantly since the advent of cART, including those with anal cancer. The overall principles of managing HIV patients with anal cancer, from referral to the regional Anal Cancer MDT, to staging, definitive treatment and follow up should be the same as in non-HIV patients, as outlined in these guidelines.

To avoid late presentation of anal cancer in people living with HIV (PLWH), there should be a low threshold for referring all suspected cases for EUA and biopsy of the anal canal and rectum.

Recommendation grade D

The overall principles of managing HIV patients with anal cancer, from referral to the regional Anal Cancer MDT, to staging, definitive treatment and follow up should be the same as in non-HIV patients, as outlined in these guidelines.

Recommendation grade C

PLWH who are to be treated with CRT should be started on combined anti-retroviral therapy (cART) and opportunistic infection prophylaxis should be considered prior to commencing CRT.

Recommendation grade C

8.5 Follow Up After CRT

The aims of follow up after completion of CRT for anal cancer are to (Renehan & O'Dwyer, 2011b):

1 Detect local disease failure amenable to successful salvage surgery.
2 Detect the development of distant metastases where early treatment may improve the prognosis or long-term survival.
3 Identify and manage late consequences of treatment. This may be due to the radiation alone or a combination of pre-existing tumour damage and radiation, which often occurs in locally advanced tumours.

Surveillance of patients should be performed within a protocol-driven program by the Anal Cancer MDT, for early detection of local disease failure following CRT.

Recommendation grade D

8.5.1 Early assessment of response to CRT

Regression of anal cancers may be slow and can continue for up to 6 months following completion of CRT (Glynne-Jones *et al.*, 2017). A decision to investigate for local disease failure should be deferred until such an interval, during which tumours should be carefully observed by clinical examination, ideally by the same clinician at 4–8 week intervals until complete clinical response. However, clinically non-responding or enlarging tumours should be biopsied earlier, in preparation for potential salvage surgery. Very early (6–8 week) assessment by MRI or other imaging modalities is generally unhelpful and is not recommended (Goh *et al.*, 2010). However, recent data indicates that MRI assessment at 3 and 6 months may be able to identify those at risk of early relapse, who are amenable to R0 salvage (Kochhar *et al.*, 2017).

Clinical assessment at 6–8 weeks following completion of CRT, then every 4–8 weeks until clinical and radiological complete response.

Recommendation grade C

Consider initial MRI between 3–6 months post CRT, particularly in more locally advanced disease, or if there is residual palpable abnormality.

Recommendation grade C

8.5.2 Follow up after complete clinical response

Patients with local disease failure may be amenable to salvage surgery. Most failures (around 80%) occur within the first 2 years (Sebag-Montefiore *et al.*, 2012). The follow up protocol from the ACT II trial is widely adopted in the UK, consisting of clinic visits every 2 months during the first year, every 3 months during the second year and every 6 months from years 3–5, which is in keeping with this pattern of failure. Clinical

assessment should consist of inspection of the perineum, anorectal digital examination and palpation for inguinal lymphadenopathy. In the case of suspicious findings, the patient should either be re-examined by the same clinician in 4–6 weeks or be referred to the Anal Cancer MDT surgeon for EUA and biopsy.

Follow up is recommended in all patients, the primary aim is to detect disease which is amenable to salvage surgical resection; secondary aim is to manage symptoms related to the cancer and its treatment

Recommendation grade C

Once clinical and radiological complete response has been achieved, further clinical assessment at 3–4 month intervals until 24 months, then 6–9 month intervals until 60 months.

Recommendation grade C

8.5.3 Role of imaging

Following CRT, MRI pelvis is able to demonstrate tumour regression and document sustained response. The benefit of routine use of MRI in addition to clinical assessment alone remains unclear with no general consensus (Goh *et al.*, 2010; Gourtsoyianni & Goh, 2014; Kochhar *et al.*, 2012; Kochhar *et al.*, 2017). NCCN and ESMO guidelines are also discordant on this issue, with MRI pelvis indicated as an option within the ESMO but not the NCCN guidelines (Glynne-Jones *et al.*, 2014b; National Comprehensive Cancer Network, 2016). There may be merit in risk stratifying patients; with MRI being used for patients with T3/4 N+ disease at diagnosis and in those with residual changes after treatment completion. These patients are the most likely to develop locoregional failure and may be the hardest to detect clinically. In the PLATO (ACT 4 and ACT 5) trial, routine MRI pelvis has been scheduled at 3 and 6 months following CRT.

In patients with suspected or proven local disease failure, MRI pelvis together with other imaging modalities such as CT chest, abdomen, pelvis and 18F-FDG PET/CT should be performed to identify appropriate patients for salvage surgery and plan the optimal surgical approach.

The routine use of CT to diagnose distant metastases before symptoms arise may enable earlier treatment but the benefits in terms of improved quality of life and overall survival remain unproven. The NCCN guidelines indicate that this may be considered in patients at higher risk (T3-4 or N2-3) of developing pelvic lymph node recurrence or distant metastases, with annual CT over the first 3 years (National Comprehensive Cancer Network, 2016).

CT chest, abdomen and pelvis can be considered as per the colorectal cancer guidelines (first at 12–18 months, second at 24–36 months).

Recommendation grade C

Routine use of MRI pelvis beyond 12 months is not recommended, unless there is suspicion of, or proven local disease failure.

Recommendation grade C

8.5.4 Reversal of stoma

Patients who require formation of a stoma prior to CRT tend to have very advanced local disease. Such patients remain at higher risk of local disease failure following CRT and have a poorer prognosis (Cooper *et al.*, 2012). Stoma reversal is not a realistic option in a high proportion of these patients (50–80%), usually due to disease failure or extensive permanent organ damage (Cooper *et al.*, 2012; Glynne-Jones *et al.*, 2012). If reversal is being considered, cross sectional imaging should be performed to exclude the presence of pelvic lymph node failure and distant metastases.

8.6 Management of Treatment Failure

Following completion of CRT, the most frequent site of treatment failure is the primary tumour. Less common sites of disease failure are inguinal or other pelvic lymph nodes and distant metastases, including liver, lung and retroperitoneal lymph nodes. Data from the ACT II trial indicate that 209 of 924 evaluable patients relapsed. Of these failures 54% occurred in the first year, 26% in year two and 13% in year 3. In 64% of the relapsed cases the disease was localized to the pelvis alone (Sebag-Montefiore *et al.*, 2012). Local treatment failure can be divided into persistent local disease or local recurrence.

8.6.1 Local disease relapse

Up to 10% of patients will have persistent local disease, defined as biopsy proven cancer at up to 6 months following completion of CRT. Local recurrence is defined as biopsy proven local disease beyond 6 months in a patient who previously achieved complete clinical response (cCR). Most local relapses will be apparent within 24 months of completion of CRT.

Local relapses are usually palpable on digital examination, often before development of new symptoms. Obtaining histological confirmation is essential when there is suspicion of residual or recurrent disease. Post-treatment fibrotic tissue can look and feel like malignant

disease. Patients being considered for salvage surgery should be assessed and restaged with:

- Examination under anaesthesia and biopsies.
- MRI pelvis
- CT chest, abdomen and pelvis
- 18F-FDG PET/CT may be helpful to assess metabolic activity of equivocal lesions and to detect sites of occult metastases.

Salvage surgery offers a second chance of cure and should be considered for all local relapses. Published data show that the proportion of patients with locally persistent/recurrent disease undergoing salvage surgery varies between 50% and 75%, but is highest in series from centralized centres working through one MDT (Renehan & O'Dwyer, 2011b). However, despite salvage surgery <50% of patients will survive beyond 5 years. The ACPGBI audit standard for the proportion of patients with local relapse (at primary site only) being offered salvage radical surgery is >60% (Renehan & O'Dwyer, 2011b).

On clinical and/or radiological suspicion of local relapse, re-staging investigations include MRI pelvis, CT chest, abdomen and pelvis, 18-FDG PET/CT (as indicated). EUA/biopsy should be performed to confirm.

Recommendation grade C

All patients with treatment failure should be assessed by the Anal Cancer MDT. The percentage of patients with local relapse and undergoing subsequent salvage surgery should be audited.

Recommendation grade D

8.6.2 Salvage radical surgery

A detailed examination under anaesthesia and biopsy should be performed by the Anal Cancer MDT surgeon; particularly noting the size, location and fixity of the suspected disease. Salvage surgery for relapsed anal cancer is often associated with significant morbidity and a prolonged recovery period. In order to obtain maximal benefit, careful patient selection is essential. Preoperative clinical and radiological assessment of the patient should be focused on achieving clear margins (R0 resection) at salvage surgery. Presence of distant metastases is associated with a poor prognosis and usually excludes the patient from surgery.

For the majority of patients, salvage surgery involves the minimum of a radical APE. The need to extend this operation to encompass adjacent viscera and irradiated soft tissue of the perianal region, perineum and buttocks should be considered. A posterior or total pelvic exenteration is sometimes required to achieve clear margins. Wide removal of the ischiorectal fossa fat with extralevator resection is recommended when tumour has breached the puborectalis or external sphincter muscles. Delayed wound healing following salvage surgery is common (over 40%) and consideration should be given to perineal reconstruction (Renehan *et al.*, 2005).

Radical APE for anal cancer is a specific operation distinct from APE for low rectal cancer. This should be performed by an experienced anal cancer surgeon, supported by an oncoplastic team.

Recommendation grade C

8.6.3 Regional disease failure

Inguinal lymph node recurrence is considered as regional failure. Suspected inguinal lymph node recurrence should be assessed by ultrasound ± FNA and restaged with CT chest, abdomen and pelvis MRI pelvis and possibly 18F-FDG PET/CT to exclude distant metastases.

Salvage surgery with pelvic lymph node dissection should be considered. This is associated with significant morbidity especially in patients who have previously received high-dose CRT to this region. In the occasional patient who did not receive prophylactic inguinal radiotherapy, salvage CRT may be considered but this requires careful planning to avoid significant radiotherapy overlap of critical organs.

8.6.4 Further radiotherapy

There is emerging evidence showing that following initial radiotherapy, tolerance to further radiation improves with time, due to limited long-term recovery of radiation DNA damage (Stewart & van der Kogel, 1994). Patients with local recurrence of anal cancer who are not suitable for salvage resection may benefit from further radiotherapy, with or without chemotherapy to the pelvis. Treatment to a small volume, using a dose and fractionation defined by the cumulative prior doses in the organs at risk and taking into account the degree of normal tissue recovery expected over time would be appropriate. Stereotactic radiotherapy may be possible in selected cases, with the intention of delivering a tumoricidal dose where feasible. A long interval from completion of initial CRT to recurrence (>2 years) predicts for a good response to further RT. Although this approach is unlikely to be curative, it can offer medium term control of local disease and palliation of symptoms.

8.6.5 Distant metastases

The development of distant metastases in the absence of local failure in anal cancer is infrequent, estimated at up to 10% (Northover *et al.*, 2010). Distant metastases are

usually incurable and treatment with systemic chemotherapy to control disease and prolong survival should be considered. There are limited published data on the optimal systemic therapy regimens but a combination of cisplatin and a fluoropyrimidine (5FU or capecitabine) is often used. Treatment of eligible patients within clinical trials, such as InterAACT is encouraged. There is no systematically reviewed evidence to recommend resection or ablation of oligometastases. Early phase data indicate there may be a future role for immune checkpoint inhibitors in this group of patients (Morris & Eng, 2016).

8.7 Histopathology Reporting

This section should be read in conjunction with the Royal College of Pathologists (Loughrey *et al.*, 2014) dataset for colorectal cancer (3rd edition).

Process
The Welsh audit of anal cancer demonstrated poor documentation overall (Karandikar *et al.*, 2006). Use of structured proformas has been shown to improve histopathology reporting.

Local resections
The size of the lesion (usually anal margin) should be documented together with lateral and deep resection margins. All local excisions should be registered with the network anal cancer MDT. A prospective collection of local excision for anal SCC is the focus of the upcoming UK ACT3 trial within the PLATO umbrella trial. Positive margins have been defined as ≤1 mm and these patients will be offered chemoradiotherapy, with 3-year locoregional relapse as the primary endpoint.

The new terminology of Superficially Invasive Squamous Cell Carcinoma of the Anus (SISCCA) has been detailed under management of AIN.

Resection Specimen
This will usually be an anorectal excision for persistent disease following CRT, recurrence or complications. Cut up of the specimen should concentrate on size, depth of invasion (in relation to sphincters), involvement of adjacent organs and circumferential resection margins.

Histology Type
Usually squamous but other varieties can be recorded. Historically, variants such as basaloid and cloacogenic have been recorded, but these terms are no longer advocated in the WHO classification.

TNM Staging
Is different compared to rectal adenocarcinoma invading the anal canal. Pathological T staging essentially relates to size; and on clinical staging to invasion of adjacent organs and pattern of lymph node spread.

- **i** pT1 to pT3 relates to size
- **ii** pT4 is any size that invades adjacent organs. Note that the invasion of the sphincter muscle is not classified as pT4
- **iii** Regional lymph nodes. N1 is a nodal involvement in the mesorectum; N2 is unilateral internal iliac/inguinal lymph node involvement; N3 is involvement of the mesorectal/inguinal, bilateral internal iliac and/or inguinal lymph nodes.

If the patient has had neoadjuvant treatment the staging should have the prefix 'yp'.

The pathological findings should be reported using a proforma.

Acknowledgements

To Prof David Sebag-Montefiore, Dr Rob Glynne-Jones and Dr Rebecca Muirhead for reviewing this chapter and providing valuable input.

Conflicts of interest

Andrew Renehan has received lecture honoraria from Merck Serona and Sanofi and been a member of the advisory board of Beating Bowel Cancer. Mark Bower is a British HIV Association and European AIDS Clinical Society guidelines writer. None of the other authors have any conflicts of interest to declare.

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