Colorectal Disease

ACPGBI Position Statement for Management of Anal Cancer

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Anal Cancer. Position Statement of the Association of Coloproctology of Great Britain and Ireland Introduction

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Background

Development of these written guidelines followed the anal cancer consensus meeting held in October 2008 at the Royal College of Surgeons of England under the guidance of the Association of Coloproctology of Great Britain and Ireland.

Multi-disciplinary team working has become established in the last 10 years for colorectal cancer, and several sets of Local, National, and International Guidelines have been developed for the management of colorectal cancer. In the existing guidelines, anal cancer receives only limited coverage because it is a rare tumour. The relative rarity of anal cancer means that clinicians are more likely to face uncertainty in the management of these tumours when they do occur.

Anal cancer accounts for approximately 4% of large bowel malignancies; however, there is some evidence that its incidence is increasing. Over 80% of anal cancers are of squamous origin arising from the squamous epithelium of the anal canal and perianal area; 10% are adenocarcinomas arising from the glandular mucosa of the upper anal canal, the anal glands and ducts. A very rare and particularly malignant tumour is anal melanoma. Lymphomas and sarcomas of the anus are even less common but have increased in incidence in recent years, particularly among patients with human immunodeficiency virus (HIV). There has also been a rise in the incidence of other anal epidermoid tumours among patients with HIV.

Anal anatomy

Traditionally, the anal region is divided into the anal canal and the anal margin or verge. The natural history, demography and surgical management differ between these areas. There has been controversy regarding the exact definition of the anal canal. Anatomists see it as lying between the dentate line and the anal verge, whereas surgically it is defined as lying between the anorectal ring and the anal verge. For pathologists, the canal has been defined as corresponding to the longitudinal extent of the internal anal sphincter [1]. The canal above the dentate line is lined by rectal mucosa except a small zone immediately above the line called the transitional or junctional zone [2]. Inferiorly, the canal is covered by stratified squamous epithelium. Further confusion relates to the definition of the anal canal and anal margin as sites for cancer. The anal margin is variously described as the visible area external to the anal verge, or as the area below the dentate line. This argument has become less important as surgery plays a lesser role in treatment, but reports of surgical results from past decades are confused by this variation in definition.

Aetiology and pathogenesis

Anal squamous cell carcinomas are relatively uncommon tumours; there are between 350 and 400 new cases per year in England and Wales. Based on these figures, each consultant general surgeon might expect to see one anal carcinoma every 3–5 years. However, anal cancers are probably underreported as some anal canal tumours are misclassified as rectal tumours and some perianal tumours as squamous carcinomas of skin.

The Office of Population Censuses and Surveys' [3] Cancer Statistics for England and Wales recorded 289 cases of anal cancer in 1988 (*need updates figures*). The average age is 57 for both sexes but canal tumours are more common in women, whereas margin tumours are more common in men. However, these figures must be interpreted with caution because the distinction between anal canal and anal margin is poorly defined.

There is wide geographical variation in the incidence of anal cancers around the world [4], but again these figures must be interpreted with caution for reasons given earlier. Nevertheless, a low incidence (0.2 cases per 100 000 of population) is reported by Rizal in the Philippines, and the highest incidence (3.6 cases per 100 000 of population) is reported in Geneva, Switzerland. Other areas of high incidence are Poland (Warsaw) and Brazil (Recife). It is notable that these areas also have a high incidence of cervical, vulval and penile tumours (possibly reflecting the common proposed aetiological

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agent – papillomaviruses). The UK incidence of anal cancer lies between these extremes.

The increasing incidence of HIV infection in the United States has resulted in an increase in the incidence of anal cancer [5]. Areas such as San Francisco with a large gay population have reportedly seen a dramatic increase in the prevalence of anal cancers. A recent study from Denmark has reported a doubling in the incidence of anal cancer, particularly in women over the last 10 years [6]. No other countries have reported similar increases to date, but the Cancer Registry data in Denmark are renowned for their remarkable accuracy and completeness. Systemic immunosuppression is recognized as a risk factor for the development of anal cancers and transplant recipients; patients on long-term steroid therapy for autoimmune disease are at increased risk [7–9].

Recent epidemiological evidence has suggested that anal cancer may be associated with anal sexual activity; Cooper [10] observed four cases of anal cancer arising in homosexual men with long histories of anoreceptive intercourse. The occurrence of a disproportionately high incidence of anal cancer among male homosexual communities was reported from San Francisco and Los Angeles. Daling *et al.* [11] identified risk factors for the development of squamous cell carcinoma of the anus, a history of receptive anal intercourse in men increasing the relative risk of developing anal cancer by 33 times compared with controls with colon cancer. A history of genital warts also increased the relative risk of developing anal cancer (27-fold in men and 22-fold in women). These studies suggest that a sexually transmissible agent may be an aetiological factor in anal squamous cell carcinoma.

Similarly, epidemiological data and molecular biological data have shown an association between a sexually transmissible agent and female genital cancer. Using nucleic acid hybridization techniques, human papillomavirus (HPV) type 16 DNA and less commonly types 18, 31 and 33 DNA were consistently found to be integrated into the genome in genital squamous cell carcinomas [12]. Recently, the same HPV DNA types have also been identified in a similar proportion of anal squamous cell carcinomas [13]. Human papillomaviruses are DNA viruses, of which there are more than 60 HPV types capable of causing a wide variety of lesions on squamous epithelium. Common warts can be found on the hands and feet of children and young adults and are caused by the relatively infectious HPV types 1 and 2. Anogenital papillomaviruses are less infective than types 1 and 2 and are exclusively sexually transmissible. The epidemiology of genital papillomavirus infection is poorly understood, largely because of the social and moral taboos surrounding sexually transmissible infections. Anogenital papillomavirus-associated lesions range from condylomata through intraepithelial neoplasia to invasive carcinoma. The most common HPV types causing genital warts are types 6 and 11. HPV types 6 and 11 may also be isolated from low-grade intraepithelial neoplasia. HPV types 16, 18, 31 and 33 are much less commonly associated with genital condylomas but are more commonly found in high-grade intraepithelial neoplasias and invasive carcinomas. Once one area of the anogenital epithelium is infected, spread of papillomavirus infection throughout the rest of the anogenital area probably follows, but remains occult in the majority of individuals [14]. Therefore, the commonly held belief that anal cancer only occurs in individuals who practise anal intercourse is probably unfounded.

Competing interests

None.

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Position Statement

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Guidelines for Management of Anal Intraepithelial Neoplasia

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Introduction

Anal intraepithelial neoplasia (AIN) is often a precursor to invasive squamous anal carcinoma. The disease process involves both the perianal skin and the anal canal including the anal transition zone [13 III]. It is a multifocal disease process strongly associated with human papillomavirus (usually HPV types 6, 11, 16 and 18). There are strong aetiological and clinical parallels between AIN and cervical (CIN) and vulval (VIN) intraepithelial neoplasia. Less is known about the natural history of AIN than for CIN or VIN, but AIN is probably more analogous to VIN than to CIN in its natural history. The accepted figure for malignant transformation in VIN is 10% over 10 years.

Nomenclature

In clinical practice, the vast majority of AIN lesions occur in the perianal skin, and although such lesions may spread into the anal canal, anal canal lesions without evidence of perianal involvement are very unusual. Of course, the boundaries of the perianal skin and anal canal are rather poorly defined, and this can complicate description and treatment of these lesions.

The natural history of AIN [also referred to as squamous intra-epithelial lesion or squamous intraepithelial lesion (SIL) in the United States] is uncertain. It was first described in 1985 as two cases of rectal dysplasia by McCance *et al.* [24 III] and grades were defined the following year by Fenger and Nielsen [13 III]. It is characterized by cellular and nuclear epithelial abnormalities limited by the basement membrane. Histological features include increased mitotic rate, mitotic activity above the basal layer, nuclear pleomorphism, hyperchromatism and failure of normal maturation [18 IV]. AIN I and AIN II refer to nuclear abnormalities confined to lower one-third and lower two-thirds of the epithelium, respectively, and these lesions are considered to be low-grade dysplasia [41 III]. AIN III is full thickness involvement of the epithelium and represents high-grade dysplasia or carcinoma *in situ*. The Bethesda system refers to AIN as anal SIL with low-grade lesions (LSIL) equivalent to AIN I, and high-grade lesions (HSIL) equivalent to AIN II and III [29 IV].

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Prevalence of AIN

The exact prevalence of AIN in the general population is unknown, but is thought to be < 1% [30,31 IIa], although the incidence is rising. A number of groups at high risk for AIN have been defined and include patients with HIV, those who are systemically immunocompromised such as transplant recipients and those on long-term steroids (e.g. for connective tissue disorders), women with a history of genital intraepithelial neoplasia and those with extensive anogenital condylomata.

Much of the literature on prevalence of AIN relates to patients with HIV. The nature and time course of AIN in patients with HIV pursue a more aggressive course, and the literature needs to be interpreted with care when applied to immunocompetent individuals.

The prevalence of AIN in HIV cohorts ranges from 26% to 89%, the more recent series report increasing prevalence with 52% of HIV-positive men having AIN2 or 3 *vs* 20% in HIV-negative men [25 III]. This is paralleled by a steeply rising annual incidence of anal cancer in patients with AIDS of 224 per 100 000 [12 III].

Conversely, the prevalence of AIN in nonimmunosuppressed patients – such as women with VIN or CIN – is around 5% [26 IIb]. The prevalence of AIN in renal allograft recipients is probably of the order of 3–5%.

Risk of progression from AIN to anal squamous cell carcinoma

Progression from low to AIN III is seen in 62% of HIV-positive and 36% of HIV-negative MSM men within 2 years [34–36 IIa]. AIN III very rarely regresses [37 III], but AIN I and II may regress [42,43 IIb].

The risk of progression of AIN to invasive anal cancer approximates 10% at 5 years. It was initially thought that 5% of AIN III progresses to invasive cancer in a median of 104 (16–273) months [21 III,22 III]. Higher progression rates are more recently reported; Scholefield *et al.* [44 III] reported 9% progression of AIN III [follow-up 63 (14–120) months], while 13% progression of AIN III to invasive disease in 60 (80–112) months was found by

Watson *et al.* [49 III]. Invasive carcinoma is found in 8.8–26% of those having AIN III excision [4 III,40 III]. Similarly, AIN III is found in 80% of cases of anal carcinoma [13 III]. These figures need to be interpreted with caution as progression rates are probably determined by treatment (such as excision) and by the host immune status.

Those most at risk of invasive cancer are those with multifocal disease or immunosuppression [44 III]. In this series, 50% of systemically immunocompromised (transplant, systemetic lupus erythematosus (SLE) and asthma) patients with AIN III developed invasive cancer within 5 years of diagnosis compared with no progression to invasive disease in the immunocompetent patients [44 III].

Presentation

A high index of suspicion is required for diagnosis of AIN. Patients may present with perianal symptoms of irritation, and the perianal skin appears abnormal but without a high index of suspicion AIN III lesions are easily missed. Around 10% of AIN lesions are diagnosed as an incidental finding after excision of a 'funny looking' anal tag. Any suspicious anal lesion must be biopsied although with increasing experience of AIN lesions the need for such biopsy may be reduced.

Low-grade anal dysplastic lesions may have the appearance of anal condyomata, but some condylomata are flat rather than filiform, this is particularly the case for dysplastic lesions. AIN III lesions are usually flat, and they may appear white, grey, purple or brown in colour. The pigmentation of such lesions is not always uniform. The presence of ulceration in an AIN lesion suggests invasion.

The prevalence of incidental AIN in routine haemorrhoidectomy specimens is just 0.05% [20 III]. The appearance of AIN lesions is very variable, hence, the need for a high index of suspicion. Symptoms include pruritus and anal discharge; other symptoms of pain, bleeding and tenesmus suggest invasion. Suspicious lesions may be raised, scaly, white plaques, erythematous, pigmented, fissured or eczematous [52 IV]. AIN is present in 28–35% of excised anal condylomata [6 III,27 III,52 IV].

Screening

There is probably no place for screening for AIN even in high-risk groups at the present time. Although some centres in the United States have started screening for AIN in HIV cohorts using anal cytology (EXPLORE study), this is not a sensitive screening test and requires highly trained cytopathologists. At present, this is probably only appropriate as part of a trial in high-risk groups in the United Kingdom.

Diagnosis

As stated earlier, diagnosis requires a high index of suspicion and then biopsy of suspicious lesions. Although colposcopy of the anus (sometimes referred to as anoscopy) can be used in conjunction with 5% aqueous acetic acid and Lugol's iodine to make an *in vivo* assessment of the presence of anal dysplasia, this is a specialist technique and one which requires training an regular practice [41] III). It is not something which is recommended for colorectal surgeons who see relatively few patients with AIN. Anal colposcopy may have a role in those practices seeing large numbers of patients with HIV where a simple test to identify high-grade dysplasia from benign anal condyloma has important implications for the patient and may reduce the need for examination under anaesthesia. Equipment and facilities for biopsy under local anaesthetic are a useful addition to this service.

The grading of AIN can only be performed by histopathological examination. Although some centres have used cytology as a diagnostic tool, this is a highly specialized diagnostic field. Indeed any anal cytological abnormalities should undergo biopsy to confirm the diagnosis of AIN [22 III,33 IIa].

Histopathological interpretation of AIN lesions is subject to interobserver variation [5 IIb,10 IIb]. Some authors have reported high incidences of invasive foci in 8.8–26% of specimens excised for AIN III alone [4 III, 40 III]. This is probably because of the difficulty in recognizing that AIN III lesions may extend down hair shafts and involve skin adenexae. When cut in a slightly tangential histological section, this can be misleading in that the adenexal involvement appears as a focus of micro invasion or frank early invasion. This dilemma may be resolved by examining adjacent tissue sections. If in doubt, discussion at a multidisplinary team (MDT) with the treating clinician and early review to check on wound healing is recommended. It is the authors' experience that most of these 'early micro-invasive' lesions subsequently turn out to be no more than AIN III extending into skin adenexae, and the patient can safely be observed provided the wound has healed readily after the primary excision.

Difficult cases involving AIN or micro-invasive disease should probably be discussed at the anal cancer MDT and may benefit from review by several histopathologists and clinicians within a network or referral to experts in other networks.

Management strategies

The aims of treatment are to minimize symptoms and prevent the development of anal cancer. The optimal management of AIN is difficult to determine as large

series comparing treatments with the prolonged follow-up required are lacking. The largest single institute experience is 47 patients over 21 years [22 III]. The various treatment options that have been subject to analysis are detailed later.

Observation alone

Expectant management extends from the fact that high recurrence rates are seen after aggressive attempts to eradicate dysplasia. This is particularly seen in HIV-positive patients and is likely to be because of persistent HPV infection. This conservative approach is based on the perceived low rate of progression of high-grade AIN to invasive cancer and aims to detect invasive disease at an early and curative stage [11 III]. Low-grade dysplasia (AIN I or II) is generally managed in an expectant way with regular follow-up [9 IIb,42 IV].

Chemo-radiotherapy

This is the standard first-line treatment for invasive anal cancer, but there is no published evidence for its use in AIN in the absence of invasion. Radiotherapy has been used for both vaginal and vulval intra-epithelial disease with good results [2]. Extensive AIN III and AIN II at the margin of invasive cancers treated by chemoradiation disappear, suggesting that this treatment may have a place in patients with extensive AIN but risks causing anal stenosis. There is no literature on its use in AIN.

Surgery

Local excision

Excision of small lesions is preferable to ablative therapies as the latter destroy the tissue and preclude histopathological examination which should dictate further management. Local excision may be suitable for localized symptomatic lesions of < 30% anal circumference [44 III]. Defects can be closed primarily or left to heal by secondary intention.

Most studies describe preoperative mapping before excision, but this does not preclude recurrence [23 III]. Brown *et al.* [4 III] described 34 patients having local excision. Despite preoperative mapping, 56% had margin positivity, and 63% recurred within 1 year. Similarly, Rasmussen reported 4 of 11 recurrences and Marchesa *et al.* [22 III] reported 53.3% local recurrence after local excision (0.5–1 cm macroscopic margin) at 38 months. Others describe multiple recurrences after conservative surgery including invasive recurrences [22 III].

Wide local excision of larger anal lesions is not usually necessary, if the worst areas are excised, the adjacent areas can often be managed by observation. Although there have been reports of wide local excision and reconstruction using a variety of flaps, these approaches carry significant morbidity [42 III], and for a condition of uncertain malignant potential is probably over-treatment.

Micro-invasive disease

Micro-invasive disease represents a challenge to the histopathologist and clinician. Careful histopathological assessment is required to ensure that micro-invasive disease is not under- or over-diagnosed. If there is a focus on micro-invasion which was incompletely excised, it is unlikely that the initial biopsy site will heal fully, and early re-excision with further histopathological examination is required. If the lesion has been completely excised, the biopsy site will heal and then regular follow-up as for AIN III is recommended. Invasive disease in a re-excision specimen should be treated as for invasive anal SCC by chemoradiation.

The extent of AIN III change in the anal epithelium dictates the management strategy. This requires multiple biopsies of the anal canal and perianal skin, a procedure sometimes referred to as 'anal mapping'. The use of a 3-mm corneal punch biopsy is recommended for this. A total of 8–12 biopsies should allow adequate mapping of disease extent in most cases. An operative mapping sheet or digital photography is helpful in this procedure. Examination of the vulval skin, vagina and cervix should be performed by a Gynaecologist, but this does not need to occur at the same time as the anal mapping procedure.

Grade and extent of anal disease determines management. Localized or focal AIN is defined as < 30% anal circumference involved, whereas extensive AIN involves more than 30% circumference [44 III]. Lesions involving < 30% anal circumference can be simply excised with the resulting wound left to granulate or sutured as appropriate. AIN III lesions involving more than 30% of the anal margin or canal cannot be excised as the risk of severe anal stenosis is significant, but excision of the most symptomatic area is possible. The remaining areas can then be observed at regular follow-up intervals of around 6 months.

Immunomodulation therapies

Imiquimod 5% cream

This nucleoside analogue of the imidazoquinoline family has pro-inflammatory, anti-tumour and anti-viral activity through a number of subcellular mechanisms [reviewed by Ref. 45]. Use of this topical treatment caused

resolution of AIN III, regression by at least two histological grades and undetectable HPV type 16 [16 III,19 III].

In a separate uncontrolled study of 27 patients, half of whom had AIN III: 77% of lesions resolved following 16 weeks of treatment [51 IIb]. Total lesion clearance has been seen in 46% of HIV-positive men at 20 weeks [39 III]. This agent is emerging as a safe effective topical treatment, even in HIV-positive patients with their high propensity for recurrence.

Cidofovir 1% gel

Cidofovir is an acyclic nucleoside phosphonate with broad spectrum anti-viral activity. It has activity against vulval, vaginal and perianal IN [48 IIb]. When used for up to 6 weeks has been shown to be more effective than electrosurgery in the treatment of anogenital warts in HIV-positive patients [32 IIb]. Cidofovir alone cleared all low-risk HPV and 57% of high-risk HPV, which translated into 35% relapse rate compared with 74% relapse in the surgery-alone group at 6 months follow-up ($P = 0.018$), although a combined electrocautery and cidofovir gave the best results (100% complete response). While these studies are of interest, the follow-up is very short and this precludes useful analysis of the long-term efficacy of this treatment and make its routine use or research interest rather than for widespread clinical application.

HPV immunotherapy

Increased understanding of the molecular biology of HPV infection has led to phase II/III trials of therapeutic vaccination. A fusion vaccine of HPV-16 E7 protein and *M. bovis* heat-shock protein 65 led to a partial or complete response in five of 15 participants with associated clearance of HPV at 48 weeks [38 IIa]. A prime-boost strategy in 29 women with anogenital IN found complete histological regression in just one patient [14 IIa]. Research efforts continue in this field. Further data are awaited.

Photodynamic therapy (PDT)

A pilot study of 12 HIV-positive patients with high-grade dysplasia used the photosensitizer δ-aminolevulinic acid followed by PDT [50 IIb]. Consistent downgrading of dysplasia was seen, and the treatment was well tolerated, although response was based on cytology and a complete response was seen in just two cases. This type of therapy is painful and often requires multiple treatments. The long-term outcomes are uncertain.

Ablation

Ablative therapies used in AIN include CO_2 laser ablation [22 III, 3 III], cryotherapy [17 III,28 Ib] and electrocautery fulgaration [7 IIb]. Many of these studies suffer from high recurrence rates and significant morbidity. For example in a study of electrocautery in HIV-positive men, the recurrence rate was found to be 79% in 12 months, with an estimated recurrence risk approaching 100% by 50 months [7 IIb]. Patients also suffered uncontrolled postoperative pain lasting for a mean of 3 weeks, although multifocal extensive abnormalities were being treated. Recurrences may be high because of persistence of HPV infection and because of deep involvement of the perianal skin and appendages by AIN [8 III,46 III], which cannot be cleared by ablation. Invasive disease cannot be identified with these destructive techniques.

Treatment algorithm (Appendix 2 and 3)

AIN I/II and AIN III have differing natural histories so are treated differently in the algorithm. AIN I/II does not require long-term follow-up, whereas patients with AIN III and multicentric intraepithelial neoplasia should be managed by clinicians with an interest in this disease and require a multidisciplinary approach (involvement of a gynaecologist to exclude vulval and cervical disease as a minimum standard).

Similarly patients with HIV are considered separately in view of the higher progression rates and poorer results and higher recurrence rates after surgery compared with immunocompetent patients. Excision of extensive high-grade AIN that was too large for topical therapy found that 23 of 29 HIV-positive patients having surgery had persistent or recurrent high-grade AIN at median follow-up of 29 months, compared to no recurrences in the eight HIV-negative patients [7]. Surgical treatment of CIN in HIV-positive women is similarly beset with significantly higher recurrence rates than that for HIV-negative women (73% *vs* 27%, $P = 0.019$) [47]. Surgery is likely to be less effective in the face of persistent HPV infection and ongoing immunocompromise. Promising results of treatment with imiquimod, particularly in HIV-positive patients, reflect its inclusion as a treatment alternative to 'watchful waiting'. Those patients with symptomatic lesions should be offered surgery if the benefits are thought to justify the morbidity (Table 1).

Follow-up/surveillance

The aims of follow-up are to detect progressive or recurrent disease after treatment or to detect invasive

Table 1 Results of wide local excision surgery (WLE) for AIN3/Bowen's disease.

Author	*n*	Follow-up	FS	Mapping	RR	Coverage
Margenthaler *et al.* [23]	23			83%	13% at 2 years	
Brown *et al.* [4]	10	41 months		Y	37% at 41 months	SSG
Marchesa *et al.* [22]	26	104 months	Y	Y	23% at 41 months	SSG/AF
Sarmiento *et al.* [40]	18	8.4 years			31% at 5 years	V-Y flap
Scholefield *et al.* [42,43]	10	20 months		Y	0	SSG
Strauss 1979	10	3 years	Y	Y	10% at 3 years	SSG

AIN, anal intraepithelial neoplasia; FS, intraoperative frozen section; RR, recurrence rate; SSG, split skin graft; AF, advancement flap.

changes in known AIN. Follow-up of patients with AIN is essential as the natural history is still uncertain. Although there is no standardized follow-up protocol for AIN, a number of aspects are agreed. AINI and II have an indolent course in the immunocompetent patients, and 12 monthly anoscopy is recommended [1 IV,52 IV]. Women should undergo 12 monthly cervical screening if there is a history of AINIII [52 IV]. HIV-positive patients are considered at higher risk of recurrence and progression, so six monthly anoscopy is recommended [1 IV, 11 III]. Extended follow-up is advised as recurrences at 9 years after surgery is described [22 III].

Issues for service providers

1 The incidence of AIN is currently unknown. Data should be obtained prospectively to determine incidence and prevalence. Such information would help determine the natural history and predict the workload from new cases and follow-up of patients detected with AIN .
2 It will need to be decided who has responsibility for management of AIN. In many parts of the United Kingdom, each colorectal surgeon in the region will see a small number each year, other networks tend to centralize the referral of AIN III cases to one centre and to one or two (preferable) colorectal surgeons.
3 Clinicians dealing with AIN need to be identified and any training requirements met. This probably does not mean that courses for anal coloscopy need to be established.
4 Colorectal surgeons with a large AIN practice in patients with HIV may require specific collaborations with their local GUM and HIV clinicians.
5 There will be training requirements for histopathologists.
6 Use of novel agents with anti-viral activity such as imiquimod and therapeutic vaccination should be encouraged possibly as part of clinical trials.

Competing interests

None.

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Recommendations

Histological assessment of suspicious lesions is essential in all patients, and targeted biopsy of anal lesions suspicious for AIN is mandatory in high-risk groups. Evidence Grade C.

Histological diagnosis of AIN III should only be made by an experienced histopathologist to reduce the risk of misdiagnosis of invasive disease. Evidence Grade C.

Women with AIN should be managed in conjunction with a gynaecologist with an interest in oncology. Evidence Grade C.

Clinicians should have appropriate training in the management of anal dysplasia. Evidence Grade C.

As the incidence of AIN is low, it is appropriate for AIN III to be managed in a centre with an interest in AIN as part of a cancer network. Evidence Grade C.

Consider testing AIN III patients for HIV particularly if recurrent or multifocal Evidence Grade C.

Appendix 1

Grading of evidence

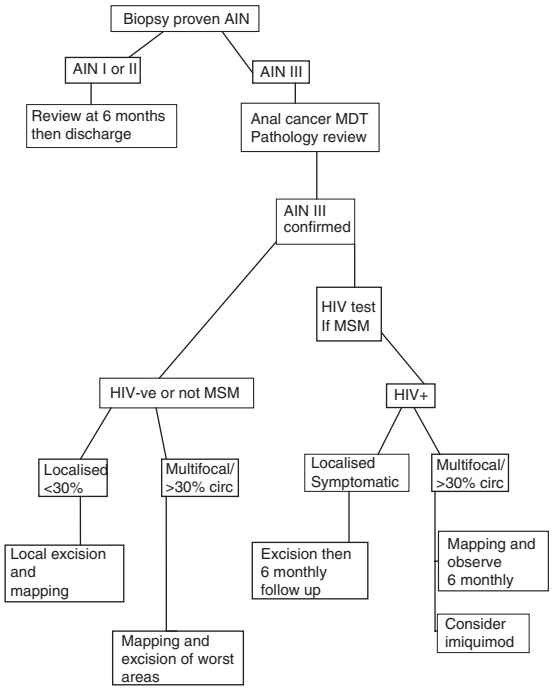
Ia: Evidence obtained from meta-analysis of randomized controlled trials.
Ib: Evidence obtained from at least one randomized controlled trial.
IIa: Evidence obtained from at least one well-designed controlled study without randomization.
IIb: Evidence obtained from at least one other type of well-designed quasi-experimental study.
III: Evidence obtained from well-designed nonexperimental descriptive studies such as comparative studies, correlation studies and case studies.
IV: Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Note: Every reference quoted in the text of the detailed version of the guidelines is graded according to this system.

Grading of recommendations

A: Requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation (levels Ia, Ib).
B: Requires the availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation (levels IIa, IIb, III).
C: Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable clinical studies of good quality (level IV).

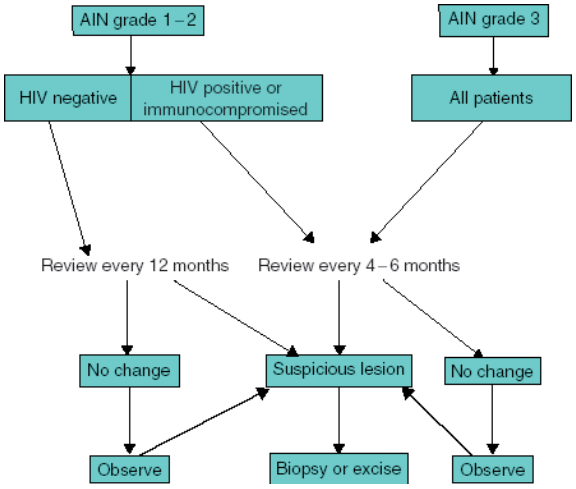
Appendix 2: Suggested protocol for the management of AIN



MSM, men who have sex with men.

Appendix 3: Protocol for AIN treatment and follow-up

From Abbasakoor and Boulos [1]



Position Statement

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Anal Cancer: Pathology, Staging and Evidence-Based Minimum Data Set

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Anatomy and terminology

1 The anal canal is the terminal part of the large intestine, which extends from the anorectal junction at the upper surface of the pelvic floor, passes through the anorectal ring and ends at the junction with the skin at the anal margin [1].

2 The anorectal ring is a palpable ring, rather than a visual landmark surrounding the anal canal at the upper surface of the pelvic floor. The mucosa below it presents 8–10 longitudinal folds called anal columns. Each column ends with an enlarged base, which are then joined by a mucosal fold to form the anal valve. The alignment of the valves forms the dentate line. The segment of the anal canal above the dentate line is the anal transitional zone (ATZ).

3 The histological anal canal (usually 3 cm in length), in an excised opened specimen, begins at the level of the histological anorectal junction and ends at the junction with the true skin at the anal margin (from the anal transition zone to the perianal skin) [2].

4 The ATZ is defined as the zone interposed between the colorectal-type mucosa above and the uninterrupted squamous epithelium below, irrespective of the type of epithelium present in the zone itself [3].

5 The surgical anal canal is a functional unit and extends from the distal intestinal tract enclosed by the internal sphincter muscle to the anal verge (from the anorectal junction down to the junction of nonkeratinized squamous epithelium with hair-bearing perianal skin).

6 The anatomic anal canal is the segment between the dentate line to the true skin around the anus (anal verge) [1,2].

The surgical definition of the anal canal is the one most widely accepted for practical reasons and is the preferred definition of the American Joint Committee on Cancer (AJCC) [4].

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Tumour location

Tumours involving the anorectal junction should be classified as rectal cancers if the epicentre is more than 2 cm proximal to the dentate line and as anal cancers if the epicentre is 2 cm or less from the dentate line [4]. Cancers that arise in the perianal skin are termed 'perianal cancers' and are biologically similar to other skin tumours and are staged according to the classification for cancers of the skin [4]. This distinction between anal canal and anal margin malignancies is important as anal canal lesions are more aggressive [5] than the latter and also the incidence of anal canal lesions is up to five times more common than that of anal margin lesions [6].

Primary tumours of the anal margin constitute 15–20% of anal squamous cell carcinoma (SCC) [7], and they have high cure rates with wide local excision alone if they are <3 cm in diameter, well differentiated and superficial [8]. It is not known if the original location of the tumour affects the outcome for salvage surgery as in most reports SCC of anal margin and canal are analysed together [8]. It is, however, important to emphasize that to determine the primary location of the tumour by biopsy alone can be difficult or impossible hence the importance of documenting location by clinical examination [9,10].

Recommendation

The distinction between anal canal and anal margin malignancies is important as anal canal lesions are more aggressive. Anal margin cancer tends to have high cure rates with wide local excision alone if they are < 3 cm in diameter, well differentiated and superficial (Level of evidence: III).

Pathology and biology

Epidermoid (squamous) carcinoma is the most common type of anal canal malignancy, seen in up to 80–85% anal canal carcinoma [11]. Most cancers of the anal margin are keratinizing and well differentiated, while those located in the canal are often nonkeratinizing and poorly differentiated. Tumours arising from the upper part of the canal, around the dentate line, have been defined as transitional,

Table 1 WHO histological classification of tumours of the anal canal: [14].

Epithelial tumours
Intraepithelial neoplasia1 (dysplasia)
Squamous or transitional epithelium
Glandular
Paget disease 8542/32
Carcinoma
Squamous cell carcinoma 8070/3
Adenocarcinoma 8140/3
Mucinous adenocarcinoma 8480/3
Small cell carcinoma 8041/3
Undifferentiated carcinoma 8020/3
Others
Carcinoid tumour 8240/3
Malignant melanoma
Nonepithelial tumours

cloacogenic or basaloid carcinoma. Adenocarcinoma of the anus is rare (5–10% of cases up to 18% in recent reviews); most of the reported cases consisted of colloid carcinomas arising in an anal fistula or low rectal tumours [12].

Traditionally, SCC of the anal canal has been divided into basaloid, large nonkeratinizing and large keratinizing variant. However, the diagnostic reproducibility of these subtypes of anal SCC has been low, and there are no significant prognostic differences between the subtypes of SCC; hence, the term cloacogenic carcinoma is now obsolete [9,13].

Therefore, the current WHO classification (Table 1) recommends that the generic diagnostic term 'SCC' be used to cover all histological variants of SCC of the anal canal [14]. However, additional descriptive comment regarding specific histological features such as predominant cell size, basaloid features or adjacent intraepithelial neoplasia is still recommended, as prominent basaloid features and small tumour cell size are usually linked with 'high-risk' human papilloma virus infection [14].

Two variants of SCC of the anal region should be mentioned separately as they differ in prognosis from typical squamous tumours [10]. One is verrucous carcinoma (giant condyloma or Buschke–Lowenstein tumour), of the anal margin which resembles a condyloma macroscopically but is larger and does not usually respond to conservative therapy. These lesions are regarded by some, as biological intermediates between condyloma and SCCs, with a better prognosis than SCC. However, nearly 50% of these lesions will eventually prove to be malignant [9]. Rare histological subtypes that can arise in the anal area include small cell carcinoma, lymphoma, melanoma, leiomyosarcoma. Melanomas contribute 1–4% of all anal cancers and 1–2% of all melanomas [12].

Premalignant changes including severe dysplasia or carcinoma *in situ* can be seen in up to 80% of cases of SCC of the anal canal, particularly those arising in the ATZ [15,16]. High-risk HPV-16 has been found in over 80% of anal canal cancers with aberrant expression of p53 and c-myc [17–20] which has also been implicated in the development of anal cancer.

In high-grade anal intraepithelial neoplasia and invasive lesions, p53 was expressed in the full thickness of the epithelium and in invasive lesions. This is in contrast to warts and normal epithelium where very few basal cells stained for p53 [21]. C-myc oncogene expression is also implicated in the pathogenesis of anal cell squamous carcinomas and may be helpful in identifying those high-grade dysplastic lesions most likely to progress to invasive tumours [19].

Grading and differentiation

Anal canal squamous carcinoma can be graded histologically into the following categories: [22]

1 Grade X = grade cannot be assessed
2 Grade 1 = well differentiated
3 Grade 2 = moderately differentiated
4 Grade 3 = poorly differentiated.

It is suggested that if there are variations in the differentiation within the tumour, the highest grade is recorded as the overall grade [9]. However, it should be stressed that neither the histology type nor the degree of differentiation have major prognostic significance [23], and therefore, have not been included in the AJCC/UICC staging system. Furthermore, chemoradiotherapy (CRT), which is the primary treatment modality for anal canal cancer, may significantly alter the morphology of the cells thus rendering the grading doubtful.

Carcinoma *in situ* or anal intraepithelial neoplasia may be graded into mild (Grade 1), moderate (Grade 2) and severe (Grade 3) dysplasia. Grade 1 is defined as nuclear abnormalities confined to the lower third of the epithelium, Grade 2 to the lower two-thirds of the epithelium and Grade 3 as abnormalities involve the full epithelial thickness [14].

Macroscopically, SCCs may appear as a small ulceration or fissure, exophytic, with indurated margins and irregular thickening. The basaloid phenotype is characterized by small to intermediate cell size, basophilic with often central necrosis comedo-like palisading and retraction artefact [24].

Adenocarcinomas arising in the anal canal have similar macroscopic and microscopic features to colorectal-type adenocarcinomas. They may be the result of a downward

infiltration of a rectal adenocarcinoma, or they may arise from the epithelium of the transitional zone [14].

Immunohistochemistry can be useful in differentiating colorectal from anal adenocarcinoma with CK7+/CK20−ve immunoprofile characterizes the typical pattern of the anal gland carcinoma, whereas colorectal adenocarcinomas are usually CK7−ve/CK20+. Prostatic carcinomas may resemble anal gland carcinomas in male patients, but they are CK7−ve/CK20−ve and either prostate-specific antigen or prostatic acid phosphatase positive [25].

Recommendation

SCC can be used to cover all histological variants of SCC of the anal canal with high risk of association with HPV-16. Immunohistochemistry can be useful in differentiating colorectal from anal adenocarcinoma (Level of evidence: III and IV).

Diagnosis

Careful digital examination of the anal region can provide essential information regarding the presence, site and extent of anal cancer, and biopsy of any suspicious area is recommended to confirm the diagnosis [12]. Suspicious inguinal nodes need to be pathologically ascertained [12].

Prognostic factors

In different studies on anal canal squamous cell cancer, sex, tumour stage, node involvement, and response to radiotherapy or combined treatment are of independent prognostic significance for overall survival and local control in a multivariate analysis [26,27]. Histological subtypes of squamous carcinoma are less relevant than tumour stage in considering prognosis [28].

Tumour size and depth of invasion

Because current recommendations for primary treatment of anal canal cancer do not involve a surgical excision, most tumours are staged clinically, with an emphasis on the primary tumour size determined through direct examination and microscopic confirmation [22]. Many studies have shown conclusively that outcome is influenced by tumour size. For patients receiving radiotherapy alone or CRT as the primary treatment, one group [29] found a significant difference in survival for tumours greater or lesser than 4 cm. In addition, tumour extent of more than one-third of the circumference of the lumen adversely affected local control in a univariate analysis [30]. Similar results have been found in patients receiving salvage anorectal excision after failed CRT, where a tumour size > 5 cm has been shown to affect adversely the survival of these patients. In this study, age of > 55 years was a bad prognostic parameter [31].

The diameter of the tumour correlated with the depth of penetration, and according to some authors, it was unclear whether the independent variable is the actual tumour size or the depth of invasion [32]. A cut-off of 4–5 cm has been proposed as the size that distinguishes good and poor prognosis [33]. Advanced T-stage and invasion through the muscle wall were accompanied by a higher rate of failure of CRT and a greater need for abdominoperineal resection (APR) [34]. In one study from Mexico, there was a specific pattern of recurrence according to the size of the tumour [35], i.e. in T1 patients, no recurrences were observed; in T2 tumours, the recurrence pattern was local; in T3 tumours, it was loco regional and to the groin area; and in T4 tumours, it was loco regional and distant.

The classical study by Boman *et al.* [36] has shown that for patients who had APR as the primary treatment, the depth of invasion is the most important pathological factor. When the disease was confined to the sphincter muscles (T1 and T2 combined), the local recurrence rate was 23% compared with 52%, when the tumour had invaded through the sphincters into the adjacent pelvic tissues. A recent prospective study showed tumour diameter of more than 5 cm as an independent prognosticator of poorer 5-year disease-free survival and overall survival and confirms nodal involvement and male sex as poor prognostic factors [37]. The study from Memorial Sloan–Kettering showed that when salvage anorectal excision was performed after radiotherapy or CRT, the depth of invasion had a major impact on outcome [38]. For most histological types of anal canal cancer, the diameter of the tumour correlates with the depth of penetration [9].

Prior to the widespread use of CRT, several large surgical series identified pathological prognostic indicators for anal cancer and several staging systems were recommended based on examination of the surgical resection specimen [36,39,40]. These studies were published prior to the widespread use of CRT and were thus not widely adopted, as there was no primary surgical specimen. One group [13] advocated that the studies of pathological prognostic factors should be interpreted with caution when applied to patients treated primarily with radiotherapy or CRT. Clinically based pretherapy staging came to predominate. Other systems have also been adopted [23].

Surgical excision remains an important treatment modality for residual or recurrent anal cancer, and there

is a need for a validated staging system for post-CRT anorectal excision specimens to provide clear prognostic information and to decide on possible further treatment after salvage surgery. Haboubi *et al.* [10] showed that in salvage surgery, the prognosis is worse in the following categories: nonresponders than recurrence, initial tumour size of 5 cm or over, depth of invasion into and beyond the lavator ani, 55 years or over age groups and lymph node involvement. They also showed that cancer of the anal margin tends to have a higher cure rate with wide local excision but only if the tumour was well differentiated, small and superficially located. Location therefore is very important and needs to be documented by the clinician. The factors, which were shown not to affect the outcome in the salvage operation, are the degree of tumour differentiation and lymphovascular or perineural invasion. Recent guidelines from the European Society of Medical Oncology suggest that local excision can be considered for small well-differentiated carcinomas of the anal margin (T1 N0), i.e. < 2 cm in diameter, without evidence of nodal spread [33].

Lymphatic, vascular and neural invasion

The presence of lymphovascular invasion does not affect the staging of the local extent of the tumour [9]; therefore, it has not been included in the AJCC/UICC staging system (Table 2). Also, there is no information available as to whether vessel invasion will affect the result of salvage surgery after failed CRT treatment.

Recommendation

Most anal cancers are staged clinically, with an emphasis on the primary tumour size which is shown to be an important prognostic parameter. In patients who had salvage APR, the depth of invasion is the most important pathological factor (Level of evidence: III).

Lymph node involvement

Lymph drainage of anal cancer tumours is dependent on the tumour location in the anal region. Cancers in the perianal skin and the region of the anal canal distal to the dentate line drain mainly to the superficial inguinal nodes; lymph drainage at and proximal to the dentate line is directed towards the perirectal nodes and to some of the nodes of the internal iliac system and more proximal cancers drain to nodes of the inferior mesenteric system [41]. Regional lymph nodes (N) stage comprises the perirectal (anorectal, perirectal and lateral sacral), the internal iliac (hypogastric) and the inguinal (superficial and deep) [22]. All other nodal groups represent sites of distant metastasis (M category). Tumours that arise in the anal canal usually spread initially to the anorectal and perirectal nodes, and those that arise at the anal margin spread to the superficial inguinal nodes [42].

Nodal metastasis was found to be associated with a worse outcome, higher local failure and decrease survival as reported by European Organization for Research and Treatment of Cancer trial [43]. Some studies predict that inguinal lymph node involvement may be present in later stages of this disease as the proximal lymphatic channels of the lower rectum become saturated with tumour cells and causing malignant cells to travel retrograde along the lymphatics [42]. In fact, the presence of inguinal but not perirectal lymphadenopathy at presentation will adversely affect the outcome of salvage surgery after CRT [38]. If nodal disease is present at the time of salvage surgery, there appears to be both an increase in recurrence and a

Table 2 AJCC staging system for anal cancer: [4,70].

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
Tumour of any size invades adjacent organ(s), eg, vagina, urethra, bladder*	
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis**
N1	Metastasis in perirectal lymph node(s)
N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes	
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Stage groupings	
Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0; T3 N0 M0
Stage IIIA	T1 N1 M0; T2 N1 M0; T3 N1 M0; T4 N0 M0
Stage IIIB	T4 N1 M0; Any T N2 M0; Any T N3 M0
Stage IV	Any T Any N M1

*Direct invasion of the rectal wall, perianal skin, subcutaneous tissue or the sphincter muscle is not classified as T4.

**Regional perirectal/pelvic lymph node dissection requires examination of at least 12 lymph nodes. However, histological examination of inguinal lymph nodes will require six lymph nodes. If the lymph nodes are negative but the required number is not met classify as pN0.

decrease in survival [44]. One group argued that the low yield of lymph nodes in resection specimens for anal cancer after radiotherapy and chemotherapy makes nodal status less important in pathological reporting [23].

For anal cancer, we are not aware of data regarding the significance of extra nodal deposits, which are tumour nodules not associated with lymphoid follicles [10]. One recent study [45] compared the use of PET scan and sentinel lymph node biopsy of inguinal lymph nodes in patients with anal cancer. Among 27 patients, PET scans detected no inguinal metastases in 20 of 27 patients and metastases in the remaining 7. Histological analysis of the sentinel lymph node detected metastases in only three patients (four PET–CT false positives). They concluded that inguinal sentinel node biopsy was superior to PET–CT for staging inguinal lymph nodes.

In another recent study by De Nardi *et al.* [46], among 11 patients studied (two T1, four T2 and five T3 tumours), sentinel lymph node biopsy detected metastases in three patients who had otherwise negative groin lymph nodes on clinically and radiologically examination.

MRI is currently the modality of choice to assess locoregional disease, but ultrasound can be useful for small lesions. PET/CT has been recommended in the current National Comprehensive Cancer Network treatment guidelines, because of high sensitivity in identifying involved lymph nodes and high specificity in immunocompetent patients [47].

Recommendation

Lymph node status is an important determinant of prognosis and recurrence which is mainly determined by clinical examination, by biopsy and CT (Level of evidence: IV). The routine use of a PET–CT scan for staging or treatment has not been validated (Level of evidence IV).

The effect of treatment on pathological staging

The standard definitive treatment for carcinoma of the anus 30 years ago was APR. Using this technique, the 5-year survival range was 38–71% [36,48–50] for SCC. In patients with small lesions, local excision was performed in an attempt to spare the anal sphincter; however, the results were poor in patients with anal canal lesions and only seemed to benefit those with anal margin lesions < 2 cm in size [51]. In 1974, Nigro *et al.* [52] introduced combined CRT in an attempt to downstage the disease prior to surgery. They were, subsequently, able to achieve 2- to 11-year survival rates of 80% reserving APR as a salvage procedure for residual or recurrent disease [53]. Reported results of primary CRT for epidermoid anal cancer reveal initial complete response rates of 75–95% [54–57]. Although this was originally developed as a neo-adjuvant protocol, the findings of complete tumour regression in the majority of patients led to its use as a primary treatment [53], with disease-free survival of 65–75% at 5 years has been reported [44]. Currently, most anal canal carcinomas are managed successfully without surgery, using combination chemotherapy and radiation therapy and therefore cannot be staged pathologically [47].

It is well known that anal cancers continue to regress well after treatment with CRT; however, the exact timing of maximal tumour regression is unclear [58]. Studies have demonstrated that up to 12 weeks are needed to see complete clinical response in the majority of patients, and it is this initial response that has been shown to be an independent factor in overall survival [59].

Routine biopsy is controversial in monitoring response to treatment with CRT, with some clinicians advocating multiple random biopsies every 3 months, whereas others biopsy only clinically suspicious lesions [58,59]. Following CRT, 10–15% of patients have a less than complete response and therefore persistent disease. An additional 10–30% of patients can be expected to recur at a later date. The usual treatment for both groups is APR [54–56,60].

Recurrent *vs* Persistent local disease

It is important to differentiate residual disease (positive biopsies < 6 months) after the completion of CRT from tumour recurrence (complete response initially, with positive biopsies > 6 months after cessation of treatment) [61]. Recurrence has a better prognosis for salvage surgery after CRT than persistent disease [61].

Risk factors for failure of surgical salvage include the presence of persistent rather than recurrent disease [44], inguinal adenopathy at presentation, < 55 Gy of radiation administered, inability to tolerate complete treatment mainly in the elderly and immunocompromised patients, and gaps in treatment owing to toxicity lead to decreased effective radiation dose distribution with resultant worse local control and worse overall survival [62–65]. Tumour size at time of presentation has also been associated with locoregional failure. Akbari *et al.* in their analysis of 62 patients who had salvage surgery owing to locoregional failure demonstrated that predictors of decreased survival were tumour size > 5 cm or adjacent organ involvement, positive nodal disease and positive margins at the time of salvage surgery. However, they showed that recurrence rather than persistence disease after CRT (when salvage is potentially curative), absence of nodal disease at salvage and negative margins were associated with favourable outcome [44].

Metastatic disease is seen in 6–10% of patients at presentation [11], and the risk for subsequent development of metastatic disease is independently associated with the ability to maintain locoregional control [59]. Schiller *et al.* [66] found in their analysis of 40 patients who underwent APR for failed CRT that male gender and tumour size with positive margins and lymphovascular invasion predicted poor disease-free survival.

Lateral margins

Analysis of the pathological data of patients from the UKCCCR trial by Hill *et al.* [23] showed that when the lateral excision margin was > 1 mm, further pelvic recurrence occurred in 25% (cancer-specific mortality 33%). These rose to 60% and 75%, respectively, when the lateral excision margins were < 1 mm. These data, however, need to be validated but for the time being, we suggest that the microscopic distance between the excision margin and the tumour is measured and recorded.

Fixation of tumour to the pelvic sidewall at operation and invasion into the perirectal fat in the resection specimen adversely affected outcome of salvage surgery after CRT [38], while negative margin is a favourable independent prognostic factor [44]. Positive surgical margins seem to be the best predictor of worse outcome in specimens from salvage surgery [64].

Recommendation

Tumour size, persistent disease and positive lateral margins are adverse prognostic parameters in patients undergoing salvage APR (Level of evidence II).

Concomitant squamous neoplasia

Women with anal cancer are more likely to have had vulval, vaginal or cervical cancers [67]. A study using data from the Danish Cancer Registry demonstrated that the probability of developing anal cancer after a diagnosis of cervical cancer or cervical intraepithelial neoplasia was three to five times as high as the probability of developing stomach or colon cancer [68]. It appears that the association between cervical cancer and anal cancer is as strong as that between cervical and vulval cancer [68] suggesting that a carcinogenic 'field effect' exists in the anogenital area.

Concomitant nonsquamous neoplasia

Based on data from the Danish Cancer Registry, Frisch *et al.* [67] have found an association between anal cancer and lymphoma/leukaemia. This association may indicate a possible role of immunodeficiency in the development of anal cancer [67]. Patients with immunosuppressive disorders such as AIDS or after solid organ transplantation are at an increased risk of developing anal cancer [69].

Staging of anal cancer

Anal cancer behaves as two distinct clinical entities, tumours of the anal canal and tumours of the anal margin. Unfortunately, the distinction between the two sites is inconsistent and their boundaries have been differently considered, making the comparison of data from different institutions very difficult.

Different classifications of anal canal carcinoma have been proposed over time, and none of them has been systematically adopted. Classifications based on depth of infiltrations are mainly postsurgical, and those based on dimensions are mainly clinical [12]. Staging should be performed in accordance with the AJCC/UICC staging system for anal cancer which includes assessment of the tumour, lymph nodes and distant metastasis. The 'T' category is assessed by clinical examination, imaging and/or surgical exploration as the 'N' and the 'M' categories. The latest TNM classification of cancer of anal canal 2009 includes the following categories [70] as seen in Table 2. Physical examination including digital rectal examination and vaginal examination should determine site and size of the primary tumour and nodal involvement. Local staging should include MRI of the pelvis. Distant metastases should be assessed with computerized tomography of the thorax and abdomen.

Recommendation

Staging should be performed in accordance with the latest AJCC/UICC staging system for anal cancer (Level of evidence: II).

Pathological examination of the surgical specimens following salvage APR

Haboubi *et al.* and Washington *et al.* [9,10] recommended minimum data set for reporting of excision specimens from salvage surgery (Table 3). These should include information regarding the site of the tumour and the tumour size (length, width and depth) recorded in mm as well as the histological type together with the histological grade. The tumour should be specified whether recurrent or persistent.

Assessment of microscopic tumour extension should include the following:

Table 3 Template for postchemoradiotherapy pathological reporting of anal cancer resectates[10].

Surname	Forename	Date of birth	
Hospital	Hospital No.	Sex	
Date of receipt	Date of reporting	Report No.	
Pathologist	Clinician		
Gross description			
Site of original tumour	Anal margin	Anal canal	Unidentifiable
Site of current tumour			
Recurrent tumour			
Persistent tumour			
Specimen length in mm			
Tumour length in mm			
Tumour width in mm			
Tumour depth in mm			
Microscopic findings			
Tumour type			
Squamous cell carcinoma			
Verrucous variant			
Mucinous microcysts variant			
Nonsquamous carcinoma			
Adenocarcinoma			
Mucinous adenocarcinoma			
Small cell carcinoma			
Undifferentiated carcinoma			
Local invasion			
T1 tumour limited to the internal anal sphincter			
T2 tumour involving the external anal sphincter			
T3 tumour extending outside the anal sphincters/muscularis propria of the rectum			
T4 tumour involving adjacent tissue			
Tumour margins from excision (mm)			
Long			
Circumferential			
Metastatic disease			
No. lymph nodes recovered			
No. positive nodes (pN1 1–3 nodes, pN2 > 3 nodes)			
Tumour nodules not associated with lymphocytic infiltrate/extra nodal deposits (END's)			
Site of histologically proven distant metastases			
Presurgical treatment modality			
Chemotherapy			
Dose			
Schedule			
Radiotherapy			
Dose			
Schedule			
Combined modality treatment			
Dose			
Schedule			
Concomitant squamous neoplasia			
Cervical			
Vaginal			
Vulval			
Perineal			
Penile			
Concomitant nonsquamous neoplasia			

1 Cannot be assessed
2 No evidence of primary tumour
3 Carcinoma *in situ*
4 Tumour invades lamina propria
5 Tumour invades muscularis mucosae
6 Tumour invades submucosa
7 Tumour invades into but not through sphincter muscle
8 Tumour invades into but not through muscularis propria of rectum
9 Tumour invades through sphincter muscle into perianal or perirectal soft tissue without involvement of adjacent structures
10 Tumour directly invades adjacent structures
11 Tumour invades perianal skin

Assessment of the state of the margins is important and should include the proximal, distal as well as the radial/circumferential margins which should be inked when the specimen is received for examination. The distance should be specified in mm. Treatment effect (response of tumour to the previous chemotherapy or radiation therapy) should be reported. Although many tumour regression grading systems exist and they are mainly being used for rectal cancers, the three-category system described by Ryan *et al.* [71] provides a good interobserver reproducibility and prognostic information. Many studies in rectal cancer specimens have demonstrated that histological quantification of tumour regression is a useful method of determining tumour response to CRT and showed its prognostic significance with regard to local recurrence and disease-free survival [72].

We suggest adopting the following scheme of grading tumour regression:

1 Grade 0*: No viable cancer cells (complete response)
2 Grade 1: Single cells or small groups of cancer cells (moderate response)
3 Grade 2: Residual cancer outgrown by fibrosis (minimal response)
4 Grade 3: Extensive residual cancer (poor response)

*A complete pathological response is combined with grade 1 in Ryan's classification.

Additional information represents documenting the presence of Condyloma accuminatum, dysplasia, associated rectal carcinoma, solid organ transplantation, HIV/AIDS and Human papilloma virus infection. Details of the neo-adjuvant therapy should also be included.

Recommendation

The use of the minimum data set for reporting of excision specimens from salvage surgery is recommended (Level of evidence: III). Tumour regression grade should also be included in the data set (Level of evidence: IV).

Competing interests

None.

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Position Statement

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Initial management through the anal cancer multidisciplinary team meeting

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Introduction

Cancers arising from the anal canal and anal margin are uncommon. In 2007, there were 790 (M, 292: F, 498) new patients (10th International Classification of Diseases (ICD) codes: 21.0, 21.1, 21.2, 21.8) with anal malignancies in England, giving a crude incidence rate of 0.65 per 100 000 [1]. Improving Outcome Guidance (IOG) accordingly defines anal cancer as a rare malignancy, which requires centralization of care to a single anal cancer multidisciplinary team (MDT) per cancer network (or per two networks if populations are small).

Anal cancer is associated with HPV infection in 70–90% of patients [2]. Incidences have been increasing in the United Kingdom (UK) over the past three decades [3,4], with greatest increases in women. This contrasts with trends in the United States, where the greater increases have been seen in men, an observation thought in part to be attributable to HIV-associated anal cancer in the antiretroviral era [5]. Nonetheless, in UK oncology clinical practice, there is emerging evidence that the proportion of anal cancers presenting in men who have sex with men, with or without HIV positivity, is steadily increasing [6].

This position statement addresses aspects of the patient pathway prior to first definitive treatment, in this instance, chemoradiotherapy. Seven sections are evaluated as follows: (i) MDT meeting and network organization; (ii) presentation and pathways to MDT; (iii) histological classification; (iv) patient assessment; (v) staging; (vi) pretreatment colostomy; and (vii) trial recruitment and prospective audit.

Methodology

Systematic searches of the Cochrane Database, MEDLINE and EMBASE (until May 2010) were performed using keywords relevant to each section of this position statement. For pragmatic reasons, searches were limited predominantly to English languages articles. Additional publications were retrieved from the references cited in articles identified from the primary search of the literature. Other guideline papers on anal cancer were reviewed [7–10]. We assigned grading of recommendations using standard levels of evidence.

Role of the MDT

Within the United Kingdom, each cancer network (or two adjoining networks if population numbers are small) should establish a network anal cancer MDT, which meets regularly. The MDT includes a team of colorectal surgeons, clinical oncologists, radiologists and pathologist, supported by a dedicated MDT coordinator, advanced nurse specialist and data manager.

All patients with a new (histological) diagnosis of anal cancer from within a network should be reviewed through the MDT prior to initial treatment. Each network MDT should establish referral guidelines ratified through the disease-relevant network Clinical Subgroup (CSG).

The National Cancer Peer Review Programme recommends that the anal cancer MDT has at least one, and no more than two consultant surgical core members, under whose care all operations for anal cancer take place for the patients of that MDT [11]. This is appropriate for most populations to ensure that individual colorectal surgeons are performing adequate numbers of cases. There may be exceptions for larger cases series where the consultant surgical core members may number more than two.

Radical salvage surgery for local disease relapse from anal cancer (Renehan & O'Dwyer, chapter 7) is invariably complex and frequently requires support from plastic surgery, urological and gynaecological surgical oncologist. The complexities of the anorectal component of radical salvage surgery for anal cancer may require the presence of two colorectal surgeons for part of some salvage operations.

The National Cancer Peer Review Programme also recommends that the anal cancer MDT has at least one, and no more than two consultant clinical oncology core members, under whose care all chemotherapy and/or radiotherapy takes place for the patients of that MDT [11].

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Recommendation

Within the United Kingdom, each cancer network (or two adjoining networks if population numbers are small) should establish a network anal cancer MDT, which meets with regularity and discusses all patients with anal cancer prior to first treatment (Level of evidence: IV).

Presentation (pathways to the MDT)

For United Kingdom and European treatment series [12–15], mean ages at presentation are between 60 and 70 years; for US series [16–18], mean ages are typically a decade earlier – an observation to take into account when comparing outcomes. For the United Kingdom, presentation before 30 years of age is uncommon (in 2007, there were only two cases registered in patients under 30 years [1]).

Symptomatic

Common presenting symptoms are anal pain, bleeding anal discharge, pruritis ani and ulceration. Once the anal sphincters are involved, patients complain of discharge and soiling before frank faecal incontinence and tenesmus. In locally advanced disease, perianal infection and fistula formation may occur. Patients may present with enlarged inguinal lymph nodes in the absence of anal symptoms. Clinically palpable (inguinal) lymph nodes occur in 16–25% of patients [13,15,16,18,19], depending on the clinical setting (Branagan, chapter 8). Distant metastases at presentation are generally reported as < 5% in treatment series [13,15,18] – the proportion for all-comer series is unclear.

Through Anal Intraepithelial Neoplasia (AIN) surveillance

Increasingly, surveillance programmes for patients with AIN disease occur in parallel with the anal cancer MDT and detect early invasive carcinomas. This is covered in detail elsewhere (Scholefield & Radcliffe, chapter2).

Incidental excision of anal tag or haemorrhoidectomy

Occasionally, the presence of invasive anal carcinoma is an unexpected finding from haemorrhoidectomy or excision of anal tags. In general, as these are not planned oncological excisions, cases should be discussed at the anal cancer MDT. Cancers < 1 cm in size with clear margins may be considered treated as local excision; larger tumours or positive histological margins warrant consideration for chemoradiotherapy.

Transplant patients

Chronic iatrogenic immunosuppression, especially in solid organ transplant patients, is associated with a higher risk of squamous cell carcinoma (SCC) of various sites, including the anal canal [20]. Recent data quantified that the relative risk of anal cancer in renal transplant patients is tenfold than that of the general population (14 per 100 000) [21]. Similar risks are likely in heart transplant patients although long-term follow-up data in large numbers of survivors are not yet reported (we found no reports in our search).

Carcinoma arising within perianal Crohn's disease

The diagnosis of anal cancer in the presence of inflammatory perianal disease is relatively rare but constitutes a specific clinical scenario. This has recently been reviewed by Devon *et al.* [22] with the addition of 14 patients from Toronto to the already reported 60 patients in the literature. Carcinomas are more commonly adenocarcinomas, mucinous in nature in over 50% of patients, occur generally in longstanding inflammatory disease, often with fistulae, but at a mean age (49 years) a decade earlier than sporadic anal cancer. Discriminating tumour from background inflammatory disease is not always possible by magnetic resonance (MR) imaging. This patient group presents specific treatment challenges: diagnosis may be delayed with locally advanced disease at presentation; chemoradiotherapy may be less effective; and surgical resection is particularly challenging, with high rates of wound complications against a background of long-term steroids and/or immune-modulating therapies.

Malignant melanoma of the anal canal

Although melanoma is not included within the World Health Organisation (WHO) classification of anal canal carcinomas (see below), it deserves brief mention here. Anorectal melanoma is rare and usually presents as advanced disease with nodal and/or distant disease. However, there are some scenarios where surgery, either local excision or abdominoperineal resection, is indicated. The Swedish National Cancer Registry recently reported a review of 251 patients with anorectal melanoma treated between 1960 and 1999 [23]. This report clearly demonstrated that positive margins were common after surgery (64%), and even in those with clear margins, 36-month overall survival was < 40%. These data suggest that surgery for anorectal melanoma does not substantially alter the natural history of this aggressive malignancy. Nonetheless, surgery may be

required palliatively for symptoms, such as pain or chronic bleeding.

Recommendation

Clinicians treating and reviewing patients with a wide variety of anal and perianal disorders should be alert to the diagnosis of anal malignancy (Level of evidence: IV).

Histopathological classification

Histological assessment of anal cancer is dealt with elsewhere in this position statement (Salmo and Haboubi, chapter 5) but a note on the WHO classification of anal canal carcinoma, as used within the AJCC Staging Manual (7th Edition) [24], is pertinent to presentation and is listed in Table 1. Melanomas, carcinoid tumours and sarcomas are not included in this classification. The commonest type (>70%) is SCC. Traditionally, SCC has been further subdivided into basaloid or cloacogenic types, but these are now recognized as a SCC variant that lacks terminal differentiation, specific prognostic significance is questionable [25], and do not indicate differences in management [10].

Adenocarcinomas are next commonest, mostly representing downward spread from an adenocarcinoma in the rectum or arising from transitional mucosa above the dentate line [25]. Additionally, over 200 cases of extramucosal (perianal) adenocarcinomas are reported in the literature – a minimum criterion for this diagnosis is an overlying non-neoplastic anal mucosa [25]. These adenocarcinomas represent a specific group – some 50% may represent secondary spread from intra-abdominal malignancy, they may be multifocal and require thorough search for a primary elsewhere before directing local treatment. Adenocarcinomas arising from anal glands are recognized although rare – their diagnosis may be supplemented using immunohistochemical profiling and specifically the positive expression of MUC5AC [26].

Rare cancers of the anal canal include verrucous and mucinous microcystic variants of SCC [27]. Rarely, SCC may present as a rectal carcinoma. These cases probably represent malignant transformation within anal canal squamous ectopic tissue. The treatment is the same as that for anal canal SCC [28].

The distinction between squamous and nonsquamous histology is prognostically relevant. Data from the US National Cancer Database show that matched for stage, nonsquamous histologies have significantly worse 5-year survival rates [24].

Table 1 WHO classification of carcinoma of the anal canal*.

	Code
Squamous cell carcinoma	8070/2
Adenocarcinoma	
Rectal type	8140/3
Of anal glands	
Within anorectal fistula	
Mucinous adenocarcinoma	8480/3
Small cell carcinoma	8041/3
Undifferentiated carcinoma	8020/3

*The term carcinoma, NOS (not otherwise specified) is not part of the WHO classification.

Recommendation

The establishment of nonsquamous histological diagnoses for anal canal malignancies is challenging. Where this is suspected, specimens should be reviewed by the central MDT (Level of evidence: IV).

Patient assessment

Following a complete medical history, patients with anal cancer should be assessed for performance status (using, for example, the ECOG/WHO 0–5 score). This is essential to audit treatment toxicity and compare outcomes with other series.

Attention to a patients age is relevant. Older age – defined as > 75 years in one series [29] and > 77 years in another [30] – is associated with reduced tolerance to chemoradiotherapy; dose reduction (of either radiation or chemotherapy), and in turn, increased risk of local disease relapse [14].

Despite the observation that anal cancer is 30 times more common in HIV-positive individuals (even in the Highly Active Anti-Retroviral Therapy (HAART) era) [31], this malignancy is a non-AIDs defining cancer. Nonetheless, testing for HIV or obtaining an up-to-date assessment of CD4 counts and viral load in known HIV-positive patients is relevant for subsequent treatment. In the absence of HAART therapy, anal canal in HIV-positive patients is associated with rapid disease progression, high chemoradiotherapy toxicity, high local disease relapse rates, high complication rates following salvage surgery and high mortality [32]. However, in the era of effective antiretroviral therapy, treatment tolerability and oncological outcomes equivalent to those in HIV-negative populations are achievable with low viral loads and high CD4 counts (typical cut-off: 200 cells/μl) [33–35].

Recommendation

All patients presenting to the anal cancer MDT should have a complete medical history and performance status assessment. HIV testing should be considered in many cases; for known HIV-positive patients, up-to-date viral loads and CD4 counts should be obtained (Level of evidence: III).

Staging

Clinical examination

Staging starts with clinical examination including inspection of the perineum, digital anorectal examination (under general anaesthetic, EUA, if painful), ano-proctoscopy and examination of the inguinal nodal area. Specifically for anal cancers, an essential prerequisite to staging is defining the tumour as either arising from the anal canal or arising from the anal margin (Fig. 1) [24,36], as the staging criteria differ between these sites. The term anal verge should be used to define the line (not the area) separating the anal canal and margin.

Anal cancers are staged in accordance with the American Joint Committee on Cancer (AJCC) system.

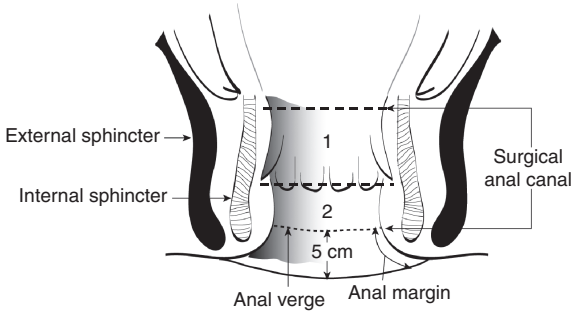

Figure 1 The anus may be divided into the *anal canal* (C21.1) and the *anal margin* (C44.5); the former is 3.5–4 cm in length in men, being shorter in women. The anal canal begins where the rectum enters the puborectalis sling at the apex of the anal sphincter complex and ends with the squamous mucosa blending with the perianal skin, which roughly coincides with the palpable intersphincteric groove. Immediately proximal to the dentate line, a narrow zone of transitional mucosa (similar to urothelium) is variably present – the *anal transition zone* (depicted as 1 in the figure). Distal to this, the mucosa consists of squamous epithelium devoid of hair and glands (depicted as 2 in the figure). Detailed anatomy found in ref. 35. The *anal margin* extends distal to the anal verge (the junction of the hair bearing skin) to a 5 cm circumferential area from it. Lymphatic drainage of the anal canal depends on location: below the dentate line drainage is to the inguinal group of nodes; above lymph drains to the mesorectal, lateral pelvic and inferior mesenteric nodes. There is considerable overlap and some tumours can follow more than one pathway.

The 7th edition AJCC has recently been published [24]. For anal canal cancers, there have been no changes in the definitions of Tumour Node Metastasis (TNM) groupings. There have been two minor changes on the 6th edition: (i) the descriptions of both the boundaries of the anal canal and anal margin have been clarified (see Fig. 1 legend); (ii) the collection of the reported status of the tumour for the presence of HPV is included. The clinical category TNM criteria for anal cancer carcinomas are listed in Table 2.

The stage groupings derived from the TNM categories are shown in Table 3. These have prognostic significance – the 5-year observed survival rates (from the US National Cancer Database) are as follows: Stage I, 69.5%; Stage II, 61.8%; Stage IIIA, 45.6%; Stage IIIB, 39.6%; Stage IV, 15.3% [24].

Anal margin tumours are classified similar to skin cancers. In the AJCC 7th edition, staging of nonmelanoma skin cancers has been comprehensively revised in line with the staging of head and neck SCCs. These category defining criteria are not applicable to SCCs arising in the anal margin, and therefore, the AJCC 6th edition is still recommended (Table 4) [37].

Table 2 AJCC 7th edition clinical category definitions for anal canal cancer.

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ* (Bowen's disease, high-grade squamous intraepithelial neoplasia II-III (AIN II-III)
T1	Tumour 2 cm or less in greatest dimension
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, bladder*
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 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
Metastasis	
M0	No distant metastasis
M1	Distant metastasis

*Note: direct invasion of the rectal wall, perirectal skin, subcutaneous tissue or the sphincter muscle(s) is not classified as T4.

Table 3 AJCC 7th edition staging system for anal canal cancer.

Group	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N1	M0
	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

For identification of special cases of TNM or pTMN classifications, the 'm' suffix and 'y', 'r' and 'a' prefixes may be used. Although they do not affect the stage category, they indicate cases that need separate analysis. **m** suffix indicates the presence of multiple primary tumours; **y** prefix indicates cases in which classification is performed during or following initial multimodality therapy; **r** prefix indicates a recurrent tumour when staged after a disease-free interval; **a** prefix designates the stage determined at autopsy.

Table 4 AJCC 6th edition clinical category definitions for anal margin cancer.

Primary tumour (T)	
TX	Primary tumour cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumour 2 cm or less in greatest dimension
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 invades deep extradermal structures (i.e. cartilage, skeletal muscle, or bone).
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Metastasis	
M0	No distant metastasis
M1	Distant metastasis

Continuation of the 6th edition of the AJCC system for skin carcinoma is recommended as the new 7th edition AJCC definitions for nonmelanoma skin carcinoma incorporate multiple terms relevant to head and neck squamous cell carcinoma, which are not applicable to anal margin carcinomas.

Rationale for accurate staging

In the TNM system, importance is given to the size of the lesion and its extent (T), the presence and extent of lymphatic disease (N) and evidence of distant metastases (M). The rationales for accurate staging of anal cancer are as follows:

1 Metastases: determination of distant metastases (for example, lungs or liver) or intra-abdominal disease outside the pelvis essentially deems the case noncurative.
2 Prognosis and treatment response: in general terms, risk of local disease relapse increases with increasing T size. Specifically, in patients treated with radiotherapy alone, T size correlates with local treatment response [38], although this is not as clear-cut with chemoradiotherapy regimens [14].
3 Gross tumour volume (GTV) – T size and immediate pelvic lymph nodes: all macroscopic primary tumour and involved nodes are considered for treatment planning purposes as GTV [39]. In most modern treatment protocols for anal cancer, chemoradiotherapy is based on the model of external beam irradiation delivered using a two-phase technique without a gap (ACT II trial radiotherapy schedule) [40]: a planned central axis dose as first phase, with inguinal or perineal boosts as the second phase if required (Glynne-Jones, chapter 4). Initial staging in part determines the GTV (this is latter refined on the CT simulator) and determines inguinal node involvement.
4 Determination of inguinal node involvement: inguinal node positivity materially changes the planned radiotherapy schedule to include the inguinal nodes in the boost (second) phase. In turn, this is associated with increased skin toxicity and long-term leg lymphoedema risk.
5 Defining follow-up: the overall risk of local disease relapse after chemoradiotherapy is in the order of 20–25% at 3 years. There are risk stratifications such that the following have increased risk and require closer follow-up: T4 size; carcinoma with fistula; age > 75 years; HIV-positive and other immunosuppressed patients.
6 Defining T1 anal margin tumours: early anal margin tumours may be amenable to local excision, although in general, this is the exception. Accurate determination of tumour size and absence of sphincter involvement are key criteria for selection of these patients.
7 Defining T size for trial entry: the comparison of treatment outcome by T size is an important subanalysis for current and future trials and will assist future trial questions and designs – for example, to reduce treatment toxicity in T1 tumours.

Imaging and staging

1 A CT scan of the thorax, abdomen and pelvis may readily delineate distant spread.

2 Pelvic magnetic resonance imaging (MRI) provides an accurate assessment of local anatomy either with an endoanal coil or with high spatial resolution external surface pelvic-phased array coils [41], but can sometimes miss early disease. MRI has the advantage of distinguishing tumour from normal pelvic structures more clearly than CT imaging [41] (the lesion is high signal intensity relative to skeletal muscle on T2-weighted images) and can assist in detecting pelvic, mesenteric and inguinal node involvement.
3 Phase array MR scanning is at an experimental stage [42].
4 Endoanal ultrasound (EUS) may accurately determine depth of tumour penetration into the sphincter complex and tumour response to treatment, but because of the limited field of view and the likelihood of missing mesorectal nodes, it is likely to be effective only in early lesions (T1-2) [43–45] and is limited by patient discomfort.
5 Clinically enlarged inguinal lymph nodes occur in up to 25% of patients (Branagan, chapter 8) and may be assessed by Fine Needle Aspiration Cytology (FNAC) or biopsy (+/− ultrasound guidance), although up to 50% show reactive change only [46].
6 Sentinel node mapping in anal SCC has been suggested to improve staging of the disease and thereby improve treatment planning [47], but has not yet attained widespread acceptance.
7 Positron emission tomography (PET) using [(18) F]-fluoro-2-deoxy-D-glucose (FDG) provides functional imaging and may have a role in the assessment of indeterminate lesions on MRI or CT and in the evaluation of suspected local disease relapse [48,49].

Recommendation

All patients presenting to the anal cancer MDT should have a staging CT scan of the abdomen, thorax and pelvis and a pelvic MR scan (Level of evidence: III).

Pretreatment colostomy

Despite improved local control with chemoradiotherapy, long-term permanent colostomy rates in series are still approximately a third of cases [14,50]. By subtraction of colostomies performed post-treatment for salvage abdominoperineal resection and other miscellaneous indications (for example, faecal incontinence), approximately 5–8% of all patients require pretreatment colostomy. Indications include incontinence, fistula formation and occasionally pain. Several series note that patients who receive a pretreatment colostomy, despite local disease control, rarely go on to successful colostomy reversal [14,50].

In a patient where pretreatment colostomy is indicated, specific surgical aspects should be considered. End colostomy is preferred to loop colostomy. Laparoscopic trephine end colostomy may be feasible but in placing the ports, consideration should be given to possible subsequent surgical procedures. Patients who require pretreatment colostomy are the same cases at increased risk of local disease relapse and may require radical salvage surgery with wide perineal excision, necessitating reconstruction – placement of the laparoscopic ports should thus avoid, for example, puncture to the rectus abdominis muscles.

Recommendation

The requirement for pretreatment colostomy is generally low. Where this is indicated, patients should be warned that such colostomies are usually permanent even in the presence of local disease control (Level of evidence: III).

Trial recruitment and prospective audit

The initial presentation of a case to the anal cancer MDT should be an opportunity to recruit patients to suitable trials. In the United Kingdom, the ACT II closed recruitment at the end of 2008, and currently there is no nationally recruiting trial. ACT III is currently under design (Glynne-Jones, chapter 4) [51].

Through the central anal cancer MDT, there are opportunities for prospective clinical audit. These include short-term and long-term outcomes, the latter in turn complements the UK National Cancer Survivorship Initiative [52].

Recommendation

The initial presentation of a case to the anal cancer MDT should be an opportunity to recruit patients to suitable trials and allow prospective clinical audit (Level of evidence: IV).

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Competing interests

None.

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Position Statement

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Staging and Management of Inguinal Nodes

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Introduction

Squamous cell cancer of the anus is a rare disease accounting for < 4% of all anorectal neoplasms, with an incidence of the order of 0.5–1 per 100 000 population [1]. The aetiology of anal cancer seems to be more closely related to genital malignancies than other malignancies of the gastrointestinal tract. Data suggest associations between incidence of anal cancer and infection with human papillomavirus, lifetime number of sexual partners, cigarette smoking, genital warts, receptive anal intercourse, and infection with HIV.

Systemic spread of anal cancer is usually via the lymphatics and less commonly via the bloodstream. Distal anal canal cancers (below the dentate line) tend to spread to the inguinal and femoral node basins, whereas proximal cancers drain to mesorectal, internal iliac and paraaortic nodes. When the primary tumour is clearly located laterally within the anal canal, inguinal metastases are almost universally ipsilateral [2]. Bilateral inguinal involvement is seen only when the tumour invades the medial part of the anal canal.

The risk of synchronous inguinal metastases is of the order of 13% [2] and increases with the size of the tumour [3]. It is < 10% for patients with T1–T2 lesions, and between 15% and 30% for patients with T3–T4 lesions [4]. The risk is lower when the entire tumour is located above the dentate line [4].

Staging of inguinal lymph nodes

There is no agreement as to the best way to determine inguinal lymph node status of patients with anal canal cancer. Traditional management relied on clinical examination supplemented by fine needle aspiration cytology (FNAC) or excision biopsy. However, lymph node size is not a reliable predictor of the presence of lymphatic metastases. Using a fat-clearing technique, Wade *et al.* [5] found that 44% of all nodal metastases occurred in lymph nodes measuring < 5 mm in diameter. Therefore, a proportion of metachronous inguinal metastases arise in nodes that actually harbour subclinical metastases at the time of the original presentation.

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As many as 50% of clinically palpable inguinal nodes are enlarged for reasons other than metastases, and therefore histological confirmation of the diagnosis is mandatory.

The challenge lies in identifying those patients that have inguinal node metastases in the absence of clinically palpable nodes. Data for many of the current modalities are sparse in relation to anal cancer but there is more experience using these techniques in cancer of the penis and vulva, which share similar patterns of lymphatic drainage.

Ultrasound +/— FNAC

High-resolution ultrasound is often able to detect subtle findings of early malignancy before node enlargement occurs [6]. The addition of FNAC of nodes suspicious on ultrasound has been shown to increase the diagnostic yield of ultrasound further. There is no data for the use of ultrasound to identify occult inguinal node metastases in patients with anal cancer.

The combination of ultrasound and FNAC has shown promise in staging patients with squamous cell cancer of the vulva with sensitivity of 80–83% and specificity of 82–100% [7–9]. FNAC has, however, been associated with false-negative results [8] and failure to obtain a sample [9].

CT and PET–CT

Computed tomography (CT) is routinely used for the assessment of intra-abdominal metastases in patients with anal cancer. However, there is no published data as to the value of CT in assessing inguinal nodes in these patients. What little comparative data there is in other pelvic cancers suggests that other modalities will have more to offer in this area [7].

Positron emission topography (PET) using the glucose analogue 2-[^{18}F]-fluoro-2-deoxy-d-Glucose (FDG-PET) has been used to improve the pre-treatment staging of anal cancers as well as to assess response to primary treatment. Detection of nodal metastases by FDG-PET relies on metabolic activity rather than size criteria or abnormal lymph node morphology. It has been demonstrated to increase the detection of abnormal inguinal lymph nodes in patients with anal cancer by 17–19% compared with a combination of clinical examination and CT staging [10,11]. However, an earlier study of 21 anal

cancer patients reported no increase in inguinal node metastases with the use of PET alone when compared with clinical examination and CT [12]. Studies of PET–CT in other pelvic malignancies have demonstrated specificity rates of the order of 93%, which suggests that PET–CT positive inguinal nodes in patients with anal cancer are highly suggestive of nodal disease [13].

MRI +/− node enhancement

Two studies report the use of MRI in patients with anal cancer but both focus on the primary tumour. Although they report pathological nodes in the inguinal regions, there is no comparison made with clinical examination and no histological confirmation of the diagnosis [14,15].

In patients with vulvar cancer, MRI has been demonstrated to be superior to clinical examination [16] and has sensitivity of between 50% and 85.7% and specificity of between 85% and 100% [16,17]. However, the results of a meta-analysis indicate that for the identification of nodal disease in the mesorectum, MRI lacks sufficient accuracy for clinical decision-making [18].

Ultra small super paramagnetic iron oxide (USPIO)-enhanced MRI is a promising technique that has been reported to improve the differentiation of benign from malignant nodes. The particles cross the capillary wall and become localized to the reticuloendothelial system of the lymph nodes giving information on lymph node morphology and function. A recent meta-analysis suggests that USPIO-MRI is superior to unenhanced MRI in the detection of lymph node metastases for various tumours [19].

There are no data for patients with anal cancer. However, in a small series of seven patients with penile cancer, USPIO-MRI was compared to histology for each node harvested at inguinal lymph node dissection, resulting in sensitivity of 100%, specificity of 97% and a negative predictive value of 100% [20]. This result suggests that it is safe not to treat inguinal nodes in patients with a negative groin by USPIO-MRI criteria, although the numbers in this study are very small.

Sentinel node biopsy

Sentinel node biopsy is based on the premise that lymphatic dissemination from a tumour occurs in a stepwise fashion, with initial involvement of a primary node, called the sentinel node, before dissemination to the remainder of the lymphatic chain. If the sentinel node is histologically negative, then the remainder of the nodes in the same anatomic region will be at minimal risk of containing metastases. Described originally in patients with carcinoma of the penis, it is now considered the standard of care for patients with malignant melanoma and is widely used in patients with breast cancer. Damin *et al.* [21] report six series reported to date of sentinel node biopsy in patients with anal cancer. The sentinel node detection rate varies from 67% to 100% (mean 91.7%). Metastases were identified in 7.1–38.5% of patients (mean 23.9%) in whom a sentinel node was identified.

The sensitivity and specificity of sentinel node biopsy in anal cancer remain unknown because of the lack of a surgical specimen. However, in a study of over 330 patients with penile cancer, sensitivity and specificity rates of 94% and 100%, respectively, have been reported for inguinal sentinel node biopsy [22]. Bobin *et al.* [23] followed up a cohort of 26 anal cancer patients who had negative sentinel node biopsies and were not given radiotherapy to the groins. After 18 months, no patient had developed metachronous inguinal metastases.

Minor morbidity associated with the procedure is seen in approximately 4% of patients [22], and no serious complications have been reported in the series of patients with anal cancer [21].

Recommendations

1 *All patients presenting to the anal Multidisciplinary Team should have staging of inguinal nodes by clinical examination and specific imaging modalities (level of evidence III)*
2 *The best modalities for increasing detection of occult inguinal metastases appear to be PET–CT and Sentinel node biopsy (level of evidence IV).*

Management of inguinal nodes

Synchronous nodal metastases

Historically, clinically palpable nodes have been evaluated by FNAC. Synchronous inguinal metastases are treated by chemoradiation schedules used for the primary tumour with a boost of radiotherapy to the groins [24]. Formal groin node dissection is reserved for residual or recurrent groin node metastases after radiotherapy. These patients have a significant risk of complications after surgery [25].

Synchronous inguinal metastases are independent prognostic indicators for reduced survival [2,3], with 5-year survival rates of approximately 73% in node-negative patients and 54% in those with nodal involvement.

Metachronous nodal metastases

The rate of metachronous nodal metastases in patients in whom the groins are not treated prophylactically with

radiation ranges from 7.8% [2] to 25% [26]. The management of metachronous inguinal disease is more difficult to clarify as it can occur within a number of different clinical scenarios, and therefore histological confirmation of the diagnosis is necessary. Management will depend on whether there is anal recurrence and whether there has been radiotherapy to the groins, the presence of metastatic disease elsewhere and the condition of the patient. Therapeutic options include radiotherapy (where none has previously been given) and block dissection of the groin.

Non-involved nodes

There is no consensus of opinion regarding the management of non-involved inguinal lymph nodes at the time of presentation. Two pathways are possible: (i) a watch-and-wait policy or (ii) elective irradiation of the groins. The watch-and-wait policy is the simplest approach but requires close follow-up to detect inguinal node recurrence after completing primary treatment. However, in approximately 10% of patients, especially those with T3–T4 tumours or tumour involving the anal margin, metachronous inguinal node metastases will occur [2] and these are known to be associated with a worse prognosis [2].

Many centres perform elective groin irradiation, resulting in a rate of metachronous inguinal metastases of < 5% in the absence of anal recurrence [26]. However, the increased dose of radiation given to this group of patients is associated with life-threatening acute toxic complications, especially when given concurrently with chemotherapy or given to elderly and frail patients. Mortality rates of 2.0–2.7% were seen in 3 randomized trials giving chemoradiotherapy to this group of patients [24,27,28]. The annual incidence of complications related to radiotherapy does not appear to decrease with time, and there may be a lifelong risk of developing late complications [29].

Recommendation

In adequately staged patients, especially those with T1 and T2 tumours, a policy of watch and wait is a suitable alternative to elective irradiation of the groins (level of evidence IV).

Conclusion

Inguinal lymph node status is a major prognostic indicator in patients with anal cancer. Any staging technique which will allow the accurate identification of the presence of nodal metastases will allow the appropriate treatment for those patients with metastases without over-treating the majority of patients that do not have involved nodes. The best placed of the current techniques under evaluation appear to be sentinel node biopsy, USPIO-MRI and FDG-PET/CT. The centralization of the management of anal cancer in the UK may set the stage for a trial to compare some or all of these techniques.

Competing interests

None.

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Position Statement

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Chemoradiotherapy in anal cancer

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Introduction

Epidermoid cancer of the anus commonly has an indolent natural history with a low rate of distant metastases [1–3]. Metastases are observed in only 5% of patients at presentation, and are rare unless the patient experiences a local failure. Hence, local control is the dominant aim of treatment. Concurrent chemoradiotherapy is now recognised to be the optimal treatment modality to achieve local control, with surgery reserved for salvage of loco-regional recurrence.

We are aware of only six randomised phase III trials [4–9] with four full papers and two abstracts (Table 1). We identified no meta-analyses based on individual-patient data. Five of these phase III trials have examined the combination of radiotherapy with 5-fluorouracil (5-FU) and Mitomycin C (MMC) – initially as the novel arm, and more recently as the control. All five studies confirm the regimen of MMC, infusional 5FU and radiotherapy provides the best outcome in terms of loco-regional recurrence, colostomy-free and overall survival [5–9]. Chemoradiotherapy with concurrent mitomycin (MMC) and 5-fluouracil (5-FU) is now widely used as the current standard of care.

This position statement aims to provide a cohesive outline of treatment strategies in terms of chemoradiation currently in use, which are supported by evidence from randomised trials, and to summarise current and future directions in the management of anal cancer. We make recommendations regarding the total dose of radiotherapy, the fraction size, the avoidance of planned gaps, the field sizes, and the choice of chemotherapy agents. We also aim to outline different patient groups that may benefit from a more tailored approach to chemoradiotherapy.

Staging for the rational delivery of chemoradiation

Physical examination including digital rectal examination (DRE) and vaginal examination should determine site and size of the primary tumour and nodal involvement. Assessment of the cervix, vagina and vulva is suggested in female patients. A defunctioning colostomy should be considered prior to starting chemoradiation in patients with transmural vaginal involvement (at risk of development of an anorectal-vaginal fistula), or faecal incontinence. Careful clinical assessment of the inguinal nodes is essential for the rational selection of field size and dose required. Physical examination is most definitive if carried out under general anaesthesia, and usually complements radiological staging.

The (TNM) clinical staging system is based on accurate assessment of size (T-stage), regional lymph node involvement (N) and metastatic spread (M) (AJCC 2002). Local staging should nowadays include MRI of the pelvis. Distant metastases should be assessed with CT Thorax and Abdomen. A PET scan may also be helpful in planning gross tumour volumes.

Assessment for selection of chemotherapy

Before selecting the chemotherapy agents and appropriate doses, patients should be assessed for performance status, renal function, and other medical co-morbidity (in particular cardiac). The New York Heart Association Classification of Heart Failure is a useful functional classification system, which relates symptoms to everyday activities and the patient's quality of life.

Sperm banking should be discussed prior to the commencement of treatment with male patients who wish to preserve fertility. Pre-menopausal women should be informed that fertility will be lost, and hormone replacement therapy may be appropriate in future for those in whom an early menopause is induced.

Position statement: Many patients with anal cancer are elderly with co-morbid conditions. Careful assessment of renal function (often with EDTA if predicted by serum creatinine to be < 50 ml/min) and performance status is advised prior to the use of the cytotoxic agents mitomycin C and cisplatin.

Radiotherapy alone

For small tumours (T1), some investigators have used external beam radiotherapy alone, followed by a small volume boost either with photons, electrons, or interstitial implantation with excellent long-term results. How-

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ever, the use of interstitial brachytherapy is a skill more associated with European training than that in the UK. The evidence from the ACT I trial suggests that even T1 tumours have a better outcome with chemoradiation than radiation alone [4].

Quality of life has also been shown to improve following chemoradiation [10] and is better following chemoradiotherapy when compared with radiotherapy alone (Slevin *et al*., 1998) and late effects have been shown to correlate with total dose received. In the UKCCR [4] and EORTC [5] trials there was no difference observed in late toxicity between the radiotherapy and chemoradiotherapy groups. More recent evidence confirms that only 10% of patients develop long-term toxicity after chemoradiotherapy, with 5% requiring a colostomy for treatment-related problems [7].

Radiotherapy dose

Doses in the range of 30 Gy with standard fractionation and concurrent MMC and 5-FU control small tumours (CCR rate of 86%) [2,12]. Poorer results were achieved in tumours over 4 cm in size. Yet we can find no dose response curves proposed in the literature either for radiotherapy or CRT.

Lower doses in the range of 30 Gy have also been shown to control sub-clinical disease [12].

The ACT II study [8] used a dose of 50.4 Gy in 28 fractions, with no gap between the first phase (30.6 Gy in 17#) of treatment and the boost (19.8 Gy in 11#). Overall 3-year disease free survival in this study was 75%. Larger cancers are more difficult to control, hence there have been attempts to increase total dose in anal cancer either with techniques such as IMRT or brachytherapy [9]. Advances in imaging such as MRI and PET have improved localisation of the cancer in terms of accuracy and precision, so it is more feasible to treat smaller volumes to a higher dose. In contrast, historical studies in retrospect demonstrate poorer technique, larger volumes treated to lower total doses and greater morbidity.

Although some studies have used higher doses (45–55 Gy for the first phase of treatment), to date there has been little demonstrable evidence of improvement in outcome with the use of higher doses. The risk of late adverse effects is associated with increasing total radiotherapy dose. Dose escalation may be justifiable in T3 or T4 disease where local failure is higher, but preliminary results of the ACCORD-03 trial [9] compared 45 Gy in 25# plus a 15 Gy boost after a 3 week gap with a higher boost dose, and found no benefit in colostomy-free survival at doses above 59 Gy. The lack of benefit from dose escalation is also supported by the RTOG 92-08 trial [13].

Position statement: Although elderly frail patients with small T1 and T2 tumours may be controlled with doses in the region of 30 Gy, a minimum dose of 50.4 Gy in 28 fractions over 5½ weeks is recommended for local control of macroscopic disease.

The gap

Chemoradiotherapy regimes have in the past routinely employed split-course radiotherapy with a gap of 6 weeks. A prolonged 6–8 week interval was originally thought necessary to allow sufficient time to assess response, to direct brachytherapy treatment and deliver radiotherapy to the smallest possible volume (and hence minimise the risk of necrosis). This interval also facilitated salvage surgery for non-responders. So a 6-week interval was advocated in the early randomised European trials [4,5].

Many studies suggested that excess acute toxicity precluded an immediate perineal boost with brachytherapy or external beam radiotherapy [11,14], and a planned gap in treatment was introduced following the observation that unscheduled treatment gaps were often necessary. More recently the interval has been reduced to 2–3 weeks, prior to the boost.

However, repopulation time is thought to be short in anal cancer, and cancer kinetics suggests a projected clonogen doubling time of about 4 days [15]. Although there are no randomised controlled trials comparing continuous radiotherapy regimes with those incorporating a gap between phase one and phase two, comparison has been made between cohorts in the RTOG 92-08 trial, treated with a short 2 week gap, and patients in the RTOG-04 trial who were treated with an initial dose of 45 Gy. The group whose regime mandated a gap at 36 Gy had a worse overall survival and disease free survival.

In contrast, the ACT II trial advocated a continuous treatment schedule of 50.4 Gy in 29 fractions over 38 days, with no planned gap, and achieved high CR (95%) and disease free survival (75% at 3 years) rates, possibly as a result of abolishing the gap in the CRT regime [8].

Position statement: Planned gaps in treatment are detrimental to local control and should be avoided.

Radiotherapy technique

Treatment should aim to encompass the primary tumour and any sites of likely nodal involvement within the high-dose volume. Most current radiation protocols for T3/T4 tumours use techniques that employ an initial wide field of radiotherapy treating the whole of the lower pelvis, including the inguinal lymph nodes and the

Table 1 Randomised phase III trials: results compared.

Studies	Sample size	Primary endpoint	Complete response	DFS	Local failure rate	OS
ACT 1 UKCCCR 1996	585	Local failure	30% for RT *vs* 39% CRT at 6 weeks	No data	61% with RT alone *vs* 39% with CRT at 3 years; (HR = 0.54, $P < 0.0001$) (includes stomas) Colostomy rate 39% *vs* 23%	58% with RT alone *vs* 65% with CRT at 3 years Not significant $P = 0.25$
ACT 1 updated James 2010	577	Local failure	As above	Relapse free survival at 5 years 34% for RT *vs* 47% CRT at 5 years	57% with RT alone *vs* 32% with CRT at 5 years Colostomy free survival 37% with RT alone *vs* 47% with CRT at 5 years	53% with RT alone *vs* 58% with CRT at 5 years; 34% with RT alone *vs* 41.5% with CRT at 10 years; $P = NS$
EORTC 22861 Bartelink 1997	110	Disease free survival	54% for RT *vs* 80% CRT at 6 weeks	No data Estimated improvement in DFS by 18% at 5 years	50% with RT *vs* 32% with 5-FU, MMC at 5 years; $P = 0.02$ Estimated improvement in Colostomy free survival by 32% at 5 years	54% RT *vs* 58% with 5-FU/MMC/RT; $P = 0.17$
RTOG 87-04 Flam 1996	291	Loco-regional control	Path CR (biopsy) at 4–6 weeks 86% 92.2% (MMC)	51% 5-FU *vs* 73% with 5-FU, MMC at 4 years	Colostomy-free survival: 59% with 5-FU *vs* 71% with 5-FU, at 4 years; $P = 0.014$ Colostomy rate: 22% with 5-FU *vs* 9% with 5-FU, MMC; $P = 0.002$	71% with 5-FU *vs* 78.1% with 5-FU, MMC; $P = 0.31$
RTOG 98-11 Ajani 2008	644	Disease free survival	No data provided	60% with 5-FU, MMC *vs* 54% 5-FU, cisplatin at 5 years; NS $P = 0.17$	25% with 5-FU, MMC *vs* 33% with 5-FU, cisplatin; Colostomy rate: 10% with 5-FU, MMC *vs* 19% with 5-FU, cisplatin; $P = 0.02$ at 5 years	75% with 5-FU, MMC *vs* 70% with 5-FU, cisplatin; $P = 0.1$ at 5 years
UKCCCR ACT II James 2009 abstract only	940	Relapse free survival	94.5% 5FU/MMC/RT *vs* 95% 5FU/Cis/RT at 18 weeks	75% in both arms at 3-years	Colostomy rate – same in both arms (5% with maintenance *vs* 4% without)	85% with maintenance at 3 years 84% without not significant
ACCORD-03 Conroy 2009 abstract only	307	Colostomy free survival	No data	NACT/70% CRT (5FU/Cis) NACT/HDRT 78% CRT (control) 67% (5FU/Cis) HDRT 68%	83% 85% 86% 0%	79% 88.5% 89% 9%

DFS, disease free survival; OS, overall survival; RT, radiotherapy; CRT, chemoradiation; 5FU, 5-fluorouracil; Cis, cisplatinum; MMC, mitomycin C; NACT, neoadjuvant chemotherapy; NS, not significant; HDRT, high-dose radiotherapy.

external and internal iliac pelvic lymph nodes in continuity with the primary cancer. Subsequent field reductions aim to encompass the primary tumour plus a margin. In the RTOG-9811 study [7] all patients received 45 Gy in 25 fractions using an anterior/posterior – posterior/anterior (AP-PA) technique or a four-field technique to include the anus, pelvis, perineum and inguinal nodes. The superior border was at L5-S1 and the inferior included the anus and tumour with a 2.5 cm margin.

The ACT II trial also used a wide (AP-PA) technique, but did not aim to encompass the common iliac nodes. Fields extended superiorly to 2 cm above the sacro-iliac joints, but to a lower dose of 30.6 Gy. The phase I dose was stipulated as 30.6 Gy in 17 fractions to ICRU intersection point (midpoint) using parallel-opposed posterior/anterior portals. For phase II, the technique used depended on the presence or absence of significant lymphadenopathy in the inguino-femoral region or in the pelvic nodes on CT scan. In the case of clinically palpable nodes, those enlarged on CT criteria, suspicious on MRI criteria, or positive on biopsy, were treated to the full dose of 50.4 Gy.

Data on site of failure is not available for these randomised trials. Retrospective studies have raised concerns that regional failures may occur in patients in whom the field did not encompass the common iliac nodes [16].

The inguinal nodes should be formally included in the radiation fields in the majority of cases, even in the absence of clearly demonstrable involvement. The incidence of nodal involvement increases with increasing primary tumour size and is at least 20% in patients with T3 disease. However, some clinicians may treat clinically uninvolved inguinal nodes only in certain circumstances (eg T3-4 primary disease, location of primary tumour within the canal, ≤ 1 cm from the anal orifice, or if there is involvement of pelvic lymph nodes (on CT or MRI criteria).

Recent studies suggest that acute and late toxicity can be reduced with more advanced 3-D or complex IMRT techniques of radiation delivery [17,18].

Tailoring radiotherapy regimes to T-stage

Small tumours and subclinical disease

Although doses in the range of 30 Gy with standard fractionation and concurrent MMC and 5-FU control small tumours and subclinical disease [2,11], late recurrence may be more frequent after a lower total dose of radiotherapy.

Larger tumours

T3 and T4 tumours have lower response rates of between 45% and 60% [19,20], and a more radical treatment approach may therefore be justified. Although the long-term results of recent trials [9,13] do not support dose escalation in CRT regimes there may be a justification for further investigating this in larger tumours. Preliminary results in abstract suggest that patients in the ACCORD-03 trial who were in the dose-escalated arms (receiving 65–70 Gy) had a higher colostomy rate, implying that normal tissue effects may be dose limiting, Widder *et al.*'s retrospective analysis [21] suggests that different prognostic factors apply to different stages of tumour. Tumour stage, and age were found to influence OS and CFS, and N stage to be a factor for DFS. It also found that in stage T1–T2 tumours local control was improved in patients receiving treatment with a shorter overall treatment time. Higher total dose and female gender were associated with improved local control in T3–T4 tumours. This implies that further investigation of higher dose regimes specifically in T3 and T4 tumours may be appropriate.

Doses of radiation should be at least 45–50 Gy in the first phase of treatment, or higher doses if a planned gap to allow skin recovery is used. It remains unclear if increasing the radiation dose > 50 Gy in patients with locally advanced anal cancer receiving combined modality therapy will improve the results – particularly if a planned gap is used [9, 13, 22]

Supportive care during radiotherapy

Tolerance to treatment can be maximised with antibiotics, anti-fungals, anti-emetics, analgesia, skin care, advice regarding nutrition and psychological support. The post-treatment use of vaginal dilators in sexually active females is recommended although the evidence for benefit is weak.

Position statement: Prophylactic antibiotics (eg ciprofloxacin) are recommended during the radiotherapy to reduce infections and promote skin healing.

Concomitant chemotherapy – mitomycin C or cisplatin?

Mitomycin C

The evidence of the RTOG 87-04 study (Flam 1996 [6]) showed addition of mitomycin is a necessary component of the chemoradiotherapy regime [23] in terms of disease free survival, and sphincter preservation [4–6] In the RTOG 87-04 study (Flam 1996 [6]) a dose of 10 mg/m^2 in weeks 1 and 5 was used (ie a total of 20 mg/m^2), compared to the European studies, which used a single dose of 12 mg/m^2 (capped at 20mg in the ACT II study). The RTOG 8704 study [6] demonstrated a pathological complete response rate of 92% in patients receiving 5-FU and MMC *vs* 87% for patients receiving 5-FU alone from biopsy at 6 weeks.

Cisplatin

The RTOG 98-11 study [7] demonstrated that colostomy rate was significantly worse with cisplatin, and the increased risk of colostomy has to be taken into consideration (Ajani 2008). Preliminary results of the ACT II trial [8] failed to confirm an advantage for cisplatin over MMC when combined with radiotherapy in terms of overall survival, disease-free survival or colostomy free survival (James 2009). However patients in the cisplatin group had significantly less acute grade 3/4 haematological toxicity (although there was no significant difference in non-haematological toxicity). Preliminary results show that 25% of patients in the group receiving MMC suffered grade 3/4 haematological toxicity, compared to only 13% in the group receiving cisplatin. This observation has persuaded some clinicians to favour the use of cisplatin.

It is important to be aware we do not yet have data for compliance to cisplatin in the ACT II trial and whether loss of compliance in the second phase of chemoradiation impacts on outcome. MMC is certainly easier to deliver even in the elderly provided renal function is adequate. Cisplatin has therefore not replaced MMC in the CRT schedule, although there may well be a role for cisplatin instead of MMC in patients who are particularly at risk from haematological toxicity.

At this time the present authors feel that 5FU and MMC (12 mg/m^2 day 1) should be recommended rather than 5FU and cisplatin, MMC and cisplatin [24], any single drug or three drugs [7,9].

The use of neoadjuvant or induction chemotherapy

Two recent trials (RTOG 98-11l [7], ACCORD-03 [9]) have clearly demonstrated that chemo-radiotherapy is superior to sequential chemotherapy and chemo-radiotherapy.

Position statement: Currently neoadjuvant chemotherapy prior to chemoradiation is not recommended, as this strategy appears associated with worse outcomes in terms of colostomy-free survival.

Consolidation chemotherapy

The ACT II trial also examined consolidation chemotherapy with cisplatin, and found that there was no significant difference in disease-free survival or overall survival in the group that received two additional cycles of cisplatin and 5-FU.

Hence, neither neoadjuvant chemotherapy nor consolidation chemotherapy are advocated in patients undergoing chemoradiotherapy for anal cancer.

The ACT II schedule is therefore the current recommended treatment schedule:

- Chemoradiotherapy with concurrent 5-FU 1000 mg/m^2 days 1–4 and 29–32, Mitomycin C 12 mg/m^2 day 1 cycle 1 (Maximum single dose 20 mg)
- Radiotherapy regimen 50.4 Gy in 28#: Phase I 30.6 Gy in 17#; phase II 19.8 Gy in 11#

Although this might be delivered with less toxicity by means of 3-D conformal radiotherapy or IMRT.

Future directions to improve colostomy-free survival for different patient groups

- Consideration of capecitabine to replace 5FU as in rectal chemoradiotherapy
- Less intensive treatment for T1/T2 disease such as smaller radiotherapy doses e.g. ~40 Gy, or smaller field sizes.
- Higher radiation doses for T3/T4 disease, perhaps facilitated by IMRT
- Addition of biological agents to chemoradiotherapy regimes particularly for T3/T4 disease

The limitations of this position statement remain that the conclusions are based on only six phase III trials, three of which were designed and conducted more than 20 years ago. Two have to date only been presented in abstract, so the published data comprises four trials with only 1628 patients. High levels of acute toxicity, insufficient detail on the radiation doses and the use of a planned gap in treatment (which may compromise efficacy) make it difficult to define the actual total dose received by patients. Finally, two of the three more modern trials defy de Ruysscher's principle of SER (the interval between the start of treatment and the end of radiotherapy) by using neoadjuvant chemotherapy [25]. This strategy may also compromise efficacy.

Conclusions

A 'one-size-fits-all' approach for anal cancer is probably inappropriate. The NCRI anal cancer group believes that early T1 tumours are currently over-treated. T3/T4 lesions have a 3-year DFS of 40–68%, and might merit escalation of treatment. Radiotherapy dose-escalation and intensification of the concurrent chemotherapy might improve local control, but is just as likely to impact adversely on colostomy-free survival (CFS). So we will need trials to clarify these concepts.

More accurate radiotherapy techniques such as 3-D conformal radiotherapy and IMRT may benefit the patient in terms of lessening morbidity. Integration of biological therapy looks hopeful. Future approaches to the management of anal cancer may include the integration of new chemotherapy combinations, and novel biological agents. Finally, it is in the interest of all patients to be offered participation in a clinical trial.

Competing interests

RJG is chair of the NCRI anal cancer research group in the UK. The author has received honoraria from lectures from Roche, Sanofi and Pfizer. He also received funding for research and support from Roche to attend international meetings in GI cancer.

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Follow up

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Introduction

Anal cancer is a rare disease, accounting for 1–2% of gastrointestinal malignancies. Therefore, the number of cases requiring follow up is relatively small at each centre. NICE guidelines on improving outcomes in colorectal cancer suggest site specialisation for anal cancer. Most cancer networks has now set up 'Anal cancer MDT' and the person responsible for follow up should be one, preferably two members of the MDT who specialise in the treatment of anal cancer. This has ensured the necessary expertise to develop in the follow up and the management of patients with anal cancer.

Following the publication of the results of UKCCCR anal cancer ACT 1 trial, chemoradiotherapy is now regarded as the standard treatment for anal cancer [1]. It is offered to most patients except for very old and frail patients where modified dose of radiotherapy alone was used. The results of the ACT 2 trial presented at the ASCO (2009) showed that the local control rates for all stages were very high (95%) [2].

The earlier stage disease obviously resulted in much better outcomes. Distant relapse is not very common and for the few patients who failed locally, radical salvage surgery offers the best chance of long term cure. Therefore, regular follow up is necessary to identify patients who can be salvage:

1 Those with loco-regional persistent disease following chemoradiotherapy.
2 Those with subsequent loco-regional failure without distant metastases.

These patients must be discussed at the regional anal cancer MDT and salvage surgery performed by designated experience surgeons with special interest who are members of the regional anal cancer MDT. Patients with anal cancer treated should be divided into low and high risk cases. The investigations carried out during follow up period depend on the predicted risk of recurrence.

High risk patients [3]

1 T4 tumours (i.e. the invasion of adjacent organs)
2 Anal cancer in the presence of fistulae
3 Immuno-compromised patients (including HIV; transplant patients)
4 Patients intolerable to treatment (elderly and medically compromised patients)
5 Anal adenocarcinoma

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Current practice

Initial definitive treatment with chemoradiotherapy allows sphincter conservation which gives the opportunity for careful loco-regional examination during follow-up. Therefore, thorough clinical examination is important since both the primary tumour and groin lymph nodes are accessible for inspection and careful palpation. This should be supplemented by endoscopy, radiology and examination under anaesthesia when necessary. However, no consensus exist regarding who should be follow up, the frequency of follow up and the type of investigations use.

Anal cancer patient follow up depends on:

1 Prediction of the risk for recurrence (high or low risk),
2 Type of treatment (chemoradiotherapy or radiotherapy alone or incomplete)
3 Treatment strategy offered (nodes treated prophylactically).

Treatment strategy

Primary tumours

Anal margin tumours

Most small (< 2 cm) discrete anal margin tumours are initially treated by local excision which confirms the diagnosis and provide the primary definitive treatment. If all the resection margins are clear no further treatment is necessary [4]. Post operative chemoradiotherapy or radiotherapy alone (elderly and frail patients) is indicated if the resection margin is close (< 1 mm). Radiation dose of 45GY in 25 fractions over 5 weeks or lower dose of 36Gy in 20 fractions in 4 weeks or 30Gy in 15 fractions over 3 weeks [5] is offered with or without chemotherapy (5FU and Mitomycin C). Patients are treated prone using three fields technique. Prophylactic groin node irradiation is not usually carried out and patients need close follow up (at least in the first 3 years). Larger tumours

(T2 and above) are treated by chemoradiotherapy following excision biopsy. There is a high risk of inguinal lymph node spread and prophylactic irradiation is offered to both groins. Those with lymph node spread at presentation will have groin node boost on the effected side and groin node dissection may be necessary if there is residual tumour after radiation.

Anal canal tumours

Most patients who are fit will be offered chemoradiotherapy using 5FU and Mitomycin C. Following the publication of RTOG [6] and ACT 2 [2] trials preliminary results, the role of cisplatin either as a neoadjuvant or adjuvant therapy has fallen into disrepute. In well differentiated T1 tumours (< 2 cm), groin nodes are not routinely irradiated outside the clinical trial unless there is extension of tumour into the anal margin. However, it is important to irradiate the pelvic and iliac lymph nodes for more advanced tumours (T2 and above). Close follow up is necessary in the first 3 years (where the relapses are most common) to detect loco regional failure which can be salvage by radical surgery [7].

Lymph nodes

Nodal drainage areas in the groins are not treated prophylactically for well differentiated T1 tumours of the anal margin and early tumours of the anal canal unless there is tumour involvement of the anal margin. Therefore, examination of the groin is important during the follow up. However, assessment of pelvic lymph node relapse needs to be assessed by radiological means. Both CT and MRI can pick up lymph node relapse; however, intra anal ultrasound alone is not useful for detection of lymph node relapse. At present, there is no consensus on the frequency of radiological examinations during the follow up.

The prognosis for patients with metachronous nodal metastases is better than those with synchronous nodal metastases. In St Mark's hospital series of 170 patients, only 19 out of 49 patients with inguinal nodal involvement at presentation were deemed suitable for bloc dissection. Following surgery, five (10.2%) of these were alive at 5 years and only four were alive at 10 years. In contrast, 17 patients in whom the groin nodal metastases developed later, nine (52%) were alive and well at 5 years following groin nodal dissection [8]. In another series, 5 years survival following groin nodal dissection was 20% for synchronous metastases against 59% for metachronous metastases [9]. Therefore, in early stage disease (T1) without nodal metastases at presentation, if the predicted risk of lymph node spread is relatively small (< 10%) prophylactic groin node irradiation can be omitted to reduce toxicity. Groin node develop at a later stage can be salvage by radical node dissection without compromising the 5 year survival [10].

Distant metastases

Haematogenous spread is not common (< 10%) in anal cancer compare to other colorectal cancers. However, ACT 1 trial indicated that 40% of the patients died from distant metastases [1]. In another series of 200 cases collected from 31 hospitals in Connecticut, 13 hepatic and six pulmonary metastases were detected. They were usually bilateral and almost exclusively observed in patients with advanced primary tumours with residual disease following initial treatment [11]. Both the neo adjuvant and adjuvant approach used in RTOG and ACT 2 trials has no influence on disease free survival. Radiological examinations are necessary to detect distant metastases and again there is no consensus on the type or the frequency of examinations used. Follow up protocol for ACT -2 trial stipulate CT scan of chest, abdomen and pelvis at 6 months. As there is no effective treatment for distant metastases at present, it is not clear whether further radiological examinations should be carried out beyond the initial 6 month period for low risk patients.

Follow-up protocol

Clinical

Most recurrences following chemoradiotherapy for primary anal cancer occurred within the first 3 years. Therefore, it is important to follow these patients closely during this period as the detection of early recurrent disease will permit aggressive salvage surgical treatment. There are no consensus exits regarding the frequency of follow-up or type of investigations or their frequency that should be used.

The follow-up protocol from ACT 2 trial consists of visits once every 2 months during the first year, every 3 months in the second year, and every 6 month from year 3 through to year 5 (Table 1). Recurrences after 5 year is rare, at which time patients can be transferred back to the care of general practitioners for annual follow-up visits. At each follow-up visit, a careful history of new or change in symptoms and thorough physical examination should be carried out. Initial non surgical approach which is adopted as standard currently allows careful local examination of perianal region, anus and rectum. Serial digital examination by one experience observer is most useful. This is supplemented by proctoscopy or sigmoidoscopy (for higher lesions). Any

Table 1 Follow up of patients with anal cancer.

	Year				
	1	2	3	4	5
Clinic visit	6	4	2	2	2
Physical exam	6	4	2	2	2
Proctoscopy	6	4	2	2	2
Flexi sigmoidoscopy	1	0 (1)	0	0	0
CT scan	1	0 (1)	0 (1)	0	0
MRI	1 (2)	0 (2)	0 (2)	0	0
PET/CT scan*	0 (*)	0 (*)	0	0	0
Intra anal US*	0 (*)	0 (*)	0	0	0
EUA and biopsy*	0 (*)	0 (*)	0	0	0

* These examinations are done as necessary if there is suspicion of residual disease. Those shown in brackets are for high risk patients.

suspicious lesion should be observed and documented carefully. The patients should be re-examined in 4–6 weeks time and if there is any change observed then examination under anaesthesia should be carried out. Biopsy of the suspicious area should be carried out by experience surgeon as repeated generous biopsies can lead to radionecrosis, especially if the patient had interstitial brachytherapy.

Radiology

Initial radiological investigations should include MRI scan of pelvis in addition to CT scan of chest, abdomen and pelvis.

MRI

Magnetic resonance imaging showed soft tissue changes much clearer and has been used successfully in lieu of CT scan in some studies. A retrospective review was performed of 27 cases of biopsy-proven anal carcinoma, where MRI was used for primary staging (nine patients) or suspected recurrence (18 patients) [12]. In all, seven patients with recurrent disease underwent surgery and subsequent histological correlation was performed. Primary and recurrent tumours were of high signal intensity relative to skeletal muscle on T2-weighted images (T2WI), and of low to intermediate signal intensity on T1-weighted images (T1WI). Lymph node metastases were of similar signal intensity to the anal cancer. Recurrent tumours were found to be more locally advanced than primary tumours and tend to extended into adjacent organs or the pelvic skeleton (T4). Recurrent lymph node disease involved perirectal, presacral and internal iliac nodes more commonly than the lymph node disease at presentation. The investigators concluded that MRI has a role in the preoperative evaluation and surgical planning of cases of recurrent disease following radiotherapy.

CT scan

In a study of 19 post treatment patients by Cohan *et al.*, [13] computed tomography correctly identified recurrent disease in 14 (74%). Local tumour recurrence detected by CT had the appearance of ischiorectal or perirectal fat stranding in association with a mass. False positive diagnosis in four patients (21%) included a pelvis abscess, radiation and surgical scar and radiation necrosis. Each verified by tissue biopsy or serial scans. CT scan is now superseded by MRI scan for local staging but is still useful for detection of distant metastases.

Recommendation (C): MRI scans 6 monthly in high risk patients or those with residual disease following chemoradiotherapy. CT scan should be done at 6 months and yearly for the first 3 years for high risk patients only (See Table 1).

PET/CT scan

There is increase trend to use PET/CT to differentiate post radiation fibrosis with recurrent tumour. In one study found post treatment PET imaging to be less useful. Nine patients had minimal residual PET activity at the primary site on the 1-month follow-up PET study, but only three of these subsequently developed local recurrences. In addition, recurrences occurred in three patients (two local, one distant) of the six who had negative post treatment PET studies. It was concluded that post treatment PET scans appear to be of little value in predicting durability of response [14]. Current practice in the UK does not include routine PET/CT for follow up. It is mainly use to exclude metastatic disease prior to salvage surgery.

Intra anal US

In anal cancer, the ultrasonic image of the tumour and the adjacent tissue correlated well with the pathological stage. This was shown by Roseau *et al.* to detect early mural recurrent disease which predicted pathological findings accurately in a group of patients subjected to salvage surgery. [15,16]. However, clinical suspicion should be verified by histological proof to avoid surgical salvage with no residual tumour on final histology.

Tumour markers

Levels of tumour marker SCC Ag are not done routinely in the UK. There is no role for measurement of CEA routinely during the follow-up period as there is no association between anal cancers and colorectal cancers [17].

Difficult special circumferences during follow-up

Delayed response

Following chemoradiotherapy of patients presenting with locally advanced disease, there can be visible or palpable residual disease at the first follow-up, usually 6–8 weeks from the end of treatment. If the symptoms are improving and if the tumour has regressed, case should be made to review the patient at a later date in approximately 4–6 weeks time. If the tumour continues to regress, wait and watch policy should be adopted as it can take up to 6 months before there is complete regression of the residual tumour [2,17].

Fibrosis or residual tumour?

Sometimes it is difficult to differentiate between radiation fibrosis and residual tumour. This is especially true in patients presenting with locally advanced disease, the distortion of normal anatomy following chemoradiotherapy resulting from tissue damage and fibrosis can be difficult to evaluate at the time of follow up. Another difficulty is in evaluating patients with chronic sepsis, scaring from previous surgical explorations or those with viral warts. Repeated EUA and biopsies may be necessary but scarring and necrosis resulting from such intervention could make the assessment much more difficult. These cases should be discussed at the regional anal cancer MDT and opinion from experience clinicians should be sought.

Development of metastatic disease during follow –up

ACT 1 trail showed 40% of the patients developed distant metastases [1]. These are usually multiple and salvage liver or pulmonary resection is not possible as in other colorectal cancers. There is no effective second line chemotherapy for metastatic disease at present and currently there are no large phase 1 or 2 trials to evaluate this problem.

Immune compromised patients and high risk groups

Patients with HIV or other immune compromised state (post renal or liver transplant) cases are difficult to treat as they do not tolerate chemoradiotherapy well. There is a higher risk of residual disease for advance tumours following treatment which may require earlier surgical salvage. On the other hand, there is no evidence that high risk groups i.e. male homosexuals practising anal receptive intercourse has higher risk of recurrent disease beyond tumour stage, completeness of treatment, and tumour response. HIV patients on full anti viral treatment do not require closer follow up than other patients.

Follow up following surgical salvage

Surgical salvage usually involved APER with perineal plastic reconstruction. Therefore, it is important to do vaginal examination including speculum inspection in women to detect further local recurrences in the pelvis. In men, serial inspection of surgical scars is important to distinguish local recurrence from healing wound. If in doubt, EUA and core biopsy is necessary. Malignant inguinal lymph adenopathy can be distinguished from reactive adenopathy by observing the firm character of the nodes, observing progressive enlargement on serial examinations and adopting a policy of early aggressive FNA or excision biopsy of suspected lymph nodes.

Recommendations

Patients with anal carcinoma following treatment should be follow up regularly to detect residual or recurrent malignancy for surgical salvage by designated surgical team. (See Table 1; Level of Evidence III). Regular follow up should be done by designated oncologists and surgeons who are members of specialist anal cancer MDT.

There is no agreement at present on the type or the frequency of radiological examinations used during follow up. Scans are repeated more frequently for high risk patients especially if there is uncertainty about residual disease which may need surgical salvage. Low risk patients should not have further scans after 6 month assessment as per ACT -2 trial follow up protocol.

Current practice in the UK does not include routine PET/CT for follow up. It is mainly use to exclude metastatic disease prior to salvage surgery. Future trials are needed to evaluate the role of serial PET/CT scan to identify patients with residual disease who need early surgical salvage.

Competing interests

None.

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Position statement

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Management of Local Disease Relapse

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Introduction

Despite refinements in chemo-radiotherapy regimens for first-line treatment of anal cancer (Glynne-Jones, chapter 4), 20–25% of cases will have local disease relapse, mainly during the first 3 years [1,2]. For these patients, salvage surgery offers the only opportunity for cure. This position statement addressed the assessment, treatment and outcome of patients with relapsed local disease from anal cancer. Nine sections are evaluated as follows: (i) assessment of the patient with local disease relapse; (ii) multidisciplinary team meeting (MDT) and patient selection; (iii) salvage radical surgery; (iv) oncological outcomes; (v) mortality and morbidities; (vi) perineal wound reconstruction; (vii) pathology reporting after salvage surgery; (viii) post-salvage surgery surveillance; and (ix) prospective audit. As a prelude to these evaluations, we address the nomenclature used in this area and make recommendations for more standardised terms.

Methodology

Systematic searches of the Cochrane Database, MEDLINE and EMBASE (until May 2010) were performed using keywords relevant to each section of this Position Statement. For pragmatic reasons, searches were limited predominantly to English languages articles. Additional publications were retrieved from the references cited in articles identified from the primary search of the literature. Other guideline papers on anal cancer were reviewed [3–5]. We assigned grading of recommendations using standard levels of evidence.

Nomenclature

In the context of relapsed anal cancer, many papers in the literature have used the categorisation – 'persistent (or residual)' and 'recurrent' local disease [6–13]. However, this dichotomisation has inconsistent impact on prognosis or management. Thus, in some studies patients categorised as persistent had survival outcomes after treatment that were better [7], no different [10,12], and worse [8,9]. Additionally, the definition cut-off for persistent and recurrent varied between 3 and 6 months after initial treatment, whereas at a biological level, the process of relapse is likely to be a continuum. Furthermore, local disease labelled as 'recurrent' occurring in the first few months after the defined cut-off time point will be determined by the aggressiveness of surveillance during this period.

The term local disease failure has also been used [14]. By corollary, the term local control is used very specifically to refer to a time-defined initial treatment response, for example, in the UK ACT II Trial [15]. To apply a uniform nomenclature, in this statement, we use the term *local disease relapse* to encompass the concept that this is a clinical problem which may occur at any time point after the commencement of chemo-radiotherapy through to several years after initial treatment.

Recommendation

The term local disease relapse is recommended when the same malignancy is diagnosed, and confirmed by histopathological assessment, after initial chemo-radiotherapy for anal cancer (Level of evidence: IV).

Assessment of the patient with local relapse

The assessment a patient who may have local relapsed disease is intrinsically linked with the surveillance programme following initial chemo-radiotherapy in patients with anal cancer. This is covered in detail elsewhere (Sun Mynt, Chapter 6) but several general principles apply, as follows:

1 The conventional argument for surveillance in patients with any cancer is that there may be benefit through the early detection of treatable relapsed disease – a second chance at cure. There is indirect evidence that this is true for anal cancer as patients with local disease relapse selected for salvage surgery have a 40–60% 5-year post-salvage survival rates (detailed later) compared with dismally poor survival rates (> 5% at 3 years) in those deemed unsuitable for salvage surgery [2,9].

2 To facilitate early detection of local disease relapse, surveillance of all patients after initial chemo-radiotherapy should be carried out within a protocol-driven

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programme at a dedicated anal cancer unit, involving integrated clinical oncology and colorectal surgery teams.

3 To streamline this protocol, stratification by risk-factors for local disease relapse may be considered. Clinico-pathological factors associated with increased risk for local disease relapse include: large T size, age > 75 years, and intolerance of treatment [2,8]. Additionally, HIV positive individuals (especially in the context of poor response or poor compliance to HAART therapy), and by extrapolation, solid organ transplant patients, are high-risk for recidivism as chemo-radiotherapy may be poorly tolerated [16].

On clinical and/or radiological suspicion of local disease relapse, a series of re-staging investigations should be put into effect. Magnetic resonance (MR) imaging should be used to accurately assess the pelvis as it is better than CT imaging for evaluating the local extent of disease prior to salvage surgery and can better distinguish between tumour recurrence and RT induced fibrosis [17]. FDG-PET CT scans may have greater sensitivity for tumour detection and/or regional nodal spread [18].

Examination under anaesthesia (EUA) and biopsy are an initial pre-requisite. Post-radiotherapy biopsy material may be difficult to interpret and will often require a specialist histopathologist within the multi-disciplinary team.

Recommendation

All patients with anal cancer should be offered a protocol-driven surveillance programme after initial chemo-radiotherapy, at a dedicated anal cancer unit, involving integrated clinical oncology and colorectal surgery teams (Level of evidence: III).

On clinical and/or radiological suspicion of local disease relapse, a series of re-staging investigations should be put into effect including MR scan (supplemented with either CT or FDG-PET CT imaging as indicated); EUA and biopsy, and discussed through the Anal Cancer MD (Level of evidence: III).

MDT and patient selection

To address the question of patient selection, two randomised trials [14,19] and two large case series [2,8], which reported the total number of local disease relapses and also reported numbers of patients who underwent salvage surgery, were evaluated (Table 1). A pattern emerged. In large trials where patients were recruited across multiple centres, the proportion of patients with local disease relapse who went on to undergo salvage surgery was approximately half. This contrasts with series from centralised settings – working through one MDT – where the proportion of patients with local relapsed disease who underwent salvage radical surgery was over 70%. These data point to a positive patient selection for salvage surgery and an opportunity for a 'second chance at cure' in centralised units.

Recommendation

All patients with local disease relapse should be evaluated through a central Anal Cancer MDT (Level of evidence: III).

The audit standard for the proportion of patients with local disease relapse being offered salvage radical surgery is greater than 60% (Level of evidence: IIB).

Salvage radical surgery

For the majority of patients with local disease relapse from anal cancer, salvage surgery takes the form of a radical abdomino-perineal resection (APR). A small

Table 1 Rates of salvage surgery for anal cancer in different series.

Authors & year	Centre/ Country	Total case no.	No. of local relapses	Salvage surgery rate
Multi-centred setting				
Intergroup trial 1996 [19]	104 institutions, USA	310	28*	13 (46%)
UKCCCR ACT I Trial 1996 [14]	Multiple UK centres	585	265	143 (54%)
Centralised setting				
Nilsson *et al.* 2002 [8]	Stockholm, Sweden	308	48	35 (73%)
Renehan *et al.* 2005 [2]	Christie Manchester, UK	254	99	73 (74%)

UKCCCR, UK Co-ordinating Committee on Cancer Research.
*Trial protocol dictated that a biopsy was performed at approximately 100 days following start of treatment.

number of cases may be treated by local resection, but this is the exception. In a further small number of cases, it is necessary to consider a posterior or total pelvic exenteration. In using the term, *radical APR*, there is recognition that it is the norm that there is a need to extend this operation to encompass adjacent viscera (for example, the vagina in women) and irradiated soft tissue of the perianal area, perineum, and buttocks.

It is important to emphasise that radical APR for local disease relapse from anal cancer is completely different to APR for low rectal adenocarcinomas, in five main aspects:

1 the perineal skin resection during salvage anal cancer surgery is wider to take account of the local spread of the squamous cell carcinoma (i.e. a larger perineal defect);
2 the key oncological margin during salvage anal cancer surgery is the lateral margin at the level of the ischial tuberosity (compared with the circumferential meso-rectal margin in rectal carcinoma);
3 the effects of radiation on perineal cutaneous tissue are greater (due to high radiation doses between 50 and 55 Gy) leading to a wider field of fibrosis and relative devascularisation. Thus, the extent of the perineal skin resection is in part dictated by the need to obtain a vascularised skin edge;
4 the en bloc resection of adjacent viscera or organs is common. Thus, for example, in series where operation procedure details are reported [13,20], 70% of women undergoing radical salvage surgery also require a posterior vaginectomy;
5 the almost universal need for reconstruction of the perineal defect.

For these reasons, the radical APR as salvage surgery for anal cancer is described as a 'port-bottle' shaped resection to distinguish it from the 'cylindrical' shaped resection used for low rectal cancer (Fig. 1).

Recommendation

Radical abdomino-perineal resection for anal cancer is a specific operation distinct from that used for low rectal cancer. It should be undertaken by an experienced anal cancer surgical team, which includes tissue reconstruction (Level of evidence: III). This also has implications for training.

Oncological outcomes after salvage surgery

A literature search for case series of salvage surgery for anal cancer was undertaken. A summary of the series, published since 1990 where oncological outcomes were reported, is shown in Table 2 [2,6–10,12,13,20–24]. The study size and duration of follow-up varied, whilst patient selection criteria were seldom explicitly stated. Some studies reported their main findings based on curative cases only, though this was generally defined post-operatively based on margin status. Where possible, the rates cited are those for all study-specific patients undergoing radical salvage surgery. Two patterns emerged:

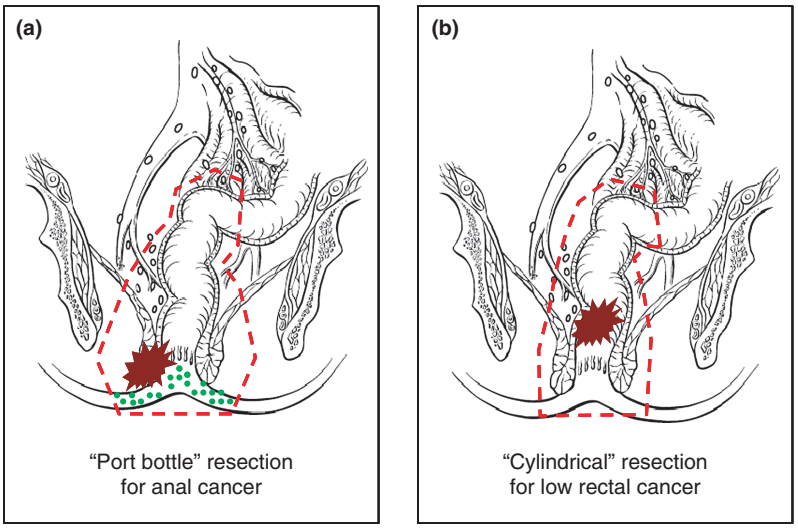

Figure 1 The abdomino-perineal resection for relapsed anal cancer (A) is fundamentally different from that for a low rectal adenocarcinoma (B) in five main aspects: (i) the perineal skin resection during salvage anal cancer surgery is wider; (ii) the key oncological margin during salvage surgery for anal cancer is the lateral margin at the level of the ischial tuberosity; (iii) the effects of radiation on perineal cutaneous tissue (indicated as green dots) are greater; (iv) en bloc resection of adjacent viscera is common, and (v) almost universal need for perineal reconstruction. For these reasons, the radical abdomino-perineal resection during salvage surgery for anal cancer is described as a 'port-bottle' resection to distinguish it from the 'cylindrical' resection used for low rectal cancer.

Table 2 Summary of oncological outcomes after salvage surgery for relapsed anal cancer.

Authors & year	Centre/Country	No. of cases	Median FU (months)	Further loco-regional disease	Survival
Ellenhorn *et al.* 1994 [6]	Memorial Sloan-Kettering Cancer Center, New York, US	38	43	23 (61%)	5-year actuarial survival: 44%
Pocard *et al.* 1998 [7]	Saint Antoine, Paris, France	21	40	Not stated	Overall 3-year survival: 58%
Allal *et al.* 1999 [21]	Geneva, Switzerland	26	22	15 (58%)	Crude 5-year survival: 45%
Smith *et al.* 2001 [22]	Toronto-Sunnybrook Regional Cancer Centre, Ontario, Canada	22	30	18 (82%)	Crude 5-year survival: 23%
van der Wal *et al.* 2001 [23]	Johns Hopkins, Baltimore, US	17	53	Not stated	5-year actuarial survival: 47%
Nilsson *et al.* 2002 [8]	Stockholm, Sweden	39	33	15 (38%)	Crude 5-year survival: 52%
Hill *et al.* 2003 [24]	Multi-centred, UKCCCR	133	30	58 (44%)	'67 (50%) died of anal cancer'
Akbari *et al.* 2004 [9]	Memorial Sloan-Kettering Cancer Center, New York, US	57*	24	79%	5-year actuarial survival: 33%
Ghouti *et al.* 2005 [10]	Marseille, France	36	67	23 (66%)	Crude 5-year survival: 69%
Renehan *et al.* 2005 [2]	Christie Manchester, UK	73	45	Not stated	5-year cancer-specific survival: 40%
Mullen *et al.* 2007 [12]	MD Anderson Cancer Center, Texas	31	29	12 (39%)	5-year actuarial survival: 64%
Lefevre *et al.* 2009 [13]	Saint Antoine, Paris, France	95	Not stated	Not stated	Overall 5-year survival: 58%
Sunesen *et al.* 2009 [20]	Aarhus, Denmark	49	Not stated	Not stated	Overall 5-year survival: 61%

FU, follow-up; UKCCCR, UK Co-ordinating Committee on Cancer Research.
*Seven cases were radical surgery for primary cancer.

1 salvage radical surgery achieves a local pelvic disease control rate of 50–60%
2 5-year post-salvage surgery survival rates are 40–60%.

Recommendation

The audit standard for the proportion of patients achieving local pelvic disease control after salvage surgery is greater than 50% (Level of evidence: IIB).

The audit standard for 5-year post-salvage surgery survival rate is greater than 40% (Level of evidence: IIB).

Mortality and morbidities

A literature search for case series of salvage surgery for anal cancer was undertaken. A summary of the series, published since 1990 where peri-operative mortality and morbidities were reported, is shown in Table 3 [2,7,8,10,12,13,20,21,23]. Despite variations in definitions of complications and morbidities, five patterns emerged:

1 radical salvage surgery has a recognised, albeit low (< 3%) level of peri-operative mortality;
2 delayed healing of the perineal wound after primary closure is very common – approximately 40–70% of cases;
3 the complication of perineal hernia after primary closure is recognised though not always stated in reports, but may be as great as 15% [13];
4 there are a range of other major morbidities associated with radical salvage surgery including general medical complications (for example, cardiovascular events, chest infections) and general abdominal surgical complications (for example, small bowel obstruction requiring laparotomy, wound infections). These are variably defined in the literature, but are estimated to occur in 15–25% of cases;
5 the use of autologous tissue reconstruction in recently reported series reduces the rate of delayed perineal wound healing to between 15% and 25%.

Recommendation

The risk of peri-operative mortality following radical salvage surgery for anal cancer needs to be appreciated – patients require thorough pre-operative anaesthetic assessment and critical care monitoring during the immediate post-operative period (Level of evidence: III).

With very high perineal wound breakdown rates and delayed healing following direct closure, autologous tissue reconstruction should be considered the norm as part of salvage surgery for anal cancer (Level of evidence: III).

Table 3 Summary of complications after salvage surgery for relapsed anal cancer.

Authors & year	No. of cases	Operation type	Peri-operative mortality	Delayed healing in primary wound	Perineal hernia	Other morbidities	Reconstruction	Comments
Pocard *et al.* 1998 [7]	21	All APR, PPr, 2	0	13* (62%)	1	5 (24%)	Omentoplasty, 16	No muscle flaps used
Allal *et al.* 1999 [21]	26	APR, 23; LE,3	0	2 (8%)	Not stated	Not estimatable	Not described	Two committed suicide
van der Wal *et al.* 2001 [23]	17	All APR	0	12 (70%)	Not stated	Not estimatable	Omenoplasty, 3; muscle flap, 9	Lower perineal breakdown in flap group ($P < 0.05$)
Nilsson *et al.* 2002 [8]	39	All APR; PPr, 2	1	23 (59%)	Not stated	13 (33%)	No primary flaps	Secondary flaps, 3
Ghouti *et al.* 2005 [10]	36	All APR	0	23 (70%)	Not stated	36 (13%)	Omentoplasty, 9; muscle flap, 13	Delayed healing, 5 (38%) in muscle flap group
Renehan *et al.* 2005 [2]	73	APR, 67; LE, 3; TE, 3	0	22 of 52 (42%)	Not stated	Not stated	No flaps pre-1998	Four muscle flaps post-1998, reduced delayed healing
Mullen *et al.* 2007 [12]	31	APR, 20; AR, 2; PPE, 9	0	5 of 15 (33%)	1	Not stated	Omentoplasty, 11; muscle flap, 16	Wound complications in six flaps (38%)
Lefevre *et al.* 2009 [13]	95	All APR; PPr, 4; ‡PV, 49 (70%)	2†	19 (44%)	8, all non-VRAM	Not estimatable	VRAM flap, 43	Wound complications in 11 (27%) VRAM patients
Sunesen *et al.* 2009 [20]	49	APR, 47; TE, 2; ‡PV, 25 (74%)	1	1	Not stated	Not estimatable	VRAM flap, 48; other flap, 1	Lost VRAM, 1.

APR, abdomino-perineal resection; PPr, partial prostate excision; LE, local excision; TE, total pelvic exenteration; PPE, posterior pelvic exenteration; VRAM, vertical rectus abdominis myocutaneous flap.

*In 10 cases, wounds were packed open and were counted as delayed healing.

†Died at 45 and 51 days.

‡PV: posterior vaginectomy. This was not routinely reported, but where reported, percentage is given based on number of women.

Table 4 Perineal wound flaps – advantages and disadvantages.

Flap type	Advantages	Disadvantages
Vertical rectus abdominis myocutaneous flap (VRAM)	Widely used flap Robust blood supply Provides good bulk	Either precluded or requires modification if previous abdominal scars High abdominal wound complication rate including hernias Poor versatility if commitment vaginal reconstruction required
Bilateral gracilis myocutaneous flap	Avoids additional abdominal complications Versatile to allow commitment vaginal reconstruction	Variable blood supply High complication rates High donor site morbidity
V-Y Bilateral gluteus maximus myocutaneous advancement flap	Robust flap Good bulk, particularly if sacrectomy part of operation	Requires patient in prone position Poor versatility if concomitant vaginal reconstruction required
Lotus petal (fatty cutaneous) flap	Relatively short procedure Wide experience in gynaecological surgical oncology Low donor site morbidity Good aesthetic – 'like' skin with 'like' Versatile to allow concomitant vaginal reconstruction	No muscle component, risk of perineal hernia

When using plastic reconstructions, the audit standard for delayed perineal wound healing is less than 25% (Level of evidence: III).

Radical salvage surgery for anal cancer is associated with major morbidities beyond the perineal wound problems. For audit standards, these morbidities should be defined using internationally recognised criteria, such as the National Cancer Institute Common Toxicity Criteria, and should be less than 30% (Level of evidence: III).

Perineal reconstruction

A variety of plastic reconstruction approaches have been described – the most commonly used are listed in Table 4, and include: vertical rectus abdominis myocutaneous flap (VRAM) [20,25,26]; bilateral gracilis myocutaneous flap [27]; V-Y bilateral gluteus maximus myocutaneous advancement flap [28,29]; and the lotus petal (fatty cutaneous) flap [30]. Detailed descriptions of these are found elsewhere [31,32] – the advantages and disadvantages of the various flaps are summarised in Table 4. Other less commonly used but described flaps for perineal reconstruction include: the anterolateral thigh-vastus lateralis muscle flap [33]; the posterior thigh flap [34]; and the inferior gluteal perforator flap [35]. The choice of flap depends on the goals of reconstruction, size of the defect, and the availability of donor tissue.

Omentoplasty is commonly used after radical abdominoperineal resection (APR) to fill the irradiated pelvis and act as a base for autologous tissue interposition of the perineal wound. It has the important advantage that it reduces prolapse of small intestine into the radiated pelvis, and may therefore reduce subsequent small bowel obstruction, fistulations, and perineal hernias.

Recommendations

There is a large variety of techniques to reconstruct the irradiated perineal wound, selection of which depends on the goals of reconstruction, size of the defect, and the availability of donor tissue. Given the versatility and selection of flap choices required, reconstruction should be assessed jointly with plastic surgical input as part of the anal cancer MDT (Level of evidence: III).

Pathological reporting

Pathological staging systems of resections were historically validated when surgery was the primary treatment for anal cancer (over two decades ago). There is therefore a need to revise pathological reporting of resections following salvage surgery (Salmo and Haboubi, Chapter 5). A post-salvage surgery staging system should take into account relevant prognostic factors. The most powerful prognostic

factor is a positive resection margin – several studies report that the majority of patients with a positive resection margin die within 2 years after salvage surgery. Histological involvement of the external sphincter muscles may also be a negative prognosticator [24], but it is unclear whether this is independently significant. It is not clear whether histological features, such as perineural invasion, a powerful negative prognosticator in head and neck squamous cell carcinoma, is relevant after salvage surgery for squamous cell anal carcinoma. The suggested reporting system of Haboubi *et al.* [11] is shown in Table 5.

Recommendation

A standardised pathological reporting system that includes potential prognostic factors should be encouraged and used within the anal cancer MDT (Level of evidence: III).

Surveillance following salvage surgery

Following salvage surgery, further disease in the pelvis may occur in 40–50% of cases (Table 2). For these patients, there is seldom an opportunity for further surgical salvage. However, for patients with isolated distant metastases to the liver and/or lungs, there may be opportunities for surgical resection of metastases [36]. Therefore, an imaging surveillance programme similar to that used for colorectal cancer may be considered.

In addition, there is a recognised risk of second primary cancers in patients following pelvic radiation and persistence of HPV infection [37], mandating the need for a long-term surveillance programme. Surveillance protocols using MR and CT imaging are justified though the optional frequencies are unclear.

Table 5 Pathological reporting after salvage surgery for relapsed anal cancer.

Surname	Forename	Date of birth
Hospital	Hospital no.	Sex
Date of receipt	Date of reporting	Report no.
Pathologist	Clinician	
Gross description		
Site of current tumour		
Specimen length in mm		
Tumour length in mm		
Tumour width in mm		
Tumour depth in mm		
Microscopic findings		
Tumour type		
Squamous cell carcinoma		
Adenocarcinoma		
Mucinous adenocarcinoma		
Undifferentiated carcinoma		
Small cell carcinoma		
Local invasion		
T1 tumour limited to the internal anal sphincter		
T2 tumour involving the external anal sphincter		
T3 tumour extending outside the anal sphincters/muscularis propria of the rectum		
T4 tumour involving adjacent tissue		
Tumour margins from excision (mm)		
Long		
Circumferential		
Metastatic disease		
No. lymph nodes recovered		
No. positive nodes (pN1 1–3 nodes, pN2 > 3 nodes)		
Tumour nodules not associated with lymphocytic infiltrate/extra nodal deposits (END's)		
Site of histologically proven distant metastases		

Modified from Haboubi *et al.* 2007 [11].

Recommendation

The anal cancer MDT is encouraged to develop a surveillance programme which recognises opportunities for salvage treatment of distant metastases, second primary cancers, and long term treatment related side-effect (Level of evidence: III).

Prospective audit and outcome standards

Through the central anal cancer MDT, there are opportunities for prospective clinical audit. These include short-term and long-term outcomes, the latter in turn complements the UK National Cancer Survivorship Initiative [38].

Recommendations

The management of patients with local disease relapse from anal cancer are complex and uncommon. Prospective clinical audit and periodic evaluation against standards (such as those stated in this document) should be undertaken through the anal cancer MD (Level of evidence: IV).

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Competing interests

None.

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