

Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence

Epidermoid anal cancer is a rare disease requiring a specialist multidisciplinary team approach for optimum results. The annual incidence is ~1 in 100 000, is higher in women and is increasing. Five-year survival in the USA was 62% in the 1980s, and has changed little in the last two decades.

aetiology

Anal cancer is strongly associated with human papilloma virus (HPV) infection. Using polymerase chain reaction (PCR), the presence of the HPV genome has been identified in 80%–85% of cases. Other important risk factors include human immunodeficiency virus (HIV), immune suppression in transplant recipients and cigarette smoking. Herpes simplex virus (HSV) may play a secondary role in disease progression. Dietary habits, chronic inflammatory diseases and the presence of haemorrhoids do not appear to predispose to epidermoid anal cancer.

Previous (gynaecological, lymphoma or leukemia) or subsequent (e.g. lung, bladder, vulva, vagina or breast) malignancy is more likely in anal cancer patients. This observation may reflect a genetic predisposition in some individuals, while in others synchronous or metachronous multicentric epidermoid tumours are related to HPV infection.

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Approved by the ESMO Guidelines Working Group: February 2009, last update February 2010. This publication supercedes the previously published version—Ann Oncol 2009; 20 (Suppl 4): iv57–iv60.

Conflict of interest: Dr Glynne-Jones has reported that in the last 3 years he has received honoraria for lectures from Roche, Pfizer and Sanofi and that he has received honoraria for advisory boards from Roche, Merck-Serono, Pfizer and Sanofi-Aventis. He also has received funding and free cetuximab from Merck-Serono for an ongoing phase I/II study integrating cetuximab into chomoradiation in rectal cancer. He has an agreement with Roche to supply bevacizumab for 3 months for 60 patients in a randomized phase II study as neoadjuvant chemotherapy in rectal cancer (due to start in 2010). He has finally received support for attending international meetings in GI cancer from Roche, Merck-Serono, Pfizer and Sanofi-Aventis; the members of the panel have reported that they have received financial support from the following pharmaceutical companies: Pfizer, Roche, Sanofi-Aventis, Novartis, Astra-Zeneca, Merck Serono and Amgen for research, attendance at international meetings, membership of advisory committees or participation in speaker's bureau; Prof. Northover and Dr Cervantes has reported no conflicts of interest.

pathology and biology

There is a spectrum of neoplastic changes in and around the anus, including the three stages of benign intraepithelial neoplasia (AIN) and invasive malignancy.

anal intraepithelial neoplasia

AIN is conventionally divided into three grades. AIN is present in 30%–40% of men who have sex with men (MSMs). Progression from AIN 1 and 2 to AIN 3 is uncommon, as is progression from AIN 3 to invasive malignancy in immunocompetent patients, while it is more likely in systemically immunosuppressed patients, and is influenced by HIV seropositivity, low CD4 count and serotype of HPV infection and therapeutic immunosuppression.

anatomy

The anal canal extends from the anorectal junction to the anal margin; around its midpoint the dentate line marks the junction between squamous and mucosal epithelium. Immediately above the dentate line there is a zone of transitional epithelium, below it the canal is lined by non-keratinizing squamous epithelium, which merges with the perianal skin. The anal margin is the pigmented skin immediately surrounding the anal orifice, extending laterally to a radius of ~5 cm.

The lymphatic drainage varies in different parts of the canal. Proximally drainage is to perirectal nodes along the inferior mesenteric artery. Lymph from immediately above the dentate line drains to internal pudendal nodes, and to the internal iliac system. Infra-dentate and perianal skin drains to the inguinal, femoral and external iliac nodes.

presentation

Small, early cancers are sometimes diagnosed serendipitously following the removal of anal tags. More advanced lesions are usually encountered in the distal anal canal, and may present with any combination of a mass, non-healing ulcer, pain, bleeding, itching, discharge and faecal incontinence. Not uncommonly lesions are palpated first by the patient. Suspicious lesions should always be biopsied.

diagnosis

A relevant history to elicit symptoms and predisposing factors should be documented. Proctoscopy and examination under anaesthesia facilitates biopsy and clarification of anatomical relations to surrounding structures. Histological confirmation is mandatory.

histology

Tumours of the anal margin are usually well differentiated, in contrast to canal tumours. Grading is subject to inter-observer variability, and considerable heterogeneity is seen in larger tumours. The reproducibility of small biopsies could well be questioned. High-grade tumours have been thought to have a worse prognosis, but this has not been confirmed in multivariate analysis. Histological subclassifications of basaloid, transitional, spheroidal and cloacogenic cell cancers have no additional confirmed bearing on management. Some authors report that a basaloid rather than squamous histological subtype has a higher risk of developing metastatic disease.

staging and risk assessment

An indolent natural history and a low rate of distant metastases means anal cancer is usually amenable to loco-regional treatment.

Physical examination including digital rectal examination (DRE) and vaginal examination should determine site and size of the primary tumour and nodal involvement. Careful clinical assessment of the inguinal nodes is important. Physical examination is most definitive if carried out under general anaesthesia; this complements staging investigations as outlined below. Local staging should include magnetic resonance imaging (MRI) of the pelvis. Distant metastases, should be assessed with computerized tomography (CT) thorax and abdomen.

Anal cancers occur rarely, and factors influencing outcome and long-term survival have proved difficult to study with multivariate analysis. The role of prognostic factors in anal cancer has only been reported only from the smallest of the four published randomized studies, which suggested that skin ulceration as well as gender and nodal status were important, but not tumour size. We emphasize that prognostic factors require validation. The EORTC 22861 and the RTOG 9811 studies have laid out some hypotheses based on size and nodal status, which look able to discriminate outcome, but these factors need to be validated on other large trial datasets.

- The TNM clinical staging system is based on accurate assessment of size (T-stage), regional lymph node involvement (N) and metastatic spread (M).
- Nodal status is based on distance from the primary site rather than the number of nodes involved—see Table 1. Nodal involvement of anal canal lesions differs from that of anal margin tumours.
- A cut-off of 4–5 cm has been proposed as the size that distinguishes good and poor prognosis.
- The level of tumour regression (>80%) after primary chemoradiation may be predictive of colostomy-free survival (CFS) and disease-free survival (DFS).

Table 1. TNM staging

Tx	Primary tumour cannot be assessed
Tis	Carcinoma <i>in situ</i>
T1	Tumour ≤2 cm
T2	Tumour >2–5 cm
T3	Tumour >5 cm
T4	Tumour invades other organ (vagina, urethra, bladder, sacrum): anal canal Tumour invades deeper structures (skeletal muscle or cartilage): anal margin
N	Regional nodes are perirectal, internal iliac and inguinal
Nx	Regional nodes cannot be assessed
N0	No regional node metastases
N1	Metastasis in perirectal nodes
N2	Metastasis in unilateral internal iliac and/or inguinal nodes
N3	Metastasis in perirectal and/or bilateral internal iliac or inguinal nodes
M0	No metastasis
M1	Metastasis present

NB: nodal N stage differs in anal margin and anal canal.

biological markers

Squamous cell carcinoma antigen (SCCAg) is a tumour marker that is expressed by carcinomas of the anal canal, but its clinical utility in diagnosis and follow-up remains controversial. Recently a retrospective study from the UK suggested the initial SCCAg level before treatment appeared to be related to tumour stage and/or nodal status, and might assist in guiding planning target volumes.

general points

- Patients should be tested for relevant infections, and other malignancies.
- Patients should be assessed for performance status, renal function, and other medical co-morbidity before treatment.
- Assessment of the cervix, vagina and vulva is suggested in female patients, and includes screening for vaginal and cervical cancer (and the penis in men), because of the common role of HPV in these tumours.
- HIV testing is recommended in any patient with a lifestyle that puts them at risk of contracting HIV infections.
- Smoking may worsen acute toxicity during treatment and lead to a poorer outcome in terms of DFS and CFS. Every effort should be made to ensure patients stop smoking before therapy.
- Sperm banking should be discussed before 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 those in whom an early menopause is induced.
- A defunctioning colostomy should be considered in patients with transmural vaginal involvement (at risk of development of an anorectal-vaginal fistula), or faecal incontinence.

radiological staging

Available imaging modalities are CT, MRI, endo-anal ultrasound (EUS) and positron emission tomography (PET) scanning. Together they allow assessment of the local extent including involvement of other structures, and spread to nodes and distant sites.

- Determination of loco-regional lymph node status may be inaccurate. Involved nodes are often clinically palpable, but historical pathology studies, using a 'clearing' technique, demonstrated that almost half of all involved lymph nodes were <5 mm in diameter.
- As a minimum it is suggested patients undergo CT of chest, abdomen and pelvis as staging for metastatic disease.
- MRI is currently the modality of choice to assess loco-regional disease, but ultrasound can be useful for small lesions.
- PET/CT with [¹⁸F]fluorodeoxyglucose (FDG-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.

primary treatment

surgery as primary treatment

Until the mid-1980s surgery was the cornerstone of treatment. Local excision was (and is) usually performed for small tumours at the anal margin, which behave in a similar fashion to skin cancer elsewhere; this procedure has not been shown to be efficacious for small tumours in the canal.

Abdominoperineal excision was formerly recommended for all other tumours. Surgery was associated with local failure in up to half of cases, and 5-year survival rates in the region of 50%–70%.

Surgical excision remains a standard for T1 cancers of the anal margin (i.e. where sphincter function will not be compromised by adequate surgical resection).

non-surgical treatment

- Recommendations are based on the results of 3 phase I, 13 phase II and 6 randomized phase III (EORTC 22861, UKCCCR ACT I, RTOG 87-04, RTOG 98-11, ACCORD-03, CRUK ACT II).
- 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.
- In contrast, Nigro *et al.* and Cummings *et al.* reported that CRT, with the addition of mitomycin C (MMC) to 5-fluorouracil (5FU), demonstrated excellent local control in small tumours
- Sequential phase II studies with chemoradiation have shown the efficacy of relatively low total radiation doses (30–45 Gy) in combination with 5FU and MMC.
- Randomized controlled studies in Europe have demonstrated that synchronous chemoradiation (SCRT), as the primary modality, is superior to radiotherapy alone.

- European trials have previously advocated a 6-week gap following chemoradiotherapy (CRT) to a dose of 45 Gy before a subsequent boost with a further 15 Gy.
- Subsequent EORTC trials have used a prolonged venous infusion (PVI) of 5FU, and reduced the gap to 2 weeks.
- The RTOG phase III study compared 5FU with 5FU and MMC in combination with radiotherapy (median dose 48 Gy), and did not use a planned gap, but boosted poor responders with a further 9 Gy. This study confirmed the superiority of the combination of MMC and 5FU.
- The UK ACT II pilot study suggested the use of a triple drug combination (MMC, 5FU and cisplatin) was poorly tolerated, and associated with sufficient morbidity, which would not allow the regimen to be taken into a subsequent phase III trial.
- It remains unclear whether increasing the radiation dose to >50 Gy in patients with locally advanced anal cancer receiving combined modality therapy will improve the results—particularly if a planned gap is used.
- Neoadjuvant chemotherapy (NACT) has not improved either loco-regional or distant control, and CFS is significantly worse. NACT should not be given outside clinical trials [I]
- The UK ACT II trial employs a continuous schedule of 50.4 Gy in 28 daily fractions, and demonstrated no difference in terms of overall survival (OS) or RFS, when MMC was replaced with cisplatin.

recommendations

- 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 [III]. More extensive lesions will have a higher risk of nodal spread.
- Combined modality chemoradiation using 5FU and MMC is recommended as first-line treatment for all other cases, with salvage surgery reserved for those who fail on this regimen. 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.
- 5FU and MMC combined with radiotherapy are recommended rather than 5FU and cisplatin, MMC and cisplatin, any single drug or three drugs [I].
- Uninterrupted treatment, avoiding a gap, is considered radiobiologically the most effective treatment [III]. Doses of at least 45–50 Gy without a gap are recommended for T1–2 N0.
- Higher doses may be required for more advanced tumours, particularly if a planned gap is used. Currently it is not possible to make a definitive recommendation (based on inter-trial comparisons of differing dose fractionations with or without a gap) on either the requirement for, the form (external beam or brachytherapy) or the appropriate doses for a boost after 50 Gy.

radiotherapy technique and treatment fields

Dogmatic definition of treatment fields is beyond the scope of this article. There are significant differences in approach

within Europe, but in general treatment should aim to encompass the primary tumour and any sites of likely nodal involvement within the high-dose volume.

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 (e.g. 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).

Some authors have advocated PET to define the dose required for the inguinal lymph nodes; PET positive nodes are assumed to be involved, but subclinical involvement cannot be ruled out even if PET is negative. They suggest doses in the region of 36 Gy may be sufficient for PET-negative lymph nodes even if these nodes are enlarged on CT criteria. However, the specificity of PET remains unknown because anal cancer is not usually treated by surgery (so no tissue confirmation is possible).

Recent studies suggest that acute and late toxicity can be reduced with more advanced and complex techniques of radiation delivery.

postoperative chemoradiation

Postoperative chemoradiation should be considered in patients who have undergone excision of perianal skin tags where completeness of excision cannot be guaranteed, or in the case of narrow margins, and re-excision is not feasible. Other indications are in the rare cases when radical surgery has been performed as primary treatment and the resection margin following surgical resection is involved,

toxicity and supportive care during radiotherapy

- Patients should be assessed, and full blood counts checked weekly if mitomycin is used, as CRT is associated with high risks of haematological toxicity.
- Patients should be informed of the negative effect of smoking before chemoradiation starts. Smoking may worsen acute toxicity during treatment and lead to a poorer outcome in terms of DFS and CFS. Every effort should be made to ensure patients quit smoking before therapy.
- Tolerance to treatment can be maximized 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.

response evaluation

Clinical response should be assessed at 6–8 weeks after completion of treatment. By this time 60%–85% achieve complete clinical response. The mainstay of clinical evaluation relies on DRE, and careful examination of the inguinal regions.

- MRI can complement clinical assessment, and act as a useful baseline. However, MRI can over-stage observed abnormalities, and should be used in context with clinical findings.
- Good partial regression can be managed by close follow-up to confirm that complete regression takes place, which may take 3–6 months. A decision regarding salvage surgery can be deferred safely in these circumstances.
- The risk of radionecrosis should be borne in mind when considering biopsy.
- Residual or 'recurrent' tumour must be confirmed histologically before considering proceeding to radical surgery.
- Complete response on PET/CT at 8 weeks following chemoradiation may predict long-term outcome.

follow-up and surveillance

Patients in complete remission at 8 weeks should be evaluated every 3–6 months for a period of 2 years, and 6–12 monthly until 5 years, with clinical examination including DRE and palpation of the inguinal lymph nodes.

Patients tend to relapse loco-regionally rather than at distant sites. Regular CT scans for metastatic surveillance outside trials remains controversial, as there is no evidence for benefit of resection of metastases as in colorectal cancer.

quality of life

Data on long-term quality of life is sparse, but appear satisfactory to patients despite objective impairment of sphincter function. Complete continence is preserved in the majority of patients (56%). Efforts should be made to document quality of life and late effects.

salvage treatment

Patients with locally persistent/progressive disease should be considered for surgical salvage with abdomino-perineal excision.

Biopsy and restaging for metastatic disease is recommended before resorting to surgery. PET/CT may have a particular role in excluding distant disease before proceeding to surgery.

Surgery following chemoradiation is often complex and may require involvement of colleagues from other disciplines including urology, gynaecology and plastic surgery.

palliative treatment

Otherwise fit patients with symptomatic metastatic or recurrent disease not amenable to surgery should be considered for chemotherapy, usually with a combination of cisplatin and 5FU. There are several other options. Responses are rarely complete and usually of short duration.

conclusion

A multidisciplinary team approach is essential for the management of anal cancer. Despite the results of four randomized phase III trials in anal cancer, the paradigm of

Table 2. Levels of evidence

IA	Evidence from meta-analysis of randomized controlled trials
IB	Evidence from results of a randomized controlled trial
IIA	Evidence from results of at least one non-randomized controlled study
IIB	Evidence from results of at least one other type of experimental study
III	Evidence from results of non-experimental descriptive studies
IV	Evidence from expert committees or opinions, and/or clinical experience

external beam radiation therapy with concurrent 5FU and mitomycin developed over 30 years ago remains the standard of care.

As anal cancer is a rare tumour, the panel strongly believes that it is in the interest of all patients to be offered participation in a clinical trial. National and international trials in this disease site are ongoing throughout Europe.

PubMed and Medline were searched for articles published between 1990 and September 2009. The search term included squamous cell carcinoma, anal cancer, anal canal carcinoma, anal margin cancer, survival, diagnosis, recurrence, surgery, chemotherapy, radiotherapy, chemoradiation, chemo-radiotherapy.

Recent reviews and guidelines are available as listed in the literature.

note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets (Table 2). Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty. The present guidelines have been formulated with the assistance of the United Kingdom National Cancer Research Institute (NCRI) multidisciplinary Anal Cancer Group.

On behalf of panel members of the NCRI Anal Cancer Group: David Sebag-Montefiore—Clinical Oncologist; Roger James—Clinical Oncologist; Jim Hill—Surgeon; Richard Adams—Clinical Oncologist; Suzy Mawdsley—Clinical Oncologist; Alec McDonald—Clinical Oncologist; Simon Gollins—Clinical Oncologist; Sun Myint—Clinical Oncologist; Phil Quirke—Pathologist; Gina Brown—Radiologist; David Cunningham—Medical Oncologist; Michael Roughton—Data manager.

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