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# Anal cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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## incidence

Squamous cell cancer (SCC) of the anus is a rare disease. The annual incidence is approximately 1 in 100 000, is higher in women than in men, and is increasing. Anal cancer is strongly associated with human papilloma virus (HPV) human immunodeficiency virus (HIV), and immune suppression in transplant recipients.

## diagnosis

Small, early cancers are sometimes diagnosed serendipitously following the removal of anal tags. More advanced lesions present as a mass, non-healing ulcers, pain, rectal bleeding, itching, discharge and faecal incontinence.

A relevant history to elicit symptoms and predisposing factors should be documented. Proctoscopy and examination under anaesthesia facilitates biopsy. Diagnosis requires histological confirmation.

### anatomic definition

The anal canal extends from the anorectal junction, through the anorectal ring and ends at the anal margin. Immediately above the dentate line there is a zone of transitional epithelium, while the lower half is lined by non-keratinizing squamous epithelium, which merges with the perianal skin. The anal margin is the pigmented skin with skin folds surrounding the anus, extending laterally to a radius of approximately 5 cm from the anal orifice.

### histology

Tumours of the anal margin are usually well-differentiated SCC, in contrast anal canal tumours are more commonly less well differentiated. Histological sub-classifications of basaloid, transitional, spheroidal and cloacogenic cell cancers have no additional bearing on management or outcome.

## staging and risk assessment

Squamous cell cancer of the anus requires a multidisciplinary specialist approach for the optimum results.

Physical examination including digital rectal examination (DRE) and vaginal examination should determine site and size of the tumour, nodal involvement and distant metastases.

- 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).
- Nodal status is based on location rather than number of nodes involved – see appendix 1. Nodal involvement of anal canal lesions differs from that of anal margin tumours.

### 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 prior to treatment.
- Assessment of the cervix and vulva is suggested in female patients because of the common viral aetiology of vulvar, cervical and anal neoplasms.
- HIV testing is recommended in any patient with a lifestyle that puts them at risk of contracting HIV infections.
- Sperm banking should be discussed prior to the commencement of treatment with male patients who wish to preserve fertility.
- 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 include computerized tomography (CT), magnetic resonance imaging (MRI) and endo-anal ultrasound (EUS), and permit assessment of tumour length, circumferential extent, and involvement of adjacent structures.

- As a minimum it is suggested patients undergo CT of chest, abdomen and pelvis as staging for metastatic disease.

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- MRI is currently the modality of choice to assess loco-regional disease.

## primary treatment of anal cancer

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 (level of evidence III) and no sphincter involvement.

- Combined modality chemoradiation is recommended as first line treatment for all other cases, with salvage surgery reserved for those who fail on this regimen (level of evidence IB).
- Uninterrupted treatment, avoiding a gap, is considered radiobiologically the most effective treatment (level of evidence III).
- Doses of at least 45 –50 Gy without a gap are recommended or higher doses if a planned gap is used (level of evidence I).
- 5FU and mitomycin C combined with radiotherapy are recommended rather than a single drug or three drugs (Ajani 2008) (level of evidence IB).
- Neoadjuvant chemotherapy has not improved either loco-regional or distant control (Ajani 2008), and should not be given outside clinical trials (level of evidence IB).

## radiotherapy technique and treatment fields

Dogmatic definition of treatment fields is beyond the scope of this recommendation. There are significant differences in approach within Europe, but in general treatment should aim to encompass the primary tumour and any sites of 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.

Some clinicians may decide to 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). The results of the ACT II trial should clarify the optimum strategy, and the dose required for microscopic disease.

## postoperative chemoradiation

Post-operative chemoradiation should be considered in patients who have undergone piecemeal excision of peri-anal skin tags where completeness of excision cannot be guaranteed, when the resection margin following surgical resection is involved, or in the case of narrow margins.

## toxicity and supportive care during chemo-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 (Ajani 2008).
- Tolerance to treatment can be maximized with antibiotics, anti-fungals, anti-emetics, analgesia, skin care, advice regarding nutrition and psychological support.
- There is no evidence to support altering treatment planning according to HIV status. However, possible interactions with anti-retroviral therapy, and the increased risk of infections warrant strict monitoring of toxicity and modifying treatment accordingly in patients with low CD4 lymphocyte counting or with AIDS.

## response evaluation

Clinical response should be assessed at 6–8 weeks after completion of treatment.

- By this time 60–85% achieve complete clinical response.
- Good partial regression can be managed by close follow-up to confirm that complete regression takes place, which may take 3–6 months.
- The advantages of biopsy should be considered against the substantial risks of radionecrosis.
- Evidence of major residual tumour or progression should be considered for biopsy.
- MRI can complement clinical assessment, and act as a useful baseline.

## follow-up and surveillance

Follow-up relies on clinical examination.

- Patients in complete remission at 8 weeks should be evaluated every 3–6 months for a period of two 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 but the results of the ACT 1 trial showed high incidence of distant spread. However, regular CT scans for metastatic surveillance outside trials remains controversial.

## salvage treatment

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

- Biopsy is mandatory and restaging for metastatic disease is recommended before resorting 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

Fit patients with metastatic or recurrent disease not amenable to surgery should receive chemotherapy – usually with a combination of cisplatin and 5-fluorouracil.

Responses are rarely complete and usually of short duration.

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.

## level 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

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## appendix I

### TNM staging

(NB Nodal N stage differs in anal margin and anal canal.)

| | |
|---|---|
| Tx | Primary tumour cannot be assessed |
| Tis | Carcinoma *in situ* |
| T1 | Tumour 2 cm or less |
| 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 – anal canal |
| | Regional node metastasis – anal margin |
| N2 | Metastasis in unilateral internal iliac and/or inguinal nodes – anal canal |
| | (No N2 for anal margin) |
| N3 | Metastasis in perirectal and/or bilateral internal iliac or inguinal nodes – anal canal |
| | (No N3 for anal margin) |
| M0 | No metastasis |
| M1 | Metastasis present |

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