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Anal carcinoma

80% of anal cancers are squamous cell carcinomas (SCCs). Other tumour types include melanoma, lymphoma and adenocarcinoma. Tumour behaviour depends on the anatomical site of the primary cancer:

- **Anal margin tumours**: are usually well differentiated. They are more common in men and have a good prognosis.
- **Anal canal tumours**: are usually poorly differentiated. They are more common in women and have a worse prognosis.

The anal canal extends from the anorectal junction to the anal margin. The dentate line marks the junction between squamous and mucosal epithelium in the anal canal. Immediately above the dentate line there is a zone of transitional epithelium. Below the dentate line, the canal is lined by non-keratinising squamous epithelium, which merges with the perianal skin. The anal margin is the pigmented skin immediately surrounding the anal orifice.[1]

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.[1]

How common is anal cancer? (Epidemiology)[2]

- Anal cancer accounts for less than 1% of all new cancer cases in the UK (2016-2018).
- Incidence rates for anal cancer in the UK are highest in people aged 80 to 84. Each year 25% of all new anal cancer cases in the UK are diagnosed in people aged 75 and over (2016-2018).

- Since the early 1990s, anal cancer incidence rates have increased by 76% in the UK. Rates in females have increased by 117%, and rates in males have increased by 26% (2016-2018).
- Anal cancer incidence rates are projected to rise by 14% in the UK between 2023-2025 and 2038-2040.
- Anal cancer incidence rates in England in females are 60% higher in the most deprived quintile compared with the least, and in males are 89% higher in the most deprived quintile compared with the least (2013-2017).

Risk factors[3] [4]

- Human papillomavirus (HPV): Squamous cell carcinoma of the anus is strongly associated with human papillomavirus (HPV) infection which represents the causative agent in 80-85% of patients (usually from HPV16 or HPV18 subtypes in Europe) as is its precursor lesion anal intraepithelial neoplasia (AIN).
- Anal intercourse and a high lifetime number of sexual partners increase the risk of HPV infection.[5]
- Anal carcinoma is more common in men who have sex with men.
- It is increased in HIV infection and in patients taking immunosuppressive drugs for HIV infection.
- Women with a history of cervical cancer or cervical intraepithelial neoplasia (CIN) are also known to have a greater risk for anal cancer.[6]
- Other important risk factors include immune suppression in transplant recipients, and cigarette smoking.

Screening[7] [8]

- Premalignant changes (AIN) occur.[9]
- Although randomised controlled trials evaluating screening and treatment outcomes are lacking, experts support routine screening for AIN in high-risk populations.

- AIN can be treated using topical therapies such as imiquimod, 5-flurouracil, and trichloroacetic acid, as well as ablative therapies such as electrocautery and laser therapy. Reductions in AIN and anal cancer rates have been shown in studies where high-risk populations were vaccinated against the oncogenic strains of HPV.

Anal cancer symptoms (presentation) [1]

- Presentation includes perianal pain and bleeding, a palpable lesion and faecal incontinence.
- Neglected tumours in women can cause a rectovaginal fistula.
- Tumours near the anal margin spread to the inguinal lymph nodes; those higher in the anal canal spread to the pelvic lymph nodes.

Editor's note
Dr Krishna Vakharia, 16th October 2023 **Suspected cancer: recognition and referral** [10] The National Institute for Health and Care Excellence (NICE) has recommended that a person should receive a diagnosis or ruling out of cancer within 28 days of being referred urgently by their GP for suspected cancer.

Investigations [1]

- Anal cancer guidelines state that a careful clinical examination, including a digital rectal examination (DRE), an anoscopic examination with biopsy, and palpation of inguinal nodes, is recommended for the assessment of T stage. [11]
- Imaging modalities used for staging include CT, MRI, endo-anal ultrasound and positron emission tomography (PET).
- Patients should be tested for relevant infections, including HIV, and other possible malignancies.

Staging[5]

The following is a staging system for anal canal cancer that has been described by the American Joint Committee on Cancer and the International Union Against Cancer. Tumours of the anal margin (below the anal verge and involving the perianal hair-bearing skin) are classified with skin tumours.

- 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.
    - T4: tumour of any size that invades adjacent organ(s) - for example, vagina, urethra, bladder (direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) - is not classified as T4).
- 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.

- Distant metastasis (M):
    - MX: distant metastasis cannot be assessed.
    - 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.

Anal cancer treatment and management[1] [3]

With a typical natural history of slow growth and a low rate of distant metastases, anal cancer is usually amenable to locoregional treatment.

- Local excision can be considered for small well-differentiated carcinomas of the anal margin.
- Primary chemoradiotherapy (CRT) results in a high level of disease control for small, early-stage SCC of the anal canal, with salvage surgery reserved for those who fail on this regimen.
- More advanced cancers still fare poorly with this treatment, and the disease relapses locoregionally in the majority of cases (30-50% of patients), resulting in an abdominoperineal resection.
- Current treatment recommendations are associated with substantial morbidity.
- Cytotoxic chemotherapy remains the standard of care for treatment-naïve patients with metastatic disease.

Radiotherapy

- Radiotherapy is given to the tumour and inguinal nodes.
- Radiation therapy alone may lead to a five-year survival rate in excess of 70%, although high doses may be required and cause necrosis or fibrosis.

Chemotherapy

- Chemotherapy concurrent with lower-dose radiation therapy has a five-year survival rate in excess of 70% with low levels of acute and chronic morbidity, and few patients requiring surgery for toxic effects (such as anal stenosis or anal necrosis).
- Radiation with continuous infusion of fluorouracil plus cisplatin is also under evaluation. However, the role of cisplatin in anal cancer is not currently clear.
- Metastatic disease is less responsive to combined chemotherapy and radiation treatment.
- HIV patients: patients with pre-treatment CD4 counts of less than 200 cells/mm^3 may have increased acute and late toxic effects and doses of radiation and chemotherapy drugs may need to be modified.

Surgery

- Surgery is required for:
    - Tumours that fail to respond to radiotherapy.
    - Large tumours causing gastrointestinal obstruction.
    - Small anal margin tumours without sphincter involvement.
- Standard salvage therapy for patients with residual disease following chemoradiotherapy has been abdominoperineal resection. Alternatively, patients may be treated with additional salvage chemoradiotherapy in the form of fluorouracil, cisplatin, and a radiation boost to potentially avoid permanent colostomy.
- Patients with anal cancer may require radical inguinal lymphadenectomy.

- NICE does not currently recommend endoscopic radical inguinal lymphadenectomy because of inadequate evidence of safety and efficacy. [12]

Complications

Complications of radiation therapy include anal ulcers, anal stenosis and necrosis.

Prognosis [2]

- 52.2% people diagnosed with anal cancer in England survive their disease for ten years or more.
- Ten-year survival in England is higher in females than males.
- 71.2% people in England diagnosed with anal cancer aged 15-44 survive their disease for ten years or more, compared with 32.3% of people diagnosed aged 75-99 (2013-2017).
- For anal cancer, like other cancer sites, survival trends reflect a combination of changes in treatment and stage distribution. These factors themselves can vary by age, sex and deprivation.

Prevention

HPV vaccination continues to be underutilised as a method of preventing HPV-associated cancers. [13]

Further reading

- Martini G, Arrichiello G, Borrelli C, et al; How I treat anal squamous cell carcinoma. ESMO Open. 2020 Sep;4(Suppl 2):e000711. doi: 10.1136/esmoopen-2020-000711.

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