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# SEOM clinical guidelines for the treatment of anal cancer

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**Abstract** Anal carcinoma is an uncommon disorder accounting for less than 2% of large bowel malignancies and 1–6% of anorectal tumours. Its incidence ranges between 0.5 and 1% per 100,000. Local staging should be done with MR imaging using an external pelvic phased-array coil. Treatment strategy should be optimally discussed in a multidisciplinary team. HIV-positive patients seem to achieve similar response rate and overall survival to HIV-negative patients but with increased toxicity and higher local recurrences. Combined modality treatment with irradiation and chemotherapy has resulted in complete response over 90% and local control over 85%. This guide gives recommendations for diagnosis, staging and treatment.

**Keywords** Anal canal · HIV · Staging · Multidisciplinary

## Introduction

Anal carcinoma is an uncommon disorder accounting for less than 2% of large bowel malignancies and 1–6% of anorectal tumours. Its incidence ranges between 0.5 and 1% per 100,000. Using polymerase chain reaction (PCR), the presence of the human papilloma virus (HPV) genome has been identified in 80–85% of cases. Infection with human immunodeficiency virus (HIV) augments HPV-associated anal disease in homosexual males [1] Combined modality treatment with irradiation and chemotherapy has resulted in complete response in over 90%, local control in over 85%, 60–65% sphincter preservation and 5-year overall survival rate between 60 and 65%.

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## Diagnosis and staging

Anal carcinoma originates between the anorectal junction above and the anal verge below. Suspicion should be established with a clinical history of bleeding, local pain, tenesmus and the presence of enlarged inguinal lymph nodes. Physical examination including digital rectal examination (DRE) and vaginal examination should determine the site and size of the primary tumour and nodal involvement. Careful clinical assessment of the inguinal nodes is important [2].

Biopsy of a suspicious lesion is mandatory. Clinically enlarged lymph nodes should be aspirated for cytologic diagnosis. The majority of anal cancers are squamous cell carcinoma. Local staging should be done with MR imaging [3] using an external pelvic phased-array coil. This technique provides optimal assessment of local extent and nodal involvement. Evaluation of tumour size and stage (see Table 1), tumour signal intensity on T2 weighted imaging, infiltration of adjacent structures (with special emphasis on anal sphincter and vagina, urethra and bladder infiltration) and nodal disease involvement should be defined before treatment, with MR imaging. A spiral thoraco-abdominal CT provides information to rule out metastatic spread.

## Treatment

Treatment strategy should be optimally discussed in a multidisciplinary team. Radiotherapy alone (50–60 Gy) is

**Table 1** Stage (defined by MR image)

| | |
|---|---|
| I | T1N0M0 |
| II | T2 or T3N0M0 |
| IIIA | T1-3N1 or T4N0M0 |
| IIIB | T4N1 or TxN2-3M0 |
| IV | TxNxM1 |

T1, tumour 2 cm or less in greatest dimension; T2, tumour more than 2 cm but not more than 5 cm without invasion of adjacent organs; T3, tumour more than 5 cm without invasion of adjacent organs; T4, tumour invading adjacent organs (urethra, vagina or bladder); *N0, no regional lymph nodes greater than 5 mm in maximum short axis diameter in the peri-rectal area or greater than 10 mm over the inguinal or iliac area; N1, metastases in peri-rectal lymph nodes; N2, metastases in inguinal or iliac lymph nodes; N3, metastases in peri-rectal and inguinal or bilateral iliac and inguinal lymph nodes; M1, distant metastases

*Nodes as defined by Koh et al. [3]

the standard therapy for patients with T1N0M0 anal canal cancer with a 5-year survival rate over 70–75% and local control over 80% [4, 5].

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. More extensive lesions will have a higher risk of nodal spread [2].

Two randomised studies showed that the administration of chemo-radiotherapy (CT-RT) with mitomycin-5-FU was better than RT alone in locally advanced disease (T2-4NxM0). The trial conducted by the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) randomised 585 patients to receive radiotherapy (45 Gy in 4–5 weeks) or the same RT regimen coupled with 5FU (1000 mg/m$^2$×4 days or 750 mg/m$^2$×5 days) for the first and last week of RT and mitomycin C 12 mg/m$^2$ on day 1. The 3-year local failure rate was 39% in the CT-RT arm vs. 61% with RT alone. There were no differences in the 3-year overall survival rate [6]. On the other hand, in the study conducted by EORTC, 110 patients were distributed to receive RT (45 Gy in 5 weeks, with an over-impression of 15 Gy in the patients with complete response (CR)) and 20 Gy if PR) or RT plus 5FU (750 mg/m$^2$ days 1–5 and 20–33) associated to mitomycin C (15 mg/m$^2$ on day 1). The CR rate was significantly greater in the group treated with CT-RT (80% vs. 54%). After 5 years of follow-up, there was still an 18% increase in the local control rate in favour of the group treated with CT-RT [7].

More recently, the preliminary results of a phase II CALGB trial were presented, suggesting that the administration of induction treatment with two cycles of cisplatin-5FU (cisplatin 100 mg/m$^2$ days 1 and 29 and 5FU 1000 mg/m$^2$ days 1–4 and 29–32) followed by chemo- and radiotherapy with 5FU and mitomycin was very promising, especially in patients with a poor prognosis, with 50% of patients colostomy- and disease-free at 48 months [8]. In a randomised study by the RTOG group (98-11), which included 682 patients, this strategy was compared with the classic concomitant chemo- and radiotherapy with 5FU (1000 mg/m$^2$ days 1–4 and 29–32) and mitomycin (10 mg/m$^2$ days 1 and 29). No differences in survival were found, but it was also detected that the colostomy rate was greater in the patients treated with the regimen containing cisplatin (HR 1.6; 95% CI: 1.008–2.63; $p$=0.04) [9]. The authors concluded that induction with cisplatin was not superior to the traditional administration of 5FU-mitomycin C with RT.

HIV-positive patients seem to achieve similar response rate and overall survival to HIV-negative patients but with increased toxicity and higher local recurrences (LR) at 2 years (>50% LR in HIV-positive vs. <20% LR in HIV-negative) [10]. It seems that HIV-positive patients with low CD4 cell counts (less than 200 cells/ml) specifically have a significant risk of toxicity [11]. In patients with important comorbidities, including HIV-positive patients and CD4 <200 cell counts/ml, radiotherapy alone (60 Gy) should be considered independently of the stage.

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. However, MRI can over-stage observed abnormalities and should be used in context with clinical findings. A new MR image should be done between 8 and 12 weeks after CT-RT. Decrease in tumour size, accompanied by reduction and stability of the MR T2 signal characteristics at 1 year, was associated with response. Radiological responses improved over time during the first 2 years after therapy. Biopsy resampling after therapy is subject to bias and it is recommended to be done after 8 weeks of therapy. However, the risk of radionecrosis should be borne in mind when considering biopsy. Disease can continue to regress for a period of many months following completion of CT-RT. Some of the indications for biopsy include new hard-edge ulcer, enlarging mass or increasing pain (ASCO guidelines). Following complete remission of disease, patients with a LR should be treated with an abdomino-perineal resection (APR) with a groin dissection if there is clinical evidence of inguinal node metastases and patients with a regional recurrence in the inguinal nodes can be treated with an inguinal node dissection, with consideration of RT with or without chemotherapy if limited prior RT to the groin was given.

Persistent disease is found in 10–15% of patients. Patients with macroscopic disease are candidates for APR, although salvage CT-RT can be sphincter-sparing despite initial failure to achieve a first-complete remission.

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, when re-excision is not feasible. Other indications are when radical surgery has been performed as primary treatment and the resection margin is involved.

ECOG PS should always be initially evaluated. Patients with ECOG PS 3–4 or unfit elderly patients should probably be treated with the best supportive care, including

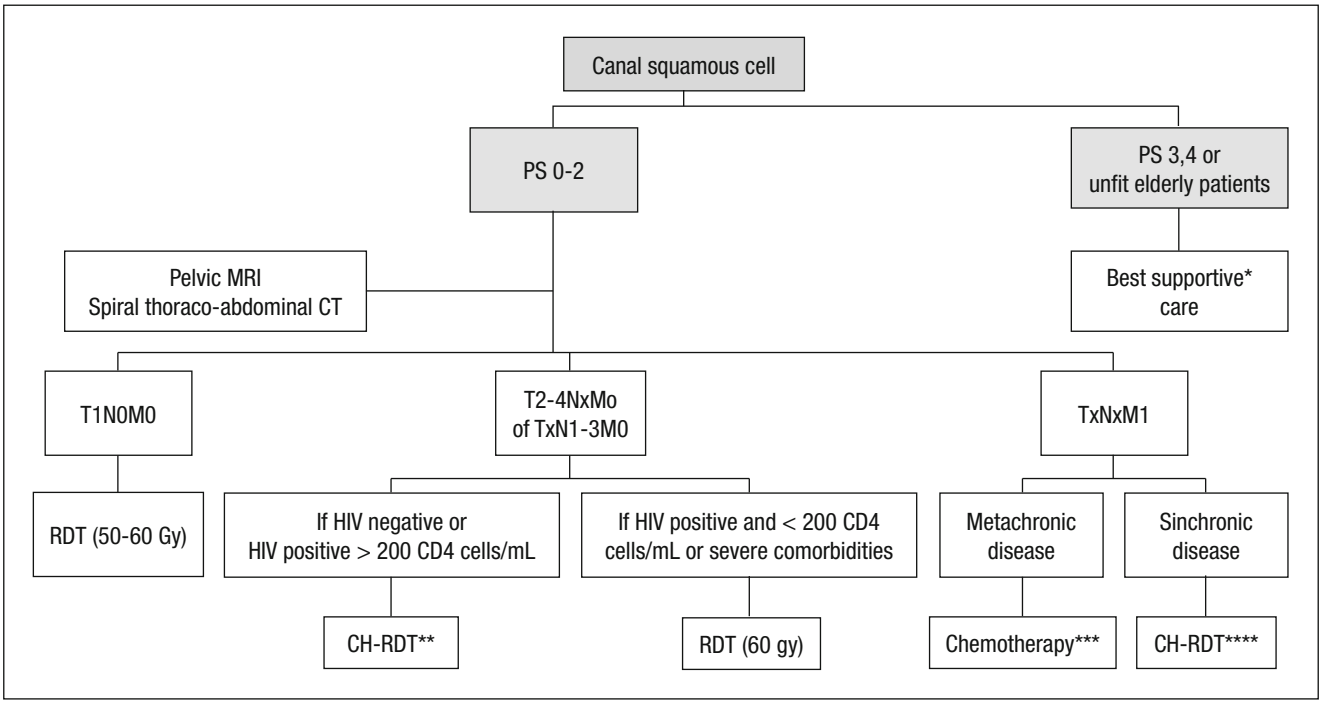


**Fig. 1** Treatment strategy

palliative radiotherapy in primary tumour. In synchronic metastatic patients, with conserved ECOG PS (0–2), full CT-RT followed by chemotherapy would probably provide better palliation than chemotherapy alone. In metachronic metastases, chemotherapy doublets with platinum and fluoropyrimidines are recommended, but median survival ranges between 7 and 10 months. Second-line strategies are investigational and include taxanes and anti-EGFR compounds (Figure 1).

## Follow-up

Patients in complete remission at 8–12 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 (ESMO guidelines).

A thoracic X-ray and a pelvic NMR should be considered annually for 3 years for patients with locally advanced disease (NCCN guidelines).

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

**Conflict of interest** The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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