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How I treat anal squamous cell carcinoma

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ABSTRACT

Squamous cell carcinoma of the anus (SCCA) is a rising health issue, strongly related to other relevant medical conditions such as (HIV) and human papillomavirus (HPV) infection. Correct assessment of patients with SCCA requires a multidisciplinary evaluation and adequate follow-up. Accurate local and systemic staging, as well as risk evaluation, are essential to optimal treatment planning. Early stage tumours can be definitively treated with a combination of chemotherapy and radiotherapy, while salvage surgery is usually reserved for patients who develop local recurrence. Distant recurrence and de novo metastatic disease are associated with poorer prognosis and require palliative systemic chemotherapy, with different single agent and combination options available. Finally, recent discoveries on the carcinogenesis of SCCA have allowed the development of innovative treatment options, the most promising being immune checkpoint inhibitors. The limited systemic treatments for SCCA and low incidence of the disease, together with insufficient data from clinical research could explain the poor outcomes of these patients, which should therefore be managed in high volume centres and enrolled in clinical trials whenever possible. This article summarises the main strategies for treating patients with SCCA.

INTRODUCTION

Anal cancer is a rare neoplasia, although its incidence has been increasing in the last decades, representing 3% of all gastrointestinal tract tumours and the 0.3% of the worldwide diagnoses of cancer.[1] Data from trials and large treatment series have shown a general improvement in survival in patients with anal cancer over the past three decades.[2] Squamous cell carcinoma of the anus (SCCA) is the most common histological subtype and is mostly attributable to human papillomavirus (HPV) infection, which represents the causative agent in 80%–85% of patients, with genotypes 16 and 18 being the most frequently involved.[3] The role of HPV infection as prognostic biomarker for SCCA has been investigated but not confirmed so far. To date, there are not standard screening programmes for anal cancer. In 2015, European Medicines Agency and Food and Drug Administration approved a vaccine for primary prevention from HPV-correlated cancers but it is still underused worldwide.[4]

Other risk factors include sexual practices that increase the risk of HPV transmission, HIV infection or other forms of immune suppression and cigarette smoking.

Eighty per cent to ninety per cent of patients presenting with locoregional disease and a good performance status could undergo definitive treatment, but 15% and 10% of patients develop local and distant recurrence, respectively.[5] Moreover, in about 10% of cases, patients have metastatic disease at the time of diagnosis, facing a particularly poor prognosis (5 years relative survival rate: 30%).[6] A specialised multidisciplinary approach involving medical oncologists, radiation oncologists, surgeons, radiologists and pathologists is, therefore, critically important for the optimal management of SCCA.

Assessment and treatment should be carried out in high volume centres.

CLINICAL APPROACH TO A PATIENT WITH ANAL CANCER

The clinical onset of SCCA is usually a combination of a mass, non-healing ulcer, pain, bleeding, discharge, faecal incontinence or fistulae, although in some cases SCCA could be asymptomatic; rarely patients present with inguinal lymphadenopathy.

Digital anorectal examination is essential to detect lesions in the anal area, but all suspicious anal lesions should be biopsied in order to achieve histological confirmation and rule out different types of malignancies (ie, adenocarcinoma, verrucous carcinoma). Immune-histochemical staining for p16 may be used as a surrogate marker for high-risk HPV infection, to predict prognosis and sensitivity to chemoradiotherapy. To this regard, a meta-analysis of 398 patients showed that HPV+/p16+ tumours have better prognosis compared with HPV– or p16– ones. Survival benefit was not demonstrated for HPV–/p16+ tumours which are not induced by HPV.[7] Other relevant and independent prognostic factors include, among others, male gender, lymph node involvement and tumour size. Three-year progression-free

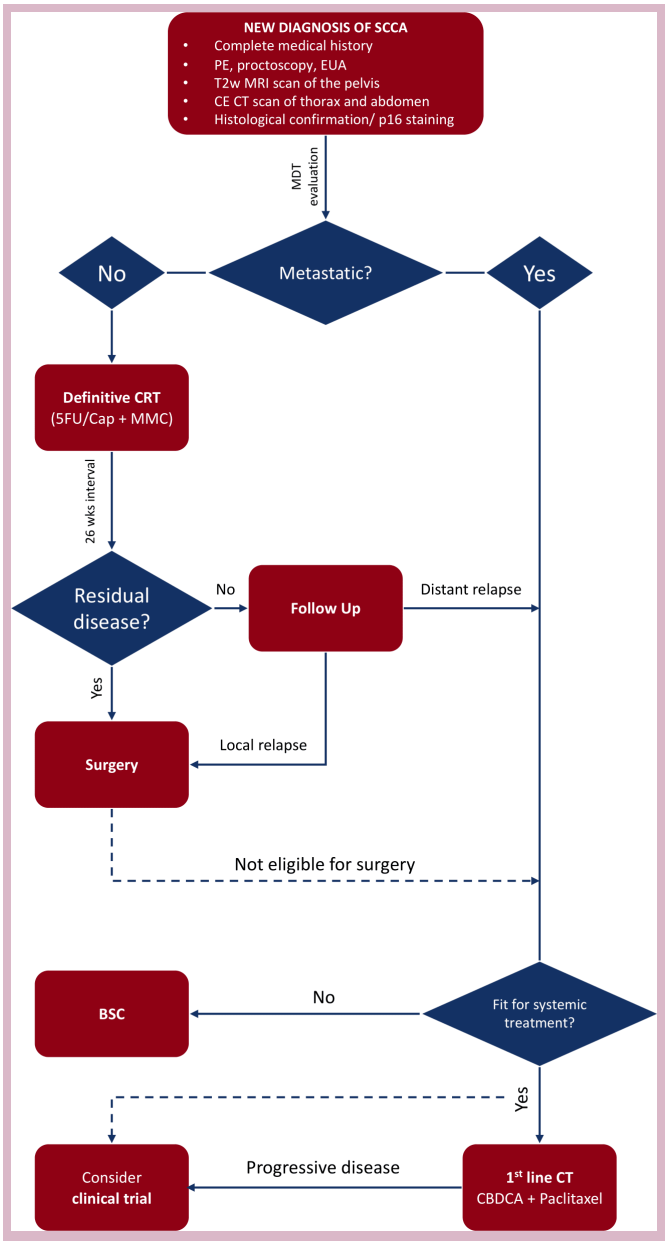

Figure 1 Algorithm for the management of newly diagnosed anal cancer. 5-FU, 5-fluorouracil; BSC, best supportive care; Cap, capecitabine; CBDCA, carboplatin; CE CT, contrast-enhanced CT; CRT, chemoradiotherapy; CT, chemotherapy; EUA, exam under anaesthesia; MDT, multidisciplinary team; MMC, mitomycin; PE, physical examination; SCAA, squamous cell carcinoma of the anus.

survival (PFS) rates range from 70%–80% to 60%–70% in localised (T1, T2, N0) and locally advanced cancers (T3, T4, N+), respectively.[8]

Clinical assessment should consist of a complete medical history and physical examination, with particular attention to inguinal lymph nodes palpation, as well as a gynaecological exam, to exclude genital involvement or the presence of a fistula. Proctoscopy with biopsy is indicated and might allow accurate clinical staging. In case of pain, examination under anaesthesia is recommended (figure 1).

Locoregional staging is usually achieved through T2-weighted MRI scan of the pelvis, to encompass areas of most frequent lymph node involvement (ie, inguinal, extern iliac, obturator, mesorectal). 18F-fluorodeoxyglucose positron emission Tomography-CT (PET-CT) scan and ultrasound-guided fine-needle aspiration can be used to further characterise suspicious lymph node lesions, such as subclinical pelvic, extra-pelvic and para-aortic nodes, an information necessary to define the radiotherapy (RT) planning.

Despite its role in staging and RT assessment, PET-CT scan has had a partial role in tumour response evaluation after chemoradiotherapy (CRT) because of variable results in terms of correct timing, deriving from small retrospective clinical trials. A unique prospective experience analysed pre-CRT and post-CRT PET-CT scan parameters of 19 patients, highlighting the potential role of PET-CT as a predictive biomarker of recurrence but clear conclusions should not be drawn due to the limit deriving from the small population in study.

Contrast-enhanced CT scan of the thorax, abdomen and pelvis is used to assess for potential metastatic disease at diagnosis and during follow-up.

The TNM staging classification should be reported according to the latest edition of the American Joint Committee on Cancer/Union for International Cancer Control guidelines and staging manual.

A fundamental role in the risk assessment of SCCA is represented by the HIV infection. HIV testing should be considered for those patients with a lifestyle that could increase the risk of contracting the virus and could be taken into account also for all patients with SCCA with unknown HIV status.

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

The principal treatment goals comprise locoregional control and anal function preservation.

Standard of care are combinations of 5fluorouracil (5-FU)-based CRT and other cytotoxic agents (mainly mitomycin C (MMC) and cisplatin (CDDP) that can lead to complete tumour regression in 80%–90% of patients (figure 1).

The role of CRT has been validated by early randomised trials, showing superiority to RT alone.[9]

The phase III RTOG 87-04 trial confirmed the superiority of the combination of MMC and 5-FU over 5-FU alone,[10] while several trials investigating the role of CDDP as a replacement for MMC failed to show an improvement in local control, disease-free survival or overall toxicity.[11] The same trials also did not demonstrate any benefit deriving from either neoadjuvant or maintenance chemotherapy (CT), which are therefore not recommended outside of clinical trials.

The recommended dose for 5-FU is 1000 mg/m^2 days 1–4 and 29–32 of RT, while for MMC is either 12 mg/m^2 (maximum dose 20 mg) day 1 or 10 mg/m^2 (maximum dose 20 mg) days 1 and 29. In recent years, several case

series have shown that capecitabine can be used instead of 5-FU at the dose of 825 mg/m^2 twice/day, 5 days per week, during RT.

The optimal radiation dose is still controversial, but doses of at least 45–50 Gy in 1.8–2.0 Gy fractions are recommended for T1-2 N0 tumours. Regarding more advanced tumours (ie, T3-4, N+), the PersonaLising Anal cancer radioTherapy dOse (PLATO) umbrella trial, comprising the ACT3, ACT4 and ACT5 trials, is currently investigating personalised RT approaches adapted to different stages and will provide more definitive answers on this issue.

Regarding HIV+ patients with SCCA, before the use of highly active antiretroviral treatment (HAART), there was a tendency in considering this subgroup of patients more susceptible of CRT toxicity and different approaches including a dose reduction or treatment breaks have been considered by clinicians, causing lower survival rates. These patients were excluded from randomised clinical trials and evidence of worse outcomes derived from very small studies. Recently, similar outcomes for HIV+ patients that receive HAART, with CD4 count <200, compared with HIV− patients have been described.[12] Undoubtedly, further prospective research in this field is necessary, to better define treatment for HIV+ patients in which the incidence of SCCA is 40–80 times higher than HIV− population.

While CRT has replaced in most anal cancers the radical abdomino-perineal excision, indications for upfront surgery may remain valid when curative RT cannot be administered (ie, previous pelvic RT).

Local excision may represent a valid treatment option for early anal margin cancers located on the pigmented skin extended within 5 cm from the anal verge; nevertheless, these tumours are highly radiosensitive and should be considered for definitive CRT, especially when a histological clearance of >1 mm cannot be achieved. In the case of early stage cancers located in the anal canal, local excision, as well as piecemeal resection, is contraindicated due to an unacceptably high proportion of margin positive resections and inadequate staging. Moreover, if the patient received a local excision, postoperative CRT should be considered, although it is associated with considerable morbidity to the anal sphincter.

Anal cancers tend to regress slowly after completion of CRT treatment. Careful clinical inspection and imaging evaluation (with pelvic MRI and CT scans) are necessary to detect recurrent/residual disease, with the optimal timepoint for response assessment at approximately 26 weeks from treatment completion.[13] There is no indication for a biopsy before this timepoint as its result would not change the strategy to wait until 6 months from CRT completion.

If residual or recurrent disease is histologically confirmed after 6 months, salvage surgery through extra-levator abdomino-perineal excision is recommended. Patients not amenable for salvage surgery should be treated as those with advanced or metastatic disease (figure 1).

MANAGEMENT OF ADVANCED/METASTATIC DISEASE

Systemic chemotherapy (CT) is recommended for this group of patients; however, optimal CT regimen and management have not been well established. Several small case series showed efficacy in favour of the combination of CDDP and 5-FU, as well as activity for carboplatin (CBDCA), doxorubicin, taxanes and irinotecan±cetuximab, either alone or in combination, to be selected based on previous treatment, disease-free interval and patient's preference. However, some of these analyses were limited to treatment-naïve patients, with no information about patients with recurrence from a systemic CRT treatment. Results from a phase II study reported a 65% overall response rate (ORR) with the combination of 5-FU/CBDCA and paclitaxel but only four patients had a metastatic SCCA[14] while a more recent phase II trial explored the combination of modified 5-FU/cisplatin and docetaxel (modified DCF), with favourable outcome data, even if not enough to define DCF as a standard of care in metastatic SCCA.[15]

No randomised clinical trials have been conducted so far for metastatic SCCA, except for the recent prospective InterAAct study. The InterAAct international multicentre phase II randomised controlled trial investigated the combination of CBDCA and weekly paclitaxel to be superior to the one of CDDP and 5-FU. The trial recruited a total of 91 patients between December 2013 and November 2017.[16] The results of the trial demonstrated similar results with CBDCA/paclitaxel combination in terms of ORR (59% vs 57%), compared with CDDP/5-FU. Secondary survival end points were PFS (8.1 vs 5.7 months, p=0.375) and overall survival (OS) (20 vs 12.3 months, HR 2.0, p=0.014), both of which were longer with CBDCA/paclitaxel, compared with CDDP/5-FU. The toxicity profile was better with CBDCA/paclitaxel combination (36% of serious adverse events (SAE) vs 62% of CDDP/5-FU (p=0.0016), supporting the combination of CBDCA and weekly paclitaxel as a new standard of care in CT-naïve advanced SCCA (figure 1).

INNOVATIVE STRATEGIES

Due to biologic implications, immunotherapy strategies for SCCA have been actively studied in the last years. Programmed death-1 checkpoint inhibitors nivolumab and pembrolizumab have shown promising activity in heavily pretreated advanced SCCA. A phase II trial (NCI9673) with nivolumab as single agent provided a 24% ORR, median duration of response of 5.8 months among responders, PFS of 4.1 months and OS of 11.5 months. Interestingly, programmed death-ligand 1 (PD-L1) expression was high among responders, compared with non-responders, even if the results are limited by the small number of population. Data from pembrolizumab therapy in the same setting deriving from the phase IB

KEYNOTE-028 trial were promising, too (17% ORR, 3 months PFS and 9.3 months OS).[17 18]

Based on these premises, nivolumab and pembrolizumab are now approved by the FDA in the treatment of patients with advanced SCCA that progressed to CT.

Recently, combinations of immune checkpoint inhibitors and RT, inducing cell death, have been considered because of the potential role to reinvigorate immunotherapy response and modulate CD8+ tumour infiltrating lymphocytes (TILs) in SCCA.[19] In patients with HPV infection, viral proteins E6 and E7 are able to promote recruitment of TILs and to trigger activation of anticancer immune response. A retrospective analysis of patients treated with CRT with curative intent, stratified for p16 expression demonstrated that tumours with high TILs presented a 92% relapse-free survival (RFS) rate compared with 63% in patients with absent or low TILs, highlighting the role of TILs as a prognostic biomarker, to stratify outcomes for HPV+/P16+population.[20]

Future approaches include the use of TILs, genetically engineered T-cell therapy and *Listeria*-based immune vaccines against E6 and E7 oncoproteins in patients with HPV+ SCCA.

Furthermore, there is accumulating evidence that up to 60% of both HPV-related and HPV-unrelated SCCA might be driven by alterations in the phosphatidylinositol 3-kinase-protein kinase B/mammalian target of rapamycin pathway, which could therefore represent a possible relevant target for future therapeutic interventions.[21]

ONGOING TRIALS

Given the positive results with innovative immunotherapy treatments, several strategies are currently under investigation such as the use of immune checkpoint inhibitors as single agents or in combinations. A clinical study is recruiting patients with refractory metastatic SCCA to receive nivolumab alone or in combination with anticytotoxic T-lymphocyte-associated protein 4 ipilimumab while another strategy is exploring the combination of atezolizumab with CT (NCT03519295). The use of immunotherapy is also currently investigated in high-risk stage II–IIIB anal cancer, after CRT (NCT03233711).

Furthermore, a combination approach with cetuximab and anti-PD-L1 avelumab is underway (NCT03944252).

CONCLUSIONS

Patients with SCCA should always be discussed in a multidisciplinary setting, owing to the multiple professional figures essential to adequate treatment.

Despite progress made in managing this disease, considerable heterogeneity remains in terms of outcomes, particularly for more advanced stages in which data from clinical trials are still insufficient for the small number of patients. Therefore, it is advisable that these patients be managed in high volume centres and enrolled in clinical trials, whenever possible.

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