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Review Article

# Treatment of Anal Carcinoma – A Review of the Literature

**Manuela Machado, Maria Leitão, Bárbara de Castro, Olga Sousa, Dora Gomes**

1. Medical Oncology Department, IPO Porto, Portugal
2. Radiation Oncology Department, IPO Porto, Portugal

**Corresponding author:** Manuela Machado, Medical Oncology Department, IPO Porto, Portugal

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**Abstract**

Anal carcinoma is a rare but clinically challenging malignancy. In the last few decades, important steps have been taken towards a better understanding of the pathogenesis and thus adequate treatment of this disease. Method A review of the literature on the treatment of anal carcinoma was carried out using PubMed and the most relevant articles were selected. Discussion The majority of these tumors are diagnosed as a locoregional disease, for which the mainstay of treatment is chemoradiation. The association of 5-FU and mitomycin remains the preferred regimen since other combinations have proved less optimal in comparison. The use of IMRT is highly encouraged as a means to decrease toxicity and improve treatment tolerability. There is scarce data on metastatic anal carcinoma, the most used regimens being carboplatin plus paclitaxel (the regimen with more robust evidence) and cisplatin plus 5-FU.Conclusion Many open issues remain in this disease; more phase III trials are needed in order to improve the quality of life and survival of this population.

## Introduction

Anal carcinoma is considered a rare tumour, accounting for 1.5% of the digestive tract tumours [1]. Historically, incidence is higher in women, but it seems to be increasing in both sexes, especially in males [2]. The most common histology is squamous cell carcinoma, which will be the focus of this review. Adenocarcinoma in this location should be managed according to the principles of rectal cancer and melanoma should be treated as such.

The last few decades have witnessed an important evolution in the understanding of the pathogenesis and adequate treatment of this entity.

Several risk factors have been described for anal carcinoma, including HPV and HIV infection, history of sexually transmitted diseases, history of anal intercourse, previous HPV-related gynecological cancers (vulvar, cervical and vaginal cancer), immunosuppressive disorders and tobacco smoking [1-6]. The usual clinical presentation is rectal bleeding, but mass sensation and/or pain can also be described [7].Staging should follow the 8th AJCC TNM classification and is mostly done clinically. Prognosis is determined mainly by the size of the tumour and involvement of lymphatic nodes, with tumours above 5cm in diameter carrying a worse prognosis [1-8]. Positivity for HPV and/or p16 are predictive of higher local tumour control and better overall survival (OS) [9].

These tumours are very responsive to chemoradiation (CRT), which is the main treatment of localized tumours, allowing organ preservation and high rates of local control and overall survival. Only a minority (around 15%) of patients present with metastized disease at the time of diagnosis and therapeutic options are limited [10,11].

### Methods

A review of the existing literature on the treatment anal carcinoma was carried out using PubMed and the most important and informative articles were selected, with special attention to existing phase III clinical trials.

### Discussion

#### Approach for non-metastatic anal carcinoma

In the past, treatment for anal carcinoma was primarily surgical in the form of abdominal perineal resection (APR). This technique resulted in high morbidity, frequent local recurrence and increased mortality, with reported OS at five-years between 40-70% [1-12].

In the 70s, the first reports of pre-operative CRT for anal carcinoma found interesting rates of tumour regression with a combination of 5-FU and mitomycin or porfiromycin, concurrent with pre-operative doses of radiation (30 Gy delivered in 15 fractions to the pelvis, medial nodes and anal canal).11 Multiple subsequent clinical trials have proved CRT without surgery to be the best treatment for anal carcinoma [13].

In 1997, the randomized clinical trial UKCCCR Anal Cancer Trial I (ACT I) established the advantage of CRT (45 Gy in 20 or 25 fractions plus a 15 Gy to 25 Gy boost) with 5-FU and mitomycin when compared to RT alone, by reducing the risk of local failure with little increase in acute side effects [14]. These findings were confirmed in a follow-up analysis conduct-

ed 13-years after treatment, with a median survival in the CRT arm 2.2 years above the RT alone arm [15].

In the following trials, various combinations of anti-neoplastic agents were tested against the standard 5-FU and mitomycin. The phase III Intergroup trial proved the superiority of the latter combination when compared to CRT with 5-FU alone, with improved 4 year disease free survival (DFS) (73 versus (Vs) 51%, p=0.0003) and improved colostomy rate (9 vs 22%, p=0.002), although at the cost of significantly higher Grade 4 and 5 acute toxicity. In this trial, patients with residual disease were treated with salvage CRT with 5-FU and cisplatin, after which 50% were free of disease [16].

The multicentric phase III ACT II trial randomized patients to CRT with 5-FU and mitomycin or 5-FU and cisplatin and then further randomized to maintenance therapy with 2 cycles of 5-FU and cisplatin or no maintenance therapy. Radiotherapy was performed on a continuous schedule at the dose of 50.4 Gy. The primary treatment arms showed no difference in complete response rate, progression free survival (PFS) or colostomy rate and there was no difference in the 3-year PFS with the addition of maintenance treatment [17].

Ajani et al compared CRT with 5-FU and mitomycin versus CRT with 5-FU and cisplatin in the RTOG 98-11 phase III trial. The platin-based arm did not improve DFS and demonstrated a worsening of the cumulative colostomy rate (15 vs 10%, p=0.02). In the long-term update of the trial results, CTR with 5-FU and mitomycin improved 5-year OS and DFS with statistical significance. However, the cisplatin arm included induction therapy, that was not contemplated in the mitomycin arm – this incongruence means that the pharmacological agent used was not the only differentiating factor between the two groups [18,19].

The possibility of chemotherapy (CT) with a triplet (mitomycin C, 5-FU and cisplatin) followed by maintenance with the same drugs was explored in a phase II trial, with reasonable OS results, but rejected due to increased toxicity and lowered compliance to treatment [20].The addition of cetuximab to CT has been evaluated in multiple trials, without added benefit and higher frequency of serious side effects [21-23].Capecitabine may also be used instead of 5-FU, according to phase II trials and retrospective studies [24,25].

In light of these positive and negative findings, CRT with 5-FU and mitomycin remained the preferred regimen, with apparently no role for systematic induction or maintenance chemotherapy.

The lack of benefit of induction chemotherapy before CRT was cemented by the UNICANCER ACCORD 03 trial [26]. The exception might be T4 tumours, which may benefit from neoadjuvant treatment (5FU plus cisplatin) with lower colostomy rates [27]. In the ACCORD 03 study, intensification of the radiation boost to 20-25 Gy (total dose of 65-70 Gy) vs 15 Gy (total dose of 60 Gy) was also tested and proved not to have a significant effect on tumour response, although there was a suggestion of better 3-year colostomy-free survival. In fact, total radiation doses above 59 Gy have proved to be detrimental in earlier trials [28], at least with ancient radiation techniques.

Intensity-modulated radiation therapy (IMRT) allows for beam shaping and has proven to be particularly useful in irregular pelvic treatment volumes, such as those of anal carcinomas. The conformality of this technique is believed to minimize dose to the pelvic organs at risk, such as bladder and small bowel. In the RTOG 0529 Phase II, dose painting IMRT was used, enabling a differential dose to cT2N0 tumours [50.4 Gy to the Planned Tumour Volume (PTV) and 42 Gy to elective nodal areas] vs cT3-T4 N0-3 (54 Gy to the primary tumour and > 3cm nodes, 50.4 Gy to ≤ 3cm nodes and 45 Gy to elective nodal areas) [29], Comparing with patients from RTOG 98-11 study, there was a significant reduction in Grade 3 genitourinary and dermatological and Grade 2 hematological acute toxicities; moreover, some reproductions of this study have showed clinical complete responses of 92% at 49 months of median follow-up. The use of IMRT also proved to reduce toxicity-related interruptions, which may be responsible to some extent for the increased local control associated with the use of this technique [30].

Although the acute side effects of pelvic irradiation with concurrent CT can be sometimes limiting, it is also important to discuss potential long-term adverse events with patients, especially given the high probability of cure of this disease. Typically, these events develop within 2 years of treatment.

Telangiectasias may occur as asymptomatic or minimally symptomatic intermittent bleeding from bladder or anorectal mucosa. Fibrosis of the irradiated subcutaneous tissue is also common and may result in anal or vaginal stenosis. Rectal symptoms, such as increased stool frequency, fecal incontinence and rectal urgency are among the most reported ones, resulting in a significant reduction in the quality of life of these patients [31]. Elderly patients, especially in those with osteoporosis and those treated with ancient radiotherapy techniques, may be at risk for femoral head and neck fracture. Sexual disfunction may manifest both in men and women, the latter mainly as dyspareunia [32]. As with any form of pelvic irradiation, the likelihood of infertility and menopause should be addressed, and proper referral to a specialist should be arranged.

Severe late effects, present in 10-15% of patients, are described as those requiring surgical intervention and may include bowel obstruction, chronic diarrhea, anal incontinence, chronic pelvic pain and fistulae.25 The need of a permanent colostomy, occurring in 2-12% of patients, is usually used as an endpoint to evaluate the efficacy of CRT, not only as an indirect measure of local recurrence resulting in an AAP, but also as an indicator of severe late toxicity [33].

Late radiation side effects are more likely when daily fractions of more than 2 Gy are used. The recent trends in decreased use of dose escalation and increased use of IMRT may reduce the frequency of these long-term adverse events typically associated with CRT [34].

**Approach for metastatic anal carcinoma**

There is a paucity of data on the ideal treatment for patients with M1 anal carcinoma, with few phase III trials conducted to date. This scarcity is partly explained by the fact that anal carcinoma is an uncommon disease that is seldom diagnosed in a metastatic stage, which carries a poor prognosis.

There is no standard for the first line of treatment, but choice of regimen should be tailored to the previous CRT treatment (if any) – the drugs used and the time since elapsed. Similarly to the

therapy for localized disease, there is some evidence to the use of cisplatin plus 5-FU [35].

The InterAACT phase II trial, published in 2018, compared cisplatin (60 mg/m2 D1q21) plus 5-FU (1000 mg/m2/24h D1-4q21) to carboplatin (AUC 5, D1q28) plus paclitaxel (80 mg/m2, D1-8-15q28) in the first line of treatment. Both arms revealed similar response rates and non-statistically significant differences in PFS, with OS favouring carboplatin/paclitaxel (OS 12.3 months vs 20 months, HR 2.0 p = 0.014) and lower rate of serious adverse events (62% vs 36%, p = 0.016) [36].

There are older or single-arm trials and retrospective studies on the use of FOLFOX, 5-FU in monotherapy and DCF, but no definite results were obtained.

In the second-line, a phase II single-arm study with nivolumab achieved a response rate of 24% (with two complete responses) and a phase Ib trial with pembrolizumab (KEYNOTE-028) in PD-L1 positive tumors showed a response rate of 17% [37,38].

## Conclusion

From the 70s until the 90s, important advancements were made in the realm of treatment for anal carcinoma, which constitutes a mostly curable illness nowadays. Locoregional disease is greatly controlled with chemoradiation, preferably a fluoropyrimidine plus mitomycin regimen in association with a IMRT technique when available.

Research is needed in this partly forgotten pathology, in order to minimize side effects of treatment and improve long-term quality of life. More trials are in demand in the metastatic setting, where data is scarce and the prognosis is still dim.

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