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MINI REVIEW

Squamous-cell carcinoma of the anal canal: Room for improvement with targeted therapy

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Summary Carcinoma of the anal canal is a rare disease accounting for 1—5% of gastrointestinal tract malignancies. However, its incidence is increasing worldwide. Chemoradiation is the standard treatment for most patients with squamous-cell carcinoma of the anal canal and was first described by Nigro et al. Since then, no other effective treatment was developed. Patients with metastatic disease should be considered candidates for clinical trials. New treatment strategies, including molecular target therapies, are warranted in order to improve disease control. Despite the rarity of this disease, it is urgent to improve its treatment by introducing targeted therapy in the arena.

Background

Carcinoma of the anal canal is a rare disease accounting for 1—5% of gastrointestinal tract malignancies. However, its incidence is increasing worldwide. Squamous-cell carcinoma (SCC) is the most frequent histology among tumors, comprising up to 80 to 85% of all lesions [1]. Epidemiological data suggests that main risk factors for anal cancer are history of persistent high-risk genotype human papillomavirus infection, HIV infection, cigarette smoking, anoreceptive intercourse and immunosupression following solid organ transplant [2].

Staging

The staging system used for anal canal cancer has been described by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer [3]. Tumors of the anal margin (below the anal verge and involving the perianal hair-bearing skin) are biologically similar to skin tumors and follow the same classification [3,4].

Clinical examination determines the size of the tumor. Inspection, palpation and biopsy of the primary tumor should be performed and when necessary biopsy of suspicious regional lymph nodes. Computed tomography (CT) of the chest, CT or MRI of the abdomen and pelvis should be done to complete staging. PET-CT scan may improve sensitivity for detecting lymph nodes metastases and should be performed if available. Winton et al. published a small study with 61 patients and demonstrated that sensitivity

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for nodal regional disease was 89% for PET-CT and 62% for conventional imaging methods [5].

The European Organization for Research and Treatment of Cancer (EORTC) phase 3 study showed that skin ulceration, nodal involvement and sex were the most important prognostic factors for local control and survival [6]. Results from the intergroup Trial RTOG 98-11, which included 644 patients, demonstrated that tumor diameter > 5 cm was associated with poorer 5-year disease—free survival ($P = 0.0003$) and poorer 5-year overall survival ($P = 0.0031$) in multivariate analysis. This study also confirmed positive lymph nodes and male sex as poor prognostic factors [7].

Treatment overview

Chemoradiation is the standard treatment for most patients with SCC of the anal canal and was first described by Nigro et al. in 1974 [8]. In their study, patients were treated with radiation therapy with concurrent 5-fluorouracil and mitomycin C. Clinical complete response to chemoradiation was observed in 86% of patients. After this, abdominoperineal resection was reserved for treatment failure after combined chemoradiation.

Patients with superficial (Tis-T1N0) and well-differentiated tumors may be treated with local resection. However, if there is involvement of the anal sphincter, the patient should receive external-beam radiation therapy with or without chemotherapy.

Patients with stage II and III should be treated with radiation therapy plus chemotherapy based on 5-fluorouracil and mitomycin C. Two randomized trials showed that concurrent chemoradiation was superior to radiation therapy alone as definitive treatment for anal cancer. The United Kingdom Coordinating Committee on Cancer Research (UKCCR) performed a trial with 585 patients who were randomized between radiation alone versus radiation plus chemotherapy. Local failure was observed in 59% of the patients in the radiotherapy (RT) arm compared to 36% in the combined modality therapy (CMT), representing a 46% reduction risk of local failure for CMT (relative risk 0·54, 95% CI 0.42—0.69, $P < 0.0001$) [9]. However, overall survival was similar between the two arms. The EORTC conducted a phase III trial to evaluate RT with or without concomitant infusional 5-FU plus mitomycin [6]. Patients in the chemoradiation arm had a higher rate of complete remission compared to RT alone; 80% for RT and chemotherapy and 54% for RT alone. This resulted in a significant improvement of locoregional control and colostomy-free interval ($P = 0.02$ and $P = 0.002$, respectively) favoring combined modality treatment. Colostomy-free rate was also in favour of chemoradiation and increased by 32% with the addition of chemotherapy to RT. The locoregional control improved by 18% at 5 years for the combined treatment. It was also observed a better progression-free survival for this group ($P = 0.05$). However, no improvement in overall survival was observed for the combined treatment group.

After these trials, Flam et al. conducted a phase III randomized trial to evaluate the importance of mitomycin in the standard chemoradiation regimen [10]. Three hundred and ten patients were randomized to RT and fluorouracil or RT, 5-FU and mitomycin. At 4 years of follow-up, colostomy rates were lower (9% versus 22%; $P = 0.002$), colostomy-free survival higher (71% v 59%; $P = 0.014$), and disease-free survival higher (73% versus 51%; $P = 0.0003$) in the mitomycin arm. Meanwhile there was no significant difference in overall survival at 4 years with the addition of mitomycin for chemoradiation regimens. These results justified the use of mitomycin in chemoradiation treatment.

Alternative regimens, including cisplatin, were evaluated in this disease. The Intergroup RTOG 98-11 trial was designed to compare fluorouracil plus cisplatin induction chemotherapy followed by the same chemotherapy and concurrent radiation and fluorouracil plus mitomycin and concurrent radiation [11]. A total of 644 patients were assessable and the study showed that cisplatin-based therapy failed to improve disease-free survival compared to mitomycin-based therapy. The disease-free survival rate was 60% (95% CI, 53—67%) in the mitomycin-based group and 54% (95% CI, 46—60%) in the cisplatin-based group ($P = 0.17$). Colostomy-free survival was also better for mitomycin-based group.

The optimal schedule and dose of RT for anal carcinoma continue to be investigated. Some studies, including RTOG 98-11 showed that administration of higher radiation doses in the treatment of anal carcinoma could improve local-regional disease control. In a retrospective review of 50 patients with anal cancer treated with concurrent 5-FU, mitomycin, and radiation, it was observed that doses of $\geq$ 54 Gy were associated with improved 5-year survival (84 vs. 47%, $P = 0.02$), disease-free survival (74 v. 56%, $P = 0.09$), and local control (77 vs. 61%, $P = 0.04$). Overall, treatment time of less than 40 days was associated with a trend towards improved outcome, but this was not statistically significant [12]. There is evidence that treatment interruptions can interfere in treatment effectiveness [13].

Standard dose recommendations with conventional external beam RT range from 45 Gy for early lesions to 59.4 Gy for T2—T4 disease. Response rate is associated with tumor T stage in multivariate analysis. T3 and T4 tumors have lower response rates, so in these cases, some advocated intensification of treatment [14].

Long-term results of the RTOG 92-08 trial and ACCORD-03 trial, which compared radiation dose-escalation from 60 Gy to 65—70 Gy, did not confirm that radiation dose escalation within concurrent chemoradiation schedule can increase local control in anal cancer. This could be explained by dose-limiting toxicities in normal tissues, which outweigh any potential tumoricidal advantages from higher radiation doses [15,16].

Regarding the role of brachytherapy, a small study including 31 patients with T3 and T4 anal carcinoma treated with combined external beam (EBRT) and chemotherapy, followed by interstitial (192)Ir implant boost showed that this treatment was well tolerated, with acceptable toxicity. However, brachytherapy use requires skill and expertise to avoid complications [17].

Advanced radiation delivery techniques can reduce treatment-associated toxicity. Intensity-modulated radiotherapy (IMRT) enables the delivery of complex radiation therapy sparing critical normal tissue, which is crucial in the treatment of anal canal carcinoma with concurrent chemoradiation. IMRT has been associated with reduced acute toxicity for anal cancer.