Anal Squamous Cell Carcinoma

Subjects: Oncology

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Anal squamous cell carcinoma (ASCC) is a rare malignancy, with most cases associated with human papilloma virus and an increased incidence in immunocompromised patients.

Keywords: anal squamous cell carcinoma ; human papillomavirus ; chemoradiotherapy

1. Introduction

Squamous cell carcinoma is the most common malignant histologic subtype affecting the anal canal (ASCC). The anal canal anatomically occurs between the anorectal junction proximally and the anal verge distally and is approximately 3–5 cm in length. The transitional zone between the columnar epithelium of the rectum and the unkeratinized squamous cells of the anal mucosa, and proximal to the dentate line, is the site of most cases of ASCC [1]. Etiologically, the vast majority of cases are associated with human papilloma virus (HPV) infection and its incidence is significantly elevated in immunocompromised patients [2][3]. There were about 8300 new cases of cancer involving the anus in the United States in 2019. While ASCC is rare, making up only 2.5% of gastrointestinal malignancies, its incidence continues to increase [4]. Social stigma, rarity of the disease and associated lack of research funding have contributed to under-recognition of the malignancy and hampered progress in its management.

2. Chemotherapy for Locoregional Disease

Historically, standard of care for invasive ASCC was abdominal perineal resection (APR). Given it involves removal of the anorectum, APR requires a permanent colostomy. Even accepting such morbidity, five-year survival after APR only ranges between 40% and 70% [5][6]. However, in 1974, three case reports published by Nigro et al. proved influential in making chemoradiation standard of care. Two patients received chemoradiation with 5-fluorouracil (5-FU) and mitomycin C (or poriferomycin), while one received radiation alone. Tumor regression was seen in all three cases with no evidence of residual disease appreciated on subsequent surgical resection. One patient refused APR and reportedly remained disease-free [7]. Such observations suggested chemoradiation could potentially obviate surgical resection and its associated morbidity. This was validated in later prospective studies [8][9][10]. A summary of landmark study results in the management of locoregional ASCC is provided in Table 1. An EORTC trial in 1997 was one of the first randomized phase III trials investigating 5-FU and mitomycin with concomitant radiation for a five-week treatment course vs. radiation alone in patients with locally advanced anal cancer. The trial enrolled 110 patients randomized between the two arms. Results confirmed the role of multimodality treatment with chemoradiation in conferring significantly increased complete response (CR) rates, lower locoregional recurrence rates, higher locoregional control, and longer colostomy-free interval [9]. Similarly, the larger ACT I phase III study also compared radiation or chemoradiation arms. This confirmed the superiority of chemoradiation as it conferred reduced local failure rate [10], while median overall survival (OS) differences could not be discerned until long-term follow-up published in 2010. This revealed reduced locoregional relapse and ASCC death with improved OS [11]. Finally, the importance of mitomycin in the chemoradiation regimen was assessed in an intergroup phase III study. Relative to 5-FU alone, the addition of mitomycin improved colostomy-free survival and disease-free survival (DFS) [12]. Taken together, since the 1970s, chemoradiation has remained the standard-of-care for all nonmetastatic ASCC cases given its improved outcomes and reduced morbidity with APR reserved as a salvage therapy.

Table 1. Landmark studies in management of locoregional ASCC.

Trial	N	Treatment Arms	Outcomes
EORTC 22861 [9]	**110**	**Randomized phase III study comparing 5-FU + mitomycin with radiation vs. radiation alone**	• Improved CR rate (80% vs. 54%) • Improved locoregional recurrence rate by 18% (p = 0.02) • Improved colostomy-free interval by 32% (p = 0.002) • Improved PFS (p = 0.05)
ACT I [11]	**500**	**Randomized phase III study comparing 5-FU + mitomycin with radiation vs. radiation alone**	• Primary endpoint of local-failure rate at 3.5 years was reduced by 46% (HR 0.54, 95% CI: 0.42–0.69, p < 0.0001) • Median follow-up of 13 years: • Reduced in locoregional relapse by 25% (HR 0.46, 95% CI: 0.35–0.60) • Reduced ASCC death by 12.5% (HR 0.67, 95% CI: 0.51–0.88) • Improved median OS at 7.6 vs. 5.4 years (HR 0.86, 95% CI: 0.7–1.04)
RTOG 87-04/ECOG 1289 [12]	**310**	**Randomized phase III study comparing chemoradiation with 5-FU + mitomycin vs. 5-FU alone**	• Improved colostomy-free survival (71% vs. 59%, p = 0.014) • Improved DFS (73% vs. 51%, p = 0.0003)
EXTRA [13]	**31**	**Single-arm phase II study using capecitabine + mitomycin chemoradiation**	• Complete response rate was 77% • Approximately 10% locoregional relapses at median follow-up of 14 months
[14]	**43**	**Single-arm phase II study using capecitabine-based chemoradiation**	• Primary endpoint of local control at six months was 86% (95% CI: 0.72–0.94)
ACT II [15]	**940**	**Randomized phase III, 2 × 2 factorial design, comparing chemoradiation with mitomycin + 5-FU vs. cisplatin + 5-FU with or without maintenance chemo**	**Comparing mitomycin + 5-FU and cisplatin + 5-FU** • Primary endpoint of CR rates at 26 weeks was not significantly different (90.5 vs. 89.6%, 95% CI −4.9–3.1, p = 0.64) **Comparing with or without maintenance chemotherapy:** • No significant difference in three-year PFS at 74% (95% CI: 69–77) and 73% (95% CI: 68–77) (HR 0.95, 95% CI: 0.75–1.21, p = 0.70)

Trial	N	Treatment Arms	Outcomes
[16]	19	**Phase II pilot study treating with 5-FU + mitomycin + cisplatin chemoradiation**	• Sixteen (84%) developed grade 3/4 toxicities with one patient dying as a complication of treatment • At median follow-up of 79 months, 84% remained disease-free • Approximately 10% locoregional relapses at median follow-up of 14 months
RTOG 98-11 [17]	649	**Randomized phase III study comparing chemoradiation with 5-FU and mitomycin vs. 5-FU and cisplatin**	• Primary endpoint of five-year DFS improved at 67.8% vs. 57.8% (p = 0.006) • Improved five-year median OS of 78.3% vs. 70.7% (p = 0.026)
ACCORD 03 [18]	307	**Randomized phase III study comparing chemoradiation with or without induction 5-FU and cisplatin**	• Primary endpoint of five-year colostomy-free survival was 76.5% (95% CI: 68.6–83.0) vs. 75% (95% CI: 67.0–81.5, p = 0.37)

5-FU, 5-fluorouracil; CI, confidence interval; CR, complete response; DFS, disease-free survival; HR, hazard ratio; N, number of patients; OS, overall survival; PFS, progression-free survival.

Attempts to improve on this treatment paradigm have been limited. In a retrospective cohort study including 299 elderly patients (median age of 72) with stage I ASCC, 200 were treated with chemoradiation vs. 99 treated with radiation alone. After propensity-score adjustments, the addition of chemotherapy did not significantly improve OS, DFS, colostomy-free survival or cause-specific survival in this select group [19]. This finding potentially supports de-escalation of therapy in carefully selected patients.

Alternatives to 5-FU and mitomycin have also been explored. For example, the oral fluoropyrimidine prodrug capecitabine has proven to be interchangeable with infusional 5-FU in the treatment of other malignancies such as with gastric cancer in the REAL-2 phase III study [20] or colorectal adenocarcinoma in the X-ACT phase III trial [21]. Several retrospective studies have demonstrated safety and efficacy of capecitabine and mitomycin in locoregional ASCC [22][23][24]. One study included 105 patients with ASCC with 47 treated with 5-FU-based chemoradiation while 58 were treated with capecitabine-based therapy. This demonstrated nonsignificant differences in CR rates, three-year locoregional control, three-year OS and colostomy-free survival [23]. While randomized prospective comparisons are lacking in ASCC, these retrospective findings are comparable to clinical outcomes and safety data from two studies. The EXTRA phase II trial included 31 patients with ASCC receiving chemoradiation with capecitabine and mitomycin and demonstrated a CR rate of 77% [13]. A later phase II, single-arm trial similarly used capecitabine-based chemoradiation in 43 patients with ASCC, demonstrating an 86% locoregional control rate at 6 months [14]. Therefore, capecitabine is considered as an appropriate alternative to infusional 5-FU for locoregional ASCC.

Improving chemoradiation by replacing mitomycin with cisplatin has also been tested. The ACT II trial was a randomized, phase III, open-label study consisting of 940 patients comparing radiation with 5-FU and mitomycin vs. 5-FU and cisplatin. It should be noted that, instead of giving mitomycin at 10 mg/m^2 for two doses, it was administered at 12 mg/m^2 as a single dose. There were no significant differences in CR rates nor grade 3–4 adverse effects between the chemotherapy regimens [15]. Therefore, feasibility of treatment escalation was tested in a phase II pilot study in which 19 patients were treated with radiation concomitantly with 5-FU, mitomycin and cisplatin. Unfortunately, given the very high toxicity rates with this regimen, triplet therapy was not considered reasonable [16]. Thus, while chemoradiation with 5-FU and cisplatin is considered an alternative to 5-FU and mitomycin, triplet therapy is deemed too toxic.

3. Role of Induction or Maintenance Chemotherapy

Chemoradiation has largely been the standard of care for locoregional ASCC since the 1970s. While the previously highlighted trials firmly support the use of chemoradiation, there have been a few attempts to advance clinical outcomes through the modification of available regimens. Two examples include the addition of either induction or maintenance

chemotherapy to chemoradiation. The aforementioned ACT II study had a 2 × 2 factorial design assessing the utility of maintenance chemotherapy following chemoradiation. In the two treatment arms, including maintenance chemotherapy, patients received an additional two cycles of fluorouracil with cisplatin at weeks 11 and 14. Of the patients who received cisplatin- and mitomycin-based chemoradiation, 222 and 226 patients, respectively, were randomized to receive maintenance chemotherapy. However, this did not significantly improve three-year PFS [15].

Akin to ACT II, the intergroup RTOG 98–11 study was a phase III trial randomizing 325 patients to chemoradiation with 5-FU and mitomycin and 324 patients to the 5-FU and cisplatin arm. Interestingly, the mitomycin arm resulted in improved five-year DFS and OS [17]. However, interpretation of these results must be made cautiously given patients in the cisplatin arm received induction 5-FU and cisplatin prior to chemoradiation while the mitomycin arm did not. Thus, it is difficult to attribute differences in outcomes purely to comparisons between mitomycin and cisplatin. In fact, in light of the ACT II trial, these results may suggest a detrimental effect of induction chemotherapy.

The ACCORD 03 study was a phase III trial that directly tested treatment intensification by adding two cycles of induction chemotherapy with 5-FU and cisplatin prior to chemoradiation. The addition of induction chemotherapy caused no significant differences in colostomy-free survival [25]. These studies, in addition to a systematic review, demonstrate no benefit of induction chemotherapy in ASCC management [18]. Taken together, there is no clear role for induction or maintenance chemotherapy in the management of nonmetastatic ASCC.

4. Systemic Therapy for Metastatic Disease

Management of locoregional ASCC is largely one-size-fits-all irrespective of precise staging due to the relative rarity of the disease. However, approximately 10–20% of patients treated with curative intent will develop metastatic disease. In addition, less than 10% of patients with ASCC present with de novo metastatic disease [10][26]. Prognosis for these patients is poor with an approximately 30% five-year survival rate [27].

Chemotherapy is routinely offered to patients with metastatic ASCC. In this setting, guidelines have historically recommended a platinum doublet including a fluoropyrimidine as first-line treatment [28][29]. There are limited data supporting the use of leucovorin, fluorouracil and oxaliplatin (FOLFOX) as well as FOLFCIS, effectively a FOLFOX schedule with cisplatin replacing oxaliplatin [30][31]. Nonetheless, until 2018, treatment recommendations have been based upon similar case series and retrospective studies. Table 2 summarizes key prospective trials in the management of ASCC. The Epitopes-HPV02 trial was a single-arm phase II study with nonoperable or metastatic ASCC treated with either standard or modified docetaxel, cisplatin and fluorouracil (DCF and mDCF, respectively). DCF treatment consisted of six cycles of docetaxel (75 mg/m^2 on day one), cisplatin (75 mg/m^2 on day one), and fluorouracil (750 mg/m^2 per day for five days) every three weeks. The mDCF regimen consisted of eight cycles of docetaxel (40 mg/m^2 on day one), cisplatin (40 mg/m^2 on day one), and fluorouracil (1200 mg/m^2 per day for 2 days) every two weeks. Choice of the two treatments was not randomized. Instead, it was determined by the patient's age and performance status. PFS between the two treatment regimens was not significantly different. However, there were significantly more grade 4 adverse events in those who received DCF vs. mDCF, making the latter a potential first line option for metastatic ASCC [32].

Table 2. Landmark Studies in Management of Metastatic ASCC.

Trial	N	Treatment Arms	Outcomes
Epitopes-HPV02 [32]	**66**	**Nonrandomized, single-arm phase II treating with either DCF or mDCF with allocation determined by age and PS**	• Primary endpoint 12-month PFS was not significantly different (61% had progressed with DCF while 60% had progressed with mDCF) • Improved locoregional recurrence rate by 18% (p = 0.02) • Improved colostomy-free interval by 32% (p = 0.002) • Improved PFS (p = 0.05)

Trial	N	Treatment Arms	Outcomes
InterAAct [33]	**91**	**Randomized phase II study comparing carboplatin + paclitaxel vs. cisplatin + 5-FU**	• Comparable ORR at 59% (95% CI: 42.1–74.4%) vs. 57% (95% CI: 39.4–73.7%) • Improved PFS (8.1 vs. 5.7 months) and OS (20 vs. 12.3 months) (HR 2.00, 95% CI: 1.15–3.47, p = 0.014) with carboplatin + paclitaxel • Increased serious adverse events cisplatin + 5-FU arm (62% vs. 32%, p = 0.016)
KEYNOTE-028 [34]	**25**	**Single-arm phase Ib study of pembrolizumab in second line**	• Primary endpoint of ORR was 17% (95% CI: 5–37%) • Duration of response that was not reached at median follow-up of 10.6 months • Median PFS was 3.0 months (95% CI: 1.7–7.3 months) • Median OS was 9.3 months (95% CI: 5.9 months—not available)
NCI9673 [35]	**37**	**Single-arm phase II study of nivolumab in second line**	• RR was 24% (95% CI: 15–33)

5-FU, 5-fluorouracil; CI, confidence interval; CR, complete response; DCF, docetaxel + cisplatin + 5-fluorouracil; mDCF, modified DCF; N, number of patients; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; RR, response rate.

The phase II InterAAct study was the first randomized trial for patients with unresectable, metastatic ASCC. Patients were treated with either carboplatin and paclitaxel or cisplatin. While ORR values between the regimens were comparable, carboplatin and paclitaxel conferred superior median PFS and OS. Furthermore, there was a significant increase in more serious adverse events in the cisplatin and fluorouracil arm [33]. Taken together, while mDCF is a promising option, the higher quality data supports using carboplatin and paclitaxel in the first line for metastatic ASCC.

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