Randomized Clinical Trials in Localized Anal Cancer

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KEYWORDS

• Anal • Cancer • Radiotherapy • Chemotherapy • Chemoradiation • Randomized

KEY POINTS

- Combined chemotherapy and radiation therapy reduce rates of anal cancer recurrence, need for colostomy, and anal cancer specific survival over radiotherapy alone.
- 5-Fluoracil (5-FU) and mitomycin C (MMC) concurrent with radiation therapy provide superior disease-free and colostomy-free survival over single agent 5-FU and radiotherapy alone.
- Phase III trials of induction chemotherapy, radiation dose intensification, and maintenance chemotherapy have not been shown to improve outcomes over standard chemoradiation for anal cancer.
- Concurrent cisplatin in place of MMC may be a reasonable alternative in patients who are unable to tolerate MMC.
- Planned treatment gaps in radiotherapy may have a negative impact on disease control. Modern radiation techniques significantly reduce acute toxicity and the need for treatment breaks.

INTRODUCTION

Historically, squamous cell carcinoma of the anal canal was treated with surgical resection by abdominoperineal resection. This produced overall survival rates of approximately 50%, but resulted in a permanent colostomy and high rates of locoregional recurrence.[1,2] In an effort to reduce the rates of local recurrence after surgery, Nigro and colleagues[3] pioneered a neoadjuvant regimen combining radiation therapy (30 Gy in 15 fractions) and chemotherapy with 5-fluorouracil (5-FU; 25 mg/kg continuous infusion) and mitomycin C (MMC; 0.5 mg/kg bolus). In a report of 28 patients undergoing this regimen, 26 patients underwent either abdominoperineal resection or

Disclosure Statement: The authors have nothing to disclose.

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Surg Oncol Clin N Am ■ (2017) ■–■

http://dx.doi.org/10.1016/j.soc.2017.05.009

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local excision after chemoradiation.[4] Of the patients, 80% were found to have pathologic complete response. In a subsequent series of 38 patients treated with chemoradiation as definitive therapy, an 84% complete response rate was achieved.[5] After these promising results, randomized clinical trials of anal cancer treatment have sought to validate definitive chemoradiation as the primary treatment for anal cancer, to establish the optimal systemic agents, and to assess the potential benefit of adjuvant chemotherapy or increased radiation dose, with the overarching goal of providing maximal colostomy-free survival while reducing treatment-related morbidity (**Table 1**).

RADIATION VERSUS COMBINED MODALITY THERAPY

Anal Cancer Trial I

The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Anal Cancer Trial I (ACT I) was designed to compare radiation therapy alone with combined modality therapy with radiation and concurrent 5-FU and MMC.[6] There were 585 patients (51% clinical T3 disease, 20% positive nodes) accrued between 1987 to 1994 and randomized to (1) radiation therapy of 45 Gy in 20 to 25 fractions with anteroposterior-posteroanterior (AP-PA) opposed fields targeting the anus and perineum, lower pelvic nodes, and optionally inguinal nodes, or to (2) the same radiation therapy given concurrently with 5-FU 1000 mg/m^2/d continuous infusion on days 1 to 4 or 750 mg/m^2 on days 1 to 5 and MMC 12 mg/m^2 bolus on day 1 of radiation. During the final week of radiation therapy, 5-FU was given as a second cycle. Response to treatment was assessed by clinical examination 6 weeks after completion of radiation. Patients with less than 50% response were referred for surgical resection and patients with greater than 50% response received a boost to the primary site of 15 Gy in 6 fractions with external beam therapy or 25 Gy over 2.5 days by iridium-192 brachytherapy implant.

At the initial response assessment 6 weeks after completion of the primary radiation treatment, there were comparable rates of patients with greater than 50% response (92% in both arms). With a median follow-up of 42 months at first reporting, 3-year local failure was 61% in the radiation alone arm versus 39% in the combined modality arm ($P<.0001$), demonstrating significant improvement with the combination of radiation and chemotherapy. Three-year cancer-specific survival was also improved significantly by combined modality therapy (72% vs 61% in patients treated with radiation alone; $P = .02$); however, there was no difference in 3-year overall survival between groups (58% vs 65%; $P = .25$). Early morbidity, including hematologic, skin, gastrointestinal, and genitourinary toxicity, was significantly worse with the addition of chemotherapy (48%) versus radiation alone (39%; $P = .03$). Late morbidity did not differ between concurrent therapy and radiation alone (42% vs 38%; $P = .39$).

In the long-term update, with a median follow-up of 13 years, the 5-year locoregional failure rate was 57% for radiation alone versus 32% for chemoradiation ($P<.001$), with this difference maintained out to 10 years.[7] The 5-year cancer-specific survival was 58% for radiation alone versus 70% for concurrent therapy ($P = .004$). As in the initial report, there was no difference in overall survival between groups at 5 years (53% vs 58%; $P = .12$). One outcome not reported in the initial publication was the colostomy-free survival rate, which reflects both the disease-free rate as well as lack of significant late morbidity from treatment that may prompt colostomy in the absence of tumor recurrence. The 5-year colostomy-free survival was increased significantly in patients receiving concurrent therapy (47%) versus radiation alone (37%; $P = .004$). In addition, examination of late morbidity found no difference between arms in rates of ulcers and radionecrosis (23% chemoradiation vs 18%