Treatment of the Primary Tumor in Anal Canal Cancers

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KEYWORDS

• Squamous cell carcinoma of the anus • Anal carcinoma • Chemotherapy
• Radiotherapy • Chemoradiation • Combined modality • Immunotherapy
• Local recurrence

KEY POINTS

- Squamous cell carcinoma of the anus is generally a localized disease with a relatively low risk of metastatic disease at presentation; thus, local control is the overriding aim of treatment.
- Randomized phase III trials have established the combination of 5-fluorouracil–based chemoradiation concurrent with mitomycin C as the standard of care rather than primary surgery.
- The TNM clinical staging system is based on accurate assessment of size (T stage), regional lymph node involvement, and metastatic spread.
- Assessment and management of anal cancer are best determined by specialist multidisciplinary teams, and treatment should be carried out in specialized centers.
- Future research should attempt to integrate novel biomarker-driven targets, such as anti-CTLA4, anti–programmed cell death, and programmed cell death-ligand 1, into chemoradiation schedules.

INTRODUCTION

Squamous cell carcinoma of the anus (SCCA) is an uncommon malignancy representing approximately 2% of all gastrointestinal malignancies. The incidence has been increasing over the past decade, probably reflecting more widespread infection with the main causal factor human papillomavirus (HPV).

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SCCA is generally a localized disease with a low risk of metastatic disease at presentation. Retrospective studies and randomized trials suggest that locoregional failure is the predominant pattern of relapse,[1–4] usually in the radiotherapy high-dose volume, and often within the first 2 years following completion of chemoradiation (CRT) treatment. Uncontrolled local recurrence is ultimately responsible for most cancer-related deaths, making local control the primary aim of treatment.

Surgical resection was the standard treatment in the 1970s, which involved removal of the anal canal and a permanent stoma. In the past, radiation alone was also often used to treat SCCA using high doses with split-course schedules and interstitial brachytherapy. The pioneering work of Nigro and colleagues[5,6] and subsequent confirmatory studies in the United States highlighted the efficacy of CRT using relatively low doses of fractionated radiotherapy (30–45 Gy) combined with 5-fluorouracil (5-FU) and mitomycin C (MMC). Subsequently, 2 randomized trials[7,8] compared a radiotherapy schedule of 45 Gy boosted with a further 15 to 25 Gy after a gap of 6 weeks against an identical regimen with concurrent 5-FU/MMC. These trials showed radiation alone could result in local control in approximately 45% to 55% of patients. However, both trials confirmed chemoradiotherapy significantly improved outcomes over radiation alone.

Significant toxicity was reported for MMC. So concurrent 5-FU and MMC or 5-FU alone were randomly compared in the CRT component in the RTOG 8704 trial.[9] The addition of MMC significantly improved both disease-free survival (DFS) and colostomy-free survival (CFS).[9] Thus, a series of randomized trials[7–11] all confirmed the efficacy of concurrent CRT with 5-FU/MMC and relegated the role of surgery to salvage of CRT failures. The small Action Clinique Coordonees en Cancerologie Digestive (ACCORD-03) trial, in contrast, used concurrent 5-FU/cisplatin.[12]

The standard of care both in Europe and North America is 5-FU/MMC CRT and is recommended in guidelines.[13,14] This schedule results in complete tumor regression in 80% to 90%, with a high level of permanent disease control particularly for cT1/T2 tumors. The 5-year overall survival (OS) reached 78% in the MMC arm of the RTOG 9811 trial,[15] 71% in the CRT-alone arms without neoadjuvant chemotherapy (NACT) in ACCORD-03,[12] and 79% in the MMC arm of Anal Cancer Trial II (ACT II).[11]

Preservation of sphincter function is usually achieved; but with doses of 50 to 60 Gy, there is a risk of fecal incontinence.[16] In more advanced T3/T4 cancers with nodal metastases, it is more difficult to achieve local control[17]; a substantial proportion of such patients will fail within 2 years. In the ACT II, patients with cT3/T4 cancers and nodal metastases had a 3-year progression-free survival (PFS) of 63%.[11]

Randomized phase III trials by RTOG 9811,[10] the ACCORD-03 phase III trial,[12] and the ACT II trial[11] failed to show any additional benefit in terms of PFS/DFS by increasing the radiotherapy boost dose or replacing MMC with cisplatin during CRT. Additional cisplatin-based chemotherapy given as induction before CRT[10,12] or as maintenance or consolidation after CRT[11] has not improved outcomes (**Table 1**).

SCCA regresses slowly following radiation or CRT. In early trials a 6 to 8 week planned gap between the completion of CRT and a radiotherapy boost allowed the acute toxicity of skin and mucosal surfaces to resolve.[7,8] During this interval the tumor would shrink, and permit an interstitial implant to the smallest possible volume - minimizing the risk of radiation induced necrosis. This strategy also allowed selection of nonresponders for salvage either by dose-escalation of the radiotherapy boost or by surgical resection. Later trials continued this approach although shortened the interval.[10,12] However this practice defied radiobiological principles, because the gap