Evolution and Management of Treatment-Related Toxicity in Anal Cancer

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KEYWORDS

• Anal cancer • Chemoradiation • Radiotherapy • Chemotherapy • Toxicity
• Intensity-modulated radiotherapy • Mitomycin-C • Cisplatin

KEY POINTS

- Definitive chemoradiation (CRT) regimens in the treatment of anal cancer have evolved over successive clinical trials.
- Although cure rates are high with these regimens, they result in hematologic, dermatologic, gastrointestinal (GI), and genitourinary (GU) toxicities.
- Alternative strategies, including novel radiotherapy approaches as well as novel chemotherapeutics, are aimed at reducing treatment-related toxicity without having a negative impact on disease-related outcomes.
- Toxicity management often requires algorithmic and multidisciplinary approaches; contemporary studies are focusing on long-term quality-of-life sequelae following anal cancer treatment.

INTRODUCTION

Anal cancer is an uncommon malignancy whose incidence has been rising over the past several decades.[1] In 2016, it is expected that more than 8000 new cases of anal cancer will be diagnosed in the United States, resulting in more than 1000 deaths.[2] Since the 1970s, curative treatment of nonmetastatic anal cancer has increasingly centered on definitive RT, which now is established as the primary treatment. Although anal cancer is largely curable with CRT, these treatments are associated with a substantial toxicity profile. Many of the large randomized clinical trials (RCTs) for anal cancer have focused on mitigating toxicity without compromising

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outcomes. This review focuses on the evolution of treatment-related toxicity for anal cancer with the progression of RCTs over the past several decades. As the standard of care has changed with the results of these RCTs, so too has the toxicity profile for anal cancer treatment. Management of these adverse effects is reviewed as are future directions in the treatment of anal cancer and their impact on toxicity.

TOXICITY DURING THE SURGICAL ERA

Prior to the advent and acceptance of definitive nonsurgical treatment options for anal carcinoma, abdominoperineal resection (APR) represented the standard of care. From an outcomes perspective, definitive APR alone resulted in recurrence rates of approximately 40% in patients treated with curative-intent.[3] Similarly, 5-year overall survival (OS) rates with APR alone averaged 62%, ranging between 51% and 71% in most studies.[3–5] In addition to these limitations, APR entails significant morbidity: as a non–sphincter-preserving procedure (ie, the entire anal sphincter complex is removed), permanent colostomy rate is 100%, along with high rates of urinary/sexual dysfunction, wound morbidity, and additional perioperative morbidity and mortality.

With this in mind, Nigro and colleagues[6] at Wayne State University piloted an effort in the early 1970s to assess the role of neoadjuvant CRT, combining 30 Gy to 35 Gy external-beam radiotherapy (EBRT) with concurrent 5-fluorouracil (5-FU) and mitomycin-C (MMC). In their initial report, these investigators demonstrated pathologic complete response (CR) in 2 patients treated with neoadjuvant CRT followed by APR.[6] The possibility of definitive CRT obviating subsequent APR resulted in the expansion of their efforts, culminating in a report of 45 patients treated with 30 Gy EBRT plus concurrent 5-FU/MMC. Remarkably, post-CRT biopsy specimens demonstrated CR in 84% of patients, with no subsequent recurrence in those with biopsy-proven CR. Of these 45 patients, 11% experienced grade 3 or higher hematologic toxicity. The investigators also reported "low-grade stomatitis" and "moderate diarrhea" as part of the acute toxicity profile of their regimen.[7,8] With these promising results, definitive surgical management of anal carcinoma ultimately gave way to definitive CRT; subsequent RCTs have therefore focused on the optimal nonsurgical approach for anal cancer.

In the modern era, the role of definitive surgical treatment of previously untreated anal lesions is primarily in the setting of T1N0 well-differentiated anal margin cancer.[9,10] These lesions, with highly favorable prognoses, may be treated with wide local excision; radiotherapy (RT) (with or without concurrent chemotherapy) is reserved for cases where re-excision (for positive or close margins) is not possible.[9,10] Given this limited scope for definitive surgery, the remainder of this review focuses on the toxicities associated with definitive CRT regimens for these patients.

FIRST-GENERATION TRIALS—RADIOTHERAPY VERSUS CHEMORADIOTHERAPY

Concurrent with the Nigro protocol, other experiences suggested that RT alone could also achieve promising outcomes.[11] Similarly, the toxicities associated with the Nigro chemotherapeutics (in particular MMC) further spurred the question as to whether RT could be as efficacious as CRT but with fewer adverse effects. Two RCTs were conducted to assess outcomes and toxicity profiles with RT versus CRT as definitive treatment of anal cancer: the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Anal Cancer Trial (ACT I), and the European Organisation for Research and Treatment of Cancer (EORTC) trial.[12–14] Both ACT I and EORTC trials used a 45 Gy RT regimen and prescribed similar concurrent 5-FU/MCC chemotherapy regimens for the CRT arms. Both trials involved a 6-week post-treatment