Clinical Trials in the Management of Anal Cancer

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ABSTRACT

Our understandings of anal canal cancer pathogenesis and treatment have undergone significant changes due to continuing research into its pathogenesis and the results of major clinical trials conducted over the past 20 years. Anal canal cancer can be cured by combined modality chemoradiation therapy, a treatment that preserves continence and reserves abdominoperineal resection of the rectum and anal canal in patients with recurrent or residual disease after primary chemoradiotherapy. The research into more effective, less toxic therapies is continuing. Future challenges include an increasing incidence of human papillomavirus infection, the AIDS epidemic, diagnosis of early disease, and optimization of chemotherapy and radiation regimens. This article aims to provide a summary of recently completed and ongoing clinical trials in the management of anal canal cancer.

KEYWORDS: Anal canal cancer, chemotherapy, radiation therapy

Objectives: On completion of this article, the reader should have an understanding of the recently completed and ongoing trials in the management of squamous cell cancer of the anal canal and be able to apply study results in the treatment of anal cancer.

Carcinoma of the anal canal is an uncommon malignancy and accounts for ~2 to 4% of all large bowel cancers. There were estimated to be 5,070 new cases of anal canal squamous cell carcinomas in the United States resulting in 680 deaths in 2008.¹ Tumor size >2 cm and lymph node involvement at initial diagnosis portends poor prognosis. Anal canal cancer incidence is rising in certain populations with high risk sexual behaviors and human immunodeficiency viral (HIV) infection. Human papillomavirus (HPV) infection is strongly associated with anal cancer and partly contributes to its pathogenesis.²

Abdominoperineal resection was the treatment of choice for anal cancers before 1980. It was associated with acceptable 5-year cancer-specific survival rate of

60%, but at the cost of significant perioperative morbidity and local recurrence rates up to 47%.^{3,4}

Based on prior experience of fluoropyrimidines as radiosensitizers in different gastrointestinal malignancies, Nigro et al⁵ in 1974 investigated the use of preoperative chemotherapy with 5-fluorouracil (5-FU) and mitomycin C (MMC) plus radiation therapy (RT) given in doses of 30 Gy in patients with anal canal cancer. Interestingly, the first three patients achieved a complete pathologic response on evaluation of postsurgical specimens, and this resulted in the concept of anal sphincter preservation strategies. Subsequent case series supported using chemoradiation protocols for anal sphincter preservation, reserving surgery for instances

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where residual disease persisted after combined modality chemoradiation therapy. These series showed 5-year overall survival of ~70% and colostomy-free survival of ~60%.^{6,7} These investigation results were followed by several large randomized clinical trials, which confirmed the role of combined modality therapy and now form the basis of our current standard of care in management of squamous cell cancer of the anal canal.

LANDMARK CLINICAL TRIALS

Two European Phase III randomized clinical trials were conducted in late 1990s to evaluate the benefits of chemoradiation therapy versus RT alone. At the same time, two United States trials looked at efficacy of different chemotherapeutic regimens in chemoradiation protocols in the treatment of anal canal cancers. The results and conclusion of these four trials are summarized in Table 1.

United Kingdom Coordinating Committee on Cancer Research-based Anal Cancer Trial

The United Kingdom Coordinating Committee on Cancer Research-based Anal Cancer (UKCCCR) Trial Working group⁸ compared RT alone versus RT, 5-FU, and MMC in a multicenter clinical trial in 1996. Five hundred eighty-five patients with stage T1 to T4 anal canal carcinomas, with and without lymph node involvement, were randomized. Patients received either 45 Gy of RT in 20 or 25 fractions over 4 to 5 weeks (290 patients), or the same regimen of RT combined with 5-FU (1000 mg/m² for 4 days or 750 mg/m² for 5 days) by continuous intravenous (IV) infusion during the first and the final weeks of RT and MMC (12 mg/m²) on day 1 of the first course (295 patients). Clinical response was assessed at 6 weeks after initial treatment. Good responders received an additional boost of radiation and poor responders underwent salvage surgery. The main endpoint was local-failure rate (>or=6 weeks after

Table 1 Results of the Landmark Completed Trials for Management of Anal Cancer

Clinical Trial	Pts.	Stage	Treatment Arm	F/U	Results	Conclusions
UKCCCR multi center randomized trial	577	T1-T4 with any N	CMT (5FU + MMC + RT vs. RT(45Gy) alone	42 mo	CR 62% vs. 53% OS 65% vs. 58% LFR 15% vs. 30%	CMT is better than RT alone.
EORTC Phase III randomized trial	110	T1-T4 with any N	CMT (5FU + MMC + RT) vs. RT(45Gy) alone	60 mo	CR 80% vs. 54%	CMT results in better loco-regional control and colostomy free survival.
RTOG-87-04 study Phase III randomized trial	310	T1-T4 with any N	(5FU + MMC + RT) vs. 5FU + RT (45-50Gy)	48 mo	CR 9% vs. 2% DFS 73% vs. 51%	Despite greater toxicity, the use of MMC in CMT is beneficial.
RTOG 98-11 Multicenter Phase III randomized trial	644	T1-T4 with any N	5FU + MMC + RT vs. 5FU + cisplatin + RT (45-59Gy)	60 mo	DFS 60% vs. 54% (P = 0.17) OS 75% vs. 70% (P = 0.10) LFR 25% vs. 33% CR 10% vs. 19%	Cisplatin-based therapy failed to improve disease-free-survival compared with mitomycin-based therapy, and resulted in a significantly worse colostomy rate.
EXTRA Multicenter Phase II study	31	T1-T4 with any N	Capecitabine plus MMC plus RT(50.4Gy)	14 mo	CR in 70%	Capecitabine with MMC and RT is well tolerated, with minimal toxicity and acceptable compliance.

RT, radiotherapy; MMC, mitomycin C; DFS, disease-free survival; OS, overall survival; LFR, local failure rates; CR, complete response.

initial treatment); secondary endpoints were overall and cause-specific survival. Only 577 patients were eligible for assessment after randomization. Chemoradiation therapy resulted in less local failure rates (36% versus 59%, $p \leq 0.0001$) and decreased cancer-related risk of death (0.71, $p = 0.02$). There was no significant difference statistically in overall survival between the two therapies at 36 months (65% versus 58%). Investigators concluded that chemoradiation therapy results in better survival and tumor control than RT alone.

European Organization for the Research and Treatment of Cancer Study

The European Organization for the Research and Treatment of Cancer (EORTC)⁹ randomized 110 patients to chemoradiation versus RT alone. They used 5-FU and MMC (750 mg/m² and 15 mg, respectively, instead of 1000 mg/m² and 12 mg in the UKCCCR Study). The addition of chemotherapy to RT resulted in a significant increase in the complete remission rate from (54% for RT alone versus 80% for combined modality chemoradiation therapy). Significant improvement in locoregional control and colostomy-free survival was noted ($p = 0.02$ and $p = 0.002$, respectively). The locoregional control rate improved by 18% at 5 years, while the colostomy-free survival at that time increased 32% with the addition of chemotherapy to RT. No significant difference in severe therapy-related toxicity was noted, although anal ulcers were more frequently observed in the combined-treatment arm. The overall survival rate remained similar in both treatment arms. The results of this study supported the UKCCCR trial conclusions.

While United Kingdom investigators were establishing the role of chemoradiation therapy in anal canal cancer, in North America investigators were concentrating on evaluation of the need for MMC in combined modality therapy. As MMC is not a known radiosensitizer and is associated with higher renal, pulmonary, and bone marrow toxicities, U.S. investigators designed trials to compare chemoradiation therapy without MMC or replacing it with cisplatin.

Radiation Therapy Oncology Group

RTOG 87-04

The Radiation Therapy Oncology Group¹⁰ (RTOG) randomized 310 patients to 5-FU plus radiation or 5-FU and MMC plus radiation. 5-FU was infused at a rate of 1000 mg/m² IV and MMC at 10 mg/m² IV. Radiation doses ranged from 45 to 50.4 Gy. Posttreatment biopsies were positive in 15% of patients in the 5-FU arm versus 7.7% in the MMC arm ($p = 0.135$). At 4 years, colostomy rates were lower (9% versus 22%; $p = 0.002$),

colostomy-free survival higher (71% versus 59%; $p = 0.014$), and disease-free survival higher (73% versus 51%; $p = 0.0003$) in the MMC arm. A significant difference in overall survival was not observed at 4 years. Toxicity was found to be greater in the MMC arm (23% versus 7% grade 4 and 5 toxicity; $p < 0.001$). From these results, investigators reached the conclusion that despite more toxicity, MMC still plays an important role in combined modality therapy by reducing local recurrence and colostomy rates.

RTOG 98-11

RTOG¹¹ conducted a multicenter phase III trial comparing 5-FU plus MMC and RT versus treatment with 5-FU plus cisplatin and radiotherapy in 682 patients with anal canal carcinoma. The MMC group received 5-FU (1000 mg/m² on days 1 to 4 and 29 to 32) plus MMC (10 mg/m² on days 1 and 29) and RT (45 to 59 Gy). The cisplatin group received fluorouracil (1000 mg/m² on days 1 to 4, 29 to 32, 57 to 60, and 85 to 88) plus cisplatin (75 mg/m² on days 1, 29, 57, and 85) and radiotherapy (45 to 59 Gy; start day = day 57). The median follow-up for all patients was 2.51 years. The 5-year disease-free and overall survival rate was not significantly different ($p = 0.17$ and $p = 0.10$). However, the 5-year locoregional recurrence, distant metastasis, and cumulative colostomy rates were significantly better for the MMC-based therapy group compared with the cisplatin-based treatment group (10% versus 19%; $p = 0.02$). Severe hematologic toxicity was higher with MMC-based treatment ($p < 0.001$).

The two European trials have shown the superiority of chemoradiation over RT alone, while the two U.S. trials endorse the use of MMC in combined modality therapy, which significantly reduces local recurrence and colostomy rates, despite a higher toxicity rate.

HIV AND ANAL CANAL CANCER

Combined modality therapy is accepted as the standard treatment for anal canal cancer in HIV-positive patients. However, this infection poses a challenge due to higher treatment-related toxicity in this population. This has been shown recently in a multicenter cohort study and retrospective analysis of 40 HIV-positive and 81 HIV-negative patients. They were either treated with chemoradiotherapy or radiotherapy alone.¹² The results revealed no difference in 5-year overall survival rates in either group (61% in HIV-positive and 65% in HIV-negative patients). However, the local control was significantly lower in the HIV-positive population ($p = 0.008$). Acute skin toxicity was associated with higher dose of radiotherapy >30 Gy. This leads to the conclusion that chemoradiation therapy is generally well tolerated in HIV-positive

patients, but can result in more treatment-related toxicity especially in patients who receive more than 30 Gy of radiation.

ONGOING CLINICAL TRIALS DETERMINING FUTURE DIRECTION IN MANAGEMENT OF ANAL CANAL CANCER

Current trials are evaluating combination therapies designed to reduce toxicity and increase response rate by incorporating molecular targeted therapies, or possibly replace MMC with cisplatin and infusional 5-FU with oral capecitabine. Some data from a phase II study done by Glynne et al suggests that capecitabine can be substituted successfully for 5-FU to minimize IV infusion and hospital stay for patients with anal canal cancers.¹³ Below is a brief summary of ongoing trials comparing different chemotherapeutic combinations in the management of squamous cell cancer of the anal canal.

NCT00093379

The National Cancer Institute (NCI) funded a phase II study by the University of Texas M. D. Anderson Cancer Center. Investigators are evaluating the combination of capecitabine and oxaliplatin with RT in patients with stage II and III anal canal cancer. This study is currently recruiting patients.

NCT00025090

A phase III randomized clinical trial by UCL Cancer Institute (London, UK) is comparing the response rates in patients with primary epidermoid anal cancer treated with RT and 5-FU with either MMC or cisplatin, with or without maintenance therapy. The endpoint of study includes local control and prevention or delay of disease dissemination in patients treated with these regimens. This study is actively recruiting patients.

NCT00068744

Another similar phase II/III study by the EORTC is evaluating RT with MMC together with fluorouracil versus RT, MMC, and cisplatin in treating patients with locally advanced anal canal cancer. This study is active, but not recruiting more patients.

NCT00423293

A phase II trial by RTOG/NCI is actively recruiting patients. This trial will study the side effects and efficacy of giving intensity-modulated RT together with fluorouracil and MMC in invasive anal cancer.

ONGOING TRIALS IN HIV-POSITIVE POPULATION

There are two major ongoing trials. One trial is looking at biological therapy and combination chemotherapy plus RT. The other is assessing the prevention of anal cancer in an HIV-positive population.

NCT00324415

A phase II study by AIDS-associated Malignancies Clinical Trial Consortium is recruiting patients with HIV disease and stage I, stage II, or stage III anal canal cancers to evaluate the efficacy of combination of cisplatin, fluorouracil, and cetuximab with RT.

NCT00316888

A similar trial by EORTC in non-HIV-positive patients has been suspended as of November 2008. They were also evaluating the combination cisplatin, fluorouracil, and cetuximab with RT in advanced anal cancer.

NCT00798265

A phase I trial by NCI to assess the immunogenicity and safety of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in HIV-infected and HIV-preadolescents, adolescents and young adults. This study is active and currently recruiting patients.

SUMMARY

All completed large randomized trials to date suggest that combined modality therapy consisting of concurrent 5-FU, MMC, and RT is the standard of care for the management of squamous cell cancer of the anal canal. However, remarkable progress has been made in understanding the etiology and pathophysiology of anal canal cancers in the past 30 years. HPV has been clearly associated and partly implicated in the development of anal cancers. This has given direction to future studies to look at preventive therapies like vaccination and screening programs, which may allow us to diagnose premalignant lesions.

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