International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation: Gastrointestinal Cancer

Twenty-Five-Year Experience With Radical Chemoradiation for Anal Cancer

Jonathan M. Tomaszewski, M.B.B.S., B.Med.Sc.,* Emma Link, DPhil.,† Trevor Leong, F.R.A.N.Z.C.R., M.D.,*,‡ Alexander Heriot, F.R.A.C.S., M.D.,‡,§ Melisa Vazquez, M.B.B.S., B.Med.Sc.,¶ Sarat Chander, F.R.A.N.Z.C.R.,* Julie Chu, F.R.A.N.Z.C.R.,* Marcus Foo, F.R.A.N.Z.C.R.,* Mark T. Lee, F.R.A.N.Z.C.R.,* Craig A. Lynch, M.Med.Sci., F.R.A.C.S.,§ John Mackay, F.R.A.C.S.,‡,§ Michael Michael, F.R.A.C.P., M.D.,‡,‖ Phillip Tran, F.R.A.N.Z.C.R.,* and Samuel Y. Ngan, F.R.A.N.Z.C.R.*,‡

**Department of Radiation Oncology, †Centre for Biostatistics and Clinical Trials, §Division of Cancer Surgery, ¶Research Division, and ‖Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne; and ‡The University of Melbourne, Parkville, Victoria, Australia*

Received May 31, 2011. Accepted for publication Jul 5, 2011

Summary

Chemoradiation is a very effective organ-sparing approach in anal cancer, particularly in early stage disease. However, despite treatment according to standardized protocols using moderately high radiation doses with no planned treatment breaks, subgroups of patients have unsatisfactory outcomes. Novel strategies are needed to improve results for these patients. Elective inguinal irradiation can be safely omitted in patients with Stage I disease only. Important late effects

Purpose: To evaluate the prognostic factors, patterns of failure, and late toxicity in patients treated with chemoradiation (CRT) for anal cancer.

Methods and Materials: Consecutive patients with nonmetastatic squamous cell carcinoma of the anus treated by CRT with curative intent between February 1983 and March 2008 were identified through the institutional database. Chart review and telephone follow-up were undertaken to collect demographic data and outcome.

Results: Two hundred eighty-four patients (34% male; median age 62 years) were identified. The stages at diagnosis were 23% Stage I, 48% Stage II, 10% Stage IIIA, and 18% Stage IIIB. The median radiotherapy dose to the primary site was 54 Gy. A complete clinical response to CRT was achieved in 89% of patients. With a median follow-up time of 5.3 years, the 5-year rates of locoregional control, distant control, colostomy-free survival, and overall survival were 83% (95% confidence interval [CI] 78−88), 92% (95% CI, 89−96), 73% (95% CI, 68−79), and 82% (95% CI, 77−87), respectively. Higher T stage and male sex predicted for locoregional failure, and higher N stage predicted for distant metastases. Locoregional failure occurred most commonly at the primary site. Omission of elective inguinal irradiation resulted in inguinal failure rates of 1.9% and 12.5% in T1N0 and T2N0 patients, respectively. Pelvic nodal failures were very uncommon. Late vaginal and bone toxicity was observed in addition to gastrointestinal toxicity.

Conclusions: CRT is a highly effective approach in anal cancer. However, subgroups of patients fare relatively poorly, and novel approaches are needed. Elective inguinal irradiation can be safely omitted only in patients with Stage I disease. Vaginal toxicity and insufficiency fractures of the hip and pelvis are important late effects that require prospective evaluation.

Reprint requests to: Dr. Jonathan M. Tomaszewski, Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria 8006, Australia. Tel: (+61) 3-9656-1111; Fax: (+61) 3-9656-1424; E-mail: jonathan.tomaszewski@petermac.org

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 83, No. 2, pp. 552−558, 2012
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2011.07.007

requiring prospective evaluation include vaginal toxicity and insufficiency fractures of the hip and pelvis.

Keywords: Anal cancer, Chemoradiation, Inguinal irradiation, Patterns of failure, Late toxicity

Introduction

The pioneering work of Nigro *et al*. (1, 2) resulted in the widespread adoption of definitive chemoradiation (CRT) as a sphincter-sparing approach for localized squamous cell carcinoma (SCC) of the anal canal. Subsequent randomized Phase III trials confirmed the superiority of CRT with 5-fluorouracil (5FU) and mitomycin (MMC) over radiotherapy (RT) alone (3, 4) and the importance of MMC in the regimen (5), with efficacy at least equivalent to that in historical surgical series. Neither induction or maintenance chemotherapy, nor the replacement of MMC with cisplatin, have produced any additional benefit (6–8).

Except for recent reports analyzing the Radiation Therapy Oncology Group (RTOG) randomized trials (9–11), much of our knowledge regarding prognostic factors in anal SCC comes from either small retrospective series or series using heterogeneous combinations of radiation and chemotherapy.

Chemoradiation for anal cancer produces significant acute morbidity, which has been well documented. However, far less is known about late morbidity and quality of life outcomes. There is increasing interest in the use of conformal techniques such as intensity-modulated radiotherapy (IMRT) to reduce toxicity while maintaining (or potentially improving) tumor control, and early reports are encouraging. The use of IMRT depends on accurate target volume delineation, which requires a precise knowledge of the failure patterns in anal cancer. To date, however, data on patterns of failure in the published literature have been very limited.

At the Peter MacCallum Cancer Centre, patients with anal SCC have been treated with a combination of RT and 5FU/MMC without a planned treatment break since the 1980s (12), and this remains the standard of care in most cancer centers worldwide. The standardized approach used at our center over 25 years provides an opportunity to explore the clinical biology of anal cancer in a large cohort of patients treated in a homogeneous fashion. The aim of this retrospective study was to analyze prognostic factors for tumor control and survival, patterns of relapse, and late toxicity in patients with anal SCC treated with definitive CRT.

Methods and Materials

Hospital records of patients with localized SCC of the anal canal or margin treated with definitive CRT at the Peter MacCallum Cancer Centre between February 1983 and February 2008 were retrospectively reviewed. Data collection was approved by the institutional ethics committee.

Staging procedures

Disease was staged according to the American Joint Commission on Cancer staging system, 7th edition (2010). Pretreatment assessment included history, physical examination, examination under anesthesia, proctoscopy and biopsy of the primary site, chest radiography or computed tomography (CT) of the chest, and CT of the abdomen and pelvis. Suspected inguinal lymph node involvement was confirmed with fine needle aspiration or excisional biopsy. Endorectal ultrasound, magnetic resonance imaging of the pelvis, and 18-fluorodeoxyglucose positron emission tomography (PET) were performed in the latter part of the study period.

Treatment

Except for 1 patient, all were treated with definitive CRT without a scheduled treatment interruption. The standard regimen consisted of RT to a total dose of 50.4 to 54 Gy by use of a three-phase technique. Phase 1 used parallel-opposed anterior and posterior fields to a dose of 36 Gy in 20 fractions. The superior field border was 1 centimeter above the inferior sacroiliac joints or 5 centimeters proximal to the primary tumor, whichever was more proximal. The lateral borders were at the lateral acetabulum (if inguinal nodes were negative) or the anterior superior iliac spine (if inguinal nodes were positive). The inferior border was 3 centimeters below the primary tumor. Phase 2 used a three-field technique with posterior, left lateral, and right lateral beams to a dose of 45 Gy in 25 fractions. The superior and inferior borders were as for Phase 1, with lateral borders 2 centimeters beyond the pelvic brim, the anterior border 3 centimeters anterior to the primary tumor, and the posterior border 2 centimeters posterior to the anterior sacral margin. Phase 3 used a three-field technique to boost the anal canal and primary tumor with a 3-centimeter margin to a total dose of 50.4 to 54 Gy. Involved inguinal nodes were boosted to the same dose as the primary site using electron fields. In patients with Stage I disease, elective inguinal irradiation was omitted, and a two-phase technique using posterior, left lateral, and right lateral beams was used throughout the treatment. A minority of patients during the 1980s and early 1990s were treated with alternative techniques and/or different doses, and during this time elective inguinal irradiation was not routinely used. Eighty percent of patients received doses between 50.4 and 54 Gy.

Standard concurrent chemotherapy was infusional 5FU 1 g/m^2 for 4 days in Weeks 1 and 5, with MMC 10 mg/m^2 on Day 1. From 1997 onward, many patients received protracted infusional 5FU 300 mg/m^2 for 96 hours each week within a clinical trial. Treatment characteristics are presented in Table 1.

Follow-up

After the completion of CRT, patients were reviewed regularly to ensure resolution of acute toxicity and for response assessment. After complete response was documented, patients were seen every 3 months for 2 to 3 years, and less frequently thereafter. At each visit, physical examination including digital rectal examination and inguinal node palpation was performed. Biopsy was performed in the context of persistent or progressive disease clinically or radiologically. Posttreatment PET became routine