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Original Article

# Implementing Intensity-modulated Radiotherapy with Simultaneous Integrated Boost for Anal Cancer: 3 Year Outcomes at Two Sydney Institutions

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## Abstract

*Aims:* Modern chemoradiotherapy used for the treatment of anal cancer has significant acute toxicity. Intensity-modulated radiotherapy (IMRT) may reduce these side-effects. We report our experience implementing IMRT with simultaneous boost at the Sydney Cancer Centre and Royal North Shore Hospital.
*Materials and methods:* We retrospectively collected acute toxicity data on all consecutive patients treated definitively with IMRT between January 2008 and December 2011. Patients received concurrent 5-fluorouracil and mitomycin-C. The radiotherapy dose varied by stage in accordance with the Radiation Therapy Oncology Group (RTOG) 0529 protocol. The first 30 plans were evaluated for adherence to RTOG 0529 dose specifications. Locoregional control and survival outcomes were analysed in July 2014.
*Results:* We included 42 patients (stage I 12%; II 41%; III 45%) with a median follow-up time of 43 months. At 3 years the locoregional control was 94% (95% confidence interval: 78–99), overall survival was 92% (95% confidence interval: 78–97), disease-free survival was 89% (95% confidence interval: 73–96), metastasis-free survival was 89% (95% confidence interval: 73–96) and colostomy-free survival was 89% (95% confidence interval: 72–96). There was no acute grade 4 toxicity. Acute grade 3 toxicity rates were: dermatological (33%), gastrointestinal (14%) and haematological (19%). Twenty-six per cent of patients were hospitalised for treatment-related toxicity. Only 12% required a treatment break greater than 3 days. All patients achieved RTOG 0529 planning target volume dose specifications. Most critical organ dose constraints were either met or met with minor deviation. The exception was 76% major deviation in small bowel constraints. Despite this no increase in gastrointestinal toxicity was observed.
*Conclusions:* IMRT with simultaneous integrated boost is safe and well tolerated in an unselected population. Most dose specifications are achievable. Excellent locoregional control and survival outcomes are achievable outside of a clinical trial setting.


*Key words:* Anus neoplasms; chemoradiotherapy; combined modality therapy; intensity-modulated; radiotherapy; squamous cell

## Introduction

Concurrent chemoradiotherapy is the standard of care for anal cancer. The pioneering work of Nigro and Gunter Seydel [1] showed equivalent local control and survival rates compared with surgical resection with chemoradiotherapy having the advantage of sphincter preservation. The subsequent United Kingdom Coordinating Committee on Cancer Research (UKCCR), European Organisation for Research and Treatment of Cancer (EORTC) and Anal Cancer Trial II (ACT II) and a systematic review confirmed the efficacy of radiotherapy combined with 5-fluorouracil and mitomycin-C [2–5].

However, concurrent chemoradiotherapy is associated with significant acute toxicity. Historically, the large opposed

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radiotherapy fields, such as those described in the ACT II trial protocol, delivered a high dose to the midline pelvic structures [6]. The resulting toxicity limits the total dose that may be safely given and patients often need a treatment break. Furthermore, local control may be compromised by these breaks that lengthen overall treatment time [7]. Intensity-modulated radiotherapy (IMRT) has the potential to further improve outcomes by reducing acute toxicity and therefore minimising treatment interruption.

IMRT has a dosimetric advantage over conventional radiotherapy. Brooks *et al.* [8] compared IMRT and conventional plans using the UK ACT II protocol, revealing a significant reduction in the dose delivered to the external genitalia, small bowel, bladder and femoral heads using IMRT. International retrospective trials have confirmed these findings. These trials also show excellent local control rates, reduced treatment interruption and acceptable toxicity [9–12]. Given these potential advantages, at the Sydney Cancer Centre, anal cancer was the first site to be chosen for IMRT outside the head and neck.

Anal cancer has been treated with IMRT and simultaneous integrated boost at the Sydney Cancer Centre and Royal North Shore Hospital since 2008. The results achieved in international trials are not always readily transferable to single institutions and this paper reports our experience. Here we retrospectively analysed the 2008–2011 cohort and report our acute toxicity and 3 year cancer outcomes.

## Materials and Methods

We included all consecutive patients who commenced definitive chemoradiotherapy between 1 January 2008 and 31 December 2011 (Figure 1). The study was approved by the relevant local ethics committees. A sample size of greater than 40 patients was chosen to be consistent with other reported international series. The data were collected by retrospective chart review of electronic records and plan evaluation. Where clinical notes were unavailable the patient or their general practitioner was contacted to determine disease and survival status. The study was completed on 31 July 2014, allowing for a median follow-up time of greater than 3 years for the cohort. This was selected as a clinically relevant time point as very low failure rates were reported after 3 years in the ACT II trial [4].

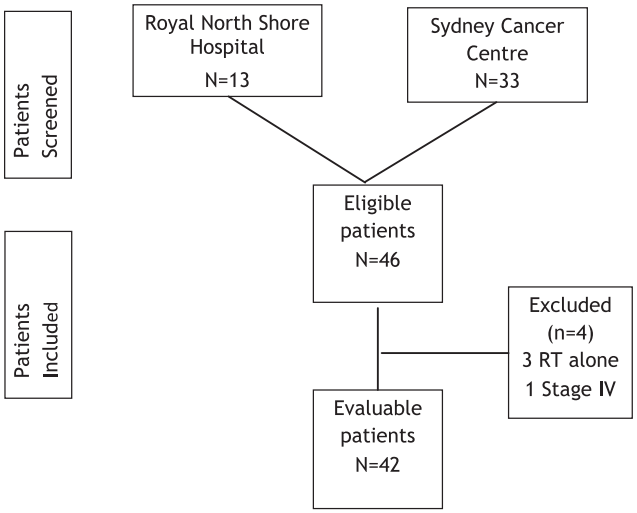


**Fig 1.** Flow diagram.

All patients had biopsy proven anal squamous cell carcinoma (inclusive of basaloid and cloacogenic) and were staged with computed tomography, positron emission tomography (PET; $n = 34$), colonoscopy and/or Transrectal Ultrasound (TRUS; $n = 9$). All patients were treated definitively with IMRT and concurrent chemotherapy. A treatment break or dose reduction was at the discretion of the treating physician, usually in the case of multiple grade 3 or grade 4 toxicity. Patients were admitted to hospital for supportive care in an attempt to minimise treatment breaks. Patients were reviewed weekly during treatment and followed up at 4 weeks. They were monitored closely until a clinical response was achieved and then reviewed 3 monthly for 2 years and 6 monthly up to 5 years. A clinical examination was carried out at each appointment and imaging was at the discretion of the clinician. PET was only used in follow-up if a recurrence was suspected.

### *Radiotherapy Planning and Treatment*

The radiotherapy technique was the same at both institutions. Computed tomography simulation was in the supine position, under knee block and ankle stocks for immobilisation, with an anal marker and a comfortably full bladder.

Australasian Gastrointestinal Trials Group (AGITG) guidelines [13] were used to assist the delineation of the primary and nodal volumes. The primary gross tumour volume was defined with reference to imaging, the clinical examination and, when available, with PET fusion. The primary clinical target volume (CTV) included the gross visible tumour, the entire anal canal from the anorectal junction to the anal verge including the internal and external anal sphincters with a 1.5 cm expansion. The elective nodal CTV, including the mesorectal, presacral and ischiorectal spaces, bilateral inguinal, obturator, internal and external iliac lymph nodes, was created by expanding the involved and uninvolved nodal regions by 1.0 cm. All CTV expansions were modified to respect anatomical boundaries. A 0.5–1.0 cm margin was added to the CTV to form the planning target volume (PTV). Critical structures (small bowel, femoral heads, iliac crests, external genitalia and bladder) were also contoured. For the small bowel, the entire peritoneal cavity was contoured at Royal North Shore Hospital. At the Sydney Cancer Centre, contouring included both individual loops of bowel and the peritoneal cavity.

All patients were treated with seven-field IMRT. Both institutions specified doses (Table 1) and dose constraints (Table 2) in accordance with the Radiation Therapy Oncology Group (RTOG) 0529 protocol [14]. Radiotherapy was delivered daily at 1.5–1.8 Gy per fraction, five fractions per week with no planned treatment breaks. Cone beam computed tomography was used for treatment verification and image guidance.