Clinical Oncology xxx (2018) 1–8

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Intensity-modulated Radiotherapy for Anal Cancer: Dose–Volume Relationship of Acute Gastrointestinal Toxicity and Disease Outcomes

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Received 14 April 2018; received in revised form 29 June 2018; accepted 4 July 2018

Abstract

Aims: Intensity-modulated radiotherapy (IMRT) is increasingly used in the treatment delivery of chemoradiotherapy in anal cancer with the ability to reduce toxicity. We report on 4 year outcomes since the introduction of IMRT and identify the most predictive bowel organ at risk that correlates with acute diarrhoea.
Materials and methods: Fifty-eight patients receiving definitive chemoradiotherapy for squamous or basaloid cell anal carcinoma (T1-4NanyM0) were reviewed. Fifty-four per cent of patients had stage III disease and most (79%) were treated with a dose of 54 Gy in 30 fractions. Patient acute gastrointestinal toxicity was recorded using Common Terminology Criteria of Adverse Events (CTCAE) diarrhoea grading. Four different methods of bowel were re-contoured for each patient and correlated with acute diarrhoea. Locoregional control and overall survival were analysed.
Results: CTCAE grade 3 or more diarrhoea occurred in 11/58 patients (19%). Seven patients did not complete treatment; 10 patients (17%) required a treatment break of 3 or more days. 'Bowel cavity' was the best predictor of acute grade 3 toxicity using volume ($P = 0.002$) or volume to bowel cavity in 5 Gy bins (V5–V50Gy); $P < 0.05$. Bowel cavity V30Gy $\leq$ 300 cm^3 predicts a 6% grade 3 diarrhoea risk versus $>$ 300 cm^3 predicts a 42% risk. Four year progression-free survival was 84% (95% confidence interval 73–92%) and overall survival was 88% (95% confidence interval 75–95%).
Conclusion: Chemoradiation using IMRT provides excellent local control and acceptable acute gastrointestinal toxicity. Bowel cavity is the most sensitive predictor for grade 3 versus grade 0–2 diarrhoea, with any volume receiving 5–50 Gy discriminatory.

Key words: Anal cancer; diarrhoea; dose–volume relationship; gastrointestinal toxicity; intensity-modulated radiotherapy

Introduction

Chemoradiation (CRT) is the standard of care for the curative treatment of localised anal squamous cell carcinoma, which permits sparing of the sphincter by avoidance of surgery and a permanent stoma. Previous trials have shown the benefit of CRT versus radiotherapy alone [1,2]. The radiation techniques used in these previous trials involved treatment fields delivered with traditional planning techniques, such as two- and three-dimensional conformal radiotherapy (2D/3DCRT), often delivering excessive dose to the small bowel and skin, which resulted in diarrhoea and skin desquamation and increased risk of treatment breaks. The CRT arm of the RTOG 98-11 trial reported a grade 3 diarrhoea rate of 23.4% [3]. Radiotherapy treatment breaks have been associated with inferior local control [4].

Intensity-modulated radiotherapy (IMRT) has become the increasingly accepted treatment technique in anal cancer as it allows more conformal dose delivery, enabling better target dose coverage while lowering dose to the surrounding organs at risk (OAR), particularly the bowel, reducing the risk

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https://doi.org/10.1016/j.clon.2018.07.020
0936-6555/

of developing severe radiation diarrhoea. The use of IMRT in anal cancer is increasingly showing comparable local control rates with less toxicity. Particularly, the RTOG 05-29 phase II trial of IMRT in anal cancer showed excellent local control and reduced acute gastrointestinal toxicity and shorter treatment breaks compared with the RTOG 98-11 trial, which used 2D/3DCRT techniques [5].

Devisetty *et al.* [6] reported a correlation of bowel dose with acute bowel toxicity. Knowledge of the bowel dose–volume relationship in patients undergoing CRT can better allow dose optimisation to minimise gastrointestinal toxicity and assist clinicians to better predict and manage which patients may be at greater risk of severe gastrointestinal toxicity.

We started IMRT in the treatment of anal cancer at GenesisCare Victoria in 2009. Our aims were to report on acute radiation-induced diarrhoea and correlate with dose–volume metrics and to report 4 year disease outcomes using IMRT.

Materials and Methods

Study Design

Our local institution board approved the study prior to commencement. All patients' electronic medical records were retrospectively reviewed and previous archived treatment plans were restored for dose–volume analysis.

Participants

Patient and tumour characteristics are given in Table 1. Fifty-eight patients with histologically confirmed squamous cell carcinoma or basaloid histology treated with definite CRT between 1 July 2010 and 30 June 2014 were identified. The AJCC 7th edition clinical stages included T1-T4N0-N3M0. The median age was 60 years; 72% of patients were female. Most patients were staged with computed tomography of the abdomen and pelvis ± computed tomography of the chest (95%), magnetic resonance imaging (MRI; 55%) and fluorodeoxyglucose positron emission tomography (FDG-PET; 71%). Only 12% had T1 disease and 53% were node negative (N0) with stage breakdown: I ($n = 4$), II ($n = 23$), IIIA ($n = 12$) and IIIB ($n = 19$).

Radiotherapy Planning and Treatment

All patients were immobilised in the supine position using either knee supports with ankle stocks or a vacuum immobilisation device. Patients were encouraged to have a comfortably full bladder where possible.

There were six radiation oncologists, who treated the patients across six networked radiotherapy centres. Contouring guidelines including OAR were made available at the time of introduction of IMRT at our centres and were based upon the Australian Gastrointestinal Trials Group (AGITG) national consensus guidelines published in 2012 [7]. The gross tumour volume was defined by clinical examination, MRI and PET. The primary clinical target volume included the anal canal with at least a 1 cm circumferential margin. The clinical target for gross nodal disease included a margin of at least 1 cm. Elective nodal irradiation included the mesorectum, pre-sacral, obturator, internal iliac, external iliac and inguinal lymph nodes. A margin of 5–10 mm was used to expand all clinical target volumes to planning target volumes (PTVs).

Table 1
Patient and tumour characteristics

			n	%
Gender	Male		16	28
	Female		42	72
Age at the start of radiotherapy	Median (range)		60 (31–82)	
Histology	Squamous cell carcinoma		52	90
	Basaloid squamous cell carcinoma		6	10
Grade	Well differentiated		3	5
	Moderately differentiated		12	21
	Poorly differentiated		24	41
	Not graded		19	33
Investigations	CT		55	95
	PET		41	71
	MRI		33	55
Staging AJCC 7th Edition	I	T1N0	4	7
	II	T2N0	16	28
		T3N0	7	12
	IIIA	T1–T3N1	8	14
		T4N0	4	7
	IIIB	T4N1	1	2
		TanyN2	17	29
		TanyN3	1	2

CT, computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging.

Please cite this article in press as: Ng M, et al., Intensity-modulated Radiotherapy for Anal Cancer: Dose–Volume Relationship of Acute Gastrointestinal Toxicity and Disease Outcomes, Clinical Oncology (2018), https://doi.org/10.1016/j.clon.2018.07.020