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Original Article

Intensity-modulated Radiotherapy and Anal Cancer: Clinical Outcome and Late Toxicity Assessment

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Abstract

Aims: To assess the potential impact on long-term consequences of treatment (intensity-modulated radiotherapy with concomitant chemotherapy) in patients diagnosed with anal cancer.
Materials and methods: We identified 43 eligible patients treated with concomitant chemoradiotherapy (pelvic intensity-modulated radiotherapy) at the Royal Marsden Hospital between 2010 and 2013. We determined late genitalia and bowel side-effects using specific questionnaires [Pelvic Symptom Questionnaire, Vaizey Incontinence Questionnaire, Inflammatory Bowel Disease Questionnaire (IBDQ) and IBDQ-B]. Using descriptive statistics, we report clinical outcomes in all patients, by time, since the end of treatment (grouped as 1–1.5, 1.5–2.5 and 2.5–3.5 years).
Results: Twenty-seven of 43 (63%) patients were identified as available for questionnaire follow-up. Reasons for unavailability were death ($n = 3$), lost to palliative care service ($n = 1$), referred to surgery ($n = 4$), lost to follow-up ($n = 8$). In the 27 patients studied, bowel toxicity was assessed by IBDQ, IBDQ-B and the Vaizey Incontinence Questionnaire. The median value was 208 for IBDQ, 38 for IBDQ-B and 3.0 for the Vaizey Incontinence Questionnaire, as assessed at 1 year or more post-completion of treatment. Treatment was reported to affect quality of life/sexual function in two of the female patients ($n = 21$) and three male patients ($n = 6$). No insufficiency fractures have been reported. Bone marrow function remained stable over the time of the follow-up.
Conclusions: Although there are data supporting a reduction in acute effects using intensity-modulated radiotherapy in anal cancer, there is very little in the literature to establish the late toxicity profile. Our results indicate that there is an effect on bowel and sexual function, but it does not increase over the period observed. These data provide a benchmark against which to compare outcomes with future manipulation in treatment, and provide us with real information to give patients as to the expectation of their functional outcome after treatment.

Key words: Anal cancer; IMRT; radiotherapy; toxicity

Introduction

Intensity-modulated radiotherapy (IMRT) is an advanced radiotherapy technique that allows more precise radiation delivery to the target volume while minimising dose to adjacent normal tissues [1–4]. It therefore has the potential to maintain or increase tumour control rates via dose escalation, while reducing the consequences of treatment. Its application to different tumour sites requires evaluation in order to establish its role, and potential superiority, in clinical practice.

The standard of care for patients with anal cancer is chemoradiation, but the complex target volume, multiple adjacent normal tissues and the large treatment volume carries with it high rates of treatment-related morbidity [1,5–7]. IMRT probably has most to offer in treatment sites with the characteristics mentioned above and its role has been evaluated in a number of sites where normal tissue exclusion and late effects of treatment remain challenging. In these settings, it has been possible to show a reduction in late toxicity, and good examples of these are head and neck studies and prostate cancer trials [8–13].

The complex anatomical target volume arises because the anal canal is an inferior–posterior pelvic structure, whereas nodal spread is both anteriorly (inguinal nodes) and superiorly (mesorectal, external iliac and internal iliac

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nodes). Covering these target volume components appropriately with conventional radiotherapy techniques means the inclusion of large volumes of bowel, bladder and genitalia. IMRT techniques offer the potential to reduce the dose to these normal structures while maintaining, or improving, the dose distribution to the target volume. Several studies have already shown the effect of IMRT on acute toxicity (a reduction in grade 3/4 toxicity for gastrointestinal and genitourinary effects) [4–6,14–18]. In a rare cancer such as anal cancer, and with a number of other treatment questions to be addressed, it is critical to document outcomes from patients treated with IMRT in order to reliably inform patients of the probable effects and to provide baseline data on late toxicity as a benchmark against which future technical modifications can be compared.

With this in mind, we conducted an evaluation of outcomes in anal cancer patients treated with IMRT between 1 and 3.5 years previously. The outcomes reported cover function, local control, metastatic recurrence and survival.

Materials and Methods

This study was carried out as a service evaluation and was approved by the Royal Marsden Committee for Clinical Review. The service evaluation incorporated asking evaluable patients to complete three questionnaires related to bowel function and one questionnaire related to genitalia/sexual function. Tumour outcomes were assessed from clinical follow-up data and normal tissue doses from radiotherapy plans.

In this prospective observational study, we identified a population of 43 patients (Table 1) with squamous cell anal cancer who were treated with radical intent. None of the patients had surgery/colonostomy before starting chemoradiotherapy. The population comprised consecutive patients treated between late 2010 and 2013, all being treated with pelvic IMRT and concomitant chemotherapy. The radiotherapy was giving in two phases, with the dose fractionation being that used in ACT II anal cancer protocol [19]. The target volumes were gross primary anal tumour volume (GTVa), which was expanded 15 mm isotropically to create clinical anal target volume (CTVa), edited to ensure coverage of anal canal from the anorectal junction to the anal verge, including external and internal sphincters, and to exclude bone. If nodal disease was present, a GTVn was drawn (involved nodal region) and expanded 10 mm isotropically to create CTVn (edited off bone).

The elective nodal areas (bilateral inguinal, external iliac, internal iliac, obturator, mesorectal and pre-sacral lymph nodes) were outlined as CTVe.

CTVa, CTVn and CTVe were then combined and expanded 10 mm to create a planning target volume (PTV)-elective, while a 25 mm margin was added isotropically to the GTVa to create a PTVa.

CTVn, if present, was expanded with 10 mm of uniform margin to obtain PTVn.

Phase I used an IMRT technique to deliver 30.6 Gy in 17 fractions, encompassing the identified primary tumour and any involved nodes, and also the elective pelvic nodes (PTV-elective). Phase II delivered 19.8 Gy in 11 fractions to the primary tumour area (PTVa) and positive nodes (PTVn), and this was either delivered using an IMRT technique, if it was a large complex volume, or by a conventional conformal technique for smaller node-negative tumours. In our cohort of patients, 23 received a conformal phase II and 10 patients received an IMRT phase II. Chemotherapy comprised capecitabine 1250 mg/m^2 /day in two divided doses, continuously throughout the radiotherapy, with mitomycin C 12 mg/m^2 (maximum 20 mg) on the first day of radiotherapy only. Two patients who were not able to tolerate oral chemotherapy switched from capecitabine to 5-fluorouracil 1000 mg/m^2 continuous infusion days 1–4 and days 29–32 (weeks 1 and 5).

Table 1
Demographics

			Patients completing questionnaires ($n = 27$)
Gender	Female	31 (72%)	21 (78%)
	Male	12 (28%)	6 (22%)
Performance status	0	25 (58%)	22 (81%)
	1	12 (28%)	5 (19%)
	2	1 (2%)	0 (0%)
	Not known	5 (12%)	0 (0%)
T-stage	1	9 (21%)	7 (26%)
	2	21 (49%)	13 (48%)
	3	3 (7%)	2 (7%)
	4	10 (23%)	5 (19%)
N-stage	0	31 (72%)	20 (74%)
	1	4 (9%)	3 (11%)
	2	4 (9%)	3 (11%)
	3	4 (9%)	1 (4%)
Age	Minimum	47	47
	Median	60	58
	Maximum	84	84

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