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Short Report

Early-stage Favourable Anal Cancer: A Retrospective Analysis of Clinical Outcomes of a Moderately Low Dose Elective Nodal Intensity-modulated Radiotherapy Schedule

L. Lestrade [*§], T. Zilli [*§], M. Kountouri [*], R. Jumeau [†], O. Matzinger [‡], J. Bourhis [†], R. Miralbell [*], M. Ozsahin [†¶], B. De Bari [†¶]

[*] *Radiation Oncology, Geneva University Hospital – HUG, Geneva, Switzerland*
[†] *Radiation Oncology, Centre Hospitalier Universitaire Vaudois – CHUV, Lausanne, Switzerland*
[‡] *Radiation Oncology, Riviera Hospital, Vevey, Switzerland*

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Abstract

In this retrospective study we evaluated the long-term results of 35 early-stage favourable T1-2 N0 M0 anal cancer patients treated with intensity-modulated radiotherapy techniques combining low dose prophylactic inguinal-pelvic irradiation with dose-escalated boost. Optimal locoregional control and good tolerance makes this treatment a valuable alternative to brachytherapy boost and involved-field radiotherapy plans.

Key words: Anal cancer; early-stage; IMRT; local control; radiotherapy; toxicity

Introduction

Early T1-T2, node-negative anal cancers represent a heterogeneous disease entity and their outcome has been frequently associated with the primary tumour diameter, the extension of anal circumference and tumour mobility [1,2]. Node-negative, not-fixed anal tumours ≤3 cm in size involving less than three-quarters of the anal circumference characterise a subset of early-stage favourable tumours [2] that are potential candidates for small-volume radiotherapy treatments, brachytherapy boost implants or dose de-intensified concomitant chemotherapy regimens.

However, the best therapeutic approach for early-stage more favourable anal cancers is still unknown, with large variability of management [3]: the role of inguinal irradiation [4–6], the use of concomitant chemotherapy [7,8] and modern radiotherapy techniques [9,10], as well as the optimal treatment field arrangement [11,12], boost modality [13–15] and radiotherapy dose [11,16] remain open issues that need further investigation.

The purpose of this study was to assess the outcome and the side-effect profile of rotational and static intensity-modulated radiotherapy (IMRT) techniques delivering a moderately–low dose to the pelvic and inguinal nodes for patients presenting a favourable early-stage anal cancer.

Materials and Methods

Thirty-five early-stage, favourable anal cancer patients (i.e. clinically node-negative, not-fixed, diameter ≤3 cm and involving less than three-quarters of the anal circumference) were identified among 139 histologically proven anal tumours consecutively treated with curative IMRT between March 2006 and February 2014 in two academic radiotherapy departments.

The median age at diagnosis was 60 years (range 36–87 years), with a male:female ratio of 7:28. All patients underwent a pre-treatment evaluation with a digital rectal

Author for correspondence: T. Zilli, Radiation Oncology Department, Geneva University Hospital, CH-1211 Geneva 14, Switzerland.
Tel: +41-22-37-27-090; Fax: +41-22-37-27-117.
E-mail address: Thomas.Zilli@hcuge.ch (T. Zilli).
§ These authors equally contributed as first authors to this study.
¶ These authors equally contributed as senior authors to this study.

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examination, ano-rectal echo-endoscopy and radiological staging by abdominal-pelvic computed tomography scans, pelvic magnetic resonance imaging (MRI) ($n = 20$) and/or ^{18}FDG positron emission tomography-computed tomography (PET-CT; $n = 12$).

According to the American Joint Committee on Cancer 6th Edition staging classification [17], 19 patients (54%) presented a T1 lesion, whereas 16 patients (46%) were classified as having a T2 disease. The median tumour size determined by combining clinical and radiological data was 2 cm (range 0.8–3 cm). The primary histology was, in all patients, squamous cell carcinoma with different tumour grading (grade 1 in seven patients, 20%; grade 2 in five patients, 14%; and grade 3 in 23 patients, 66%), including basaloid features in six patients (17%). The anal canal was involved in 24 patients (69%), whereas the anal margin and anorectal junction were the tumour location in six (17%) and five patients (14%), respectively.

An elective dose of 36 Gy (20×1.8 Gy per fraction, five times a week) was delivered to the pelvic nodal regions from the L5–S1 level down to the inguinal nodes, including a 0.5 cm expansion to create the planning target volume using either rotational ($n = 23$) or static ($n = 12$) IMRT techniques. The clinical target volume (CTV) was initially defined by encompassing the mesorectum and the internal iliac, external iliac and inguinal vessels with a 0.7–1 cm margin. Starting from 2009, the Radiation Therapy Oncology Group (RTOG) atlas guidelines for anorectal cancers were used to define the elective CTV [18].

After a planned gap of 1 or 2 weeks, a sequential boost to the anal tumour defined as the gross tumour volume including two 0.5 cm isotropic expansions for CTV and planning target volume was delivered five times a week to 23.4 or 24 Gy in 1.8 or 2 Gy per fraction, respectively. The median total delivered dose to the anal tumour was 59.4 Gy. Treatment verifications were made using daily image-guided radiotherapy (IGRT) modalities. Concomitant chemotherapy was delivered to most patients ($n = 28$, 80%). In the remaining seven patients, based on the decision of the medical oncologists, chemotherapy was not delivered for the following reasons: T1 anal disease in four patients; one 87-year-old patient with multiple comorbidities; one frail patient with a pre-existing chronic kidney disease; and one patient's refusal. Table 1 summarises the treatment characteristics.

The follow-up consisted of a physical examination, including an anorectal inspection 4–6 weeks after the end of the treatment and every 3 months during 12 months. Once complete regression had been documented, follow-up consisted of 6 monthly visits. PET-CT or MRI was only carried out if there was doubt about local or distant recurrence. The median follow-up was 46 months (range 6–98). Acute and late toxicities were retrospectively scored using the CTCAE v.4.0 grading scale, whereas haematological toxicities were graded using the European Organization for Research and Treatment of Cancer (EORTC)-RTOG scoring system for acute side-effects. The statistical analysis was carried out using the SPSS statistical software package (IBM SPSS v.22). Four year actuarial survival rates with corresponding standard errors for clinical outcomes were calculated using the Kaplan–Meier method.

Table 1
Treatment characteristics ($n = 35$)

Characteristics	*n* (%)
Overall treatment time, days	
Median (range)	56 (48–71)
Planned gap between courses	
Yes*	30 (86)
No	5 (14)
Gap duration, days (n=30)	
Median (range)	10 (5–26)
Radiotherapy total dose (elective+boost), Gy	
Median (range)	59.4 (59.4–63)†
Radiotherapy elective dose, Gy	
Median (range)	36 (36–39.6)†
Radiotherapy technique pelvis	
IMRT	12 (34)
VMAT	3 (9)
Helical tomotherapy	20 (57)
Radiotherapy boost dose, Gy	
Median (range)	23.4 (23.4–24)
Radiotherapy technique boost	
3D-CRT	25 (72)
IMRT	2 (6)
VMAT	4 (11)
Helical tomotherapy	4 (11)
Concomitant chemotherapy	
Yes	28 (80)
No	7 (20)
Chemotherapy type	
MMC/5-FU	17 (61)
MMC/capecitabine	7 (25)
Capecitabine alone	2 (8)
MMC/capecitabine/panitumumab	1 (4)
MMC/5-FU→capecitabine	1 (4)

IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; MMC, mitomycin C; 5-FU, 5-fluorouracil.

* Until 2011.

† One patient treated with definitive radiotherapy to a cumulative dose of 63 Gy (39.6 Gy + 23.4 Gy boost).

Results

All patients completed treatment as planned, with 30 patients treated by a split course with a median gap of 10 days between the elective and the boost treatment phases. At the time of this analysis, one patient with a T1 poorly differentiated anal canal tumour treated with exclusive radiotherapy without concomitant chemotherapy presented a local recurrence occurring 12 months after the end of radiotherapy. He was salvaged with abdomino-perineal resection with no evidence of disease at the last follow-up, 97 months after the end of radiotherapy. The corresponding 4 year local relapse and colostomy-free survival rates for the whole population were $96.6 \pm 4.3\%$ (Figure 1) and $96.3 \pm 3.6\%$, respectively. No pelvic, inguinal or distant recurrences have been observed, otherwise. Two deaths

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