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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.

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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.

examination, ano-rectal echo-endoscopy and radiological staging by abdominal-pelvic computed tomography scans, pelvic magnetic resonance imaging (MRI) ($n = 20$) and/or ^{18}F 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

Table 1Treatment characteristics ($n = 35$)

Characteristics	<i>n</i> (%)
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).

corresponding standard errors for clinical outcomes were calculated using the Kaplan–Meier method.

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

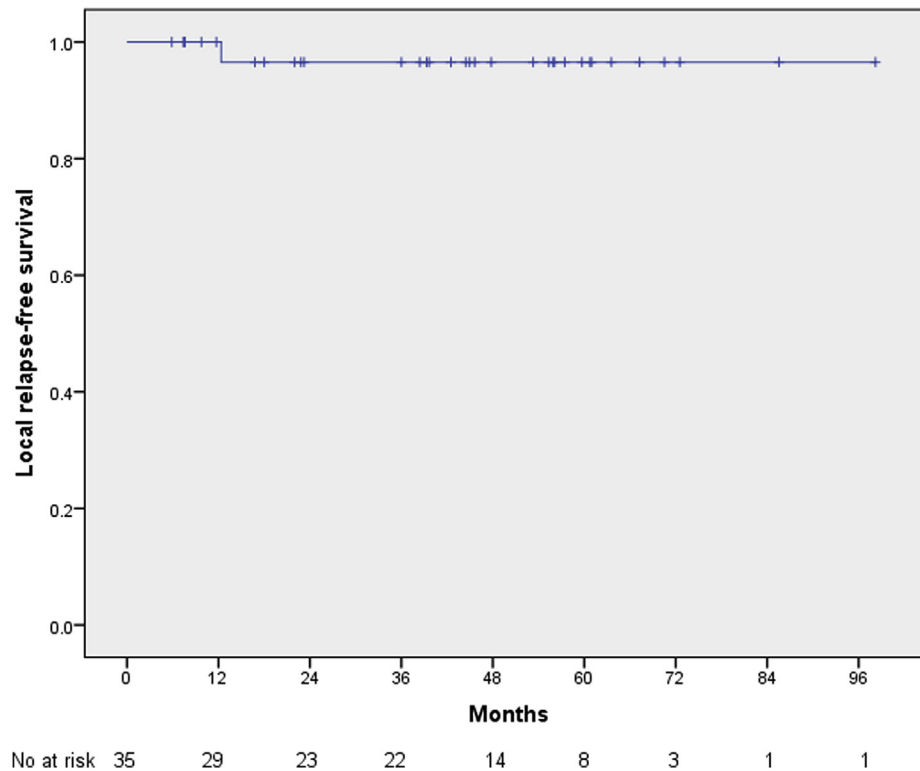


Fig 1. Local relapse-free survival Kaplan–Meier estimates.

from other causes were observed (death from colon and gastric metastatic cancer). The 4 year overall survival rate for the study population was $93 \pm 4.8\%$.

Overall, grade 3 acute toxicity was observed in seven patients (19.4%), consisting of erythema ($n = 4$) and/or diarrhoea ($n = 4$). No grade 4 acute toxicity was recorded. During treatment, haemoglobin levels and neutrophil and platelets counts remained in the normal range in 32 (92%), 30 (86%) and 28 (80%) patients, respectively. Only three patients presented with a grade ≥ 2 acute haematological toxicity, including one case of grade 3 neutropenia.

At the time of analysis, no grade ≥ 3 late side-effects were observed. Only five of 34 patients locally controlled presented with a grade 1 faecal incontinence for gas ($n = 2$) or liquid stools ($n = 3$) requiring the occasional use of pads.

Discussion

Despite the inherent bias of this small retrospective series, the results of this study are noteworthy as they provide new data and raise provocative questions concerning the best management of early-stage favourable anal cancers.

The results of the CORS-03 study showed that in anal cancer patients with lymph node involvement and even locally advanced disease there was a 20% better local control rate in patients treated with a brachytherapy boost compared with those treated with conventional two- or three-dimensional conformal external beam radiotherapy (EBRT) [13]. Despite the liberal selection criteria used in the

CORS-03 study to carry out brachytherapy implants (only 26% of the patients presented a T1-2 disease), higher precision and conformality of brachytherapy techniques as well as the possibility for dose escalation have been advocated to explain this difference. Nonetheless, long-term severe side-effects affecting sphincter function and quality of life have been reported using a brachytherapy boost technique [19,20]. In our series, all analysed patients were also potential candidates for a brachytherapy implant (tumours ≤ 3 cm in size, not-fixed, with less than three-quarters of anal circumference involvement). Using modern IMRT and IGRT techniques, up to 96% of our patients were locally controlled and colostomy-free at 4 years.

Overall treatment time (OTT) and treatment gap are major prognostic factors for disease control, as confirmed by preliminary results of the PARADAC EORTC pooled analysis [21]. Good tolerance to a moderately low elective irradiation dose using IMRT allowed an OTT reduction, thus omitting the planned gap and potentially improving the therapeutic ratio. In the CORS-03 trial, the median OTT in the EBRT group was 82 days, probably too long to get an optimal outcome for this group of patients [13]. Moreover, no difference in local control was observed in a single centre observational study between patients treated with EBRT versus EBRT + brachytherapy boost [8]. Indeed, the median OTT for patients in this study was 62 days, including a planned gap of 15 days in the EBRT group and of 46 days in the EBRT + brachytherapy group.

As far as the treatment field is concerned, a question arises on the role of prophylactic inguinal irradiation [12] compared with exclusive local involved-field radiotherapy

[4,11]. The inguinal failure rate for early-stage anal cancers varies from 7% to 22.5% when omitting coverage of the groins [4–6]. In our series, by delivering 36 Gy with IMRT to the elective regions prevented all nodal failures, with acceptable acute haematological toxicity rates and grade 3 skin toxicity limited to the anal margin, as previously reported [9,12]. Overtreatment is, however, not excluded, thus molecular imaging techniques [22] and sentinel node mapping [23] may help an optimised staging to better select candidates for small-volume strategies.

In our series, patients were treated with relatively high radiotherapy doses (59.4 Gy) delivered to the anal tumour. Although the existence of a linear quadratic-dose response model has been shown in anal cancer, dose individualisation with dose reduction in early-stage tumours may also be considered as a minimal effect of dose escalation is expected for early-stage disease [16]. Excellent local control and disease-free survival rates have been observed using low dose (30 Gy in 15 fractions) involved-field chemoradiotherapy regimens in patients with residual microscopic or very small volume tumours [11]. Interesting data on this issue are expected in the future from the results of the forthcoming ACT4 PLATO (Personalising Anal cancer radioTherapy dose) trial exploring prospectively in patients with early disease up to 4 cm the role of dose de-escalation radiotherapy to the anal tumour (41.4 Gy in 23 fractions) and to the elective nodal regions (34.5 Gy in 23 fractions, similar to the prophylactic radiotherapy dose used in our study) [24].

Although concomitant chemotherapy may be potentially reduced or omitted in this population at low risk of occult distant metastases, a synergistic or additive effect on local control has been observed for these early-stage tumours [7,8], supporting our strategy to deliver concomitant chemotherapy also in patients with early-stage disease.

In conclusion, IMRT techniques combining moderately low dose elective inguinal-pelvic irradiation with dose-escalated boost provide an effective balance between locoregional control and side-effects for early-stage favourable anal cancer, making this treatment a valuable alternative to brachytherapy boost and involved-field radiotherapy plans.

References

- [1] Myerson RJ, Outlaw ED, Chang A, et al. Radiotherapy for epidermoid carcinoma of the anus: thirty years' experience. *Int J Radiat Oncol Biol Phys* 2009;75:428–435.
- [2] Myerson RJ. Favorable anal cancer: does it include T2N0 disease? How might the electively irradiated nodal volume be reduced? *Int J Radiat Oncol Biol Phys* 2013;87:13–15.
- [3] Muirhead R, Drinkwater K, O'Cathail SM, et al. Initial results from the Royal College of Radiologists' UK National Audit of Anal Cancer Radiotherapy 2015. *Clin Oncol (R Coll Radiol)* 2017;29:188–197.
- [4] Matthews JH, Burmeister BH, Borg M, et al. T1-2 anal carcinoma requires elective inguinal radiation treatment – the results of Trans Tasman Radiation Oncology Group study TROG 99.02. *Radiother Oncol* 2011;98:93–98.
- [5] Ortholan C, Resbeut M, Hannoun-Levi JM, et al. Anal canal cancer: management of inguinal nodes and benefit of prophylactic inguinal irradiation (CORS-03 Study). *Int J Radiat Oncol Biol Phys* 2012;82:1988–1995.
- [6] Zilli T, Betz M, Bieri S, et al. Elective inguinal node irradiation in early-stage T2N0 anal cancer: prognostic impact on locoregional control. *Int J Radiat Oncol Biol Phys* 2013;87:60–66.
- [7] De Bari B, Lestrade L, Pommier P, et al. Could concomitant radio-chemotherapy improve the outcomes of early-stage node negative anal canal cancer patients? A retrospective analysis of 122 patients. *Cancer Invest* 2015;33:114–120.
- [8] Zilli T, Schick U, Ozsahin M, et al. Node-negative T1-T2 anal cancer: radiotherapy alone or concomitant chemo-radiotherapy? *Radiother Oncol* 2012;102:62–67.
- [9] Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys* 2013;86:27–33.
- [10] Ugurluer G, Ballerini G, Moeckli R, et al. Helical tomotherapy for the treatment of anal canal cancer: a dosimetric comparison with 3D conformal radiotherapy. *Tumori* 2015;101:268–272.
- [11] Hatfield P, Cooper R, Sebag-Montefiore D. Involved-field, low-dose chemoradiotherapy for early-stage anal carcinoma. *Int J Radiat Oncol Biol Phys* 2008;70:419–424.
- [12] Lepinoy A, Lescut N, Puyraveau M, et al. Evaluation of a 36 Gy elective node irradiation dose in anal cancer. *Radiother Oncol* 2015;116:197–201.
- [13] Hannoun-Levi JM, Ortholan C, Resbeut M, et al. High-dose split-course radiation therapy for anal cancer: outcome analysis regarding the boost strategy (CORS-03 study). *Int J Radiat Oncol Biol Phys* 2011;80:712–720.
- [14] Moureau-Zabotto L, Ortholan C, Hannoun-Levi JM, et al. Role of brachytherapy in the boost management of anal carcinoma with node involvement (CORS-03 study). *Int J Radiat Oncol Biol Phys* 2013;85:e135–e142.
- [15] Oehler-Janne C, Seifert B, Lutolf UM, et al. Clinical outcome after treatment with a brachytherapy boost versus external beam boost for anal carcinoma. *Brachytherapy* 2007;6:218–226.
- [16] Muirhead R, Partridge M, Hawkins MA. A tumor control probability model for anal squamous cell carcinoma. *Radiother Oncol* 2015;116:192–196.
- [17] Anus. *AJCC cancer staging manual*, 6th edn. New York: Springer; 2002. p. 125–128.
- [18] Myerson RJ, Garofalo MC, El Naqa I, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. *Int J Radiat Oncol Biol Phys* 2009;74:824–830.
- [19] Lestrade L, De Bari B, Pommier P, et al. Role of brachytherapy in the treatment of cancers of the anal canal. Long-term follow-up and multivariate analysis of a large monocentric retrospective series. *Strahlenther Onkol* 2014;190:546–554.
- [20] Papillon J, Montbarbon JF, Gerard JP, et al. Interstitial curietherapy in the conservative treatment of anal and rectal cancers. *Int J Radiat Oncol Biol Phys* 1989;17:1161–1169.
- [21] Matzinger O, Haustermans K, Maingon P, et al. Sphincter preservation in anal cancer: The EORTC PARADAC study. *Radiother Oncol* 2013;106:S146.
- [22] Jones M, Hruby G, Solomon M, et al. The role of FDG-PET in the initial staging and response assessment of anal cancer: a

- systematic review and meta-analysis. *Ann Surg Oncol* 2015; 22:3574–3581.
- [23] Tehranian S, Treglia G, Krag DN, et al. Sentinel node mapping in anal canal cancer: systematic review and meta-analysis. *J Gastrointest Liver Dis* 2013;22:321–328.
- [24] Sebag-Montefiore D, Adams R, Bell S, et al. The development of an umbrella trial (PLATO) to address radiation therapy dose questions in the locoregional management of squamous cell carcinoma of the anus. *Int J Radiat Oncol Biol Phys* 2016;96: E164–E165.