Sphincter-conserving Treatment of Carcinomas of the Anal Margin

Sabine Bieri, Abdelkarim S. Allal and John M. Kurtz

From the Cantonal Department of Radiation Oncology, Oncology Institute of Southern Switzerland (S. Bieri) and Division of Radiation Oncology, University Hospital, Geneva, Switzerland (A.S. Allal, J.M. Kurtz)

Correspondence to: Sabine Bieri, MD, Radiation Oncology, Hospital Sion-Hérens-Conthey, 1951 Sion, Switzerland. Tel: +41 27 603 4520. Fax: +41 27 603 4501. E-mail: sabine.bieri@hopsion.vsnet.ch

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Between April 1982 and December 1997 24 patients with carcinoma of the anal margin were treated with radiation therapy (RT) (10 patients) or RT-chemotherapy (CT) (14 patients). External beam RT (EBRT) was delivered in 18 patients, combined with brachytherapy in 5 patients, while one patient was treated with brachytherapy alone. Inguinal nodes were irradiated in 17 patients. Chemotherapy was based on 5-fluorouracil and mitomycin-C. At 5 years, the overall survival rate was 56% and the locoregional rate was 69.5%. Anal sphincter was preserved in 16/24 treated patients. Grade 4 late complications were observed in 3 patients. This study reinforces the notion that radical RT ± CT provides a high probability of cure and sphincter preservation in patients presenting with this rare condition. Major late toxicity is uncommon; a better adaptation of treatment technique to the individual clinical situation may prevent some of the more severe complications in the future.

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Anal margin carcinoma is a very rare disease, representing less than 15% of anal cancers (1, 2). While the definition of the anal canal has a sound anatomical basis (3, 4), perianal or anal margin cancers are defined arbitrarily as cancers arising from the skin within a 5–6 cm radius of the anal verge (5). Few series have described treatment results of anal margin carcinoma as defined above (2, 6–10). Thus, most of these tumors are included in series of anal cancers, where the results reported concern both canal and margin subsites. The anatomic definition of the anal margin has varied from one center to another, making a direct comparison between different treatment approaches difficult. Moreover, in advanced disease, the two subsites of the anus are both involved, making determination of the origin difficult or even impossible. While this distinction may be of some value when considering the approach to treatment (2, 11), recent data indicate that these two subsites probably share common etiopathogenic aspects (12), and a similar treatment outcome may perhaps be expected. However, some carcinomas arising in the anal margin may have other etiological factors, similar to carcinomas originating from the skin. On the other hand, tumor spread of anal margin carcinomas differs from those of the anal canal, leading to the use of a different UICC classification. Because few series in the literature specifically address the question of sphincter-conserving treatment in anal margin carcinomas, we undertook a retrospective study of patients with this rare condition treated in two Swiss radiation oncology departments.

MATERIAL AND METHODS

Patients

Twenty-four patients with carcinoma of the anal margin were treated by radiation therapy with or without chemotherapy between April 1982 and January 1998. For tumors involving both canal and margin, only those that clinically were judged to have originated in the anal margin were considered for this study. The primary tumor was classified according to the 1987 UICC (Union Internationale Contre le Cancer) system (4). Diagnosis was made by incisional biopsy in 21 cases and by excisional biopsy in three cases. Pre-treatment patient characteristics are given in Table 1. All the tumors were squamous cell carcinomas, well differentiated in 10, moderately differentiated in 5, poorly differentiated in 5, and unknown in 4 patients. Four patients had regional lymph node involvement (detected either clinically or by CT); perirectal in one and ipsilateral inguinal in three patients. Inguinal lymph node involvement was confirmed by cytology in only one patient.

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Table 1

Patients characteristics (24)

Median age (range)	59.4 years (43–87)
Male/Female (ratio)	12/12 (1)
TN classification (UICC 1987)	
T1	2 (8%)
T2	16 (66%)
T3	3 (13%)
T4	3 (13%)
N0	20 (84%)
N1	4 (16%)
Median tumor diameter (mm) (range)	35 (15–60)
Circumferential invasion of anal margin	
$<1/3$	12
$>1/3$ and $\leq 2/3$	10
$>2/3$	1
Unknown	1

Radiation therapy

All patients but three were treated with split-course external beam irradiation (EBRT), either alone (16 patients) or combined with a brachytherapy (BT) boost (5 patients). One patient who had previously received pelvic irradiation was treated with BT alone, and two patients were treated with continuous-course EBRT. Megavoltage photon beams (Co60 or x-rays ≥ 6 MV) were used in all patients treated with EBRT in the first RT sequence, except for one patient, who was treated with an electron beam. For the boost, the EBRT consisted of electron beams of appropriate energy in seven cases and megavoltage photon beams in nine cases. Inguinal areas were treated in 17 patients with a median dose of 45 Gy (range 30–60 Gy). Table 2 summarizes the characteristics of the RT techniques. The details of treatment have been published previously (13).

Table 2

Radiotherapy characteristics

	No. of patients
Fields and doses for 1st course of EBRT	
AP/PA pelvic fields	14
Perineal field $\pm$ sacral field	5
Others	4
Median dose/fraction/days for EBI	41.4/22/35
Fields and doses for 2nd course (boost)	
Without boost	3
EBRT	16
Perineal field alone (^{60}Co or electrons)	10
Two lateral and 2 AP/PA fields (box)	3
Others	3
Median dose/fraction/days for EBRT	16.2/9/11
BT	5
Median number of ^{192}I wires	6
Median dose–median dose rate	19 Gy–0.83 Gy/h
Median interval between course 1 and 2	12 days
Median total treatment length	59 days

EBRT: external beam radiation therapy; BT: brachytherapy; AP/PA: antero-posterior opposed fields.

Chemotherapy

Fourteen patients (58%) received concomitant chemotherapy (CT). Ten patients received 5-fluorouracil (5-FU, 600–800 mg/m^2 per day) and mitomycin-C (MMC, 10 mg/m^2), one patient received MMC alone, and 3 patients 5-FU alone. CT started on day 1 with MMC in bolus injection and 5-FU in continuous 96-h intravenous infusion. Nine patients received a second cycle of MMC and 5-FU, administered during the second RT sequence. 5-FU was given at full dose in all patients, whereas MMC was reduced by 20% in one patient because of the severity of the acute reactions.

Follow-up, toxicity grading, and statistical analysis

Acute and late complications were scored according to the Radiation Therapy Oncology Group (RTOG) grading system (14). Classification of late complications was modified in order better to describe complications involving the anorectal region. Thus, severe complications (stenosis, necrosis, incontinence) requiring abdominal–perineal resection (APR) or diverting colostomy were classified as grade 4 and those that were persistent but managed conservatively as grade 3.

The actuarial overall and disease-free survival rates as well as actuarial locoregional control rate were calculated by using the Kaplan–Meier method (15). Local control was defined as control in the anorectal region and regional control as pelvic and inguinal control, without taking into account the contribution of salvage surgery. Death from any cause was considered as an event, when assessing overall survival, whereas death from cancer or complications was considered for disease-free survival. Locoregional control was taking into account events that occurred in local and regional regions.

RESULTS

Survival

No patient was lost to follow-up. At the time of this analysis 9 patients had died and 15 were alive without active disease. Anal margin carcinoma was considered the cause of death in four patients, intercurrent diseases without cancer in four, and complications because of subsequent chemotherapy for recurrence in one. With a median follow-up of 37 months (range 5–176), the actuarial 5 year overall and diseases-specific survival rate was 56% (Fig. 1) and 69.5%, respectively.

Locoregional control

The actuarial locoregional control rate was 69.5% at 5 years (Fig. 2), with a plateau after 15 months. Seven patients failed the initial treatment; six presented with local failure alone, and one with local failure and multiple distant metastases. There was no regional failure. Salvage therapy consisted of one local excision, and four APR, in

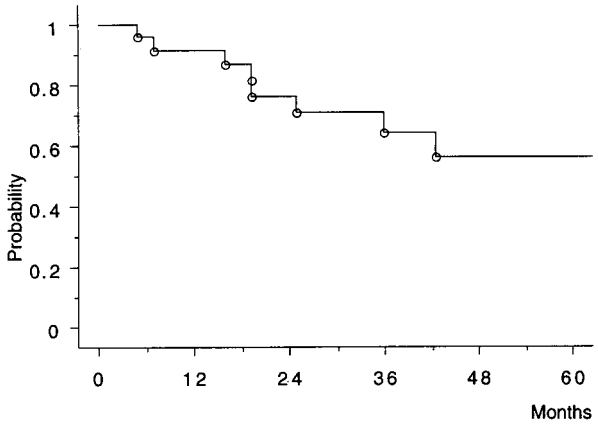

Fig. 1. Actuarial overall survival.

one case associated with chemotherapy. No further treatment was given in two patients because of poor general condition or advanced disease. Subsequent locoregional control was obtained in one of the five patients receiving salvage treatment. Overall, 16/24 treated patients preserved their anal sphincter.

Treatment morbidity

Information on acute reaction was available in 21 patients. Grade 1–2 toxicity was scored in 6/21 (29%) and grade 3 in 15/21 (71%) patients. The most frequent grade 3 acute toxicities were confluent moist perianal skin reactions, followed by proctitis and/or diarrhea. In the group treated with chemotherapy, one patient had a thrombotic complication and one patient a grade 4 leukopenia.

Twenty-two patients with a minimum follow-up of 3 months were evaluated for late complications. Ten patients presented with no or asymptomatic late complications (grade 0–1). Nine patients had one or more late complications with a maximum of grade 2. Grade 2 complications consisted of diarrhea in three patients, fibrosis or telangiectasia of the skin/anal mucosa in four patients, anal sphincter incontinence in one patient, anal mucosa bleeding in one patient, and vaginal atrophy with dyspareunia in one patient. In addition, erectile dysfunction was observed in one patient, who subsequently responded favorably to treatment with sildenafil (Viagra).

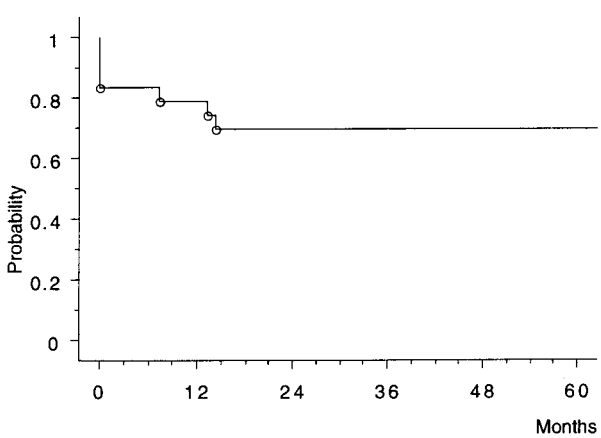

Fig. 2. Actuarial locoregional control.

Three patients (14%) presented with severe late complications (grade 4). In one patient a bladder mucosal necrosis was managed conservatively (patient treated with 63 Gy by using an antero-posterior technique in the two RT courses). One patient, who had received pelvic irradiation 30 years previously and was treated with brachytherapy alone (59.2 Gy), presented with perianal skin necrosis that required a diverting colostomy. Finally, one patient treated with EBRT (30 Gy) and brachytherapy (15 Gy) underwent an APR for anal necrosis that mimicked a local failure.

DISCUSSION

In contrast with anal canal cancers (16), uniform treatment guidelines for carcinomas of the anal margin have not been clearly established. This situation reflects the difficulties presented by the rarity of the disease, the lack of uniformity in anatomical definitions (1, 17, 18), the accessibility of tumors of the anal margin to surgical treatment, and the paucity of published experience with non-surgical approaches. However, the clinically frequent involvement of both canal and margin and the important objective of sphincter preservation have progressively led to the inclusion of anal margin lesions into the treatment approaches that have gained acceptance for carcinomas originating in the anal canal. Indeed, during the last decade combined radio–chemotherapy (RT–CT) with preservation of anorectal function has been adopted as the treatment of choice (13, 19, 20), and carcinomas originating in the anal margin have been included in prospective trials studying sphincter conservation in anal cancers (19, 20).

As a consequence, it seems justified to favor non-surgical treatment for most cancers of the anal margin, reserving surgery for the salvage of oncological or functional failures. While the surgery remains a viable option for selected small lesions (< 3 cm in diameter) amenable to local excision (11, 21–25), APR, which is the recommended surgical approach for deeply infiltrative lesions, is no longer an attractive option as first-line therapy. Local control is about 70% following surgical treatment, with a 5-year overall survival rate of 40% for patients with large lesions and of 60–90% for those with small lesions (1, 18, 21, 26). These results are similar to those reported in radiotherapy series (Table 3). Thus, the choice between radical RT or local surgery to treat T1–T2 tumors may depend on patient or institutional preferences, whereas RT–CT represents the preferred modality in more advanced disease. The retrospective nature of the present study, the small number of patients and the heterogeneity

Table 3

Results of radiation therapy series

	Patients	Median age (years, range)	Male/female	Overall survival (5 years) (%)	Local control (initial) (%)	Specific survival (5 years) (%)
Touboul et al. (10)	17	57 (31–80)	10/7	82	86.5	86.2
Cutuli et al. (7)	21	73 (56–88)	9/13	52	48	72
Peiffert et al. (2)	31	70 (39–93)	10/22	67	77	89
Cummings et al. (6)	29	N.S.	N.S.	N.S.	60	N.S.
Papillon et al. (8)	57	72	15/32	59	88	79.7
Bieri et al. (present series)	24	59 (43–87)	12/12	56	69	72.6

[1] Eleven patients were treated with local excision alone.
N.S. Not specified.

of the treatment schedules over a long period make the conclusions rather difficult (27).

The superiority of the combined RT–CT over RT alone in locally advanced anal carcinomas has been demonstrated in two randomized trials (19, 20). Although no specific data exist about the role of CT in anal margin carcinoma, it is important to note that anal margin cancers were included in these latter two randomized trials, constituting 23% of patients in the UKCCCR trial (20). The conclusions of the trials were considered to be applicable to lesions of both the anal canal and margin. Thus, speculation regarding the lack of evidence for the efficacy of concomitant CT must be interpreted with caution (2). No valid conclusions can be drawn from a comparison between subgroups of patients treated with RT or RT–CT in the individual small series in the literature, because patients selected for RT–CT, as in the present study, were more likely to have advanced disease.

Compared with patients with anal canal carcinomas treated in Geneva (13), patients in the present series tended to be younger. This observation is supported by the majority of authors, but is not a universal finding (2). Patient selection may have contributed to this discrepancy. On the other hand, a clear difference in the gender ratio is noted in the present series, where half of the patients were male, whereas among anal canal cancer patients only one-fourth to one-third were male. This observation was also reported by Svensson et al. (9), suggesting that anal margin carcinomas are equally distributed between the sexes. Concerning the treatment results, the 69% locoregional control rate at 5 years is similar to the reported ratres obtained in anal canal carcinomas (28, 29). Moreover, in the EORTC trial (19), when analyzing prognostic factors, no differences in local control or overall survival were noted between anal margin and anal canal groups.

Lymph node involvement at diagnosis is reported to be an adverse prognostic factor (6, 8, 17, 22). Although our series is limited, we observed three locoregional failures among the four patients who presented initially with nodal involvement. For N0 patients not receiving prophylactic inguinal treatment, isolated inguinal lymph node recurrence is not a rare event. Failure subsequently to control such a recurrence has led some authors to suggest prophylactic groin irradiation except for T1 tumors (6, 8, 10). Although recommendations have changed with time, in the present series, only seven patients were not irradiated at the inguinal area, perhaps explaining the absence of inguinal failures.

Fourteen percent of our patients suffered severe late complications, which is comparable with other published

Table 4

Late complications after irradiation of anal margin carcinoma

	No of patients	Late complications (grade 3–4)
Touboul et al. (10)	2/17	1 anal and perineal necrosis 1 permanent incontinence after local excision (not related to irradiation)
Cutuli et al. (7)	2/21	1 anal necrosis 1 femoral neck fracture
Peiffert et al. (2)	1/31	1 radionecrosis requiring a non-definitive colostomy
Cummings et al. (6)	3/29	1 local necrosis requiring surgery 2 local necrosis treated conservatively
Papillon et al. (8)	2/57	2 radionecrosis requiring colostomy
Bieri et al. (present study)	3/24	1 bladder necrosis treated conservatively 1 skin necrosis requiring colostomy (patient had RT previously) 1 necrosis of the anal canal requiring APR

APR: abdomino-perineal resection.

reports (Table 4). Serious complications were restricted to patients treated in the initial period of this study. At least one complication (bladder mucosa necrosis) might have been avoided if the EBRT technique had been optimal. Anal complications occurred in two patients treated with brachytherapy, one as a boost and the other as a radical treatment after a previous RT of the anal region. In the absence of a clear difference in the oncologic results between the different RT techniques used, differences in complication rates may prove useful to guide the choice of RT dosage and technique. Without the appropriate controlled trials, it is difficult to draw formal conclusions from existing retrospective studies. However, many authors underline the limited role of brachytherapy in this disease (2, 8), particularly as the sole therapeutic modality.

In conclusion, the results of the present study are consistent with the notion that radical RT, with or without comcomitant CT, offers a good probability of cure with conservation of sphincter function. The late complication rate seems acceptable. Some severe complications may be prevented by refinements in treatment technique. For small tumors the optimal treatment, either surgery or RT, remains to be defined. For more advanced disease RT, preferably associated with concomitant CT, seems to be the preferable choice, with surgery reserved for salvage therapy.

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