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Anal cancer chemoirradiation with curative intent – a single institution experience

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Results of radiochemotherapy in 50 patients with squamous cell carcinoma of the anal canal, treated with radical radiochemotherapy between January 2003 and September 2007, at the Institute of Oncology Ljubljana are presented. The treatment schedule consisted of 3-D conformal external beam radiotherapy (45 Gy in 25 fractions), with two cycles of concurrent chemotherapy (5-fluorouracil (5-FU) / Mitomycin C), followed by brachytherapy or external beam boost (15-30 Gy) to the primary tumor. Locoregional control (LRC), disease-free survival (DFS), disease-specific survival (DSS), overall survival (OS) and colostomy-free survival (CFS) rates and the rate of acute and chronic side-effects were estimated. The impact of individual tumor- and therapy-related factors on treatment outcome was assessed.

Treatment was completed according to the protocol in 72% of patients. The median follow-up time of 40 survivors was 22 months (range 1.7-53.2 months). At 2 years, LRC, DFS, DSS, OS and CFS rates were 68%, 67%, 87%, 76% and 85%, respectively. In the multivariate analysis, nodal stage was identified as an independent prognostic factor for LRC, DSS and CFS and application of Mitomycin C for OS. The most frequent acute side-effect of treatment was radiodermatitis (grade 3 in 66% of patients, grade 4 in 2%). Late anal stenosis, chronic ulceration and grade 2-3 incontinence developed in 3 (6 %), 2 (4 %) and 5 (10 %) of colostomy-free survivors, respectively.

Radiotherapy with concurrent 5-FU / Mitomycin C chemotherapy is feasible, with acceptable toxicity. The presented treatment outcome is comparable to other published results.

Key words: anal cancer, radiochemotherapy, survival, toxicity.

Carcinoma of the anal canal represents 2-4% of all cancers of colorectum and anus [1]. It is predominantly a locoregional disease [2] with increasing incidence in developing countries, mostly in younger homosexual men [1]. In Slovenia, 15 new cases were reported in 2004 (1 male and 14 females). The disease was located in the anal canal in 6 patients (35.3%), 7 patients (41.2%) had locoregional disease, 2 patients (11.8%) had distant metastases, and in 2 patients (11.8%), the disease stage was not defined at the time of the diagnosis [3].

In the past, abdominoperineal resection (APE) with permanent colostomy was the standard treatment for anal canal cancer. Local excision was recommended for well-differentiated tumors smaller than 2 cm and/or in case of mucosal or submucosal infiltration only. After APE, local failures occured in 30-50% of patients and 5-year survival rates ranged from 40 to 70% [4–6]. The major turning point in the treatment approach was made by Nigro et al., who introduced a combined concurrent chemoradiotherapy regimen, using 5-fluorouracil (5-FU) and Mitomycin C [7]. Since then, three randomized trials have demonstrated a considerable benefit of this approach, with continence-preservation rates and outcomes similar as in surgery [8–10]. In these studies, the original Nigro protocol underwent several modifications in radiation dose, volume of tissue encompased in the treatment fields and choice of the chemotherapy agents. Consequently, radical radiochemotherapy became the treatment of choice for cancer of the anal canal. Surgery is indicated in cases of residual or recurrent tumor or complications of radiotherapy [1].

The objective of this study was to evaluate the results of radiochemotherapy in the patients with squamous cell carcinoma of the anal canal treated at a single institution, as well as to analyze some prognostic factors and toxicity.

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Patients and methods

Patients. Between January 2003 and September 2007, 50 patients (21 males, 29 females; aged 34-87 years, mean age 63 years) with biopsy proven carcinoma of the anal canal were treated with concomitant chemoirradiation with curative intent at the Institute of Oncology Ljubljana, Slovenia. The patients with carcinoma of the anal margin were not included in this analysis. Since our Institute is the only center with radiotherapy facilities in Slovenia, this number represents the total population of radically irradiated patients with cancer of the anal canal in the country.

Tumor characteristics. Tumors were staged according to the International Union Against Cancer (UICC) [11]. In 5 (10%) patients, the tumor was staged as cT1, in 26 (52%) as cT2, in 13 (26%) as cT3 and in 5 (10%) as cT4. In 1 patient, the stage was not determined because the primary tumor was removed by transanal excision prior to irradiation.

Fourteen (28%) patients had N+ disease. Fourty-two (84%) tumors were squamous cell carcinomas and 8 (16%) were basaloid variant of squamous cell carcinoma (Table 1).

Table 1. Tumor characteristics

Characteristics		N (%)
cT – stage	1	5 (10%)
	2	26 (52%)
	3	13 (26%)
	4	5 (10%)
	Unknown	1 (2%)
cN – stage	0	36 (72%)
	1	5 (10%)
	2	7 (14%)
	3	2 (4%)
Overall stage	I	4 (8%)
	II	32 (64%)
	III a	5 (10%)
	III b	8 (16%)
	IV	0
	Unknown	1 (2%)
Pathohistological type	Squamous cell	42 (84%)
	Basaloid	8 (16%)

N= number of patients, cT= clinical T stage, cN= clinical N stage

Pre-treatment evaluation. Pre-treatment work-up comprised complete history and physical examination, blood count, serum biochemistry, chest radiography, ultrasonography (US) and/or abdominopelvic computer tomography (CT). Locoregional disease extent was evaluated with anorectal examination by two independent examinors (surgeon and radiation oncologist), rectoscopy, endoscopic US and/or magnetic resonance imaging (MRI) of the pelvis. In the cases, suspicious for inguinal lymph node involvement, fine needle aspiration biopsy was performed. For the purpose of brachytherapy (BT) treatment planning, detailed pre-treatment (before external beam radiotherapy (EBRT)) clinical drawings and photographs were taken and tumor borders were tattooed on the perianal skin.

All patients were presented to a multidisciplinary advisory team, consisting of a surgeon, radiation oncologist and medical oncologist, that was in charge to assess the prospects of treatment. The patients with significant comorbidity, and/or poor performance status (≥ 2, according to the World Health Organization (WHO)), were not considered as eligible for concurrent chemotherapy and were therefore treated only with radiotherapy.

Treatment. Treatment schedule consisted of 3-D conformal EBRT with concurrent chemotherapy (ChT), followed by BT or EBRT boost. EBRT was delivered using CT-based treatment planning and a four-field technique at a linear accelerator (15 MV, planned total dose of 45 Gy, dose per fraction 1.8 Gy, five fractions per week). Clinical target volume (CTV) included the anal margin, anal canal and posterior pelvis up to the S2-S3 vertebral junctions. To reach the planned target volume, an additional margin of 1 cm in all directions was applied to CTV. In case of metastases in inguinal lymph nodes, the involved areas were boosted with separate electron fields to a total dose of 60 Gy. Gelatinous, 1 cm thick bolus was used if the tumor protruded outside the anus.

Concurrent ChT was planned in all but the stage I patients and the patients with significant medical comorbidities. It consisted of two cycles of 5-FU (daily dose of 1000 mg/m^2 in 96 hours continuous infusion), given during week 1 and 5 of EBRT. Mitomycin C (10 mg/m^2 in bolus intravenous injection) was administered on day 1 of the first ChT cycle.

In case of severe treatment-related toxicity, irradiation and/or ChT doses were modified and adapted to each patient's physical condition or laboratory findings. When necessary, ChT application was delayed, or EBRT was temporarily interrupted or even terminated.

After the completion of EBRT +/- ChT, an interstitial pulsed-dose rate BT boost was planned. CTV at the time of BT corresponded to initial tumor extension, as documented by pre-treatment clinical drawings, imaging examinations (CT, MRI, US), photographs and tattoo-markings of tumor borders on perianal skin. Metal needles were implanted through a perineal template homogeneously in the CTV, respecting the rules of the Paris system. The distance between the needles and ano-rectal mucosa was 5 mm or more. This was assured by palpation during the insertion of needles and by transrectal US, performed after the insertion. An anal cylinder was inserted to displace uninvolved ano-rectal mucosa from the high dose region. Until 2006, the treatment planning was based on two orthogonal radiographs, and later, CT-based treatment planning was introduced. The dose was prescribed to the reference isodose line (85% of mean basal dose). Biologically equivalent dose of 15-30 Gy was prescribed (linear quadratic model, assuming an a/b of 10 Gy for the tumor, sublethal damage repair half time of 1.5 hours, reference dose rate of 0.5 Gy per hour), depending on the initial tumor burden and pattern and extent of regression during EBRT. After introduction of CT into treatment planning, a subtle individualized 3-D optimization of dose distribution was performed to increase the dose to CTV, while

Table 2. Acute treatment toxicity

Toxicity	NCI-CTC grade (%)					
	0	1	2	3	4	Total
Stomatitis	56	18	16	10	0	100
Nausea, vomiting	80	8	6	6	0	100
Diarrhoea	62	12	12	14	0	100
Radiodermatitis	4	18	12	64	2	100
Infection	50	16	20	10	4	100
Leucocyte count	42	34	16	6	2	100
Hemoglobin level	44	42	14	0	0	100
Platelet count	72	24	0	4	0	100

NCI-CTC= National Cancer Institute Common Toxicity Criteria [12]

respecting normal tissues tolerance. In the tumors, larger than 5 cm or in N2-3 disease, the boost was applied with EBRT.

Follow-up. During treatment, the patients were examined clinically on a weekly basis to evaluate acute toxicity and compliance with the treatment schedule. Acute toxic side effects were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 2.0) [12].

The first post-treatment follow-up appointment with a senior radiation oncologist was scheduled to be held 6 weeks after the completion of radiotherapy. Response to treatment was evaluated by clinical examination, appropriate imaging studies (MRI and/or endoscopic US) and biopsies, when indicated. Complete response was defined as total disappearance of tumor, partial response as regression of >50% in the single large diameter of the tumor, no response as no regression in size of tumor, and progressive disease as an increase greater than 25% in the single large diameter of the tumor or appearance of any new lesions. In case of incomplete response with less than 50% volumetric regression of the primary tumor, surgery (APE) was recommended. In other patients, clinical evaluation was repeated every 6 weeks until complete remission was recorded. In cases of evident progression or recurrence, surgery was recommended. In the patients with complete remission, follow-up investigations were carried out at 3-month intervals for the first 2 years and then every 6 months until the end of fifth year.

Chronic side effects were assessed at each follow-up evaluation, employing the NCI-CTC (version 2.0) [12].

Statistical analysis. Statistical analysis was performed using personal computer and software statistical package SPSS, version 13 (SPSS Inc., USA).

The main endpoints of the study were as follows: response to the therapy, locoregional control (LRC, the event was local and/or regional recurrence), disease-free survival (DFS, the event was local, regional or systemic recurrence), disease-specific survival (DSS, the event was death due to the carcinoma of the anal canal), overall survival (OS, the event was death from any cause) and colostomy-free survival (CFS, the event was the need for colostomy).

The survival of patients was computed from the date of treatment start to December 31, 2007 (close-out date). The survival probability was calculated using Kaplan-Meier estimate [13], and log rank test [14] was used to evaluate the differences between individual groups of patients (age, performance status, T-, N- and overall stage, radiotherapy and chemotherapy dose). Independent prognostic values of the factors that appeared statistically significant on univariate analysis were tested by multivariate Cox regression analysis model [15]. Two-sided tests were used and the differences at $p<0.05$ were considered as statistically significant.

Results

Course of treatment. Median duration of EBRT and total treatment time was 36 (range: 29-71) and 57 (range: 30-98) days, respectively. Thirty six (72%) patients completed the treatment according to the protocol. The planned EBRT dose of 45 Gy was applied in 49 (98%) patients. In one, EBRT was stopped at 18 Gy due to acute toxic effects. In 9 patients (18%) with inguinal lymph nodes metastases, the boost of a median total dose of 59.4 Gy (55.8-61.2Gy) to the involved areas was applied with separate electron fields.

During EBRT, two cycles of concurrent 5-FU and Mytomicin C were administered in 37 (74%) patients. Seven (14%) patients received one cycle only due to acute side effects. Concomitant capecitabine (825 mg/m^2 bid) was administered in one patient who was primarily operated for locoregionally advanced colorectal carcinoma, but during preoperative investigations, a synchronous anal carcinoma was found. ChT was omitted in 5 (10%) patients due to stage I disease (3 patients) and severe comorbidity (2 patients).

A boost to the primary tumor was applied through reduced photon fields in 19 (38%) patients, delivering additional median dose of 15.3 Gy (range: 6-20 Gy) to the primary tumor with 1.5 cm margin in all directions. Interstitial BT boost after EBRT was performed in 36 (72%) patients with a mean interval of 27 days (range: 18-57 days). Mean number of implanted needles was 7 (range: 3-14) with a mean active length of 4.2 cm (range: 2-6 cm). Biollogically equivalent dose of 19.4 Gy (range: 14-28 Gy) was prescribed to the reference isodose line.

Acute side effects. Treatment was well tolerated by the majority of patients and no treatment-related mortality was observed. Frequency and intensity of acute adverse side efects are listed in Table 2. The most frequent grade 3 side-effect was radiodermatitis, occurring in 32 (64%) patients during EBRT. One patient developed grade 4 radiodermatitis. All cases of radiodermatitis were healed without consequences.

Outcome. Median follow-up time was 19 months (range: 0.3-53.2 months) in all patients and 22 months (range: 1.7-53.2 months) in survivors.

Fifteen weeks after the end of the treatment, complete remission, partial response and stable disease were recorded in 36 (72%), 9 (18%) and 4 (8%) patients, respectively. In one patient, the tumor progressed.

All 14 patients without complete response later developed local (10 patients) or locoregional recurrence (4 patients) af-

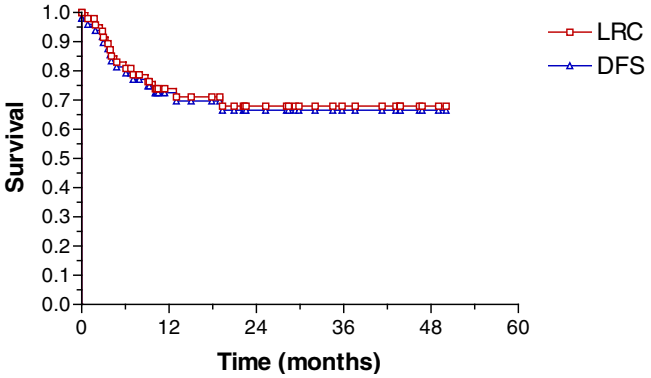

Figure 1. Locoregional control (LRC) and disease-free survival (DFS)

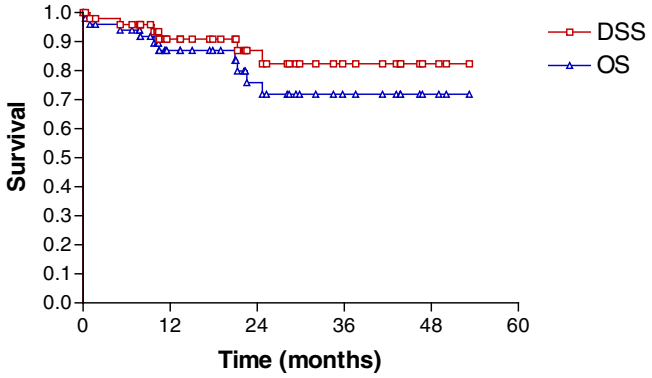

Figure 2. Disease-specific survival (DSS) and overall survival (OS)

ter a median period of 3.6 months (range: 0-9.1 months). In one patient with complete response, distant metastases without local or regional recurrence occurred.

No cases of inguinal nodal failure as the only site of recurrence were observed. Seven (54%) out of 13 patients with locoregional recurrence were treated surgically, whereas other patients had locally or locoregionally unresectable disease. One patient without recurrence was operated on because of serious side effects after radiotherapy (anal sphincter dysfunction). Two of the operated patients died of carcinoma while others are without any signs of the disease.

On the close-out date, 40 (80%) patients were alive, 32 (80%) of them being free of the disease. Six (12%) patients died from anal canal cancer. One (2%) patient, who experienced locoregional recurrence, died from metachronous bronchus carcinoma, two patients (4%) died from stroke and, in one (2%) patient, the cause of death could not be determined.

The 2-year follow-up survey showed that LRC, DFS, DSS, OS and CFS were 68%, 67%, 87%, 76% and 85%, respectively (Figures 1-3).

Chronic side effects. Three (6%) patients experienced post-treatment anal stenosis, requiring repeated dilatations and two (4%) developed chronic non-healing ulcer at the anal verge. Five (10%) patients had grade 2-3 incontinence of anal sphincter. In one patient without recurrence, colostomy was performed due to severe anal sphincter dysfunction.

Prognostic Factors. On univariate analysis, T-, N- and overall TNM-stage emerged as statistically significant prognostic factors for DFS, DSS and CFS rates, whereas ChT with Mitomycin C was identified as a statistically significant prognostic factor for LRC and OS ($p<0.005$). For other analysed factors (sex, age, performance status, histological type, overall treatment time and radiotherapy boost) no impact on the outcome was found.

On multivariate analysis, N- stage was identified as an independent prognostic factor for LRC, DSS and CFS, and Mitomycin C application retained its independent prognostic value for OS (Table 3).

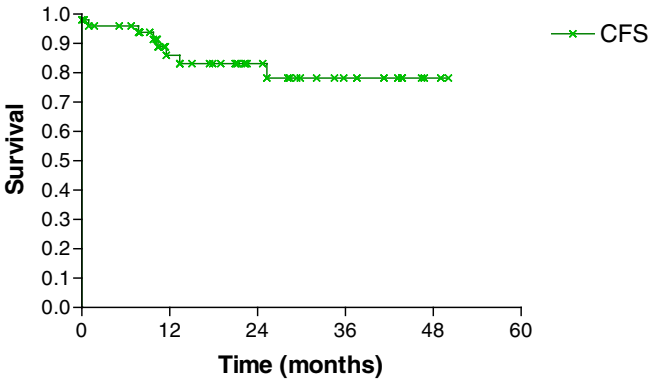

Figure 3. Colostomy-free survival (CFS)

Discussion

Radiotherapy with concomitant chemotherapy represents a standard treatment of anal cancer. Complete response and 5-year OS is recorded in 80-90% and 95-100% of patients with early stage disease and in 50-75% and 35-70% of patients with tumors larger than 5 cm [8, 10, 16-18]. In our study, complete response was recorded in 72% of treated tumors. Survival rates and observed toxicity are similar to the results of other authors [8-10] as well, although we are aware that the follow-up time in our series is rather short.

According to the literature, the most important prognostic factors in anal cancer are T-stage [1, 18, 21–23] and N-stage [8–10, 18]. In our study, similar results were obtained. On multivariate analysis, N-stage proved as a significant independent prognostic factor for LRC, DSS and CFS. As far as the independent prognostic value of T-stage is concerned, a borderline significance was demonstrated for DFS, DSS and CFS.

In three (8.3%) patients, complete response was recorded not earlier than 15 weeks after the completed treatment. There

Table 3. Multivariate analysis of survival

Prognostic fators	N	Locoregional control (p-value)	Disease-free survival (p-value)	Disease-specific survival (p-value)	Overall survival (p-value)	Colostomy-free survival (p-value)
cT – stage						
cT 1+2	30		0.086	0.068		0.073
cT 3+4	19					
cN – stage						
cN 0	36	0.036	0.068	0.035		0.041
cN 1+2+3	14					
Mitomycin C						
Yes	42				0.047	
No	8					

N= number of patients, cT= clinical T-stage, cN= clinical N-stage, MVA= multivariate analysis

are several other reports of very slow disease regression where further complete response was observed even up to 6–12 months after the treatment was completed [1, 10, 21].

In our study, only the involved inguinal lymph nodes were treated and no elective treatment of the uninvolved areas was performed, but no case of isolated inguinal-nodal failure was observed. No effect of elective irradiation of the uninvolved inguinal lymph nodes on survival rates was determined [19, 20]. Although the number of our patients was small, these findings suggest that no need for elective RT at the inguinal node region was necessary.

APE was perfomed in 8 (16%) patients (in 7 beacuse of the residual or recurrent disease and in 1 due to the sphincter incontinence after treatment) which is comparable to the results of Peiffert et al. with the APR rate of 16% following radiochemotherapy [17].

It is a well established fact that treatment intensity may affect the disease outcome. Randomized trials have demonstrated superior local control and DSS, but not OS, in the patients treated with radiochemotherapy with 5-FU and Mitomycin C, compared to those treated with radiotherapy alone [8, 9]. In our study, lower LRC and OS were observed in the patients who did not receive Mitomycin C, when compared to the patients who were treated according to the protocol. Flam et al. found out that the patients who recived Mitomycin C had a higher complete response rate (92 % vs. 85%), a significantly lower colostomy rate (95% vs. 22%) and a correspondingly significant increase in a colostomy-free survival than the patients without it [10]. Unfortunately, the last finding could not be confirmed in our study. Although there are several reports on poorer outcomes with longer overall treatment time, we did not come across this correlation.

The choice of the boost approach (EBRT or BT) did not have any impact on the treatment outcome in our patients.

According to the multivariate analysis there is no impact of patients' age, sex, performance status and histological subtype on the survival or local control. The age at diagnosis was found to be of prognostic significance for outcome in some [24], but not in all studies [25]. Some authors suggest that women have better prognosis than men [8, 18, 25], but the reason is unknown. Performance status and histological subtype of squamous-cell carcinoma have generally not been found to be independent prognostic factors for survival and local tumor control [18].

The rate of acute treatment-related toxicity is comparable to other reports [20, 26], with radiodermatitis grade 3 which occurred in 32 (64%) patients during EBRT, as the most frequent one.

Late side-effects are less frequent and their frequency is comparable to other reports [16, 20]. In our analysis, 6% of patients experienced post-treatment anal stenosis, 4% developed chronic non-healing ulcer at the anal verge and 10% patients had grade 2-3 incontinence of anal sphincter. We suppose a longer follow-up is needed to arrive at firmer conclusions about late morbidity.

In conclusion, it is to be expected that, in the future, improvement in disease control and survival will depend on early tumor detection. In locally advanced disease, innovative approaches to 3-D image-based BT boost offer a potential for individualized escalation of the target dose while respecting normal tissue tolerance. For the treatment of unresectable recurrences and distant metastases, the development of more active systemic therapies may be an option.

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