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ORIGINAL ARTICLE

Radical radiotherapy in the treatment of carcinoma of the anal canal – single center experience

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Summary

Purpose: *Radiotherapy ± chemotherapy is the first-line treatment for carcinoma of the anal canal in most oncology institutions. The aim of our study was to evaluate the efficacy and toxicity of radical radiotherapy in the treatment of this carcinoma.*

Patients and methods: *Definitive radiotherapy was performed in 41 patients with squamous cell anal carcinoma. The majority (51.2%) of them were in T3 stage. Positive inguinal lymph nodes were found in 10 (24.4%) patients. Initially, all patients received external beam radiotherapy with pelvic fields, followed, after a 2-week gap in some patients or in continuity, by local external beam or brachytherapy boost. The total tumor dose ranged from 55-75 Gy.*

Results: *Acute complications were noticed in 32 (78%) patients with moist skin perineal desquamation being the most frequent (63.5%). On the first follow-up examination (2 months after the end of radiotherapy) 65.9% of the patients were in complete remission (CR), 31.7% in partial remission (PR), while in one (2.4%) patient locoregional disease progression (PD) was registered. With a mean follow-up time of 38.4 months (range 12-90 months) 75.6% of the patients were disease-free, while local or distant disease progression was diagnosed in 24.4% of them. Local disease control was achieved in 82.9% of the patients. The 5-year overall survival was 76.59%. Late sequelae, which were of low grade (1 and 2), were registered in 22 (53.7%) patients.*

Conclusion: *Our study confirmed good treatment results and acceptable toxicity of definitive radiotherapy in the treatment of anal canal carcinoma.*

Key words: anal carcinoma, radiotherapy, response, squamous cell, survival, toxicity

Introduction

The goals in the treatment of epidermoid cancer of the anal canal are cure, local control and sphincter salvage, while attempting to minimize morbidity.

Carcinoma of the anal canal has long been considered to be predominantly locoregional disease, but surgical series over the past half century revealed that only around 50% of the cases survived for 5 years after radical or local excision [1]. Results of many studies showed that radiotherapy had at least the same potential as surgery to cure anal cancer whilst avoiding colostomy in more than two-thirds of the patients [2]. This is the reason why in most oncology institutions radiotherapy is been applied as the standard first-line treatment for anal canal carcinoma [3]. Surgical treatment is been reserved only for patients relapsing after radiotherapy or for residual disease [4].

Radiotherapy has been applied alone, but also, more frequently, in combination with chemotherapy. The studies carried out so far have shown good treatment results and high sensitivity of squamous cell carcinoma of the anal canal using radiotherapy alone or radiochemotherapy [5-8]. However, some dilemmas and open questions still remain in connection with

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the elucidation of the optimal radiation techniques, adequate dose and the most optimal concomitant chemotherapy regimen.

The purpose of this study was to analyze the treatment results of patients with squamous cell anal canal carcinoma and to evaluate the role of radiotherapy in the local disease control, overall survival, treatment toxicity, and postirradiation of the anal sphincter function.

Patients and methods

Between February 1995 and August 2002 a prospective study was conducted at the Institute for Oncology and Radiology of Serbia, which included 41 patients with squamous cell anal carcinoma.

The following inclusion criteria were applied: histologically proven squamous cell carcinoma of the anal canal; tumor of any T or any N stage according to the TNM classification (1997); absence of distant metastases; no previous treatment of the anal canal carcinoma; and Karnofsky index ≥ 80.

All patients had a detailed pretreatment clinical examination of the anorectal region and a general physical examination; rectoscopy with tumor biopsy; chest x-rays; abdominal and pelvic ultrasonography; gynecologic examination in female patients; complete blood count and basic serum biochemistry.

External beam megavoltage radiation therapy was applied with a linear accelerator (energy 6, 10, 18 MeV) in all patients. Primary tumor, lower third of the rectum and regional lymph nodes were included in the radiation volume. The upper field border was at the level of the lower end of the sacroiliac joint or L5-S1 intervertebral space, while the lower field limit included the skin of the perineum. The lateral field margins included external iliac and inguinal lymph nodes. The patients were irradiated with two parallel fields (anteroposterior and posteroanterior - AP/PA), and extended pelvic inguinal fields, with a dose ranging from 40 to 50 Gy, delivered in 20-25 fractions, 1.8-2 Gy per fraction. Thereafter the patients received a boost dose, the amount of which was planned on the basis of the achieved tumor regression with the previously applied radiotherapy. Boost was delivered in continuity or after a 2-week interval. Twenty patients received a boost dose by external beam radiation therapy by a direct posterior or reduced AP/PA fields. The dose ranged from 10 to 16 Gy and was applied in 5-8 fractions, 2 Gy per fraction. For 21 patients a boost dose was given by brachytherapy with a Mikroselektron with Ir192 radioactive source in high dose rate therapy. The doses ranged from 10 to 25 Gy and were given in 2-5 fractions (5 Gy per fraction). The total tumor dose ranged from 55 to 75 Gy.

After the completion of radiotherapy the first and second follow-up examination were done after 2 months, every 3 months thereafter during the first year, every 4 months during the second year, and every 6 months after the second year. Follow-up included general clinical and rectal examination, rectoscopy, abdominal and pelvic ultrasound, chest radiography, complete blood count and serum biochemistry.

Tumor response was evaluated on the first and second follow-up examination.

Acute complications during irradiation were registered and analyzed according to WHO toxicity criteria [9], and included dermatitis, diarrhea, cystitis, nausea, vomiting, and acute proctitis. Late post-radiation complications in the form of skin atrophy, hyperpigmentation, telangiectasias, colitis, proctitis, hemorrhagic cystitis, stenosis, fistulas and strictures were registered and scored according to RTOG/EORTC criteria [10].

Disease-free survival and overall survival were analyzed by the Kaplan-Meier method [11].

Results

The mean age of the patients was 57.7 years (range 28-82 years), with a significant female predominance (4.8:1). The general condition of all patients was good with a Karnofsky index over 80. T2 stage was diagnosed in 13 (31.7%) patients, T3 in 21 (51.2%) and T4 in 7 (17.1%), while 10 (24.4%) patients had positive inguinal lymph nodes. In 31 (75.6%) patients only biopsies were taken before starting treatment, while in 10 (24.4%) patients histologic diagnosis was determined after local tumor excision or hemorrhoidectomy.

Acute complications were noticed in 32 (78%) patients, while 9 (22%) patients completed radiotherapy without acute complications (Figure 1). The most frequent acute complication was moist perineal skin desquamation (grade 3), seen in 26 (63.5%) patients. Diarrhea (grade 1 and 2) was observed in 9 (22%) patients, nausea and vomiting (grade 1) in 4 (9.8%) patients and dry skin desquamation (grade 2) in 1 (2.4%) patient. Eleven (26.8%) patients had more than one complication (Table 1). Acute complications were of lower grade and they appeared at the end of radiotherapy (moist desquamation). However, no patient had his/her treatment interrupted because of acute complications.

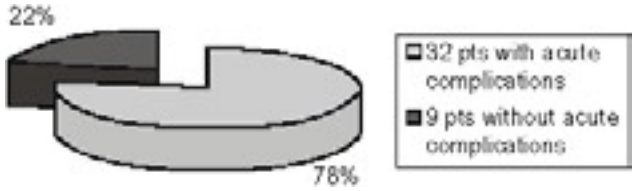

Figure 1. Distribution of patients according to acute complications.

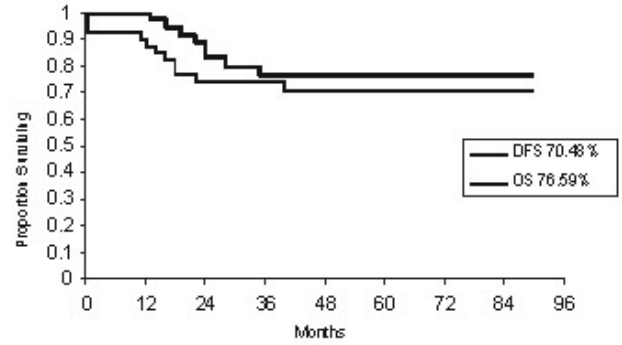

Figure 2. Five-year overall (OS) and disease-free survival (DFS) in 41 patients with anal carcinoma treated with radiotherapy.

On the first follow-up (2 months after the end of radiotherapy) 27 (65.9%) patients were considered to be in CR, 13 (31.7%) patients in PR, and 1 (2.4%) patient showed locoregional PD. On the second follow-up (4 months after the end of radiotherapy) 7 of 13 patients, initially showing PR, were considered to be in CR, increasing the total number of patients with CR to 34 (82.9%) (Table 2). Out of the 6 remaining patients with residual tumor, 4 were operated on with Milles abdominoperineal resection of the rectum and 2 patients did not continue any specific anticancer therapy due to their poor general condition (Table 2).

With a mean follow-up time of 38.4 months (range 12-90 months) 31 (75.6%) of the total 41 patients were disease-free, while local or distant disease progression was diagnosed in 10 (24.4%) patients. Only local recurrence was diagnosed in 3 patients, local recurrence plus inguinal nodal metastases in 1 patient, local recurrence plus liver metastases in 1 patient and residual disease in 2 patients. Distant metastases only were registered in 3 patients (1 in the lung and 2 in the liver). Local disease control was achieved in 34 (82.9%) patients. Two patients with residual disease and one with local recurrence were rendered disease-free by surgery.

Five-year disease-free survival was 70.48% (Figure 2). Seven patients died as a result of local disease progression or distant disease dissemination. Five-year overall survival was 76.59% (Figure 2).

During regular follow-up, postirradiation complications were diagnosed in 22 (53.7%) patients, while 19 (46.3%) patients were without late complications (Table 3). The majority of these complications were skin-related (18 patients, 43.9%) and were grade 1 (6 patients) in the form of mild skin atrophy, pigmentation, or partial epilation, and grade 2 (12 patients) in the form of partial skin atrophy, moderate telangiecta-

Table 1. Acute complications (WHO)

Acute complication	*Grade*	*No. of patients*	*%*
Skin			
moist perineal desquamation	3	26	63.5
dry perineal desquamation	2	1	2.4
Gastrointestinal			
diarrhea	1-2	9	22
nausea, vomiting	1	4	9.8

Note: 11 (26.8%) patients had more than one complication

Table 2. Response to radiotherapy

Response	*No. of patients*	*%*
CR	34	82.9
PR	6*	14.6
PD	1	2.4

* 4 of them underwent abdominoperineal resection

Table 3. Late complications (RTOG/EORTC)

Late complication	*Grade*	*No. of patients*	*%*
Skin			
mild skin atrophy, pigmentation, partial epilation	1	6	14.6
partial skin atrophy, moderate teleangiectasias, complete epilation	2	12	29.2
Small intestine and colon			
periodic rectorrhagias	2	1	2.4
Anal canal and sphincter			
mild reduction of the sphincter tonus without incontinence	1	7	17.1
stenosis of the anal sphincter not requiring dilatation, moderate tonus reduction	2	4	9.8

Note: 6 (14.6%) patients had more than one complication

sias, or complete epilation. Complications connected to the small intestine and colon were seen in 1 (2.4%) female patient only as periodical grade 2 rectorrhagias. Postirradiation complications of the anal canal were observed in 11 (26.8%) patients. A mild reduction of the sphincter tonus without incontinence (grade 1) was registered in 7 (17.1%) patients. In 4 (9.8%) patients stenosis of the anal sphincter not requiring dilatation, with moderate tonus reduction (grade 2) was noted. Six patients had 2 late sequelae each. No patient develop higher grade (3 and 4) complications.

Discussion

This report presents the treatment results of 41 patients with squamous cell carcinoma of the anal canal, treated prospectively with definitive radiotherapy. The mean age of the patients was 57.7 years with females predominating over males (4.8:1). Touboul et al. [12] in their study had patients with a mean age of 67.5 years with a female to male ratio of 5.7:1. Newman et al. [13] reported a mean patient age of 63.6 years with a female to male ratio of 1.7:1.

Disease stages and tumor grades of the patients included in this study were similar to the findings of other authors [12-14].

Many authors analyzed acute complications during radiotherapy. Wagner et al. [14] presented acute complications in the form of skin reactions in all of their patients treated with radiotherapy. Newman et al. [13] published similar results in their study. The patients included in these studies did not interrupt their radiation therapy because of acute complications. Cummings et al. [4,15,16] registered acute toxicity in 10 out of 57 patients treated with radiotherapy alone. Dogett et al. [3] reported that 65% of their patients had complications of the small intestine and 77% of the skin, while 31% of the patients required interruption of their therapy due to acute complications. In our study the acute toxicity was of lower grade and radiotherapy was not interrupted.

Touboul et al. [12] reported local disease control in 71% of their patients; Dogett et al. [3] published that the local control was 77%; Newman et al. [13] reported local control in 55 (76.4%) patients. In our study local disease control was achieved in 82.9% of the cases.

In our group of patients 5-year overall survival was 76.59%, quite similar with the results of other authors. The study by Cummings et al. showed 5-year overall survival of 56% for patients treated by irradiation alone [16], Touboul et al. reported 74.3% [12] and Newman et al. 66% [13].

During the regular follow-up late complications were also observed. Cummings et al. [16] presented that out of 57 patients treated by the radiotherapy, 11 had grade 3 and 4 complications such as anal strictures or ulcerations, proctitis and small intestine complications. Newman et al. [13] diagnosed grade 3 and 4 late complications in 6 (8%) out of 72 patients in the form of anal sphincter fibrosis or vaginal stenosis. In our study, with a mean follow-up time of 38.37 months, only lower grades of late complication were noted.

Further investigations must define many questions related to the combined use of radiotherapy with chemotherapy in patients with anal cancer.

Questions regarding total tumor dose are still awaiting a definite answer. Data from the available literature indicate that prognosis of the disease and local control are much better by delivering higher radiotherapy doses. In their retrospective study Nigh et al. [8] reported local disease control in 64% of the patients treated with less than 45 Gy, in 77% of the patients treated with 45-55 Gy and even in 92% of the patients after the application of a therapeutic dose over 55% Gy. Eschwege et al. [5] presented local control in 81% of their patients after the application of a therapeutic dose of 60-65 Gy.

Defining the optimal radiation techniques and dose per fraction is very important for the prevention of serious complications (strictures, stenoses, necroses), the frequency of which ranges between 10 to 20% [16]. Also, the size of the target volume varies in different radiation techniques and is not the same for various disease stages, while it is correlated with the development of complications.

Establishing the best chemotherapy regimen represents another step forward in the treatment of the anal canal carcinoma. Some previous studies have indicated better local control results but also higher toxicity by administering chemoradiotherapy. In an EORTC study [17] complete regressions were much higher (80%) in the group of patients that received radiotherapy combined with chemotherapy than in the group of patients receiving radiotherapy alone (50%). The local disease progression-free interval was longer in the combined treatment group, and acute toxicity was higher, while the overall survival was the same in both groups [17]. In the UKKCR trial conducted on 585 patients, the percentage of local relapses after a follow-up period of 3 years was higher in the patient group that received irradiation alone against the group with concomitant chemoradiotherapy (59 *versus* 36%), while no statistically significant difference was seen in overall survival [18].

A good local control of the disease can be achieved

by radical radiotherapy with an acceptable rate of acute and late sequelae. For more precise quantification and comparison of possible benefits and complications using radiotherapy alone or chemoradiotherapy, randomized controlled studies with greater number of patients and longer follow-up time are necessary.

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