ORIGINAL ARTICLE

Anal canal squamous cell cancer: surgıcal therapy, when?

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ABSTRACT

Aim To describe a therapeutic approach, indications for abdominoperineal resection (APR), survival and oncological results for patients who received treatment in our surgical clinic for anal canal squamous cell cancer (SCC).

Methods Patients were randomized into two groups according to the treatment method: Group 1- Chemoradiotherapy (CRT) without surgery, Group 2- CRT + APR.

Results Eighteen patients with anal canal SCC were included in the study; 11 (61.1%) patients were in Group 1 and 7 (38.8%) in Group 2. Reasons for APR was as follows: three patients had insufficient CRT, two had recurrence after CRT, one had complete faecal incontinence and one patient had rectovaginal fistula. Overall five year survival (OS) and disease free survival (DFS) was 77.7% and 72.7%, respectively. Comparing two groups five year OS was 90.9% and 57.1%, whereas DFS was 81.8%, 57.1%, respectively (p=0.389 and 0.324, respectively).

Conclusion Gold standard therapy for anal canal SCC is CRT. However, APR should be applied as an escape treatment for patients suffering from tumour progression, insufficient CRT and recurrence (30%).

Key words: abdominoperineal resection, local excision, Nigro protocol

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INTRODUCTION

Anal canal cancer is a very rare clinical entity (1-1.5/100000) (1). Only 1-4% of all colorectal cancers are localized in this area (2). Histopathologically, two main categories are detected: 85-90 % epidermoid (squamous cell) and 10-15% adenocarcinoma from anal cushions. Small cell neuroendocrine carcinoma and melanoma could be seen very barely. HIV, human papilloma virus (HPV 16), multiparity, homosexuality, female gender, tobacco use and immunosuppression are risk factors for anal canal cancers (3-5).

Patients via anal canal squamous cell cancer (SCC) are mainly suffering from rectal bleeding (%45), rectal pain (%30) or feeling of a rectal mass (6). Pelvic pain, tenesmus, urgent defecation requirement are signs of an advanced disease (7).

Former literature until 1970 was in favour of abdominoperineal resection (APR). However, recurrence rate (%25-50), low survival rates (%24-62) and mortality (%3) remain major obstacles for successful treatment via APR (8,9). Current literature describes application of APR only in selected cases, mainly as an escape treatment for patients suffering from insufficient CRT (8,9). In selected cases, where invasion of lymph nodes was directly proportional to tumour size and depth of invasion, local excisions were applied (10). Berry et al. reported that local excisions in earlier stages are very sufficient with good oncological results, whereas Ortolon et al. remain suspicious for local excisions, even in small size tumors (11,12). Local excision is not a therapeutic choice for anal canal cancers, according to National Comprehensive Cancer Network (NCCN) guidelines (13,14).

Only radiotherapy was applied for anal canal cancers for a period of time (15). However, local recurrence rates were so high (44-51%) (16). Current literature is in favour for combined CRT. Nigro et al. reported in 1972 successful application of external pelvic radiation with chemotherapeutic agents, 5-fluorouracil and mitomycin C (17). Histopathological examinations reveal negative margins and complete response for specimens retrieved via APR following CRT (18).

In the following years CRT become a gold standard therapy for anal canal cancers due to advances in chemo and radiotherapy doses (19,20). Also radical surgical excision remains an escape treatment for recurrences and residual tumours (21).

The aim of this study was to describe therapeutic approach, indications for abdominoperineal resection (APR), survival and oncological results for patients who received treatment in our surgical clinic for anal canal squamous cell cancer (SCC).

PATIENTS AND METHODS

Patients and study design

Eighteen patients diagnosed with anal canal cancer in the Department of General Surgery, Kartal Training and Research Hospital, Istanbul, Turkey, between January 2008 and December 2017 were retrospectively analysed. All patients were divided into two groups according to the treatment method: CRT group involved patients who received only chemoradiotherapy and CRT + APR group involved patients who underwent escape treatment including chemoradiotherapy and APR after a single period of time.

Demographic data, tumour specific treatment methods, clinical and pathological data, overall and disease free survivals were analysed.

Methods

The approach to anal canal cancers in our oncologic clinics is as follows: gross total volume (GTV) and clinical target volume (CTV) was created through scanning (2.5 mm) via abdominal computed tomography (CT') of the area between lower abdomen and perinea. These results were reevaluated via positron emission tomography–computed tomography (PET-CT) fusions. Radiotherapy was applied in three phases. Pelvic area, anus, perineal and inguinal lymph nodes received 30.6 Gy dose (Phase 1). In absence of inguinal lymph node invasion, radiation was discontinued with 36 Gy. In phase 2 the treatment area was decreased, inguinal lymph nodes were kept outside the application space, and the dose was increased to 45 Gy. According to the American Joint Commission on Cancer (AJCC) TNM system (22), in T2-T3-T4 or N+ patients, phase three was utilized. With 2 cm margin to GTV and attached lymph nodes, the total dose was 54-59. After 6-8 weeks a treatment control scanning was performed. In patients with progression, recurrences after 6 months, complete faecal incontinence or

rectovaginal fistulas, APR was applied as an escape treatment. In the first week and fifth week during radiotherapy regimen, 5-fluorouracil (5-FU) infusion for 120 hours and mitomycin bolus injection was used.

Management and treatment of anal canal cancer in our surgical department was applied according to the American Joint Cancer Committee (AJCC) criteria (20). The patients, who were unresponsive to CRT or had recurrent disease which was defined as initial complete response to the therapy, with subsequent positive biopsies more than six months after completion of the treatment, underwent surgery in our clinic.

Statistical analysis

Normal distribution data were analysed via t-test. Abnormal distributional data were evaluated via median and deviation, and Mann-Whitney U test. $\chi 2$ test was also used. Data normality was analysed via Kolmogorov-Smirnov test.

RESULTS

A total of 18 patients were included in our study. Eleven (61.1%) patients were in the CRT group, seven (38.8%) in the CRT+APR group. Female/male ratios in the groups were %54.5/%45.5, 57.1%/42.9%, respectively (p=0.914). Tumour size was 4.8 (±2.6) cm in CRT group, whereas it was 7.7 (±4.8) cm in CRT+APR group (p=0.362). There was no statistical difference between groups, according to TNM classification (tumour size, p=0.252; tumour stage, p=0.817; tumour metastases, p=0.113). The time between admittance and diagnosis was 8.9 (±3.0) months and 14.1 (±10.1) months in the CRT and CRT+APR group, respectively (p=0.538). Reasons for APR was as follows: insufficient CRT in three patients, recurrence after CRT in two, complete faecal incontinence and rectovaginal fistula in one patient each.

Locoregional recurrence was noticed in 27% of patients during the mean follow-up of 60.5 (6-124) months. Two (28.5%) patients were diagnosed with local recurrence after 7 and 17 months in the CRT group. Distant metastases were found in one patient (lung) (9%) in CRT group, three patients (two liver, one bone+extrapelvic lymph node) (42.8%) in the group CRT-APR (p=0.093) (Table 1).

Table 1. Distribution of two groups of patients with anal canal squamous cell cancer according to the treatment method

Variable	Chemoradiotherapy (CRT) group	Abdominoperineal resection (APR)+CRT) group	p
Gender (No, %)			0.914
Females	6 (54.5)	4 (57.1)	
Males	5 (45.5)	3 (42.9)	
Age (years)	57.5 (± 7.6)	55.9 (± 6.7)	0.543
Tumour size (T) (cm)	4.8 (± 2.6)	7.7 (± 4.8)	0.362
T stage (No, %)			0.252
T1	1 (9.1)	-	
T2	7 (63.6)	2 (28.6)	
T3	2 (18.2)	2 (28.6)	
T4	1 (9.1)	3 (42.9)	
Tumour stage (N) (No, %)			0.817
N0	5 (45.5)	4 (57.1)	
N1	4 (36.4)	2 (28.6)	
N2	1 (9.1)	1 (14.3)	
N3	1 (9.1)	-	
Tumour metastases (M stage) (No, %)			0.113
None	10 (90.9)	4 (57.1)	
Lung	1 (9.1)	-	
Liver	-	2 (28.6)	
Bone+ lymphnode	-	1 (14.3)	
Differantiation (No, %)			0.248
Not known	4 (36.4)	3 (42.9)	
Good	5 (45.5)	1 (14.3)	
Bad	1 (9.1)	3 (42.9)	
Invasive	1 (9.1)	-	
Overall five year survival (OS) (%)	90.9	57.1	0.389
Disease free survival (DFS) (%)	81.8	57.1	0.324
Time until diagnosis (month)	8.9 (± 3.0)	14.1 (± 10.1)	0.538
Application complaint (No, %)			0.224
Mass	5 (45.5)	3 (42.9)	
Fistula	1 (9.1)	3 (42.9)	
Pain	-	1 (14.3)	
Bleeding	7 (63.6)	2 (28.6)	
Abscess	-	1 (14.3)	
Hemorrhoid	1 (9.1)	-	
Constipation	1 (9.1)	-	
Local recurrence (No, %)			0.017
Yes	11 (100)	5 (57.1)	
No	-	2 (42.9)	
Distant metastasis (No, %)			0.093
None	10 (90.9)	4 (71.4)	
Yes	1 (9.1)	3 (28.6)	
Follow-up time (months)	60.5 (6-124)	38.4 (12-112)	0.326

Overall five year survival (OS) and disease free survival (DFS) was 77.7% and 72.7%, respectively. Comparing the two groups five year OS was 90.9% and 57.1%, whereas DFS was 81.8% and 57.1%, respectively (p=0.389 and 0.324, respectively) (Figure 1 and 2). Mean follow time was 51.9 (6-124) months.

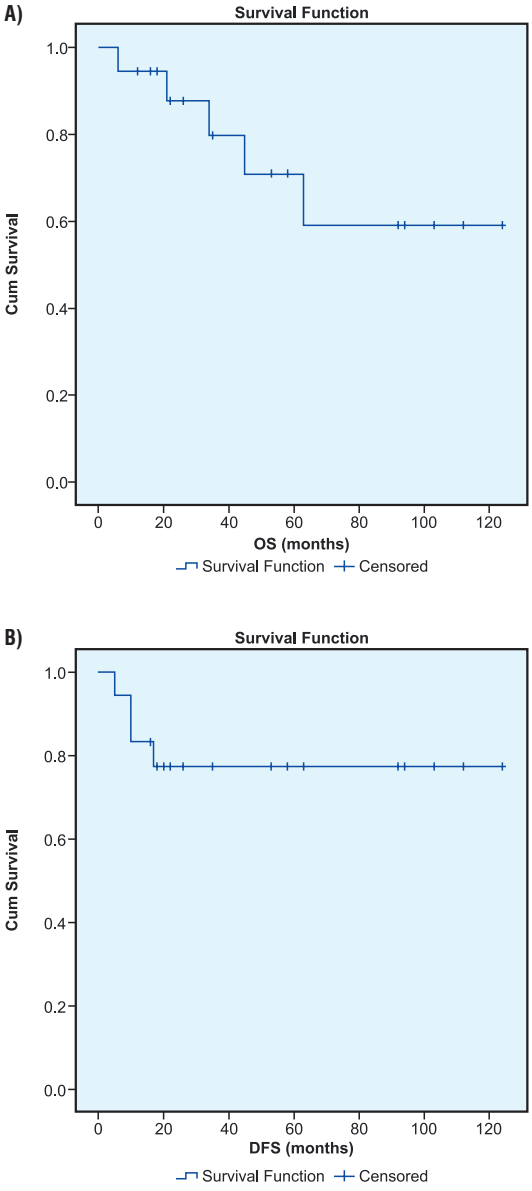

Figure 1. Overall survival (OS) (A) and disease free survival (DFS) (B) of patients with anal canal squamous cell cancer

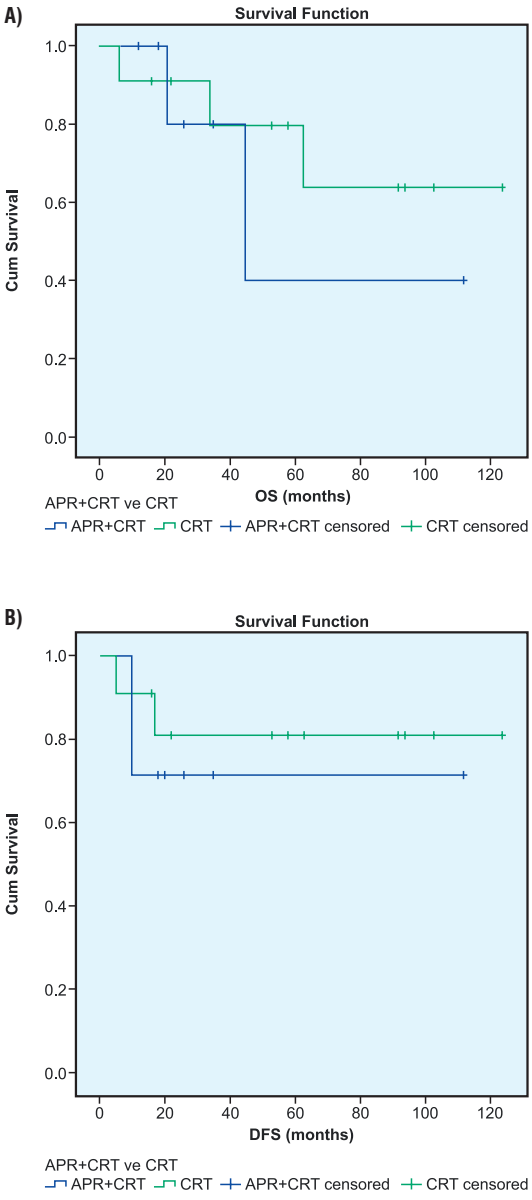

Figure 2. Comparison of chemoradiotherapy (CRT) and abdominoperineal resection (APR)+CRT group for overall survival (OS) (A) and disease free survival (DFS) (B)

DISCUSSION

Chemoradiotherapy compared to abdominoperineal resection is a preferred method in anal canal squamous cell cancer treatment due to better local control, lower recurrence rates and prolonged survival rates (6). Therefore, APR is used as salvage therapy in recurrent and persistent cases. According to NCCN guidelines CRT is a recommended essential treatment method for non-metastatic SCC (23). Five year OS in anal SCC after CRT is 60%, whereas recurrence rate is 40% (24). According to the literature, five year OS rates with combined CRT could reach 90%. In the cases without complete response recurrences occur within a short period of time. The only effective treatment modality is APR, with 5 year survival rates of 50% (2,25). In this study, five year OS and DFS were 77.7% and 72.7%, respectively. The RTOG 8704 study showed that pathologic complete response rate of anal SCC is 92% with CRT (26). In our study, pathologic complete response via CRT was 72%.

Formerly, patients who were diagnosed with anal canal carcinoma were routinely treated with APR. Nevertheless, local recurrence was

high and 5-year survival was 40-70% (6). Some of these patients were treated with preoperative 5-fluorouracil including either mitomycin C or porfiromycin and radiotherapy (chemoRT), and complete tumour regression was seen by Nigro et al, proposing that it may be possible to cure anal carcinoma (17). Current literature is in favour for combined CRT (4). Histopathological examinations reveal negative margins and complete response for specimens retrieved via APR following CRT (17). During the following years, in the light of various studies, doses of chemo-and radiotherapy were adjusted. Chemoradiotherapy is a gold standard therapy method for stage I-III anal canal SCC, whereas stage I cases in the absence of sphincter involvement could be treated with local excision (27).

Seventy-two percent of the patients who did not receive complete response in the 11th week, were disease free in the 26th week according to treatment of squamous-cell carcinoma of the anus (ACT II) study (18). Therefore, in the absence of progression, patients could be followed after 6 months of CRT. Twenty-six weeks should pass until complete response could be achieved. However, these patients should receive biopsies every 6 months, and in case of recurrence, APR should be applied (28).

Distant metastases are usually treated with systemic chemotherapy, radiation is reserved for healing of locoregional symptoms (27). In combined therapy with radiation, mitomycin/5-FU, mitomycin/kapesitabin or 5-FU/cisplatin is usually applied. Distant metastases were usually treated via 5-FU/cisplatin (29). The most common sites for distant metastases for anal canal cancer are liver, lung and extrapelvic lymph nodes (30). In our study one case had lung and another case had bone+extrapelvic metastases. We also detected 2 liver metastases. There are no published data in favour of surgical excisions of metastases (29).

Despite effective therapy via CRT for anal canal cancers, there are still high rates of locoregional insufficiency (10-30%) (31,32). Locoregonal recurrence rate was similar in our study (27%). According to the literature, this is related to tumour size, high grade of T stage and N level and we also found similar results.

All patients diagnosed with anal canal cancer should be carefully followed after primary therapy. Additional curative treatment modalities could be applied. Following primary therapy, all cases with local advanced disease proven by biopsies, and local recurrences after complete response should receive APR as an escape treatment. Salvage APR will help in controlling locoregional findings in approximately 77% of the cases with persistent or recurrent diseases (27). If invasion of inguinal lymph nodes occurs, radiotherapy (RT) should be applied. Inguinal lymph node dissection should be added in the absence of RT. Patients with extrapelvic metastases should be treated via 5-FU/cisplatin.

In conclusion, although the gold standard therapy for anal canal squamous cell cancer is chemoradiotherapy, abdominoperineal resection should be applied as an escape treatment for patients suffering from tumour progression, insufficient CRT and recurrence.

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