

The results of 21-year experience of treating anal squamous cell carcinomas

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ABSTRACT

Objective: Anal squamous cell carcinomas are one of the rare cancer types. Due to the developments in the past 35 years, surgery is no longer the first treatment of choice. The aim of this study was to retrospectively examine the outcomes of 24 patients treated in a single center in the last 21 years in terms of applied treatment, local relapse, distant metastasis, post-treatment complications, and survival.

Material and Methods: Data obtained from 24 anal squamous cell carcinoma patients, who were treated in Ankara Oncology Research and Education Hospital between 1990 and 2010, were retrospectively evaluated.

Results: Of the 24 patients, 16 had anal canal squamous cell carcinoma and eight had perianal squamous cell carcinoma. All of the patients with anal canal squamous cell carcinoma (n=16) received chemoradiotherapy. Three of these patients who did not respond to treatment, underwent abdominoperineal resection. The patients with perianal squamous cell tumors were treated by local excision. During the follow -ups, seven patients experienced local relapse, and one patient had distant organ metastasis. Only one patient died. Five-year disease free survival rate was found as 66%.

Conclusion: Our findings suggest that the first alternative in the treatment of anal squamous cell tumors should be chemoradiotherapy; and surgery seems to be the appropriate approach for the non-responsive and relapsing cases.

Key Words: Anal tumors, squamous cell carcinomas, chemoradiotherapy, abdominoperineal resection

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INTRODUCTION

Cancer of the anal region is rare. Squamous cell carcinomas are the most frequent, whereas adenocarcinomas are the second most common lesions. 1-4% of all colorectal adenocarcinoma are located in the anal area (1). More rarely, malignant melanoma may be detected. The malignancies in the anal region are examined in two different sections as the anal canal and the anal margin cancers. The anal canal forms the proximal portion of the anal region. The region between the anal verge and the pelvic diaphragm is defined as the anal canal. The region approximately 5-6 cm from the anal verge is called the perianal area. 70 to 80% of the anal area cancers arise from the anal canal, and 20% to 30 originate from the perianal region. Histologically the perianal region composed of keratinized skin where hair and sweat glands are located. The anal canal is mainly lined with squamous epithelium from the anal verge up to 1-2 cm cranial to the dentate line. A 1-2 cm section in the upper part of the dentate line is the transitional epithelium. Squamous cell tumors arising from this section do not contain large cell keratin and are called basaloid type. In proximal tumors, the lymph node drainage is to the perirectal lymph nodes along the superior hemorrhoidal artery and inferior mesenteric lymph nodes. In anal canal tumors the lymph node drainage is to anorectal, perirectal and inferior iliac lymph nodes. With perianal tumors, lymph nodes drain to superficial inguinal lymph nodes.

In 2011, 5820 anal cancer was diagnosed in the United States (2). HIV infection HPV infection, immunodeficiency, anal sex, history of cervical-vaginal-vulvar cancer are risk factors for anal cancer (3).

The diagnosis of cancer of the anal region usually is made by physical examination and rectoscopy. In 15-20% of cases, regional lymph node metastases are present on diagnosis (4-6). Endorectal ultrasound and / or pelvic MR should be done to evaluate tumor depth and regional spread. Hematogenous spread at the time of diagnosis is rare, but 40% of deaths during the course of the disease are due to distant metastases (7). Carcinomas of the anal region are staged with the TNM system (8).

MATERIAL AND METHODS

In this study, data on 24 patients who were diagnosed and treated for squamous cell cancer of the anal region in Ankara Oncology Training and Research Hospital between 1990-2010 were retrospectively analyzed. Age, gender, tumor size, lymph node status, disease stage, treatment method, presence of local recurrence, distant metastasis, treatment complications, and disease-free survival were analyzed. Informed consent was obtained from all patients and their relatives for this study.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) Version 15.0 software program for Windows computers was used for statistical calculations. Survival rate was calculated using the Kaplan-Meier method.

RESULTS

The data on clinical and pathological features are shown in Table 1. The median age was 65 years (44-86), median follow-up was 54 months (range 13-83) and there were 13 female (54.2%), and 11 male patients (45.8%). Tumor characteristics of the patients were as follows: median tumor diameter was 3.1 cm (1.5-6 cm) and when evaluated according to T stage; 14 patients had T2 tumors (58.3%), seven patients had T3 tumors (29.2%), and three patients (12.5%) had T4 lesions. According to lymph node status, 12 patients were N0 (50%), six were N1 (25%), four were N2 (17%), and two were N3 (8%). According to the TNM staging system, 12 of the (50%) were at Stage 2, nine were at stage 3A (37.5%), and three were at stage 3B (12.5%).

Analysis of the treatment methods revealed that 16 patients originating from the anal canal were treated with chemoradiotherapy and that in three of these 16 patients who failed to respond to chemoradiotherapy an abdominoperineal resection was later performed. In two of eight patients originating from the perianal region local excision plus radiation therapy was done, while in six local excision with chemoradiotherapy was preferred. In a patient with bilateral inguinal lymph node metastases at the time of diagnosis, bilateral ilioinguinal lymph node dissection was performed simultaneously.

Local recurrence was seen in seven patients (29.2%) during follow-up. The median time to local recurrence was 37 months

(12-63 months). Four patients with local recurrence had been treated with chemoradiotherapy, while three were patients who had undergone abdominoperineal resection. Three of four patients with local recurrence underwent abdominoperineal resection. Distant metastases was observed in only one patient. This patient was diagnosed with perianal squamous cell cancer with a tumor diameter of 5 cm and bilateral inguinal lymph node metastases at the time of diagnosis. The treatment consisted of excision, bilateral ilioinguinal lymph node dissection and radiotherapy. Twelve months later local recurrence, and 17 months later liver and lung metastasis developed. She died in the 22th month. There was no other mortality.

The data on disease-free survival curves are shown in Figure 1. Five-year disease-free survival rate was 66%, and the mean survival time was 51 months (95% confidence interval: 43-59). Radiotherapy was administered as conventional radiotherapy in 20 patients, and as intensity-modulated (IMRT) tomotherapy in four patients. In chemotherapy, two patients were given 5-fluorouracil (FU) (8.3%), 18 patients 5-FU + mitomycin (75%), and two patients 5-FU + cisplatin (8.3%).

Treatment complications were detected in four patients (16.7%). Radiation induced dermatitis developed in two patients, one patient had rectovaginal fistula and one experienced lower gastrointestinal bleeding. Three of these complications occurred during and in the early period after conventional radiotherapy, and one occurred in the late period. No complications were seen in patients treated with IMRT.

DISCUSSION

In squamous cell carcinoma of the anal area, abdominoperineal resection was the standard method of treatment before 1980. With this operation, 5-year recurrence rates of 40-70% and 5-year overall survival rates of 24-62% have been reported (5). To achieve better treatment results Nigro et al. (9) reported that by combined chemotherapy and radiotherapy the overall survival rate is similar to surgical treatment, and the requirement for colostomy was reduced. Currently, radiotherapy combined with 5-FU and mitomycin is used as the standard treatment in anal canal tumors (10). Surgical treatment is con-

Table 1. Clinical and pathological properties of 24 patients with anal cancer

Property		n	%
Age (median)	65 (44-86)		
Gender	F/M	13/11	54/46
T stage	T2/T3/T4	14/7/3	58/29/13
N status	N0/N1/N2/N3	12/6/4/2	50/25/17/8
Stage	2/3A/3B	12/9/3	50/37,5/12,5
Treatment	CRT/S+RT/S+CRT	16/2/6	67/8/25
Recurrence	local/distant	7/1	29/4

n: number of patients, T: tumor size, N: lymph node involvement; CRT: chemoradiotherapy; S: surgery

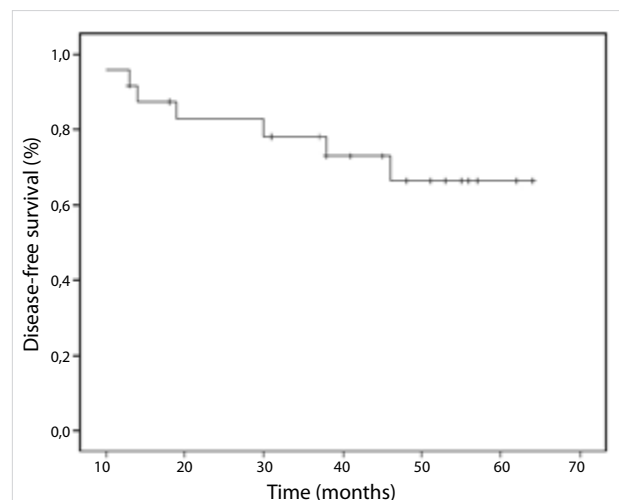


Figure 1. Disease-free survival plots

sidered only in relapsed cases or cases that do not respond to chemoradiotherapy. In many studies, patients treated with combined chemoradiation without colostomy, mean five-year survival has been reported as 70-85% with a five-year overall survival rate of 72-80% (11). Although combined chemoradiotherapy achieves better local control, and longer disease-free survival as compared to radiotherapy alone; it does not increase the overall survival. It is thought that abdominoperineal resection applied in recurrent cases has an effect on this finding. United Kingdom Coordinating Committee on Cancer Research (UKCCCR) study randomized 585 anal cancer patients and determined 4-year disease-free survival in 290 patients who received RT alone as 61%, and in the group receiving combined RT +5-FU + mitomycin of 295 cases as 72%. In our study, the five-year survival rate was found to be 66% and this rate is consistent with the literature (12). If response to chemoradiation is below 50% abdominoperineal resection can be performed. In this study, three patients who did not respond to treatment underwent abdominoperineal resection. Three more patients with recurrence also underwent abdominoperineal resection after detection of recurrence. Although in the literature, recurrence rate due to persistent disease in patients who underwent abdominoperineal resection has been reported as 40-66% (12), in this study, all three patients who were treated in the same way developed local recurrence. This situation may be attributed to the limited number of cases and higher disease stages. Primary treatment of perianal squamous cell skin cancer is surgical resection. In most cases, a large total excision is adequate, but chemoradiotherapy can also be added to treat cancer that extends into the anal canal. Five-year survival after local excision ranged from 60-95% in different series (13). In this series, eight patients who were diagnosed with perianal region squamous cell cancer were treated with wide local excision. In these patients, neither recurrence nor mortality was detected during follow-up, and this was consistent with the literature. Chemoradiotherapy-related complications can be divided into early and late complications. Early complications include diarrhea, mucositis, pain, erythema, dermatitis, and myelosuppression. While the first five early complications are more related to radiotherapy, myelosuppression is related to the toxic effects of chemotherapy. Late complications can be listed as anal ulcers, fistula, incontinence, and stenosis. In this study, three patients had early complications, and one patient developed late complications. All complications were found in patients undergoing conventional radiotherapy. There were no complications in patients undergoing IMRT. This may be due to the less toxic effects of IMRT or insufficient number of patients. Larger studies are needed regarding this issue.

Currently, new radiotherapy options like IMRT are evaluated in the treatment of anal canal tumors. In chemotherapy, cisplatin, carboplatin, oxaliplatin, docetaxel, and the new generation of targeted agents are being tested (14). It may be predicted that at the end of these evaluations, abdominoperineal resection treatment will be less administered.

Study Limitations

The number of patients in this study and the number of patients who died during follow-up is not sufficient in terms of

statistics to demonstrate powered results. Larger studies are needed to evaluate overall survival.

CONCLUSION

According to the results of this study, with chemoradiotherapy, surgery and radiation therapy planned according to localization of anal region tumors, long disease-free survival results can be achieved.

Ethics Committee Approval: Because this was a retrospective study, we did not apply for an ethical committee approval, and obtained the data from patients' files.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.İ., U.B., H.A., B.K., Y.G.; Design - K.G., H.A., G.A.; Supervision - U.B., K.G., H.A., Y.G., B.K.; Data Collection and/or Processing - F.İ., H.A., G.A., B.K.; Analysis and/or Interpretation - U.B., F.İ., K.G., Y.G.; Literature Review - F.İ., G.A.; Writer - F.İ., Y.G., B.K., U.B., K.G.; Critical Review - U.B., K.G.

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