Treatment of Squamous Cell Carcinoma of the Anal Margin: Single Center Experience

항문 가장자리 편평세포암종의 치료적 경험

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Introduction

The anal margin is defined as the skin starting at the distal end of the anal canal to a 5-cm margin surrounding the anal verge.^(1,2) The distinction between the anal margin and anal canal has become more important as they are increasingly considered different entities with separate treatments and prognosis. Squamous cell carcinoma (SCCA) of the anal cancer is rare disease representing 3 to 5% of lower gastrointestinal malignancies.⁽³⁾ Squamous cell carcinomas of the anal margin are relatively rare, at least 3 to 5 times less frequently than squamous cell carcinoma of the anal canal.⁽⁴⁾ The most common of anal margin cancer is keratinizing squamous cell carcinoma, and other tumors include Bowen disease (SCCA in situ), basal cell carcinoma, verrucous carcinoma, melanoma, and Paget disease (adenocarcinoma in situ). Nonkeratinizing SCCA are more commonly found in the cuboidal and columnar epithelium of the anal canal, proximal to the dentate line.^(5,6) Presenting symptoms include anal pain, bleeding, palpable mass, pruritus, tenesmus, change in bowel habit or discharge.⁽⁴⁾ The median time from symptom onset to diagnosis is 3 to 144 months.⁽⁴⁾ Anal margin cancers progress slowly and are commonly mistaken for benign conditions.

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In general, anal margin cancer has been characterized by a delay in diagnosis because of their location and indistinct features. Almost one-third are misdiagnosed at their first physician visit. There were given erroneous diagnoses of hemorrhoids, anal fissure, fistulas, eczema, abscesses, or benign tumor.⁽⁷⁾ The aim of this study is to present experience with radiation therapy alone or adjuvant chemoradiation therapy for anal margin cancer of the single center in Korea.

Material and Methods

Patients

A total of 16 patients treated curatively with either definitive radiation therapy(RT) alone (5 patients; 31.3%) or RT combined with chemotherapy (9 patients; 56.3%) and 2 patients (12.4%) treated only excision without RT or RT combined with chemotherapy at OOO between January 2000 and December 2010, were retrospectively analyzed. Between the two excision patients, one patient underwent wide excision and the other local excision only. The median follow up was 62 months (range, 13-148 months).

Treatment

The radiation therapy alone was performed to treat TisN0 or T1N0 diseases. The radiation therapy combined with chemotherapy was performed to treat T2-4, N0 and Any T,

N+ lesions. Five patients (31,3%) received definitive RT alone; 3 patients received RT to the pelvis only and 2 patients to the pelvis plus both inguinal areas. Nine patients (56,3%) received RT combined with chemotherapy; 2 patients received RT to the pelvis only and 7 patients to the pelvis plus both inguinal areas. The median total RT dose was 5,300 cGy (range, 4,320-6,300 cGy). The concurrent chemotherapy regimens were as follows: 5-FU/mitomycin (MMC), 5 patients; 5-FU/cisplatin (DDP), 4 patients. Patients received two 4-day cycles of continuous intravenous infusion of 5-FU (1000 mg/m²/d) combined with bolus intravenous MMC (10 mg/m²) or DDP (100 mg/m²) on the first day of each cycle. Clinical complete response (cCR) is defined as no evidence of residual disease by examination and/or imaging study. Complete Clinical complete response was observed in 13 patients and partial response was in 1 patient. Patient with partial response treated with systemic chemotherapy after RT combined with chemotherapy.

Two of all patients underwent excision only (Between them, one patient underwent wide excision and the other excision of condyloma acuminata.)

Statistical Analysis

Data were analyzed using the SPSS statistical program (Statistical Product and Service Solution 18 for Windows, SPSS Inc., Chicago, IL).Cumulative-incidence methods

Table 1. Characteristicsof patients (n=16)

Characteristic	Number of patients (%)
Sex	
Male	6 (37.5)
Female	10 (62.5)
Age(mean± SD, (range)) (year)	61.8±10.9 (38-83)
Weight(mean± SD, (range)) (kg)	56.9±8.9 (46-71)
Height(mean± SD, (range)) (cm)	157.3±7.9 (144-172)
BMI(mean± SD, (range)) (Kg/m ²)	23.0±3.1 (16.5-28.6)
CRT	
Clinical complete response(cCR)	13 (81.3)
Clinical partial resoponse	1 (6.3)
Not performed CRT	2 (12.4)
Stage	
0	1 (6.3)
I	7 (43.7)
II	4 (25.0)
III	4 (25.0)
Previous diagnosis	
Hemorrhoid	10 (62.5)
Condyloma acuminata	1 (6.3)

BMI: body mass index, CRT: chemoradiation therapy

Table 2. Treatment Results

Age(years)	Sex	AJCC	Histology	Radiotherapy	Chemotherapy	Follow-up
81	M	T2N0	SCCA+focalbasolid	4500cGy pelvis+both inguinal area	5-FU/DDP	AWD, 72 months
63	F	T1N0	SCCA	5940cGy pelvis	None	NED, 35 months
51	F	T1SNO	SCCA	4500cGy pelvis	None	NED, 96 months
82	F	T2N0	SCCA	5400cGypelvis+both inguinal area	None	AWD,132 months
78	M	T1N1	SCCA	5400cGy pelvis+both inguinal area	5-FU/MMC	NED, 28 months
44	F	T2N0	SCCA	5040cGy pelvis	5-FU/MMC	NED, 72 moths
75	M	T2N1	SCCA	5400cGy pelvis+both inguinal area	5-FU/DDP	AWD, 42 months
73	F	T1N0	SCCA	5400cGy pelvis+both inguinal area	None	NED, 148 months
71	F	T1N0	SCCA	5400cGy pelvis+both inguinal area	5-FU/DDP	NED, 65 months
72	F	T2N1	SCCA	4320cGy pelvis+both inguinal area	5-FU/DDP	NED, 51 months
57	M	T1N1	SCCA	5940cGypelvis+both inguinal area	5-FU/MMC	NED, 36 months
74	M	T1N0	SCCA	4990cGy pelvis	None	AWD, 27 months
74	F	T1N0	Cloacogenic	6300cGy pelvis+both inguinal area	5-FU/MMC	NED, 19 months
58	F	T2N0	SCCA	5940cGy pelvis	5-FU/MMC	AWD, 13 months
80	M	T1N0	SCCA	None	None	NED, 62 months
38	M	T1N0	SCCA	None	None	NED, 41 months

SCCA: squamous cell carcinoma, MMC: mitomycin, DDP: cisplatin, NED: no evidence of disease, AWD: alive with disease

were used to estimate the rate of cancer recurrence. Overall survival and disease free survival were analyzed using the Kaplan–Meier method.

Results

Patients characteristics

The median age was 61.8 years (range, 38–83 years). The sex distribution was 6 male (35,6%) and 10 female (62,5%). The median weight was 56.9 kg (range, 46–71 kg). The median BMI was 23.0 kg/m²(range, 16,5–28,6 kg/m²). The American Joint Committee on Cancer (AJCC) T–stage distribution was as follows: Tis, 1 patient (6,3%); T1, 9 patients (56,3%); T2, 6 patients (37,4%). 3 patients (18,8%) had N1 disease. No patients had T3 or T4 disease or distant metastasis. Clinical stage of all patients was stage 0 (TisN0) in 1 (6,3%), stage I in 7 (43,7%), stage II in 4 (25,0%), and stage III in 4 patients (25,0%).

Initial diagnosis of most patients was not anal margin cancer. Eleven of 16 patients were initially diagnosed with hemorrhoid (10 patients, 62,5%) and condyloma acuminata (1 patient, 6,3%). But these patients were pathologically proven squamous cell carcinoma after surgery.

Symptoms of patients were palpable inguinal node (2 patients, 12,4%), palpable perianal mass (1 patient, 6,3%), and anal bleeding (1 patient, 6,3%).

Oncologic outcomes

The 5–year disease free survival was 74,0% (Figure 1.). The 5–year overall survival was 100%. 5 patients (31,3%) was recurrence. The sites of recurrence were 2 (12,4%) anus only, 1 (6,3%) anus + vulva, 1 (6,3%) inguinal node only, 1 (6,3%) lung + pelvic wall node (Table 3.). Treatment of recurrence patients: Three patients were treated with systemic chemotherapy and 1 with RT combined with chemotherapy. Two patients refused salvage therapy. The reasons of refusal salvage therapy were old age and recipient renal allograft. Among patients who received salvage therapy, 1 patient had clinical remission and 2 patients had stable disease.

Fig. 1. Disease Free survival at 5 years for anal margin cancer

Table 3. Pattern of recurrence of anal margin cancer

Variable	N (%)
Anus only	2 (12.4)
Anus + vulva	1 (6.3)
Inguinal node only	1 (6.3)
Pelvic node + Lung	1 (6.3)

Patients who received only excision and wide excision showed no evidence of disease until last follow up.

Discussion

The median age of diagnosis of anal margin cancer is typically 60 to 70 years old.⁽⁴⁾ In present study, the median age was 61.8 years (range, 38–83 years). Jensen et al. observed that an erroneous diagnosis was made at first physician visit in 29% of patients of patients with squamous cell carcinoma of the anal margin.⁽⁸⁾ Definitive diagnosis of a squamous cell carcinoma of anal margin should be made by incisional or excisional biopsy.⁽²⁾ However, in present study, misdiagnosis rate was 68,8% (11/16 patients). Most common misdiagnosis was hemorrhoid (10 patients). Squamous cell carcinoma of the anal margin is staged according to the American Joint Committee on Cancer (AJCC).⁽¹⁾ Prognosis of patient

correlates with tumor size and lymph node involvement at diagnosis.^(9–11) The inguinal lymph nodes drain to the inguinal–femoral nodes and then to the external and common iliac lymph nodes. Pretreatment evaluation of the patient should evaluate to presence lymph node metastases used by computed tomography of abdomen and pelvis. In present study, inguinal–femoral lymph node metastasis was found in 8 patients (50%) during pretreatment evaluation. The goals of treatment are to cure the patient and also preserve anal sphincter function. Treatment of anal margin squamous cell carcinoma traditionally consisted of surgical resection with wide local excision for smaller–sized tumors and APR for larger, invasive tumors. Nigro et al. started treating anal carcinoma with chemoradiation therapy in the 1970s.⁽¹²⁾

Wide local excision is a viable treatment option for T1N0 anal margin cancer. The inguinal lymph nodes are not dissected unless they are clinically positive. Beahrs and Wilson reported that 5–year overall survival rate of 27 patients who underwent local excision was 100%.⁽¹⁴⁾ Al–Jurf et al. reported 5–year survival rate of 90% and local recurrence rate of 70% in 10 patients.⁽¹⁵⁾ The present study, 2 patients treated local excision only. Their tumor size was less than 1 cm and margin was more than 1 cm after excision. Their follow up period was 41 months and 62 months. They had no evidence of disease at the last

follow–up visit. Well to moderately differentiated, superficial T1N0 cancer and early T2N0 cancer should be treated with radiation therapy to the anus and perineal field. For T3–T4, N0–N1 or poorly differentiated cancer, radiation therapy should be given to the inguinal and pelvic area as well as primary lesion. Concurrent chemotherapy should be considered for T2Nx cancer.^(16,17) Touboul et al. reported that 5–year overall survival, sphincter preservation, and local recurrence rates were 86,2%, 82%, and 87%, respectively in 17 anal margin cancer patients treated with radiation therapy.⁽¹⁸⁾ Local control rates for radiation therapy reported by T stage were as follows: T1, 50–100%; T2, 60–100%; T3, 37–100%.^(9–11, 18–19) In comparing chemoradiation therapy with radiation alone, there was a significant reduction in the local failure rate in patients treated with chemoradiation therapy(36% vs. 59%).⁽²⁰⁾ Chapet et al. reported 71% 5–year overall survival rate and 61,4% local control rate in 26 patients treated with radiation therapy or concurrent chemoradiation therapy.⁽²¹⁾ Bieri et al. also reported that 5–year overall survival and local failure rates were 56% and 30%, respectively in 24 patients treated with radiation therapy or chemoradiation therapy.⁽²²⁾ In present study, 5–year disease free survival rate (DFS) was 74,0%, 5 years overall survival rate (OS) was 100% and recurrence rate was 31,3% (5/16) (Table 4).

Table 4. Review literature of outcomes for treatment squamous cell cancer of anal margin

Author	Institution	Treatment	Number	DFS	OS	Sphincter Preservation
Papillon and Chassard[10]	Centre Leon Berard	RT ± CTx	54	69%	59%(5 yr)	100%
Cummings et al[19]	Princess Margaret Hospital	RT ± CTx	29	79%	-	
Cutuli et al[18]	Institute Curie	RT	21	52%	52% (5 yr)	90%
Peiffert et al [8]	Centre Alexis Vantrín	RT ± CTx	32	71%	67% (5 yr)	84%
Touboul et al[17]	Tenon Hospital	RT	17	87%	86% (5 yr)	82%
Bieri et al[22]	Oncology Institute of Southern Switzerland	RT ± CTx	24	70%	56% (5 yr)	67%
Chapet et al[21]	Centre Hospitalier	RT ± CTx	26	58%	71% (5 yr)	66%
Balamucki et al[23]	University of Florida	RT ± CTx	26	81%	92%(10 yr)	81%
Present study	Yonsei University Collegeof Medicine	RT ± CTx	14	74%	100% (5 yr)	79%

DFS: disease free survival, OS: overall survival, RT: radiation therapy, CTx: chemotherapy

Conclusion

Based on literature review, the RT or RT combined with chemotherapy for squamous cell carcinoma of anal margin seems to be effective for oncologic outcome and sphincter preservation. Postoperative permanent pathology is mandatory in patients with benign anorectal disease such as hemorrhoid and condyloma acuminata since it may report squamous cell carcinoma.

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Abstract

Propose : Squamous cell carcinomas of the anal margin are rare disease among anorectal malignancies. The aim of this study is to define treatment of patients with squamous cell carcinoma of the anal margin.

Material and Method : This is a retrospective study of 16 patients with squamous cell carcinoma of the anal margin diagnosed in our hospital between January 2008 and December 2011 who received different treatment options including surgery, as well as chemotherapy and/or radiotherapy. Total radiation dose ranged from 4,320 to 6,300cGy. The radiation fields were included to pelvis alone or pelvis plus both inguinal areas. The chemotherapy regimens were 5-FU in combination with either mitomycin-C or cisplatin.

Results : Fourteen patients were treated by radiation or chemoradiation therapy. Two patients were performed local excision. Thirteen patients achieved clinical complete response and one showed a partial response. Partial response of patient was treated with systemic chemotherapy after chemoradiation therapy. Previous diagnosis of 10 patients was hemorrhoid and 1 patient was condyloma acuminata. Two patients presented with palpable inguinal nodes, one with perianal mass, and another one with anal bleeding. Ten hemorrhoids and one condyloma acuminata were determined to be squamous cell carcinoma by postoperative permanent pathology. One case was categorized as stage 0 (TisN0 : 6.3%), 7 were stage I (43.7%), 4 were stage II (25.0%), and 4 were stage III(25.0%). After a median follow up of 62 months (range, 13-148 months), recurrence was found in 5 patients (31.3%). anus only (n = 2, 12.4%). The sites of recurrence were as follows: anus + vulva (n = 1, 6.3%), inguinal node only (n = 1, 6.3%) and lung + pelvic wall node (n = 1, 6.3%). The 5-year disease free and overall survival rates were 74.0% and 100%, respectively.

Conclusion : The radiation or chemoradiation therapy for treatment of squamous cell carcinoma of anal margin was effective for oncologic outcome and sphincter preservation.

Key Words : squamous cell carcinoma, anal margin, radiation or chemoradiation therapy

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