Original Article

Anal Squamous Cell Carcinoma: 10-year Experience of a Single Center

Tsung Chuang[1]
Xuan-Yuan Huang[1]
Zhi-Cheng Chen[1]
Wei-You Chen[1]
Ya-Ling Huang[1]
Yu-Yao Chang[1,2]
[1]*Division of Colon & Rectal Surgery, Department of Surgery, Changhua Christian Hospital, Changhua,*
[2]*Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan*

Key Words
Anal squamous cell carcinoma;
Anal cancer;
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Purpose. To evaluate the presentation, management, and outcomes of patients with anal squamous cell carcinoma in a single institution.
Methods. We retrospectively identified patients diagnosed as having anal squamous cell carcinoma (ASCC) between 2009 and 2019. Diagnosis coding and chart review were conducted to identify patients with a pathologically confirmed diagnosis of ASCC and obtain their data on presentation, stage, and treatment. Main outcomes were overall survival (OS) and disease-free survival (DFS).
Results. A total of 18 patients (50% men; mean age: 60.8 year, range: 31-95 years) were identified. The most common presentations were anal bleeding (58%) and anal mass sensation (42%). The tumor was located in the perianal region in 6 (33%) patients and at the anal canal (above the anal verge) in the remaining patients (66%). Furthermore, we noted early-stage (stage 0-II), stage III, and stage IV disease at diagnosis in 13, 4, and 1 patients, respectively. Among 14 (77%) patients who underwent surgery, 13 received local excision and 1 abdominal perineal resection; 12 (66%) patients received chemoradiotherapy (CRT). Among the 12 patients who received chemotherapy, 8 received cisplatin + fluorouracil as the first-line treatment. The median follow-up period was 46 months. The median OS and DFS periods were both 68 months, respectively.
Conclusion. ASCC is a rare cancer, and anal bleeding and mass sensation are its most common presentations. CRT remains the main treatment for ASCC.

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Anal cancer is a relatively rare cancer with an incidence rate of approximately 1.9 per 100,000 men and women per year in the United States.[1] An increase in the incidence rate has been noted since the 1980s. In terms of the histological subtype, anal squamous cell carcinoma (ASCC) accounts for approximately 80% of cases.[2,3] Human papillomavirus (HPV) infection, which is a common risk factor for ASCC, may play a key role. Risk factors include receptive anal intercourse, sexual activities between men, HPV-related vulvar or cervical cancer/dysplasia, condyloma acuminata, HIV infection, smoking, and immunosuppression status.[4]

In the 1970s, abdominal perineal resection (APR) for ASCC was gradually replaced by the Nigro protocol, which used a mitomycin-based regimen. Dr. Norman Nigro initially started chemoradiotherapy (CRT) for patients with ASCC, followed by APR. Patients

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Correspondence to: Dr. Yu-Yao Chang, Division of Colon and Rectal Surgery, Department of Surgery, Changhua Christian Hospital, No. 135, Nanxiao St., Changhua City, Changhua County 500, Taiwan. Tel: 886-4-723-8595; Fax: 886-4-723-2942; E-mail: 177176@cch.org.tw

who received CRT had satisfactory outcomes.[5,6] Another study reported that patients who received a modified Nigro's protocol had lower recurrence and permanent colostomy rates than those who received CRT alone.[7] In the context of CRT treatment, studies have compared cisplatin- and mitomycin-based regimens, and results either have favored a mitomycin-based regimen or have revealed no statistical differences between the two.[8,9] Therefore, a mitomycin-based regimen is recommended as the first-line treatment in the National Comprehensive Cancer Network (NCCN) guidelines.[10] APR is currently performed as a salvage surgery for patients with recurrent or residual ASCC. In this study, we describe a 10-year experience of patients with ASCC who underwent treatment in Changhua Christian Hospital in terms of their presentation, management and outcomes.

Materials and Methods

A retrospective chart review of patients diagnosed with ASCC between 2009 and 2019 was performed at Changhua Christian Hospital. This study was approved by the institutional review board of this hospital (IRB number: 200610). We included patients who had a pathologically confirmed diagnosis of ASCC. Patients without any follow-up after their diagnosis of ASCC were excluded. We collected data on the patients'age, sex, symptoms, cancer location, cancer stage, treatment (surgery, chemotherapy, and radiotherapy [RT]), resection margin (R0, R1, or R2), time of diagnosis, time of loss to follow-up or death, and time of cancer recurrence. The patients were treated with CRT with chemotherapy regimen of 5-fluorouracil + cisplatin and radiotherapy dose ranges from 4140 to 6850 cGy; the regimen and radiotherapy doses were decided by hematologists and radiotherapists in accordance with the patients' conditions and wishes. Overall survival (OS) was defined as the time from the date of pathological diagnosis to the date of death from any cause. Disease-free survival (DFS) was defined as the time from the date of pathological diagnosis to the date of recurrence or death from any cause. OS and DFS were analyzed using the Kaplan-Meier method.

Results

After the chart review was completed, in the analysis, we included 21 patients who were diagnosed with ASCC between 2009 and 2019. We then excluded 3 patients who were immediately lost to follow-up after their diagnosis. The mean age of the 18 patients (9 men and 9 women) included in this study was 60.6 (range, 31-95) years. The most common symptoms were anal bleeding (n = 11, 58%), anal palpable mass (n = 8, 42%), painful mass (n = 2, 11%), and difficult defecation (n = 1, 5%); 2 (11%) patients were asymptomatic. Among the 18 patients, 1 had stage 0 carcinoma, 4 had stage I carcinoma, 8 had stage II carcinoma, 4 had III carcinoma, and 1 had stage IV carcinoma (Tables 1 and 2).

Table 1. Characteristics of 18 ASCC patients

	ASCC (n = 18)
Age (mean)	60.6
Gender (female)	9
Symptoms	
Anal bleeding	11
Mass sensation	8
Pain	2
Difficult defecation	2
Asymptomatic	2
Primary stage (AJCC 8th)	
0	1
I	4
II	8
III	4
IV	1
Surgery	
No	4
Local excision	13
APR	1
Chemoradiotherapy	
Combined	13
RT alone	3
No	2
Surgical margin	
R0	6
R1	7
Recurrence	
No	13
Local	2
Distant	2
Persistent	1
Death	6

ASCC, anal squamous cell carcinoma; RT, radiotherapy.

In addition, 13 of the 18 patients received local tumor excision with further CRT, 1 received APR, and 4 received only CRT. Furthermore, among the 13 patients undergoing local tumor excision, 8 received CRT, 3 received RT alone, and 2 did not receive any chemotherapy or RT (Fig. 1). The main chemotherapy regimen used was 5-fluorouracil + cisplatin; capecitabine and uracil–tegafur were also used. The chemotherapy regimen and dosage of RT for each patient is presented in Table 2.

Table 2. All 18 patients received therapy and current status

	No.	Age	Gender	Tumor size (cm)	Treatment	Chemotherapy regimen	Radiotherapy dose (cGy)	Cancer status	Current status
Local	1	31	M	3.2×1.7×1.2	Local excision	x	x	Cancer free	Alive
(stage 0-II)	2	39	F	1.0×0.7×0.6	Local excision + RT	x	6000	Cancer free	Alive
	3	56	M	2.5×1.5×1.0	Local excision + RT	x	6000	Cancer free	Alive
	4	61	M	x	CRT	5-FU + cisplatin	6000	Cancer free	Alive
	5	69	M	3.0×2.0×1.2	Local excision + CRT	5-FU + cisplatin	6000	Cancer free	Alive
	6	56	F	2.4×2.2×1.4	Local excision + CRT	Uracil–Tegafur	6000	Cancer free	Alive
	7	56	F	4.3×4.0×3.0	Local excision + CRT	5-FU + cisplatin	6000	Cancer free	Alive
	8	57	M	3.5×2.5×1.5	Local excision + CRT	5-FU + cisplatin	6000	Cancer free	Alive
	9	67	F	7.0×2.2×1.7	Local excision + CRT	Capecitabine	6120	Cancer free	Alive
	10	69	M	2.4×1.4×0.6	Local excision + CRT	5-FU + cisplatin	6000	Distant recurrence	Death (cancer)
	11	73	F	2.5×2.0×1.5	Local excision + CRT	Capecitabine	5800	Local recurrence	Alive
	12	88	M	4.0×1.0×0.7	Local excision + RT	x	6000	Cancer free	Alive
	13	95	F	3.0×2.0×1.0	Local excision	x	x	Cancer free	Death (Resp failure)
Regional	14	40	M	5.5×5.0×2.6	APR + CRT	Uracil–Tegafur	5040	Local recurrence	Death (cancer)
(stage III)	15	54	F	x	CRT	5-FU + cisplatin	4140	Cancer free	Alive
	16	61	M	x	CRT, then local excision	5-FU + cisplatin	6850	Distant recurrence	Death (cancer)
	17	75	F	x	CRT	5-FU + cisplatin	5040	Cancer free	Death (sepsis)
Distant (stage IV)	18	45	F	x	CRT	FOLFOX + bevacizumab 5-FU + cisplatin	6000	Progression	Death (cancer)

RT, radiotherapy; CRT, chemoradiotherapy; APR, abdominal perineal resection.

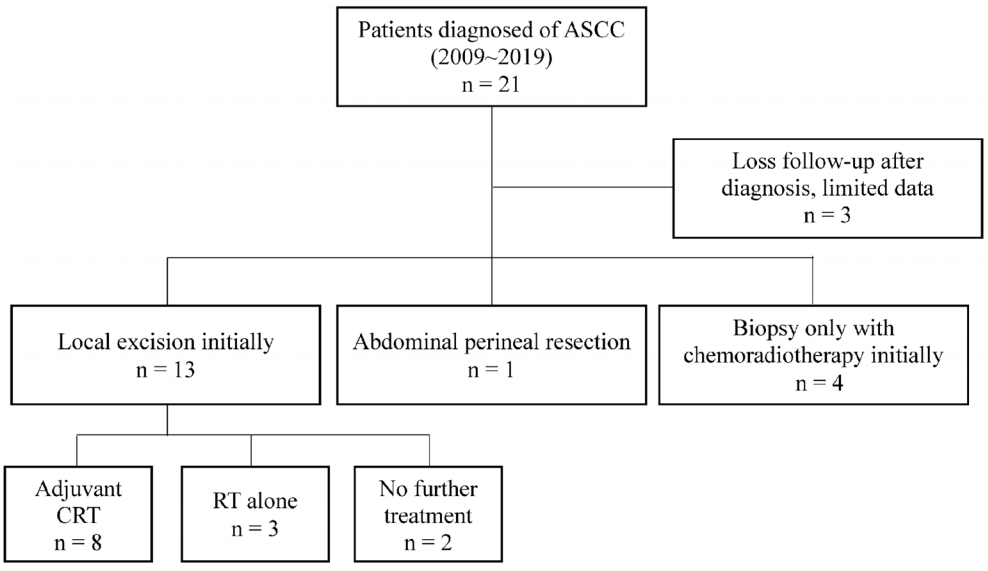

Fig. 1. Flowcharts of patients received treatment.

In terms of outcomes, the median follow-up period was 46 months. Two patients who underwent local excision only were cancer free, and 11 of the remaining 16 patients were cancer free after treatment during the follow-up period. A total of 4 (4/16) patients developed recurrence (2 developed local recurrence and 2 developed distant metastasis). The remaining patient (1/16) was a 45-year-old woman initially diagnosed with ASCC with multiple liver metastases. Chemotherapy with 5-fluorouracil + oxaliplatin + bevacizumab was administered; this regimen was then changed to cisplatin + 5-fluorouracil with radiotherapy (6000 cGy/30 fractions). We conducted abdominal CT every 6 months. Partial response was noted with shrinkage of primary tumor and liver metastases. Extended right hepatectomy + S2S3 partial hepatectomy was performed. However, an abdominal CT scan conducted 3 months later revealed liver metastasis progression. Thus, palliative chemotherapy (cisplatin + 5-fluorouracil) was prescribed. The patient died of hepatic failure 9 months after surgery. A total of 6 patients died. Four patients died of ASCC, and two patients died of pneumonia and respiratory failure. The Kaplan-Meier survival curves for OS and DFS rates are presented in Figs. 1 and 2, respectively. The 5-year OS and DFS rates of the patients were 61.2% and 60.2%, respectively. The median OS and DFS were both 68 months, respectively (Figs. 2 and 3).

Discussion

Anal cancer is a relatively rare cancer, accounting for 3% of digestive tract cancer cases.[11] Squamous cell carcinoma is the most common histological subtype of anal cancer, but it has more favorable prognosis than adenocarcinoma. In this study, we present a 10-year experience of patients with ASCC from a single center in terms of their management and outcomes. The most common symptom of ASCC was bleeding, followed by mass sensation and anal pain. This finding is consistent with that of a retrospective study that examined 107 patients in Norway.[12]

In the NCCN guidelines, the main recommended treatment for locoregional ASCC is CRT with mitomycin-C + 5-fluorouracil/capecitabine as the first-line regimen. For metastatic disease, carboplatin + paclitaxel is a first-line regimen and is associated with a higher DFS and OS and a lower toxicity relative to cisplatin + 5-fluorouracil. When local control is required for metastatic disease, RT may be considered. Local excision without CRT can be applied only in specific situations (discussed in a subsequent subsection). In our study, most patients were administered 5-fluorouracil + cisplatin for their CRT regimen. In the NCCN guidelines, a mitomycin-based regimen is recommended as the first-line treatment on the basis of the RTOG 98-11 trial, which demonstrated improved OS and DFS in a mitomycin-based group compared

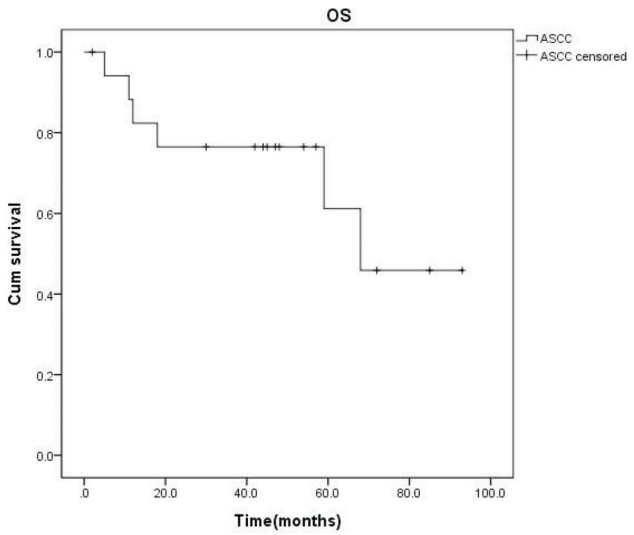

Fig. 2. Survival curve for overall survival (OS).

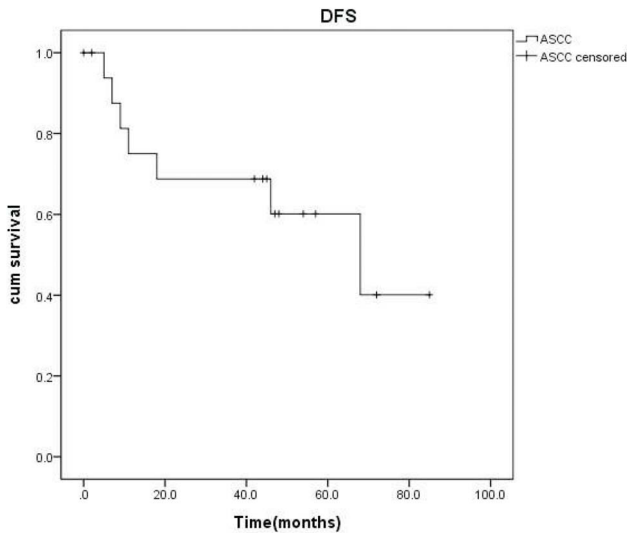

Fig. 3. Survival curve for disease-free survival (DFS).

with a cisplatin-based group.[8] The Act II trial (Second UK Phase III Anal Cancer Trial) indicated that the two CRT regimens are equivalent.[9] Therefore, the most effective regimen has yet to be identified.

A total of 13 patients primarily received CRT after a pathological diagnosis of ASCC. Among the remaining 5 patients who did not receive CRT, 1 rejected further treatment because of old age, 3 received RT after local tumor excision, and 1 received local tumor excision only. The benefits of CRT over RT alone have been under debate since the 1980s.[13] In their retrospective cohort study, Cumming et al. compared the outcomes of patients with anal canal carcinoma receiving RT alone versus CRT. They observed favorable local control in the CRT group (93%) compared with the RT alone group (60%) at the 6-month follow-up.[14] Furthermore, the first randomized clinical trial UKCCCR compared the outcomes of patients receiving CRT with 5-FU and mitomycin regimens with those of patients receiving RT alone. After 46 months of median follow-up, the local failure rate was 59% in the RT alone group compared with 36% in the CRT group.[15] However, tumor excision alone would still be favorable for patients with smaller tumors and early-stage disease. Touboul et al. suggested that RT alone is adequate for tumor sizes of ≤ 4 cm.[16] Furthermore, a recent study reported that local tumor excision alone is adequate in selective patients. They noted no decrease in the OS rate in patients with stage I disease.[17] According to the NCCN guidelines, local excision without CRT is adequate if excisional margin is adequate under two conditions: Superficially invasive anal cancer and small perianal cancer that does not involve the anal sphincter.[10]

The 5-year OS rate of patients with ASCC was reported to be approximately 68%; those with localized disease, regional disease, and distant metastasis had 5-year OS rates of 81.9%, 65.5%, and 34.5%, respectively.[1] In the RTOG 98-11 trial, the OS and DFS rates for mitomycin-based chemotherapy and cisplatin-based chemotherapy were compared. The cisplatin-based group had 5-year OS and DFS rates of 70.7% and 57.8%, respectively; these results were inferior to those of the mitomycin-based group, which had 5-year OS and DFS rates of 78.3% and 67.8%, respectively.[8]

The limitations of this study are its small sample size and retrospective design.

In conclusion, bleeding and mass sensation are the most common presentations of ASCC. CRT still remains the standard treatment for most patients with ASCC patients. Although a mitomycin-based regimen is suggested as the first-line treatment, a cisplatin-based regimen appears to be an acceptable choice.

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原　著

肛門鱗狀上皮細胞癌：一醫學中心十年的治療經驗

莊縱[1]　黃玄遠[1]　陳志誠[1]　陳威佑[1]　黃雅苓[1]　張譽耀[1,2]

[1]彰化基督教醫院　外科部　大腸直腸外科

[2]國立中興大學　醫學院　學士後醫學系

目的　整理並分析彰化基督教醫院的肛門鱗狀上皮癌病人的臨床表現、接受的治療以及整體的預後。.

方法　我們透過回溯性的病歷收集分析了在西元 2009 年到西元 2019 年被診斷為肛門鱗狀上皮癌的病人。我們使用診斷碼來蒐集病人資料也確定每個病人都有肛門鱗狀上皮癌的病理診斷。我們記錄了各個病人的症狀、癌症分期和接受的治療。我們使用整體存活率和無病存活期來估量病人的預後。

結果　總共有 18 個病人，平均追蹤的時間為 46 個月。平均年齡為 60.6 歲。最常見的症狀為肛門流血 (58%)，其次為肛門腫塊 (42%)。初始癌症分期為 0 到 2 期的有 14 位；第三期的有 3 位，而第四期則有 1 位。有 13 位病人接受局部手術切除，有 1 位病人接受經腹部和會陰切除手術。總共有 12 位病人接受化學合併放射治療，其中最常用的化學藥劑為 5-氟尿嘧啶加上順鉑。追蹤期間總共有 4 位病人復發；2 個為局部復發；2 個為遠端復發。追蹤期間總共有 6 位病人死亡；整體存活中位數為 68 個月，整體無病存活中位數為 68 個月。

結論　肛門鱗狀上皮癌是一個少見的癌症，其通常是以肛門流血和肛門腫塊來表現。化療合併放射治療仍然是主要且有效的治療方式。

關鍵詞　肛門鱗狀上皮癌、肛門癌、化學治療。