Original Article

Outcomes of Anal Squamous Cell Carcinoma: A Case Series from a Single Center

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Key Words
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Chemotherapy;
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Purpose. Anal canal cancer is a relatively rare cancer, accounting for 2-4% of all anorectal carcinomas. The current standard treatment for anal squamous cell carcinoma (SCC) is concurrent chemoradiotherapy (CCRT) based on 5-FU, rather than abdominoperineal resection (APR) and permanent colostomy. This case series study aimed to review the treatment and outcomes of patients with anal squamous cell carcinoma treated at MacKay Memorial Hospital.

Methods. A retrospective case series review was conducted of consecutive patients with anal squamous cell carcinoma treated from June 2012 to December 2019 at a single institution. Patient age, TNM stage, chemotherapy regimen, radiotherapy dose, toxicity, surgery, and survival time were recorded.

Results. Fifteen cases of anal SCC were treated during the 8-year study period. The cardinal symptoms were rectal bleeding and a palpable mass or lesion in the anal region. Fourteen (93%) patients received radiotherapy, with a dose range of 45-60 Gy in 25-28 fractions of intensity-modulated radiotherapy. Eleven (73%) patients received CCRT with 5-FU-based regimens. Three (20%) patients received radiotherapy only due to advanced age and poor health. One (6%) patient underwent Mohs surgery for tumor excision without additional treatment and had no evidence of tumor recurrence. Four (26%) patients underwent colostomy; one also underwent APR and permanent colostomy. Two (13%) patients died during the study period, at 56 months and 5 months after diagnosis, respectively. The median follow-up period was 51.87 months. The 3-year overall survival, metastasis-free survival, and colostomy-free survival rates were 93%, 92%, and 73%, respectively. The complete response rate to CCRT was 53%; when the oral precursor of 5-FU group was excluded, the complete response rate was 75%.

Conclusion. The treatment for anal SCC at MacKay Memorial Hospital during the study period resulted in favorable outcomes. Concurrent chemoradiotherapy for anal SCC can reduce APR and permanent colostomy, and thereby improve patients' quality of life.

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Anal cancer is an uncommon malignancy of the gastrointestinal tract. The most common type of anal cancer is squamous cell carcinoma (SCC), followed by adenocarcinoma and cloacogenic carcinoma.[1]

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Historically, the treatment for anal cancer has been surgery, specifically abdominoperineal resection (APR) with permanent colostomy. This procedure resulted in a 5-year overall survival rate of 57.8% for patients with anal SCC.[2] However, the conventional treatment for anal tumors is inconvenient for patients and leads to a decline in their quality of life. In 1974, Dr. Norman Nigro and colleagues developed and published the results of a radical chemoradiotherapy protocol for patients with anal cancer to avoid APR and colostomy.[3] Concurrent chemoradiotherapy (CCRT) is now the standard treatment for anal cancer and APR has become a salvage treatment for patients whose local lesions do not respond to CCRT. Several trials have demonstrated the benefits of CCRT. Chemotherapy regimens with 5-fluorouracil (5-FU) and mitomycin C are the current standard primary treatment for anal SCC. The major advantage of CCRT is preservation of the anal sphincter without reducing the cure rate.[4-6]

In Asia, Takashima et al.[7] reported that only 45% of patients with anal squamous cell carcinoma in Japan underwent definitive CCRT between 2000 and 2004, while 46% were treated surgically. As anal SCC is a rare disease, we present a case series of 15 patients from our hospital who were diagnosed and treated for anal SCC over an 8-year period. This case series includes information on the patients' characteristics, such as cancer stage, treatment modality, and outcomes after CCRT. Associated published studies were also reviewed.

Methods

Patients and methods

Patients diagnosed with anal SCC at MacKay Memorial Hospital were included in this case series review. Patients with other malignancies or who did not receive treatment at our hospital were excluded. All diagnoses were verified through examination of histological reports. Data on specific details, such as the chemotherapy regimen, radiotherapy dose, clinical response, surgical treatment, and survival time, were extracted and documented. All cases were reviewed until completion of therapy, mortality, loss to follow-up, or end of follow-up.

Follow-up and statistical analysis

Patients were regularly monitored to assess locoregional control and detect distant metastasis after treatment. The evaluations included a clinical physical examination, CT scan, and either flexible sigmoidoscopy or colonoscopy. Pelvic MRI and PET scans were also conducted, depending on the patient's symptoms. If tumor recurrence was suspected, a biopsy was routinely performed to confirm the presence of tumor tissue.

Microsoft Excel was used for data analysis.

Results

Patient demographics

From June 2012 to December 2019, MacKay Memorial Hospital diagnosed 15 patients with anal SCC. Among these cases, there were four males and eleven females, accounting for 27% and 73% of patients, respectively (Table 1). The median age of the patients was 67.8 years with a standard deviation of 10.8 years. The cardinal symptoms were rectal bleeding and a palpable mass or lesion in the anal region.

Staging of disease

The T and N stages of the 15 cases of anal SCC cases are documented in Table 2. All patients underwent an examination by colorectal surgeons for clinical staging, which included flexible sigmoidoscopy, colonoscopy, laboratory tests, computed tomography, magnetic resonance imaging, and/or positron emission tomography. Cases were staged according to the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. Four patients (26%) had stage I, 2 patients (13%) had stage II, 3 patients (20%) had stage IIIA, 4 patients (26%) had stage IIIB, and 2 patients (26%) had stage IV anal cancer (Table 2).

Table 1. Patient characteristics and summary of treatment

Pt	Age	Sex	T	N	M	Stage	Chemotherapy regimen	RT dose	Acute toxicity	Response	Local-regional recurrence/metastasis	Survival time	Surgery
1	70	F	1	2	0	IIIB	5FU + Cisplatin	60 Gy	Dermatitis	CR	-	> 134 months	None
2	66	M	1	0	0	I	5FU	50 Gy	None	CR	-	> 51 months/loss	None
3	70	F	2	0	0	II	RT alone	59.4 Gy	Dermatitis	CR	-	> 20 months/loss	None
4	68	F	2	0	0	II	5FU + Cisplatin	54 Gy	None	CR	-	> 36 months/loss	None
5	55	F	2	3	0	IIIB	5FU + Cisplatin	56 Gy	Diarrhea, mucositis	PR	-	> 87 months	Colostomy, sigmoidectomy
6	62	F	1	0	0	I	5FU	45 Gy	Anemia	CR	-	> 71 months	None
7	81	M	4	2	1	IV	Ufur	50.4 Gy	Diarrhea, anemia	SD	+/left thyroid and mediastinum	56 months/expired	None
8	61	F	2	2	0	IIIB	5FU	60 Gy	Anemia, mucositis	CR	-	> 62 months	None
9	60	M	3	2	1	IV	Capecitabine	45 Gy	None	PD	+/lung and bone	5 months, expired	None
10	59	F	4	1	0	IIIB	5FU + Cisplatin	50 Gy	Anemia, cystitis	PR	-	> 60 months	Colostomy
11	77	F	1	0	0	I	5FU + Cisplatin + Mitomycin C	45 Gy	Diarrhea	CR	-	38 month, expired due to liver cancer	None
12	88	M	4	0	0	IIIA	RT alone	50.4 Gy	None	SD	-	> 12 months (loss)	None
13	53	F	0	0	0	I	Surgery	Surgery	None		-	> 45 months (loss)	Mohs surgery
14	86	M	4	0	0	IIIA	RT alone	45 Gy	None	SD	-	> 45 months	Colostomy
15	78	F	4	0	0	IIIA	Ufur (Tegafur + Uracil)	45 Gy	None	SD	-	> 45 months	Colostomy, APR

RT: radiotherapy; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Treatment

Fourteen (93%) patients received radiotherapy, eleven (73%) patients received CCRT, and three (20%) patients received RT only due to old age and poor health. The dose of radiotherapy ranged from 45-60 Gy in 25-28 fractions of intensity-modulated radiotherapy. In the eleven patients who received CCRT, six (54%) achieved a complete response in subsequent examination. The chemotherapy regimens at our hospital are based on 5-FU combined with cisplatin and/or mitomycin C (Table 2). The most commonly reported toxicities were radiation dermatitis, diarrhea, and anemia. One patient (patient number 15) refused the chemotherapy regimen with 5-FU and cisplatin due to concerns related to side effects. Four (26%) patients received a colostomy before CCRT due to a large bowel obstruction or tumor bleeding. One patient underwent emergency surgery due to ischemic colitis. One patient underwent APR after completing the course of CCRT.

Clinical outcomes

The 3-year overall survival, metastasis-free survival, and colostomy-free survival rates were 93%, 92%, and 73%, respectively (Table 3). The median

Table 2. TNM stage

T stage	Numbers of patients (%)	Stage	Numbers of patients (%)
T1	5 (33%)	Stage I	4 (26%)
T2	4 (26%)	Stage II	2 (13%)
T3	1 (6%)	Stage IIIA	3 (20%)
T4	5 (33%)	Stage IIIB	4 (27%)
N stage	Numbers of patients (%)	Stage IV	2 (13%)
N0	9 (60%)		
N1	1 (6%)		
N2	3 (20%)		
N3	1 (6%)		
M stage	Numbers of patients (%)		
M0	13 (87%)		
M1	2 (13%)		

Table 3. Type of treatment and outcomes

	Number (%)
Treatment	
Primary tumor excision	1 (6%)
RT alone	3 (20%)
CCRT	11 (73%)
Radiation dose	
Range	45-60
Median ± SD	51.09 ± 5.88
Chemotherapy regimen	
Total	11
5FU alone	3 (27%)
Cisplatin/5FU	4 (36%)
MMC/cisplatin/5FU	1 (9%)
Oral chemotherapy	3 (27%)
Follow up period	Average 51.8 months ± 31.50
Mortality	2 (13%)
Complete response of CCRT	6 (54%)[a]
3-year overall survival	14 (93%)
3-year metastasis-free survival	11 (92%)[b]
3-year colostomy-free survival	11 (73%)

RT, radiotherapy; CCRT, concurrent chemoradiotherapy, APR, abdomminoperineal resection; SD, standard deviation; 5-FU, 5-flurouracil; MMC, mitomycin-C.

[a] The patient No. 3, No. 12, No. 13 and No. 14 were excluded because they didn't receive CCRT.

[b] The patient No. 7 and No. 9 were excluded because of in M1 stage.

follow-up period was 51.87 months (range: 5-134 months). The complete response rate to CCRT within 3 months after completing treatment was 54% (6 of 11 patients). One patient (6%) treated with CCRT was documented as having treatment failure, with lung and bone metastases detected 2 months after diagnosis. One patient treated with CCRT initially had stable disease, but thyroid and mediastinal metastases were subsequently detected and this patient died 56 months after diagnosis of anal SCC. Four patients had a partial response or stable disease, with tumor shrinkage and no progression of the lesions observed at last follow-up. Four patients underwent surgery to receive a permanent colostomy due to obstruction or bleeding. One patient underwent emergency Hartmann's procedure surgery due to radiation-related ischemic colitis. One patient had possible tumor recurrence 4 months after complete CCRT and underwent APR. One patient was diagnosed at an early stage (T1N0M0, stage I) and received CCRT; this patient achieved a complete response. Unfortunately, this patient passed away 34 months after diagnosis of anal cancer due to liver cancer.

Discussion

In this case series review of 15 patients with anal SCC treated at MacKay Memorial Hospital, only one patient underwent Mohs micrographic surgery for complete tumor resection. This patient had T1N0M0, stage I anal cancer with a tumor sized approximately 2.0 cm × 1.7 cm and 2 mm in depth. Follow-up imaging showed no evidence of tumor recurrence in this patient. Local excision for early-stage anal SCC has been reported in some studies but is not currently recommended by major guidelines. However, Sakti Chakrabarti et al. reported that local excision might be a safe and effective treatment for a highly selected group of patients with stage I anal SCC.[8]

The other fourteen patients in this case series underwent radiotherapy; eleven of these patients underwent CCRT. The dosage of radiotherapy ranged from 45 Gy to 60 Gy in 25-28 daily fractions. Many trials of chemotherapy regimens for anal SCC have been reported, including 5-FU/mitomycin C, 5-FU/cisplatin, and cisplatin/mitomycin C.[9] The current study demonstrates that the combination of 5-FU and mitomycin C leads to a high cure rate.[9,10] However, the toxicities of mitomycin C have been reported as thrombocytopenia, leukopenia, pulmonary toxicity, nephrotoxicity, and hemolytic uremia.[9] CCRT was associated with some toxicities in this study; the major acute toxicities included hematologic toxicities, dermatitis, and gastrointestinal toxicities, which can cause significant morbidity and, rarely, death. Clinically, mitigating these toxicities, optimizing survival, and individualized treatment remain major challenges.

Four major chemotherapy regimens were used in this case series of patients at MacKay Memorial Hospital: 5-FU alone (3 patients, 27%), 5-FU/cisplatin (4 patients, 36%), 5-FU/cisplatin/mitomycin C (1 patient, 9%), and the oral 5-FU precursor (3 patients, 27%). All three patients who received the 5-FU che-

motherapy regimen achieved a complete response. In the four patients who received the 5-FU and cisplatin chemotherapy regimen, two patients had a complete response and two had partial responses. The patient who received the 5-FU/cisplatin/mitomycin C chemotherapy regimen achieved a complete response. Among the three patients who received the oral 5-FU precursor, two had stable disease and one had progressive disease. Unfortunately, two of these patients passed away 56 and 5 months after diagnosis, respectively. The high mortality rate of the oral 5-FU precursor group may be due to older age and advanced disease stage. The local failure rate for CCRT in anal SCC is reported to be 10-20%.[11] In our case series, the complete response rate for CCRT was 53% (6 of 11); if the oral 5-FU precursor group is excluded, the complete rate was 75% (6 of 8).

Not surprisingly, two-thirds of the patients who received radiotherapy had stable disease and only one patient showed a complete response. This may be due to the fact that these patients were diagnosed at an advanced stage, with both patients having T4N0M0, stage IIIA disease. One of these patients was lost to follow-up 12 months later and the other patient continued to have stable disease at regular follow-up visits in the outpatient department.

Four patients underwent colostomy prior to radiotherapy or chemoradiotherapy due to obstruction and tumor bleeding. One patient underwent Hartmann's procedure following ischemic colitis of the sigmoid colon and lower rectum and was still alive with colostomy at last follow-up, at least 7 years later. One patient completed the course of CCRT, but abdominal magnetic resonance imaging revealed a potential residual tumor. APR is considered a viable salvage therapy for patients with residual or recurrent anal SCC. Fortunately, the surgical pathology revealed no residual tumor, and this patient remained disease-free at 40 months after surgery. One patient with colostomy died 60 months after diagnosed as anal SCC and among the four patients, no one had underwent colostomy reversal.

Eleven (73%) of the patients diagnosed with anal SCC and treated at MacKay Memorial Hospital were able to avoid permanent colostomy.

In our country, Taiwan, Yi-Wei Chen et al.[12] reported that the three-year overall survival rate for 42 patients with anal cancer who received anus-preserving treatment was 53% and the disease-free survival rate was 64%. The five-year rate for preservation of a functional anus was 64%. Although there was a relatively small number of patients in our case series, the clinical outcomes were at least as good as those of previous studies. The 3-year overall survival rate was 93%, the colostomy-free survival rate was 73%, and the median follow-up period was satisfactory. Only two patients (13%) died due to progression of anal SCC during the study period. Patient number 9, who was diagnosed with stage IIIC anal SCC, was treated with oral capecitabine and radiotherapy. However, follow-up imaging revealed multiple bone and liver metastases, and this patient passed away 5 months after initial diagnosis. Patient number 7, who was diagnosed with stage IV anal SCC, was treated with oral UFUR (tegafur + uracil) and radiotherapy. This patient passed away 56 months after initial diagnosis due to complications from radiation proctitis-related ischemic colitis and septic shock.

Overall, this study indicates that treating anal SCC with RT or CCRT can effectively control the local tumor, prolong survival, preserve anal sphincter function, and improve quality of life. The outcomes of anal squamous cell carcinoma for this series of patients treated at MacKay Memorial Hospital are as good as those of previous reports.[12]

The major limitation of our study is the relatively small sample size, which limits the statistical power and generalizability to other populations or locations. In addition, the follow-up duration was only three years for some patients, which did not allow for the long-term evaluation of all patients. Further prospective, multicenter studies are required to validate the current findings.

Conclusion

This case series of patients with anal cancer treated between 2012 and 2019 at our institution supports the use of CCRT for anal squamous cell carcinoma; this

treatment can reduce the need for APR and lead to favorable treatment outcomes. Moreover, the outcomes of treatment for anal SCC at MacKay Memorial Hospital during the study period are comparable to previous studies.

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Conflicts of Interest

No potential conflicts of interest were reported by the authors.

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References

1. Klas JV, Rothenberger DA, Wong WD, Madoff RD. Malignant tumors of the anal canal: the spectrum of disease, treatment, and outcomes. *Cancer* 1999;85(8):1686-93.
2. Beahrs O. Janeway Lecture. Management of cancer of the anus. *AJR Am J Roentgenol* 1979;133:790-5.
3. Nigro ND, Vaitkevicius VK, Buroker T, Bradley GT, Considine B. Combined therapy for cancer of the anal canal. *Dis Colon Rectum* 1981;24:73-5.
4. UKCCCR Anal Cancer Working Party. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil and mitomycin. *Lancet* 1996;348:1049-54.
5. Bartelink H, Roelofsen F, Eschwege F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol* 1997;15: 2040-9.
6. Flam M, John M, Pajak TF, et al. Role of mitomycin in combination with fluorouracil and radiotherapy and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. *J Clin Oncol* 1996;14:2527-39.
7. Takashima A, Shimada Y, Hamaguchi T, et al. Current therapeutic strategies for anal squamous cell carcinoma in Japan. *Int J Clin Oncol* 2009;14(5):416-20.
8. Chakrabarti S, Jin Z, Huffman BM, Yadav S, Graham RP, Lam-Himlin DM, Lightner AL, Hallemeier CL, Mahipal A. Local excision for patients with stage I anal canal squamous cell carcinoma can be curative. *J Gastrointest Oncol* 2019; 10(2):171-8. doi: 10.21037/jgo.2018.12.12. PMID: 31032082; PMCID: PMC6465491.
9. Ludmir EB, Kachnic LA, Czito BG. Evolution and management of treatment-related toxicity in anal cancer. *Surg Oncol Clin N Am* 2017;26(1):91-113. doi: 10.1016/j.soc.2016.07.004. PMID: 27889040.
10. James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, Maughan T, McDonald A, Essapen S, Leslie M, Falk S, Wilson C, Gollins S, Begum R, Ledermann J, Kadalayil L, Sebag-Montefiore D. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial. *Lancet Oncol* 2013;14(6):516-24. doi: 10.1016/S1470-2045(13)70086-X. Epub 2013 Apr 9. PMID: 23578724.
11. Hannes S, Reinisch A, Bechstein WO, et al. Salvage abdominoperineal excisions in recurrent anal cancer–impact of different reconstruction techniques on outcome, morbidity, and complication rates. *Int J Colorectal Dis* 2016;31(3):653-9.
12. Chen YW, Yen SH, Chen SY, Huang PI, Shiau CY, Liu YM, Lin JK, Wang LW. Anus-preservation treatment for anal cancer: retrospective analysis at a single institution. *J Surg Oncol* 2007;96(5):37480. doi: 10.1002/jso.20747. PMID: 17492635.

原　著

單一醫學中心對肛門鱗狀上皮細胞癌之治療及預後 – 病歷回溯研究

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目的　肛門鱗狀上皮細胞癌的標準治療是以氟尿嘧啶 (5-FU) 和 Mitomycin C 合併放射治療。本篇的目標是了解在馬偕醫院對於此疾病之治療及預後是否如同文獻上一樣。

方法　本篇為病歷回溯研究，資料蒐集自單一醫學中心，時間從 2012 年 7 月到 2019 年 11 月等 8 年間。記錄病人腫瘤期別、化學及放射治療的方法、手術個案數、併發症及存活時間。

結果　8 年研究期間共納入十五個病例。主要臨床症狀為肛門口腫塊或直腸出血。有十四個病人接受同步化學放射治療，放射線治療為強度調控放射治療 (IMRT)，強度為 45-60 戈雷，分 25-28 次照射。三個病人因為年紀跟身體狀況只接受放射線治療，11 個病例接受 5-FU 為基底的化學治療及放射線治療。有四個病人因腸阻塞或腫瘤出血接受了永久性的大腸造口，有一個病人在完成化學及放射治療後因腫瘤未完全消除行腹部會陰聯合切除術。一個病人接受莫氏顯微切除手術，後續追蹤均無復發跡象。十五個病人中，僅有兩個因肛門鱗狀上皮細胞癌進展死亡 (分別是診斷後五個月及診斷後四年八個月)，四個病人追蹤時間不足五年但目前仍於門診持續追蹤且疾病控制良好。三年的存活率 (Overall Survial) 為 93%，三年無疾病轉移存活率 (Metastasis-free Survival) 為 92%，三年無肛門造口存活率 (Colostomy-free Survival) 為 73%，整體對同步化學放射治療的完全反應率 (Complete Response) 為 53%，若排除口服化療藥物則為 75%。

結論　馬偕醫院在治療肛門鱗狀上皮細胞癌的預後和之前的研究相當。使用同步化學放射治療肛門鱗狀上皮細胞癌是有效的，可減少病人做腹部會陰聯合切除術及永久人工肛門的比例並增進病人的生活品質。

本篇呈現我們中心的肛門鱗狀上皮細胞癌經驗。雖然資料簡短而有限，我們期望能在本篇的基礎上，對未來進行更詳細的分析以供研究及參考。

關鍵詞　肛門鱗狀上皮細胞癌、化學放射治療、腹部會陰聯合切除術。