Original Article

The Oncologic Outcome of Anal Squamous Cell Carcinoma and Adenocarcinoma

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Key Words
Anal cancer;
Oncologic outcome

Introduction. Most patients with anal cancer were recommended to treat with chemoradiotherapy. However, some patients may still receive surgery in the hope of improving oncologic outcomes. In this study, we analyze the oncologic outcome of patients with anal cancer from different types of treatment and review the literature.
Method. We collected patients with anal cancer and have been treated in the colorectal department in Chung Gung Memorial Hospital from 1997 to 2020. Clinicopathologic variables were collected. We performed univariate and multivariate analyses for overall and disease-free survival. For subgroup analysis, all patient was classified into three groups according to treatment type: operation only, CCRT only, and operation plus CCRT.
Result. In univariate analysis, patients with SCC have significantly better overall survival than adenocarcinoma. Patients with distant metastasis have significantly worse overall survival and disease-free survival than those without. There was no significant difference between different T stages and N stages. In multivariate analysis (Table 3), only patients with distant metastasis showed significantly worse overall survival than others. In subgroup analysis, in patients with stage I-II anal cancer, there was no significant difference between these patients undergoing CCRT with or without operation (0.57 vs. 0.72, $p = 0.206$, Fig. 1A). No difference was found between these patients undergoing local excision with or without CCRT (0.89 vs. 0.67, $p = 0.243$, Fig. 1C). Worse overall survival for patients with stage III-IV disease treated with operation plus CCRT than with CCRT only (0.08 vs. 0.66, $p < 0.05$).
Conclusion. Early anal cancer can be treated with local excision or definite CCRT without significant difference. Surgery has no benefit but worse survival for patients with uncontrolled distant disease.

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Anal cancer is a rare malignancy, around 2.7% among all gastrointestinal cancer in U.S.[1] The pathology of anal cancer included carcinoma (eg. squamous cell carcinoma (SCC) and adenocarcinoma), neuroendocrine tumor, mesenchymal tumors, melanoma, and so on.[2] Among these types of anal cancer, anal carcinoma, like SCC and adenocarcinoma, were mostly localized and regional disease. According to current NCCN guideline, the treatment of anal SCC was recommended to treat with definitive concurrent chemotherapy and radiotherapy (chemoradiotherapy, CCRT).[3] Although anal adenocarcinoma has been recommended to treat as rectal cancer according to guideline, some have advocated that, for early disease, definite CCRT can preserve the patient's sphincter and avoid permanent colostomy.[4]

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On the other hand, for patients with early disease, local excision only may achieve non-inferior oncologic outcomes compared with definite CCRT, and the patient can spare from long-term toxic effects, like radiation proctitis or dermatitis, from CCRT.[5] Furthermore, patients who have done CCRT but with severe side effects and viable cancer may still need further surgery to treat the disease. To investigate these issues, we analyze the oncologic outcome of patients with anal SCC and adenocarcinoma from different types of treatment and review the literature in this study.

Method

We collected patients diagnosed with anal adenocarcinoma or squamous cell carcinoma and have been treated in the colorectal department in Chung Gung Memorial Hospital from 1997 to 2020. Clinicopathologic variables, including age, sex, staging, histology, treatment, dates of diagnosis/death/first recurrence/operation, types of surgery, and HPV/HIV infection, were collected.

Definition of incidental finding

When anal cancer was incidentally found in pathologic reports after elective anal surgery for benign diseases like hemorrhoidectomy or fistulectomy, we called it an incidental finding. When the cancer was incidentally found, the T stage was classified as Tx, N stage, and the M stage was classified according to the finding of CT images. The final stage was stage IV (TxNxM1) or the unknown stage (TxNxM0).

Subgroup analysis

All patient was classified into three groups according to treatment type: operation only, CCRT only, and operation plus CCRT. Patients with different stages and treatment type were compared in the subgroup analysis, but patient with no treatment (n = 2) was not shown in the subgroup analysis. These two patients' cancers were found incidentally and received no further treatment. Patients with operation only or operation plus CCRT were distributed to two groups: local excision or APR. Patients with CCRT only were classified as a primary diagnosis or an incidental finding. Patients who had just received a hemorrhoidectomy or a fistulectomy and had CCRT afterward were distributed to the group labeled CCRT only. *p*-value was not calculated in the subgroup analysis due to each group's relatively tiny patients number.

Statistical analysis

Oncologic outcomes were presented using 5-year overall (OS) and 5-year disease-free survivals (DFS), which were calculated using the Kaplan-Meier (KM) method. We use a log-rank test to compare survivals between subtypes of different variables. Patients with unknown stages were excluded from multivariate analysis. We use Cox proportional model for multivariate analysis. All statistical analysis was done by using SPSS 25.

Result

We have collected a total of 79 patients with a mean age of 62.4, ranging from 34-92 years old. The median follow-up time was 5.1 years. Most patients were squamous cell carcinoma (n = 67, 84.8%). Female patients (n = 52, 65.8%) were more than male. According to treatment types, 9 (11.4%) patients received operation only, 41 (51.9%) patients received CCRT, and 27 (34.2%) patients had operation plus CCRT. There were 15 (19.0%) patients diagnosed incidentally after hemorrhoidectomy or fistulectomy, and most of them received CCRT after surgery (n = 12), two had no treatment, and one had a radical resection. Although we have collected variables on whether patients had HPV or/and HIV infection, only a few patients have been examined for these two infections. Most patients remained unknown for these viral infections. Table 1 shows all patients' clinicopathologic features.

Patients with SCC or adenocarcinoma are analyzed separately. In the univariate analysis of anal

SCC, patients with distant metastasis have significantly worse overall and disease-free survival than those without. Overall survival and disease-free survival are correlated with advanced staging. There was no significant difference between different T stages. N1 has worse overall survival than N0, but it is insignificant (OS: 46.3% vs. 71.0%, $p = 0.15$) (Table 2A). For patients, anal adenocarcinoma, T stage, and distant metastasis have significantly worse overall survival ($p < 0.05$, Table 2B). The overall and disease-free survival are not linear depending on staging in these patients. It may be due to the small case number.

All patients with unknown stages were excluded from multivariate analysis. We did not perform a multivariate analysis for adenocarcinoma due to the small case number (n = 7). In a multivariate analysis of SCC (Table 3), only patients with distant metastasis showed worse overall survival and disease-free survival.

In subgroup analysis, the overall survival rates of patients with stage I-II were 72.2 % of patients with CCRT only, 66.6% with local excision, and 88.9% with local excision plus CCRT. There was no signifi-

Table 1. Clinicopathologic features of all patients with anal cancer

	Number	Percentage (%)
Total	79	100.0
Age (years old)		
Mean	62.4 ± 11.5	
Range	34-92	
Sex		
Female	52	65.8
Male	27	34.2
Histologic type		
Adenocarcinoma	12	15.2
SCC	67	84.8
Stage		
I	8	10.1
II	26	32.9
III	16	20.3
IV	11	13.9
Unknown	18	22.8
T stage		
Tx	20	25.3
T1	8	10.1
T2	35	44.3
T3	8	10.1
T4	8	10.1
N stage		
Nx	5	6.3
N0	54	68.4
N1	20	25.3
M stage		
Mx	2	2.5
M0	66	83.5
M1	11	13.9
Treatment type		
No treatment	2	2.5
Operation only	9	11.4
CCRT only	41	51.9
Operation plus CCRT	27	34.2
Neoadjuvant CCRT	22	81.5
Adjuvant CCRT	5	18.5
HPV infection		
Not examined	69	87.3
No	8	10.1
Yes	2	2.5
HIV infeciton		
Not examined	72	91.1
No	4	5.1
Yes	3	3.8

Table 2A. Oncologic outcomes of anal SCC-univariate analysis

	5-year overall survival (%)	*p* value	5-year disease-free survival (%)	*p* value
Sex		0.508		0.67
Female	62.7		34.4	
Male	65.8		34.9	
Stage		< 0.05		< 0.05
I	71.4		42.9	
II	67.0		40.5	
III	66.7		40.0	
IV	14.3		0.0	
Unknown	76.2		34.2	
T stage		0.326		0.99
Tx	72.7		29.6	
T1	71.4		42.9	
T2	67.5		34.7	
T3	37.5		29.2	
T4	50.0		37.5	
N stage		0.15		0.69
Nx	50.0		0.0	
N0	71.0		43.0	
N1	46.3		23.5	
M stage		< 0.05		< 0.05
Mx	50.0		0.0	
M0	69.9		40.3	
M1	14.3		0.0	

cant difference between these patients undergoing CCRT with or without operation (0.57 vs. 0.72, $p = 0.206$, Fig. 1A). No difference was found between these patients undergoing local excision with or without CCRT (0.89 vs. 0.67, $p = 0.243$, Fig. 1C). In patients with stage III anal cancer, the overall survival rate of the CCRT only group was 90%, significantly better than 16.7% of operation plus CCRT group ($p < 0.05$). The overall survival rate of stage IV patients with CCRT only was 20%, better than 0% of patients with operation plus CCRT but without statistical significance ($p = 0.238$). In addition, there was significantly worse overall survival for patients with stage III-IV disease treated with operation plus CCRT than with CCRT only (0.08 vs. 0.66, $p < 0.05$, Fig. 1B). Only one patient with stage III disease (T4N0M0) received operation only and had no recurrence afterward. For most patients, resection of the tumor, either local excision or APR, seems to relieve symptoms without significantly improving survival in patients. All patients who received APR plus CCRT eventually died due to distant metastasis, which suspected the existence of undetectable metastasis before surgery.

Table 2B. Oncologic outcomes of anal adenocarcinoma-univariate analysis

	5-year overall survival (%)	*p* value	5-year disease-free survival (%)	*p* value
Sex		0.762		0.54
Female	33.3		0.0	
Male	22.2		22.2	
Stage		< 0.05		0.196
I	100.0		100.0	
II	0.0		0.0	
III	50.0		50.0	
IV	0.0		0.0	
Unknown	25.0		0.0	
T stage		< 0.05		< 0.05
Tx	40.0		25.0	
T1	100.0		100.0	
T2	0.0		0.0	
T3	N/A		N/A	
T4	N/A		N/A	
N stage		0.30		0.99
Nx	N/A		N/A	
N0	12.5		12.5	
N1	33.3		33.3	
M stage		< 0.05		< 0.05
Mx	N/A		N/A	
M0	37.5		28.6	
M1	0.0		0.0	

Table 3. Oncologic outcomes of anal SCC-multivariate analysis

	Overall survival			Disease free survival		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Sex						
Female	ref.	-	-	-	-	-
Male	1.8	0.3-2.0	0.60	0.8	0.4-1.8	0.58
T stage						
T1	ref.	-	-	-	-	-
T2	0.6	0.2-2.1	0.47	0.7	0.3-1.8	0.41
T3	1.0	0.2-4.2	0.97	0.5	0.2-2.5	0.26
T4	0.7	0.2-3.3	0.73	0.6	0.2-2.7	0.40
N stage						
N0	ref.	-	-	-	-	-
N1	1.3	0.5-3.9	0.64	1.5	0.6-3.4	0.37
M stage						
M0	ref.	-	-	-	-	-
M1	7.1	1.7-29.2	< 0.05*	3.3	1.0-10.5	< 0.05

Table 4. Subgroup analysis

Treatment type	Stage I-II		Stage III		Stage IV		Unknown	
	N	5-year OS (%)	N	5-year OS (%)	N	5-year OS (%)	N	5-year OS (%)
Operation only	5	80.0	1	100.0	0	n/a	3	33.0
Local excision	3	66.7	1	100.0	0	n/a	2	50.0
APR	2	100.0	0	n/a	0	n/a	1	0.0
CCRT only	15	72.2	10	90.0	5	20.0	11	70.7
Primary dignosis	15	72.2	9	88.9	4	25.0	1	100.0
Incidental finding	0	n/a	1	100.0	1	0	10	67.5
Operation plus CCRT	14	57.1	6	16.7	6	0	1	0.0
Local excision	9	88.9	0	n/a	2	0	1	0.0
APR	5	0.0	6	16.7	4	0	0	n/a

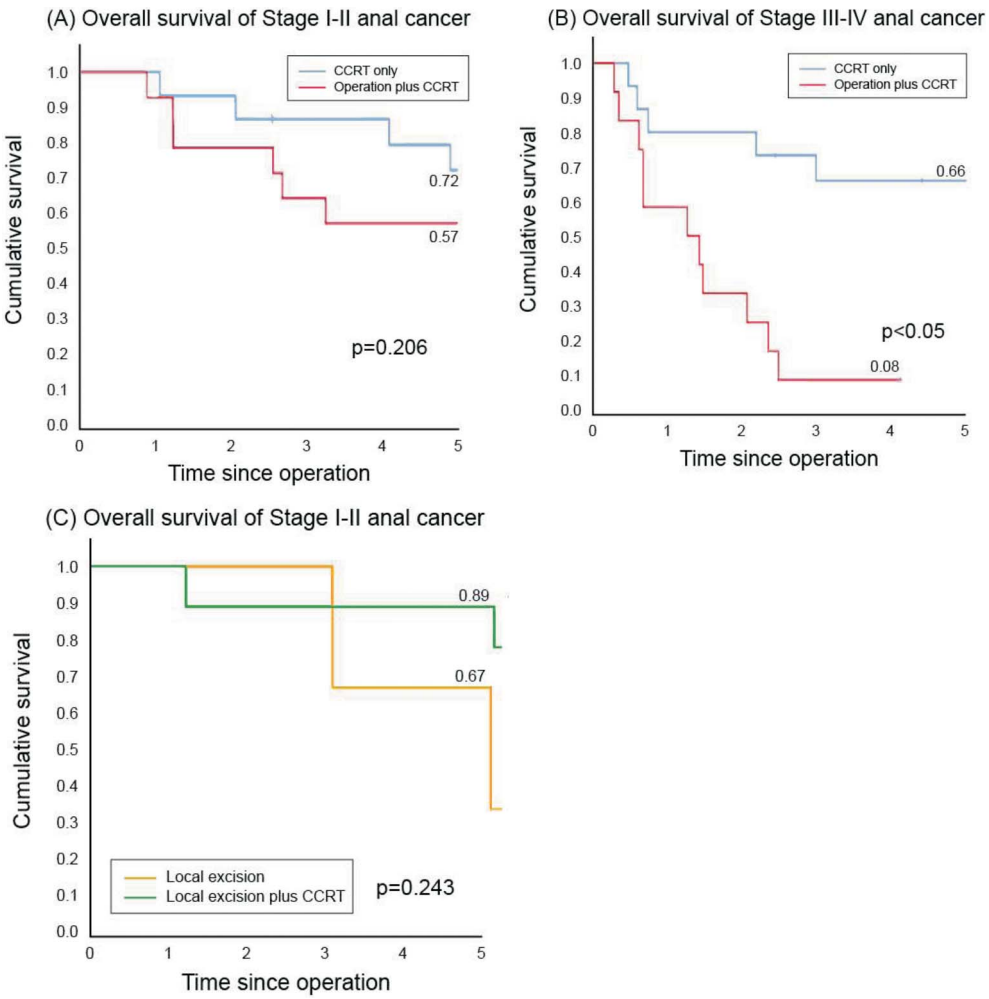

Fig. 1. Oncologic outcome of anal cancer.

Discussion

For all patients, distant metastasis was the only significant prognostic factor related to worse oncologic outcomes in both univariate and multivariate analyses. Patients with lymph node metastasis does not have significant worse outcome. The previous study has shown that anal cancer with lymph node metastasis can be cured in close to 50% of patients if the lymph node metastasis was detected and treated initially, which is compatible with our result.[6]

Adenocarcinoma was a relatively rare malignancy among anal cancer, around 5-10% of all anal cancers. It has been said to have worse overall survival than anal SCC.[7] The current guideline has shown that anal adenocarcinoma should be managed as rectal adenocarcinoma, which means radical resection can achieve better overall survival.[8] However, in our study, patient with adenocarcinoma has significantly worse OS after surgical resection (10 o, ut of 12, OS = 10%, $p < 0.05$). This may be due to a small case number (n = 12), and only two patients have stage I-II disease while the others have lymph node or distant metastasis. A retrosepctive study by Yazid et al. collecting 82 patients with anal adenocarcinoma has shown that combined radiochemotherapy has better survival rates than combined radiotheray and surgery or APR only, which is similar to our result.[4] Further investigation and more case numbers were needed to discuss this issue.

Our study showed that for stage I-II anal cancer, whether local excision with/without CCRT or CCRT with/without operation, there was no significant difference in the oncologic outcome. In a previous study published at JAMA surgery, for stage I disease, there

is no significant difference in OS between local excision (OS = 85.3%) and CCRT (86.8%). Curative intended excision with a negative margin of early disease can spare the patient from the side effects of chemotherapy. The operation resulted in worse overall survival for stage III-IV patients than CCRT only. Operation is not recommended for the uncontrolled distant disease but only for symptom control or salvage of recurrent disease.

The diagnosis of anal cancer can be incidentally found after hemorrhoidectomy. We have 19% (n = 15) patients were diagnosed incidentally. Stephen et al. has reviewed 722 patients anal SCC and found 22 patients (3.05%) were incidentally diagnosed after hemorrhoidectomy.[9] On the other hand, Pooja et al. have reviewed 1612 pathologic specimens of hemorrhoidectomy and found 72 (4.5%) had anal malignancy.[10] The result supports routine pathologic examination for the specimen of hemorrhoidectomy.

Sexually transmitted infection, especially HPV infection, was related to most anal cancer.[11] HIV-infected individuals also have a higher incidence of anal cancer.[12] The result indicated that anal cancer is preventable. The patient with the sexually transmitted disease should be routinely examined for possible anal malignancy.

Our studies have many limitations. First, the case number is small. Most patients with anal cancer were not collected in our cancer registry due to some patients being diagnosed and followed at the oncologic department for definite CCRT. Second, although HIV/HPV infection was related to anal cancer, most patients do not examine viral infections. Third, we did not discuss the subsequence treatment, like salvage surgery, for recurrent disease, which may affect the oncologic outcome.

In conclusion, early anal cancer can be treated with local excision or definite CCRT without significant difference. Surgery has no benefit but worse survival for patients with uncontrolled distant disease. Routine examination of pathology of hemorrhoidectomy or fistulectomy was suggested to detect possible anal malignancy. The study cannot be applied to a generalized population due to the small case number. Further investigation is needed.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69(1):7-34.
2. Hoff PM, Coudry R, Moniz CM. Pathology of anal cancer. *Surg Oncol Clin N Am* 2017;26(1):57-71.
3. Benson AB, et al. Anal carcinoma, version 2.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2018;16(7):852-71.
4. Belkacemi Y, et al. Management of primary anal canal adenocarcinoma: a large retrospective study from the Rare Cancer Network. *Int J Radiat Oncol Biol Phys* 2003;56(5):1274-83.
5. Chai CY, et al. Management of stage I squamous cell carcinoma of the anal canal. *JAMA Surg* 2018;153(3):209-15.
6. Gerard JP, et al. Management of inguinal lymph node metastases in patients with carcinoma of the anal canal: experience in a series of 270 patients treated in Lyon and review of the literature. *Cancer* 2001;92(1):77-84.
7. Tarazi R, Nelson RL. Anal adenocarcinoma: a comprehensive review. *Semin Surg Oncol* 1994;10(3):235-40.
8. Chang GJ, et al. A twenty-year experience with adenocarcinoma of the anal canal. *Dis Colon Rectum* 2009;52(8):1375-80.
9. O'Brien SJ, et al. Anal squamous cell carcinoma incidentally found at hemorrhoidectomy. *Surgery* 2021;169(3):610-6.
10. Navale P, Gonzalez RS, Vyas M. Incidental secondary findings in hemorrhoidectomy specimens: a 16-year experience from a single academic center. *Hum Pathol* 2021;109:12-20.
11. Frisch M, et al. Sexually transmitted infection as a cause of anal cancer. *N Engl J Med* 1997;337(19):1350-8.
12. Silverberg MJ, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. *Clin Infect Dis* 2012;54(7):1026-34.

原　著

肛門癌的治療及預後分析

蔡宗芸　蔡文司

林口長庚紀念醫院

介紹　大多數肛門癌患者推薦接受化放療。然而，一些患者可能仍會接受手術，以期改善腫瘤學結果。在這項研究中，我們分析了肛門癌患者接受不同治療的腫瘤學結果並回顧了文獻。

方法　我們收集肛門癌患者及其變量並執行單變量和多變量分析。所有患者根據治療類型分為三組：僅手術組、僅化放療組和手術加上化放療組。

結果　在單變量分析中，鱗狀細胞癌患者的存活率優於腺癌。遠處轉移患者的存活率明顯低於無遠處轉移患者。不同的 T stage 和 N stage 之間沒有顯著差異。

結論　早期肛門癌可採用局部切除或化放療，結果無顯著差異。對於有轉移的患者，手術沒有好處，會使存活率率更差。

關鍵詞　肛門癌、存活分析。