Original Article

Anal Canal Carcinoma Treatment Results: 10-year Experience in a Single Institution

Chih-Yu Kuo[1]
Po-Li Wei[2]
Li-Jen Kuo[2,3]
[1]*Department of Surgery,*
[2]*Division of Colorectal Surgery, Taipei Medical University Hospital,*
[3]*Department of Surgery, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*

Key Words
Anal adenocarcinoma;
Anal cancer;
Squamous cell carcinoma

Purpose. The anal canal has a complex anatomy and histology and gives rise to various tumor types. Challenging issues remain in regard to both the pathologic diagnosis and the clinical management of these tumors. The aim of the retrospective study was to evaluate the clinical outcome in patients with anal cancer at a single institution.
Methods. A retrospective data analysis was performed for patients with anal cancer treated in Taipei Medical University Hospital from 2008 to 2018. During this period, there were 23 patients diagnosed with anal cancer. Our analysis included data from hospital records, outpatient charts, and tumor registry data. Complete clinical responses, incomplete clinical responses, and recurrence were defined based on clinical, image and endoscopic findings.
Results. There were 16 cases of anal squamous cell carcinoma, six cases of anal adenocarcinoma and only one case of well-differentiated neuroendocrine tumor. Follow-up information was available for 22 patients, with a mean follow-up period of 4.5 years (range, 1-10 years). To anal squamous cell carcinoma, the total complete response rate was 14/16 (87.5%), and the stage III cases complete response rate was 9/10 (90%). Three anal squamous cell carcinoma cases with complete response were recurrence. According to our data about all the anal squamous cell carcinoma cases, four patients with distant metastasis died after that. The 5-year survival rate of anal squamous cell carcinoma was 81.3%, and the 5-year survival rate of anal adenocarcinoma was 80%. There were six human Immunodeficiency virus anal squamous cell carcinoma patients with concurrent chemo-radiotherapy, and the complete response rate was 5/6 (83.3%). No obvious difference was found compared to non-human Immunodeficiency virus cases.
Conclusions. To anal squamous cell carcinoma, 5-fluorouracil plus mitomycin C combined with radiotherapy leads to an outstanding clinical outcome, even in cases with human Immunodeficiency virus or stage III. Therefore, 5-fluorouracil plus mitomycin C chemotherapy combined with radiotherapy is the standard of care for all loco-regional anal cancer.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2020;31:269-275*]

Anal cancer comprises only 2.5 percent of all digestive system malignancies in the United States.[1] The incidence of anal cance (2 per 100,000) in the general population has increased over the last 30 years, both in the United States and elsewhere.[2] A higher incidence has been associated with the female gender,

Received: June 11, 2020. Accepted: August 12, 2020.
Correspondence to: Dr. Li-Jen Kuo, Division of Colorectal Surgery, Department of Surgery, Taipei Medical University Hospital, No. 252, Wuxing Street, Sinyi District, Taipei 11031, Taiwan. E-mail: kuolijen@gmail.com

infection with human papillomavirus (HPV), lifetime number of sexual partners, genital warts, cigarette smoking, receptive anal intercourse, and infection with human Immunodeficiency virus (HIV).[3,4]

Previously, anal cancer was treated with abdominoperineal resection (APR). The difficulty with surgery has been the necessity of removing the internal and external anal sphincter, with concomitant fecal incontinence. For this reason, many patients with anal cancer have required permanent colostomies.[5] However, current gold-standard therapy is chemotherapy (5-fluorouracil + mitomycin C) combined with radiation treatment to reduce the necessity of debilitating surgery.[6] This "combined modality" approach has led to increased preservation of an intact anal sphincter, and therefore improved quality of life following definitive treatment.

The aims are to study the clinical-epidemiological characteristics of the patients with anal carcinoma presented to Taipei Medical University Hospital at Taiwan from the period of 2008 to 2018. We describe the treatment outcomes of our center. The current medical advancements in anal squamous cell carcinoma (ASCC) and adenocarcinoma are also discussed in our study.

Materials and Methods

We performed a retrospective data analysis of the records of patients with anal cancer treated from 2008 to 2018 at Taipei Medical University Hospital. Our analysis included data from hospital records, outpatient charts, and tumor registry data. Patients with anal cancer treated by concurrent chemoradiotherapy (CCRT) therapy, including 4500-6400 cGy and concomitant 5-fluorouracil plus mitomycin C, were assessed for tumor response eight weeks after CCRT completion. Complete and incomplete clinical responses were defined based on clinical, image and endoscopic findings. Comparisons between groups were analyzed with t tests and $\chi 2$ tests. The overall survival curves were plotted using the Kaplan-Meier method and survival differences were evaluated using a log-rank test. $p < 0.05$ was considered as statistically significant. The statistical analysis was performed using SPSS 22.0 software.

Results

A total of 23 patients were diagnosed with anal cancer between January 2008 and December 2018 at Taipei Medical University Hospital. The characteristics and outcome of these patients are shown in Table 1. There were 16 cases of ASCC, six cases of anal adenocarcinoma and only one case of well-differentiated neuroendocrine tumor. Of the 16 ASCC cases, 10 were tumor stage III, five were stage II, and only one was stage 0 (in situ). Fifteen cases accepted CCRT

Table 1. Baseline characteristics for 16 SCC and six adenocarcinoma patient

	Squamous cell carcinoma (n = 16)	Adenocarcinoma (n = 6)
Median age (range)	54.44 (23-90)	61.83 (46-79)
Gender		
Male	10	1
Female	6	5
Anatomical site		
Anal canal	13	6
Perianal	3	0
Stage (AJCC 8th edition)		
0 and I	1	1
II	5	0
III	10	2
IV	0	2
Unknown	0	1
HIV		
Yes	6	0
No	10	6
Radiation treatment		
Yes	16	5
No	0	1
Chemotherapy		
5-FU + MMC	12	4
PFL + MMC	2	0
5-FU alone	1	2
No chemotherapy	1	0
Surgery		
APR	0	1
Wide excision	2	1
No surgery	14	4
Complete response	14	3
Incomplete response	2	1
Recurrence	3	0
Distant metastases	4	2
Alive	12	4
Death	4	2

(5-fluorouracil + mitomycin C), and only one accepted chemotherapy (5-Fluorouracil) only. Of the six anal adenocarcinoma cases, two were tumor stage IV, two were stage III, and two were stage I. Only one accepted APR. Follow-up information was available for 22 patients, with a mean follow-up period of 4.5 years (range, 1-10 years). The 5-year survival rate of anal squamous cell carcinoma was 81.3%, and the 5-year survival rate of anal adenocarcinoma was 80%. The cumulative survival rate revealed at Fig. 1 for both SCC and adenocarcinoma were no obvious difference. To ASCC, the complete response (CR) rate was 14/16 (87.5%), and the stage III cases CR rate was 9/10 (90%). Three ASCC with complete response cases showed recurrence. According to our data about all the anal squamous cell carcinoma cases, four patients with distant metastasis died after that. For anal adenocarcinoma, three cases with stage I or III showed CR, but one with incomplete response. There were two stage IV cases, and they all died after that. There were six HIV patients. The baseline characteristics and clinical outcome are shown in Table 2. All were younger patients (under 50-year-old), male, and pathological diagnosis ASCC. All six cases accepted CCRT (5-fluorouracil + mitomycin C). The CR rate was 5/6 (83.3%), and one case had recurrence. No obvious difference was apparent compared to non HIV cases.

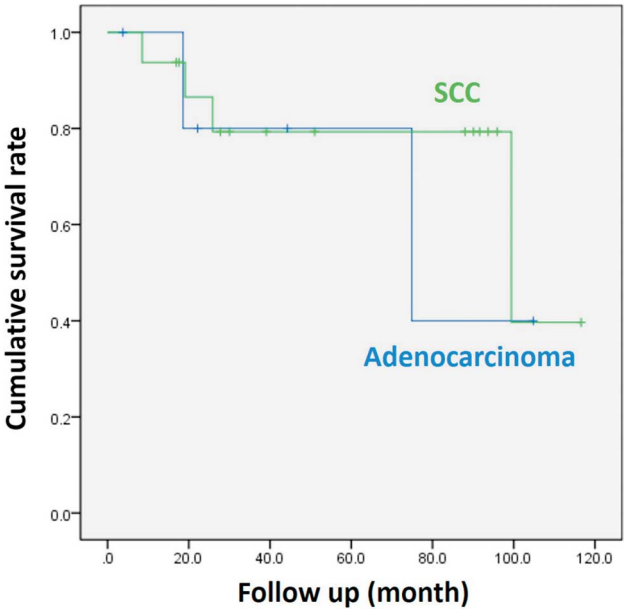

Fig. 1. Cumulative survival rate for SCC and adenocarcinoma.

Discussions

The pathologic diagnosis of anal tumors can be challenging to both pathologists and clinicians. Despite the anal canal's short length (2.5 to 3.5 cm), the anatomy of this region is complex because it represents the progressive transition from the digestive system to the skin with many different co-existing types of cells and tissues.[7] The mucosa of the proximal anal canal has an endodermal origin, but the mucosa of the distal anal canal has an ectodermal origin.[8] Histologically, the anal canal is divided into three parts on the basis of its epithelium lining: colorectal zone lined by colorectal-type glandular mucosa proximally, anal transition zone (ATZ) often lined by an epithelium that has varying appearances in the middle, and the squamous mucosa-lined distal portion.[9]

Table 2. The baseline characteristics and clinical outcome of six HIV patient

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age	23	50	42	44	40	32
Sex	Male	Male	Male	Male	Male	Male
Histological type	SCC	SCC	SCC	SCC	SCC	SCC
Stage	III	III	III	III	III	0
Radiotherapy	Yes	Yes	Yes	Yes	Yes	Yes
Chemotherapy	5 Fu + MMC	5 Fu + MMC	5 Fu + MMC	5 Fu + MMC	5 Fu + MMC	5 Fu + MMC
Surgery	No	No	No	No	No	Wide excision
Complete response	Yes	Yes	No	Yes	Yes	Yes
Recurrence	No	No	No	No	No	Yes
Death	No	No	Yes	No	No	Yes

Squamous cell carcinoma (SCC) and the variant of SCC (Basaloid carcinoma or non-keratinizing types SCC) account for about 80% of all anal cancers.[10] They originate from either the squamous epithelium of the lower part of the anal canal (most common) or the ATZ mucosa. Many epidemiological studies have identified some carcinogenic types of HPVs, mainly the HPV16 genotype, as the leading cause of most cases (~90%) of ASCC and its precursors, which are designated as anal intraepithelial neoplasia (AIN).[11] Adenocarcinomas arising from glandular elements within the anal canal are rare, accounting for approximately 5-10% of all anal canal neoplasms.[12] Various factors including chronic local inflammation, anal fistula and Crohn's disease have been implicated in the aetiology because of the chronic infection and inflammation associated with repeated epithelial regeneration.[13] Other rare histologic subtypes include melanoma, neuroendocrine tumor, carcinoid, sarcoma, gastrointestinal (GI) stromal tumor, and lymphoma, all of which account for < 3% of anal cancers.[14] Other tumors arising within the hair-bearing skin or distal to the squamous mucocutaneous junction have been referred to as perianal skin cancers. Tumors of the perianal skin are most often SCC, but other types of cutaneous malignancies (basal cell carcinoma, melanoma, Bowen disease, Paget disease) can arise within this region.[15]

Prior to 1980, surgical resection of the tumor in the form of APR had been the primary treatment for anal cancer. The overall probability of survival five years after an APR ranges from 40% to 70%.[16] However, some patients were not suitable for major operation (for unresectable disease or major comorbidity) or chose not to undergo surgery. Radiotherapy (RT) alone was thus used as an alternative treatment. Five-year survival ranged from 39-76%, with colostomy-free survival of 67-74%.[17] The use of chemotherapy in combination with RT was first evaluated in the early 1970s by a group at Wayne State University.[18] The three patients in this study were treated with 5-fluorouracil (5-FU) and mitomycin in combination with moderate-dose (30 Gy) external beam radiation therapy. Following CCRT, two patients underwent APR, and found no residual tumor cell on the specimen. In the last patient who refused an operation, there was no sign of recurrence after 14 months follow up. In 1984, Nigro treated 44 patients at Wayne State and collected data on a further 60 treated similarly at other centers around the United States. There were 104 patients in the study, and 97 were clinically free of disease at the post-therapy assessment.[19] Three randomized trials from the 1990s revealed 5-FU and mitomycin chemotherapy combined with RT is the standard of care for loco-regional anal cancer.[20-22] The trial of UKCCCR and EORTC compared radiotherapy in combination with 5-FU and mitomycin versus RT alone, demonstrating improved results in patients receiving CCRT.[20,21] The trial of RTOG/ECOG established the role of mitomycin in combination with fluorouracil and RT for anal cancer treatment.[22] CCRT leads to preservation of the anal sphincter by avoiding surgery, and it leads to complete tumor regression in 80%-90% of patients.[23] The global survival rate of ASCC was approximately 70 to 75%.[24,25] Unfortunately, CCRT fails in 20-30% of patients, resulting in persistent (10-15%) or local recurrent disease (10-15%).[26] Salvage APR is often the only option for patients with persistent or recurrent anal cancer. The prognosis after salvage APR is poor, with roughly a 40% 5-year survival.[27]

Although 5-FU plus mitomycin combined with RT is the first choice of treatment to anal SCC, the CCRT is associated with several potentially severe early and late adverse effects. Hematologic and gastrointestinal tract toxic effects, skin dermatitis, proctitis, anal and vaginal stenosis, incontinence and fecal urgency were frequently mentioned in previous studies.[28,29] Therefore, recently published data suggest less aggressive, and potentially less morbid, management options, such as local excision alone, may be feasible in select patients, in particular cases with T1N0M0.[30,31] Christy Y. Chai et al., assessed 2243 patients in the National Cancer Database (2004-2012) between 18 and 80 years of age with T1N0M0 anal SCC. A total of 503 (22.4%) were treated with local excision alone. The result revealed no statistically significant difference in survival between local excision and the CCRT group.[32] Patients who were treated surgically might incur lower costs, and have similar outcomes to those treated using CCRT or RT.[33] Therefore, local excision to T1N0M0 disease may be feasi-

ble with careful patient selection.

Compared with medical advances of anal SCC, the prognosis of anal adenocarcinoma is poor and its management remains controversial. The 5-year survival is low, only 30%, compared to rectal cancer with 52% and anal SCC with 62%.[12] Differentiating true anal canal adenocarcinoma from low rectal adenocarcinoma can be challenging. They appear to share a similar natural history to rectal adenocarcinomas and are treated similarly, with resection plus either preoperative or postoperative chemo-radiotherapy.[34] Rodney E. Wegner et al. analyzed 1729 anal adenocarcinoma cases in the National Cancer Database (NCDB) from 2004 to 2015. The result revealed the median survival rates for neoadjuvant chemoradiation + surgery, surgery + adjuvant chemoradiation, surgery alone and chemoradiation alone were 92, 83, 69, and 45 months.[35] Therefore, chemoradiation followed by abdominoperineal resection results in the best probability of long-term survival for anal adenocarcinoma.[36]

Make a summary. For ASCC, 5-fluorouracil plus mitomycin combined with RT lead to outstanding clinical outcomes, even in cases with HIV or stage III. Therefore, 5-fluorouracil plus mitomycin C chemotherapy combined with RT is the standard of care for all loco-regional anal cancer.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA: A Cancer Journal for Clinicians* 2020;70(1):7-30.
2. Islami F, Ferlay J, Lortet-Tieulent J, et al. International trends in anal cancer incidence rates. *International Journal of Epidemiology* 2017;46(3):924-38.
3. Daling JR, Weiss NS, Hislop TG, et al. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *The New England Journal of Medicine* 1987;317(16):973-7.
4. Melbye M, Coté TR, Kessler K, et al. High incidence of anal cancer among AIDS patients. *The Lancet* 1994;343(8898): 636-9.
5. Mauvais F, Sabbagh C, Brehant O, et al. The current abdominoperineal resection: oncological problems and surgical modifications for low rectal cancer. *Journal of Visceral Surgery* 2011;148(2):85-93.
6. Symer MM, Yeo HL. Recent advances in the management of anal cancer. *F1000Res* 2018;7:1572.
7. Surabhi VR, Menias CO, Amer AM, et al. Tumors and tumor like conditions of the anal canal and perianal region: MR imaging findings. *Radiographics* 2016;36(5):1339-53.
8. Shridhar R, Shibata D, Chan E, et al. Anal cancer: current standards in care and recent changes in practice. *CA: A Cancer Journal for Clinicians* 2015;65(2):139-62.
9. Shia J. An update on tumors of the anal canal. *Archives of Pathology and Laboratory Medicine* 2010;134(11):1601-11.
10. Fléjou JF. An update on anal neoplasia. *Histopathology* 2015; 66(1):147-60.
11. Herfs M, Longuespée R, Quick CM, et al. Proteomic signatures reveal a dualistic and clinically relevant classification of anal canal carcinoma. *Journal of Pathology* 2017;241(4): 522-33.
12. Franklin RA, Giri S, Valasareddy P, et al. Comparative survival of patients with anal adenocarcinoma, squamous cell carcinoma of the anus, and rectal adenocarcinoma. *Clinical Colorectal Cancer* 2016;15(1):47-53.
13. Anwar S, Welbourn H, Hill J, et al. Adenocarcinoma of the anal canal - a systematic review. *Colorectal Disease* 2013; 15(12):1481-8.
14. Klas JV, Rothenberger DA, Wong WD, et al. Malignant tumors of the anal canal: the spectrum of disease, treatment, and outcomes. *Cancer* 1999;85(8):1686-93.
15. Leonard D, Beddy D, Dozois EJ, et al. Neoplasms of anal canal and perianal skin. *Clinics in Colon and Rectal Surgery* 2011;24(1):54-63.
16. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. *The New England Journal of Medicine* 2000;342(11): 792-800.
17. Clark MA, Hartley A, Geh JI, et al. Cancer of the anal canal. *The Lancet Oncology* 2004;5(3):149-57.
18. Nigro ND, Vaitkevicius VK, Considine B, et al. Combined therapy for cancer of the anal canal: a preliminary report. *Diseases of the Colon and Rectum* 1974;17(3):354-6.
19. Nigro ND. An evaluation of combined therapy for squamous cell cancer of the anal canal. *Diseases of the Colon and Rectum* 1984;27(12):763-6.
20. UKCCCR Anal Cancer Trial Working Party. UKCCR anal cancer trial working party. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. *Lancet* 1996;348(9034):1049-54.
21. 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. *Journal of Clinical Oncology* 1997;15(5):2040-9.
22. 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 cancer: results of a phase III randomized intergroup study. *Journal of Clinical Oncol-*

ogy 1996;14(9):2527-39.
23. Glynne-Jones R, Nilsson PJ, Aschele C, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *European Journal of Surgical Oncology (EJSO)* 2014;111(3):330-9.
24. Guren MG, Aagnes B, Nygård M, et al. Rising incidence and improved survival of anal squamous cell carcinoma in Norway. *Clinical Colorectal Cancer* 2019;18(1):96-103.
25. Hur H, Jung KW, Kim BW, et al. Long-term oncologic outcome and its relevant factors in anal cancer in Korea: a nationwide data analysis. *Annals of Coloproctology* 2020;36(1): 35-40.
26. Hagemans JAW, Blinde SE, Nuyttens JJ, et al. Salvage abdominoperineal resection for squamous cell anal cancer: a 30-year single-institution experience. *Annals of Surgical Oncology* 2018;25(7):1970-9.
27. Nilsson PJ, Svensson C, Goldman S, et al. Salvage abdominoperineal resection in anal epidermoid cancer. *British Journal of Surgery* 2002;89(11):1425-9.
28. Jérôme D, Karen B, Philippe F, et al. Predictive factors for early and late local toxicities in anal cancer treated by radiotherapy in combination with or without chemotherapy. *Diseases of the Colon and Rectum* 2013;56(10):1125-33.
29. Bentzen AG, Guren MG, Vonenet B, et al. Faecal incontinence after chemoradiotherapy in anal cancer survivors: long-term results of a national cohort. *Radiotherapy and Oncology* 2013;108(1):55-60.
30. Alfa-Wali M, DallaPria A, Nelson M, et al. Surgical excision alone for stage T1 anal verge cancers in people living with HIV. *European Journal of Surgical Oncology (EJSO)* 2016; 42(6):813-6.
31. Arana R, Fléjou JF, Si-Mohamed A, et al. Clinicopathological and virological characteristics of superficially invasive squamous-cell carcinoma of the anus. *Colorectal Disease* 2015;17(11):965-72.
32. Chai CY, Cao HST, Awad S, et al. Management of stage I squamous cell carcinoma of the anal canal. *JAMA Surgery* 2018;153(3):209-15.
33. Deshmukh AA, Zhao H, Das P, et al. Clinical and economic evaluation of treatment strategies for T1N0 anal canal cancer. *American Journal of Clinical Oncology* 2018;41(7):626-31.
34. Chang GJ, Gonzalez RJ, Skibber JM, et al. A twenty-year experience with adenocarcinoma of the anal canal. *Diseases of the Colon and Rectum* 2009;52(8):1375-80.
35. Wegner RE, White RJ, Hasan S, et al. Anal adenocarcinoma: treatment outcomes and trends in a rare disease entity. *Cancer Medicine* 2019;8(8):3855-63.
36. Lewis GD, Haque W, Butler EB, et al. Survival outcomes and patterns of management for anal adenocarcinoma. *Annals of Surgical Oncology* 2019;26(5):1351-7.

原　著

肛門癌的治療結果：單一機構 10 年的臨床經驗

郭致佑[1]　魏柏立[2]　郭立人[2,3]

[1]台北醫學大學附設醫院　外科部

[2]台北醫學大學附設醫院　大腸直腸外科

[3]台北醫學大學　醫學系

目的　肛門的腫瘤類型多樣是因為其複雜的組織學型態，目前對於這類腫瘤的病理診斷和臨床治療仍有些爭議。這篇回溯性研究的目的是分析單一機構對於肛門癌患者的臨床治療結果。

方法　回溯性分析 2008 年至 2018 年台北醫學大學附屬醫院所收治的肛門癌患者的臨床資料。在此期間，有 23 個病人的診斷為肛門癌，我們針對病人的病歷記錄，門診就醫記錄和癌症中心的資料加以分析。根據病人的臨床症狀，影像學和大腸鏡的檢查結果來區分病人的治療情況，分類如下：完全有效和部分有效，且追蹤疾病是否有復發的情形。

結果　肛門鱗狀細胞癌有 16 例，肛門腺癌有 6 例，分化好的神經內分泌腫瘤有 1 例。一共追蹤了 22 位患者，平均追蹤時間為 4.5 年 (範圍為 1-10 年)。對於肛門鱗狀細胞癌，治療完全有效為 14/16 (87.5%)，III 期病例的治療完全有效率為 9/10 (90%)。在肛門鱗狀細胞癌治療完全有效的患者中有三例復發，全部肛門鱗狀細胞癌患者中有四位病人有遠端轉移並且死亡。肛門鱗狀細胞癌的 5 年生存率為 81.3%，而肛門腺癌的 5 年生存率為 80%。另外，肛門鱗狀細胞癌的患者中有六例病人患有人類免疫缺乏病毒，而這六個病人都有接受同步化學放射治療，治療完全有效率為 5/6 (83.3%)。與非患有人類免疫缺乏病毒的病患相比，沒有發現明顯差異。

結論　對於肛門鱗狀細胞癌，同步化學放射治療 (5-氟尿嘧啶加上絲裂黴素 C) 可獲得出色的臨床效果，即使在患有人類免疫缺乏病毒病患或 III 期患者中也是如此。因此，同步化學放射治療 (5-氟尿嘧啶加上絲裂黴素 C) 是局部性肛門癌的治療標準。

關鍵詞　肛門腺癌、肛門癌、鱗狀細胞癌。