Original Article

Patients with Incidental Anal Squamous Cell Carcinoma Did Not Have Poorer Outcomes Than Patients with Primary Concurrent Chemoradiotherapy

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Key Words
Anal squamous cell carcinoma;
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Background. Concurrent chemoradiotherapy (CCRT) is standard first-line treatment for anal squamous cell carcinoma (SCC). Some cases might be misdiagnosed as hemorrhoids, anal fistulas, or other anal tumors. Incidental findings of anal SCC after minor surgery (wide excision, hemorrhoidectomy, or fistulectomy) also sometimes occurs. We compared the outcomes of incidental anal SCC patients with patients initially treated with CCRT.

Materials and Methods. We retrospectively reviewed the charts of 41 patients diagnosed with anal SCC between 1982 and 2016. Tumor stage, treatment, overall survival, 5-year survival, and recurrence-free survival were compared.

Results. The 5-year-survival rate of all patients was 66%; recurrence-free survival was 57%. The 5-year survival rate of patients preoperatively treated with CCRT was 61%; recurrence-free survival was 49%. Twenty-five patients underwent surgery and 16 patients (classified as having Incidental Anal SCC) underwent a fistulectomy, hemorrhoidectomy, or wide excision before being diagnosed with anal SCC. The 5-year survival rates of patients with incidental SCC and of patients treated with CCRT as first-line therapy were 76%, n = 15 vs. 61%, n = 16, respectively; $p = 0.044$. In our retrospective study, patients with incidental anal SCC did not have a poorer prognosis than did patients given CCRT as a first-line treatment.

Conclusions. The 5-year survival of incidental SCC patients was not worse than that of anal SCC patients initially treated using CCRT.

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The incidence of anal squamous cell carcinoma (SCC) is about 1.5 cases per 100,000/people per year worldwide and is increasing: there are about 900 cases per year in the UK, and about 5000 in the USA.[1,2] The Cancer Registry Annual Report of Taiwan[3] recorded 72 cases of anal SCC in 2014.

Anal canal mucosa is predominantly formed by squamous epithelium, in contrast to rectal mucosa, which is lined with glandular epithelium.[4,5]

The terms cloacogenic, transitional, keratinizing, and basaloid carcinomas are all variants of anal SCC.[6,7]

Before 1973, an abdominoperineal resection (APR) was routinely done for tumors arising in the anal canal. In early series, the overall probability of 5-year

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survival was 40 to 70%,[4] with a perioperative mortality of 3%. Nigro et al.[5] devised a protocol of preoperative treatment for anal SCC, and reports of the first three patients were good. Two patients had complete responses and underwent APR. One patient had a complete response but refused APR. The "Nigro" regimen consisted of FU, mitomycin, and an intermediate dose of radiotherapy (30 Gy). The finding that the first three patients had complete pathologic responses led to the development of strategies that were directed at preserving the anal sphincter.

Concurrent chemoradiotherapy is now the standard first-line treatment for anal SCC. However, the tumor can be, and frequently is, misdiagnosed as a hemorrhoid, fistula, anal fissure, or other rectal lesion before being confirmed as SCC after a pathology test. Incidental findings of SCC after minor surgery (wide excision, hemorrhoidectomy, fistulectomy) also sometimes occurs. The goal of this study was to evaluate the outcomes of this group of patients and compare them with those of another group that underwent CCRT as a first-line therapy.

Materials and Methods

In this retrospective study, we retrospectively reviewed the charts of 41 patients diagnosed with anal SCC between 1982 and 2016. None had distant metastasis when they were diagnosed. Sixteen of the 41 (39%) were given CCRT as initial therapy, and the other 25 underwent surgery as their first-line therapy. Fifteen of the latter (60%) were diagnosed with incidental anal SCC after minor anal surgeries and assigned to the Incidental Anal SCC group. Since 2006, intensity modulated radiotherapy (IMRT) has been used to deliver a minimum dose of 45 Gy in 1.8-Gy fractions (25 fractions, 5 times a week, for 5 weeks) to the primary cancer. Patients were given two-dimensional radiotherapy before 1997 and three-dimensional radiotherapy between 1998 and 2005; dosages were about the same dosage. The inguinal nodes and the pelvis, anus, and perineum were included in the initial radiation fields. The superior field border should be at L5-S1, and the inferior border should include the anus with a minimum 2.5-cm margin around the anus and tumor. The lateral border should include the lateral inguinal nodes. The concurrent chemotherapy is 5-Fluorouracil (400-500/mg/day) from day 1 to day 4, plus an intravenous bolus of mitomycin (10 mg/m^2) on days 1 and 29.

Patients were evaluated based on their medical history, physical examination, digital rectal examination, abdominal computed tomography (CT), chest X-ray, and pathology reports. The American Joint Committee on Cancer TNM system, 7th edition, for anal canal squamous cell carcinoma was used for tumor staging. If a patient underwent primary CCRT, the T-stage (the size of tumor) was clinically determined using a physical examination and imaging. If the patient underwent minor surgery and the tumor was completely removed, the T-stage was determined based on information in the pathology report. If the patient underwent minor surgery but the tumor was not completely removed, the T-stage was determined based on its clinical stage.

The survival and recurrence statuses of patients were confirmed using chart reviews and, for those who had no follow-up Outpatient Department appointments for more than 2 years, telephone interviews.

Statistical analysis

Recurrence-free survival, 5 year-survival, and overall survival were estimated using the Kaplan-Meier method. Significance was set at $p < 0.05$.

Results

Demographic characteristics of patients

Demographic characteristics between patients given CCRT and patients who underwent minor surgery as a first-line therapy were not significantly different, except for mean tumor size, which was significantly larger for the latter group (3.9 cm vs. 5.2 cm, respectively; $p = 0.04$) (Table 1).

One patient had cervical cancer, 1 had an HIV infection, and 1 had a condyloma (genital wart).

Table 1. Demographic and clinical data

Variable	CCRT group (n = 16)	Incidental anal SCC group (n = 25)	Total	*p*-value
Gender				0.334
Male	7 (44%)	16 (64%)	23 (56%)	
Female	9 (56%)	9 (36%)	18 (44%)	
Mean age	62.3 (14.7)	66.3 (12)		0.556
Mean tumor size (cm)	3.9 (2.0)	5.2 (4.1)		0.04
T staging				0.356
T1	2	3		
T2	11	11		
T3	2	5		
T4	1	6		
N staging				0.166
N0	14	20		
N1	0	4		
N2	2	1		
Differentiation				0.414
Well differentiated	0	2		
Moderately differentiated	6	11		
Poorly differentiated	10	12		

CCRT: concurrent chemoradiotherapy; SCC: squamous cell carcinoma.

The 5-year survival rate of all patients was 66% and the 5-year recurrence-free survival of all patients was 57% (Figs. 1 and 2).

Twenty-five patients underwent minor surgery first: fistulectomy = 13, hemorrhoidectomy = 1, or wide excision = 1, and the latter 15 were diagnosed with SCC and assigned to the Incidental Anal SCC subgroup (Table 2). Eight of those 15 had an R0 resection, 7 had an R1 resection, and 11 underwent adjuvant CCRT to prevent recurrence. There were 4 local recurrences and salvage operations for 3 of them: 2 wide local excisions and 1 total pelvic exenteration. Finally, 1 Incidental Anal SCC subgroup patient died of the disease (Table 3).

Patients in the Incidental Anal SCC subgroup were not significantly different from those in the CCRT group, except for mean tumor size, which was significantly larger for the latter group (2.4 cm vs. 3.9 cm,

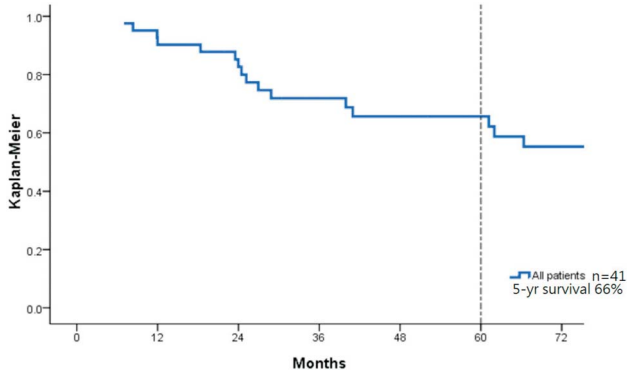

Fig. 1. Overall survival rate for all patients.

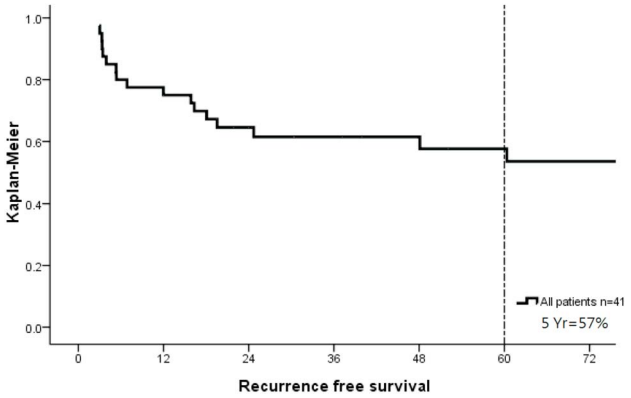

Fig. 2. Recurrence-free survival rate for all patients.

Table 2. Surgery for incidental anal SCC group patients

Surgery type	Number (%)
Fistulectomy	13 (86.7)
Hemorrhoidectomy	1 (6.7)
Wide local excision	1 (6.7)
Total	15

SCC: squamous cell carcinoma.

respectively; $p = 0.026$) (Table 4).

The 5-year recurrence-free survival rates of the two groups were not significantly different (Fig. 3). The 5-year overall survival rate of the Incidental Anal SCC group was significantly ($p = 0.044$) better than that of the CCRT group (76% vs. 61%, respectively) (Fig. 4). However, because of the small number of patients and smaller tumor sizes for Incidental Anal SCC group patients, this result should be interpreted with caution.

Table 3. Outcomes of incidental anal SCC group patients

Variable	Number (%)
Total	15
R0 resection	8 (53.3)
R1 resection	7 (46.7)
T staging	
T1	3 (20)
T2	8 (53.3)
T3	3 (20)
T4	1 (6.7)
Underwent adjuvant CCRT	11 (73.4)
Underwent salvage operation	3 (20)
Total pelvic exenteration	1 (6.7)
Wide local excision	2 (13.3)
Underwent salvage CCRT	2 (13.3)
Local recurrence	4 (26.7)
Cancer-related death	2 (13.3)

CCRT: concurrent chemoradiotherapy; SCC: squamous cell carcinoma.

Discussion

Wide excision and APR were routinely used to remove anal canal tumors before 1973. The overall 5-year survival rate was 40-70%, the perioperative mortality rate was 3%. In 1975, the first high rates of pa-

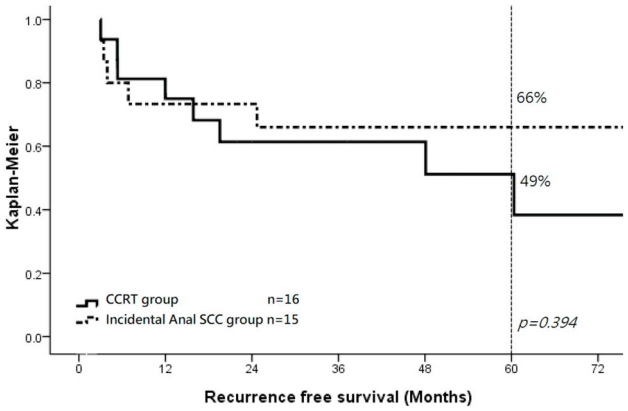

Fig. 3. Recurrence-free survival rate: incidental anal SCC vs. CCRT as first-line therapy.

Table 4. Comparison between incidental anal SCC and CCRT patients

Variable	Incidental anal SCC group (n = 15)	CCRT group (n = 16)	Total	*p*-value
Gender				0.285
Male	10 (66.7%)	7 (44%)	23 (56%)	
Female	5 (33.3%)	9 (56%)	18 (44%)	
Mean age [SD] (years)	66.4 [13.2]	62.3 [14.7]		0.423
Mean tumor size [SD] (cm)	2.4 [0.9]	3.9 [2.0]		0.026*
T staging				0.839
T1	8	2		
T2	5	11		
T3	1	2		
T4	1	1		
N staging				0.484
N0	15	14		
N1	0	0		
N2	0	2		
Differentiation				0.218
Well differentiated	2	0		
Moderately differentiated	7	6		
Poorly differentiated	6	10		

CCRT: concurrent chemoradiotherapy; SCC: squamous cell carcinoma.

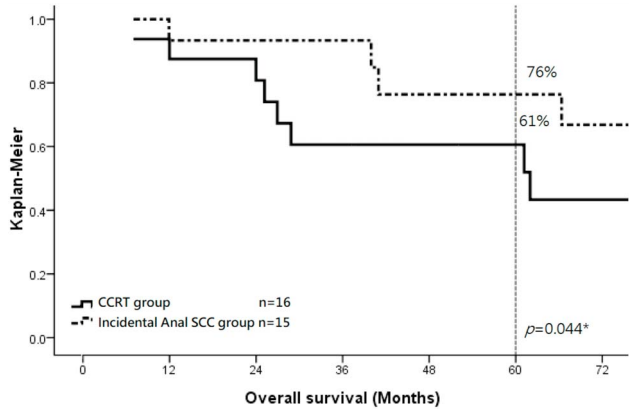

Fig. 4. Overall survival rate: incidental anal SCC vs. CCRT as first-line therapy.

thologically complete responses to CCRT were reported;[5] they also claimed that definitive CCRT was a sphincter-sparing alternative to APR. Subsequently, two randomized trials[6,7] showed that CCRT improved local control compared with radiotherapy alone. A randomized intergroup trial[8] also showed that CCRT with 5-fluorouracil (5-FU) and mitomycin C improved rates of disease-free survival and colostomy-free survival compared with chemoradiation with 5-FU. Definitive CCRT is the current standard of care for patients with locoregional anal SCC, and APR is used for persistent and recurrent SCC after CCRT.

The current recommendation primary treatment is not to do a surgical excision. A biopsy that leads to a definite diagnosis of anal SCC is recommended.

The 5-year survival rate in the CCRT group was 61%. Several studies have reported rising 5-year survival rates: 57% in 1999 (n = 19),[9] 76% in 2001 (n = 39),[10] and 75% in 2008 (n = 341).[11] These outcomes are much more acceptable compared than those reported forty years ago.

Some patients might have non-specific symptoms, like anal bleeding, itching, pain, and a rectal mass. Diagnoses might be delayed. The current National Comprehensive Cancer Network (NCCN) guidelines recommend a biopsy for diagnosis, but not an excisional biopsy. However, in daily practice, a diagnosis of might be made after a wide excision, fistulectomy, or hemorrhoidectomy. This retrospective study in our hospital showed a significant (p = 0.044) difference in the 5-year survival rate between the Incidental Anal SCC and CCRT groups (76% vs. 61%, respectively), much better than the 48% reported[14] in a 50-year-old study on patients given only a wide excision. The better outcome in our Incidental Anal SCC group might be because the tumor size and regional nodal metastasis were different between the two groups; thus, the finding should be interpreted with caution. However, it might be safe to say that incidental anal SCC treated using adjuvant CCRT might not jeopardize a patient's chances of surviving.

Although there were no significant differences in T-stage in the Incidental Anal SCC and CCRT groups, patients in the former group had significantly (p = 0.026) smaller tumors (2.4 cm vs. 3.9 cm, respectively), which might have led to better outcomes in the former group. No members of the Incidental Anal SCC group had regional nodal metastasis, but 2 members of the CCRT group developed N2 regional nodal metastasis. This also might have contributed to better outcomes for the Incidental Anal SCC group.

Eight members of the Incidental Anal SCC group had R0 resection margins and were recurrence-free at 5 years; 7 had R1 resection margins and 2 had recurrences at 5 years. Adjuvant CCRT might have contributed to this outcome. The NCCN guideline suggested a lymphadenectomy for positive nodes. However, in a study[13] on patients with anal cancer who underwent APR, pelvic node metastases were often < 0.5 cm long. Nodal metastases might be underestimated in abdominal CT and PET scans. Eleven of the 15 patients in the Incidental Anal SCC group underwent adjuvant CCRT. This might also have helped their prognoses because the inguinal nodes and the pelvis, anus, and perineum are all included in the initial radiation fields. The superior field border is at L5-S1, and the inferior border should include the anus with a minimum 2.5-cm margin around the anus and tumor (NCCN guidelines).[12] Systemic chemotherapy will also help reduce the number of residual tumor cells.

Conclusions

CCRT is the current first-line treatment of anal SCC. Patients should be treated using CCRT after a

definite diagnosis of SCC is made. Salvage APR should be used for local recurrences and persistent tumors after CCRT.

If a patient undergoes minor surgery like a local excision, hemorrhoidectomy, or fistulectomy, and is then diagnosed with anal SCC, we recommend adjuvant CCRT because our study found that the 5-year-survival rate not worse than that of the CCRT group. Because we had few patients and because this study is retrospective, a randomized controlled longitudinal trial is required to confirm our findings.

References

1. Brewster DH, Bhatti LA. Increasing incidence of squamous cell carcinoma of the anus in Scotland, 1975-2002. *Br J Cancer* 2006;5:87-90.
2. Bilimoria KY, Bentrem DJ, Rock CE, Stewart AK, Ko CY, Halverson A. Outcomes and prognostic factors for squamous-cell carcinoma of the anal canal: analysis of patients from the National Cancer Data Base. *Dis Colon Rectum* 2009;52: 624-31.
3. Cancer registry annual report, 2014 Taiwan health promotion administration of health and welfare. 2014;33-4.
4. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. *N Engl J Med* 2000;342:792-800.
5. Nigro ND, Vaitkevicius VK, Considine B Jr. Combined therapy for cancer of the anal canal: a preliminary report. *Dis Colon Rectum* 1974;17(3):354-6.
6. UKCCCR Anal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UK Co-ordinating Committee on Cancer Research. *Lancet* 1996;348:1049-54.
7. 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.
8. 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.
9. 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.
10. Kapp KS, Geyer E, Gebhart FH, et al. Experience with split-course external beam irradiation +/- chemotherapy and integrated Ir-192 high-dose-rate brachytherapy in the treatment of primary carcinomas of the anal canal. *Int J Radiat Oncol Biol Phys* 2001;49(4):997-1005.
11. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA* 2008;299(16):1914-21.
12. Anal carcinoma, NCCN Guideline 2016, version 2.
13. Wade DS, Herrera L, Castillo NB, Petrelli NJ. Metastases to the lymph nodes in epidermoid carcinoma of the anal canal studied by a clearing technique. *Surg Gynecol Obstet* 1989; 169:238-42.
14. Hardcastle JD, Bussey HJ. Results of surgical treatment of squamous cell carcinoma of the anal canal and anal margin seen at St. Mark's Hospital 1928-66. *Proc R Soc Med* 1968; 61(6):629-30.
15. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. *N Engl J Med* 2000;342:792-800.
16. Cummings BJ, Ajani JA, Swallow CJ. Cancer of the anal region. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, et al., eds. Cancer: Principles & Practice of Oncology, Eighth Edition. Philadelphia, PA: Lippincott, Williams & Wilkins; 2008.
17. Fenger C, Frisch M, Marti MC, Parc R. Tumours of the anal canal. In: Hamilton SR, Aaltonen LA, eds. WHO Classification of Tumours, Volume 2: Pathology and Genetics. Tumours of the Digestive System. Lyon: IARC Press; 2000:145-55.
18. Welton ML, Lambert R, Bosman FT. Tumours of the Anal Canal. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. WHO Classification of Tumours of the Digestive System. Lyon: IARC Press; 2010:183-93.

原　著

依照我們單一醫學中心 35 年的經驗統計，意外被小手術切除肛門鱗狀細胞癌的病人並不會有比較差的預後

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背景　同步放化療是目前治療肛門鱗狀細胞癌的第一線標準治療，但有一部份病人的表現不很典型，在確定診斷前有可能被小手術切除 (像是痔瘡切除，瘺管切除或是廣泛切除)。在這個回顧性的研究我們統計這群病人和第一線就接受同步放化療的病人做比較。

方法　從 1982 年到 2016 年，總共 41 個病人被診斷為肛門鱗狀細胞癌。我們調閱了他們的病歷。他們的期別、治療、整體存活率、五年存活率、無復發存活率都被收集並比較。

結果　所有病人的 5 年存活率是 66%，5 年的無復發存活率是 57%。以同步放化療為第一線治療的病人 5 年存活率是 61%，5 年的無復發存活率是 49%。
有 25 個病人是手術為第一線治療，其中的 15 人為確立診斷前接受了小手術 (像是痔瘡切除，瘺管切除或是廣泛切除)。這群病人被定義為意外被小手術切除。他們的 5 年存活率和以同步放化療為第一線治療的病人比較為 (76%, n = 15 vs. 61%, n = 16, p = 0.044)。在這個回顧性的研究意外被小手術切除肛門鱗狀細胞癌的病人和以同步放化療為第一線治療的病人相比，並不會有比較差的預後。

結論　雖然臨床上會遇到被小手術切除肛門鱗狀細胞癌的病人，如果病人有接受後續治療，和以同步放化療為第一線治療的病人比，我們醫院的統計結果顯示預後不會比較差。

關鍵詞　肛門鱗狀細胞癌。