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Clinical profile and treatment outcome of collision carcinoma in cervix

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Abstract

A collision tumor is defined by co-existence of two adjacent tumors which are histologically distinct. Little is known about the clinical manifestation, treatment, and prognosis of cervical collision cancer. The objective of the study was to investigate the management and prognosis of patients with cervical collision cancer.

We retrospectively reviewed and enrolled patients with cervical collision carcinoma from 2010 to 2018 in two institutions (West China Hospital and West China Second University Hospital). The clinical presentation, pathology, treatment, and prognosis of patients with collision carcinoma of the uterine cervix were retrospectively reviewed. Progression free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method.

A total of 24 patients were included in this study. The proportion of cervical collision carcinoma was 0.4% in the cervical carcinoma cohort (24/6015). The median age of the patients with cervical collision cancer was 42 years. The most common presenting symptom was cervical contactive bleeding. There were 23 patients classified as International Federation of Gynecology and Obstetrics (FIGO) stage IA1-IIB. All patients except one received radical hysterectomy, in which 21 patients received bilateral salpingo-oophorectomy (BSO) and pelvic lymphadenectomy in addition. There were 16 patients who received adjuvant chemotherapy or chemoradiotherapy. The median follow-up time was 21 months. No patient death was observed. Recurrence only occurred in two patients. The 5-year OS rates and PFS rates were 100% and 91.7%, respectively.

This study revealed that cervical collision cancer was a type of rare cervical cancer with good prognosis. Cervical collision cancer responded well to the same treatment methods as the cervical squamous cell carcinoma and was associated with few recurrence and long survival.

Abbreviations: AC = adenocarcinoma, ASC = adenosquamous carcinoma, BSO = bilateral salpingo-oophorectomy, CLS = capillary lymphatic space, CT = chemotherapy, CTV = clinical target volume, FIGO = International Federation of Gynecology and Obstetrics, GTV = gross tumor volume, HT = hysterectomy, IMRT = intensity modulated radiation therapy, MM = malignant melanoma, NK = not known, OAR = organs at risk, OS = overall survival, PALND = paraortic lymph node dissection, PFS = progression free survival, PLND = pelvic lymph node dissection, PTV = planning target volumes, RT = radiotherapy, RTOG = radiation therapy oncology group, SCC = squamous cell carcinoma, SCNC = small cell neuroendocrine carcinoma, VMAT = volumetric modulated arc therapy.

Keywords: cervical collision cancer

1. Introduction

Cervical cancer is the third common malignancy afflicting women worldwide and the most common malignant gynecologic disease in China.[1,2] Squamous cell carcinoma (SCC) along with adenocarcinoma together constitute over 98% of the cervical carcinomas diagnosed annually.[3] Cervical collision tumors are rare tumors which consist of distinct cell populations, developing in juxtaposition to one another, without areas of intermingling.[4]

The cervical collision tumors are usually comprised of two elements.[5] Collision tumors show rare coexistence of two different origin tumors presenting as one lesion. They should be differentiated from other entities like carcinosarcomas, composite tumors or cancer-to-cancer metastasis. Though both types exist in close proximity in collision tumors, they do not intermingle unlike composite tumors which originate from same pluripotent stem cell and show distinct areas of transition. The collision tumor refers to the independently coexisting neoplasms with different behavioral, genetic, and histological features that are sharply demarcated.

Since Anne-Marie F. Kersemaekers et al documented two cases from the literature, several investigators have studied the features of the cervical collision tumor.[6] The largest series of cervical collision carcinoma was reported by Hui Li et al, who described 13 cases, of which most were classified as SCC and adenocarcinoma.[4]

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Literature is comprised of case reports and a few case series, thus knowledge on them is scattered. The clinical and pathological behavior remain largely unknown as well as the appropriate diagnostic and therapeutic procedures.

In this study, we reviewed the clinical and pathological features of patients with cervical collision tumors and investigated the clinical treatment and prognosis.

2. Materials and methods

2.1. Patients

Patients who diagnosed as cervical collision tumor in two affiliated hospital of Sichuan University (West China Hospital and West China Second University Hospital) between January 2010 and January 2018 were retrospectively reviewed and analyzed.

Histopathological diagnoses and clinical information were obtained. The standard of pathological diagnosis of collision carcinoma was as follows:

1. diagnosis was made based on complete excision of the primary tumor or biopsy;
2. the carcinoma presented as coexistence of two adjacent, but histologically distinct tumor components.

Each pathological diagnosis was made by two pathologists respectively and reviewed by a senior pathologist. Every intractable case would be discussed in department to make sure that the histopathological diagnose was reliable. This study was approved by the institutional ethics committee in West China Hospital.

2.2. Treatment

The radical resection used in this cohort was radical hysterectomy with or without pelvic lymphadenectomy according to the clinical stage of disease.

The chemotherapy regimen used for the patients consisted of paclitaxel plus cisplatinum/oxaliplatin, or bleomycin plus cisplatinum. All patients received 4 cycles of chemotherapy and those patients who did not undergo surgery received 2 cycles of chemotherapy in addition.

Radiotherapy delivered in this cohort was intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT). The clinical target volume (CTV) were contoured according to consensus.[7,8] For the patients received radiotherapy after radical surgery, CTV included the proximal two-thirds of the vagina, paravaginal soft tissue lateral to the vagina and pelvic lymph nodes (common, internal and external iliac, and presacral lymph node regions). The planning target volume (PTV) was defined as the CTV plus a 10 mm margin in the axial plane except a 5 mm margin anterior to the rectum. A dose of 50–50.4 Gy/25–28 fraction was delivered to PTV.

For the patient received radical radiotherapy without surgery, the gross tumor volume (GTV) included the gross visible disease involving cervix and its extensions determined based on the contrast enhanced computed tomographic scan and the GTVnd covered pelvic/para-aortic metastatic lymph nodes. The CTV included the gross tumor, cervix, uterus, parametriun, upper part of the vagina to 3 cm below the tumor invasion and regional lymph nodes. The PGTVnd was created by extending GTVnd using a margin of 5 mm. The PTV was defined as the CTV plus an 8 to 10 mm margin and an additional 5 to 10 margin to the cervix and uterus. A dose of 45 Gy/25 fractions was delivered to PTV followed by a boost of 20 Gy/10 fractions delivered to PGTVnd, and brachytherapy of 30 Gy/5 fractions.

2.3. Follow-up

After initial treatment, the patients were required to undergo standardized follow-up, including physical examination, laboratory tests, and thoracic and abdominopelvic CT scan every 3 months for the first 2 years and every 6 months thereafter.

2.4. Statistical analysis

The endpoint of this study was OS which was defined as the time between diagnose and death from any cause. Progression free survival (PFS) was defined as the time between diagnose and the first evidence of disease progression.

3. Result

In this study, 24 patients with cervical collision carcinoma were identified in the cohort of 6015 cervical cancer patients. The median age was 42 (range, 28–69) years. All patients (100%) had good performance status (ECOG 0–1).The FIGO stage was I in 16 patients, II in 7 patients.

The commonest clinical feature was contact blooding (14/24). On imaging studies, the cervical collision carcinoma presented as cervical placeholder or cervical hypertrophy.

All patients except one received surgery. The patient who did not receive surgery had FIGO stage IB2 disease and only received chemotherapy and radiotherapy. The other 23 patients underwent radical hysterectomy with 21 patients received pelvic lymphadenectomy and bilateral salpingo-oophorectomy (BSO) in addition. There were 16 patients who received adjuvant treatments, in which 5 patients were treated with adjuvant chemotherapy only and another 11 patients were treated with adjuvant chemotherapy and radiotherapy. The detailed treatment descriptions and decisions for treatment are shown in Table 1.

3.1. Pathological feature

The two most common pathological features were adenocarcinoma (22/24, 91.67%) and squamous carcinoma (15/24, 62.50%), respectively. Small cell neuroendocrine carcinoma accounted for 33.33% (8/24). The most frequent concomitant pathological was adenocarcinoma and squamous carcinoma (14/24, 58.3%) followed by adenocarcinoma and small cell neuroendocrine carcinoma (6/24, 25%). The detailed descriptions are shown in Table 2. The histologic finding and immunohistochemical staining results of these tumors revealed mixed malignant tumor components (Fig. 1).

We found that 10 of 11 patients with HPV test results were positive for HPV infection. HPV 16, 18 were positive in the 8 patients and 2 patients, respectively.

3.2. Outcomes

The median follow-up interval was 21 (range, 6–93) months, and no patient death was observed during this time. One patient showed local recurrent disease and 1 patient showed distant

Table 1

The clinical characteristics, treatment, and follow-up of patients with collision carcinoma.

No	Age (years)	FIGO stage	Treatment	Adjuvant treatment	Follow-Up (months)	Recurrence	Survival
1	37	IA1	HT+BSO+PALND+PLND	–	93		Yes
2	29	IIA2	HT+BSO+PALND	CT	2	+	Yes
3	69	IB	HT+BSO+PALNDm+PLND	CT+RT	76	+	Yes
4	50	IIA	HT+BSO+PALND+PLND	CT+RT	70		Yes
5	42	IB1	HT+BSO+PALND	CT+RT	36		Yes
6	28	IB1	HT+BSO+PALND	–	0		Yes
7	32	IB1	HT+BSO+PALND	CT	42		Yes
8	38	IB1	HT+BSO+PALND	–	40		Yes
9	47	IB1	HT+BSO+PALND	CT+RT	39		Yes
10	38	IB1	HT	–	35		Yes
11	43	IIA2	HT+BSO+PALND	CT	26		Yes
12	44	IB1	HT+BSO+PALND	CT+RT	21		Yes
13	36	IB1	HT+BSO+PALND	CT+RT	20		Yes
14	38	IB1	HT+BSO+PALND	–	0		Yes
15	54	IIA1	HT+BSO+PALND	CT+RT	16		Yes
16	47	IB1	HT+BSO+PALND	–	14		Yes
17	42	NK	HT	CT+RT	11		Yes
18	59	IB2	–	CT+RT	12		Yes
19	69	IB	HT+BSO+PALND	–	10		Yes
20	28	IIA2	HT+BSO+PALND	CT	8		Yes
21	44	IB1	HT+BSO+PALND+PLND	–	8		Yes
22	39	IIA2	HT+BSO+PALND	CT+RT	8		Yes
23	42	IB1	HT+BSO+PALND	CT+RT	8		Yes
24	48	IIB2	HT+BSO+PALND	CT	6		Yes

BSO = bilateral salpingo-oophorectomy, CT = chemotherapy, HT = hysterectomy, NK = not known, PALND = paraortic lymph node dissection, PLND = pelvic lymph node dissection, RT = radiotherapy.

Table 2

Characteristics of pathology.

Pathological		N (n = 24)
Combination classification		
AC +	SCC	14 (58.33%)
AC +	SCNC	6 (25.00%)
AC +	ASC	2 (8.33%)
ASC +	SCNC	1 (4.17%)
SCC +	SCNC	1 (4.17%)
Pathological components		
AC		22 (91.67%)
SCC		15 (62.50%)
SCNC		8 (33.33%)
ACS		3 (12.50%)
Histologic grade		
G1: Well differentiated		2 (8.33%)
G2: Moderately differentiated		3 (12.5%)
G3: Poorly differentiated		15 (62.5%)
Stromal invasion		
Superficial half		12 (50%)
Deep half		6 (25%)
Whole stroma		1 (4.16%)
CLS		
+		14 (58.3%)
–		10 (41.6%)
Lymph node metastases		
+		1 (4.16%)
–		23 (95.8%)
HPV		
+		10 (41.7%)
–		14 (58.3%)

AC = adenocarcinoma, ASC = adenosquamous carcinoma, CLS = capillary lymphatic space, HPV = human papillomavirus, SCC = squamous cell carcinoma, SCNC = small cell neuroendocrine carcinoma.

metastasis, respectively. The presenting symptom of the local recurrent patient was cervical contactive bleeding. The patient was FIGO stage IIA and underwent laparoscopic radical hysterectomy, BSO and pelvic lymphadenectomy. The pathology showed neuroendocrine carcinoma and adenocarcinoma. The patients received 4 courses of postoperative chemotherapy. The tumor recurred in the pelvic 2 months after the end of chemotherapy. The other patient was diagnosed with collision tumor with FIGO IB. The pathological feature showed adenosquamous carcinoma and adenocarcinoma. The patient received surgery and postoperative chemotherapy and radiotherapy. The patient suffered from bone metastasis presented as pain over 3 years after the initial treatment.

The 3- and 5-year local control rates were 95.8%. The 3- and 5-year distant failure free survival rates were 100% and 95.8%, respectively. The 3- and 5-year OS rates and PFS rates were 100%, 100% and 95.8%, 91.7%, respectively.

4. Discussion

Due to the rarity of cervical collision cancer, only a few cases and case series were reported. There are no established criteria for treatment. The treatment outcome is difficult to predict with given limited information on staging and treatment from previous studies, which mainly described the pathological features. And the prognosis of cervical collision cancer is unclear either.

As shown in Table 3, we reviewed the collision cancer literature for the cervix and found there were a total of 19 patients with cervical collision cancer reported. The patients' age ranged from 32 to 60 years, and the majority of patients were FIGO stage I. There were 9 patients presenting with SCC and AC, 5 patients with SCNC and AC, 2 with ASC and AC, 4 patients with recurrence and 2 patients who died of this disease.[6,9–13]

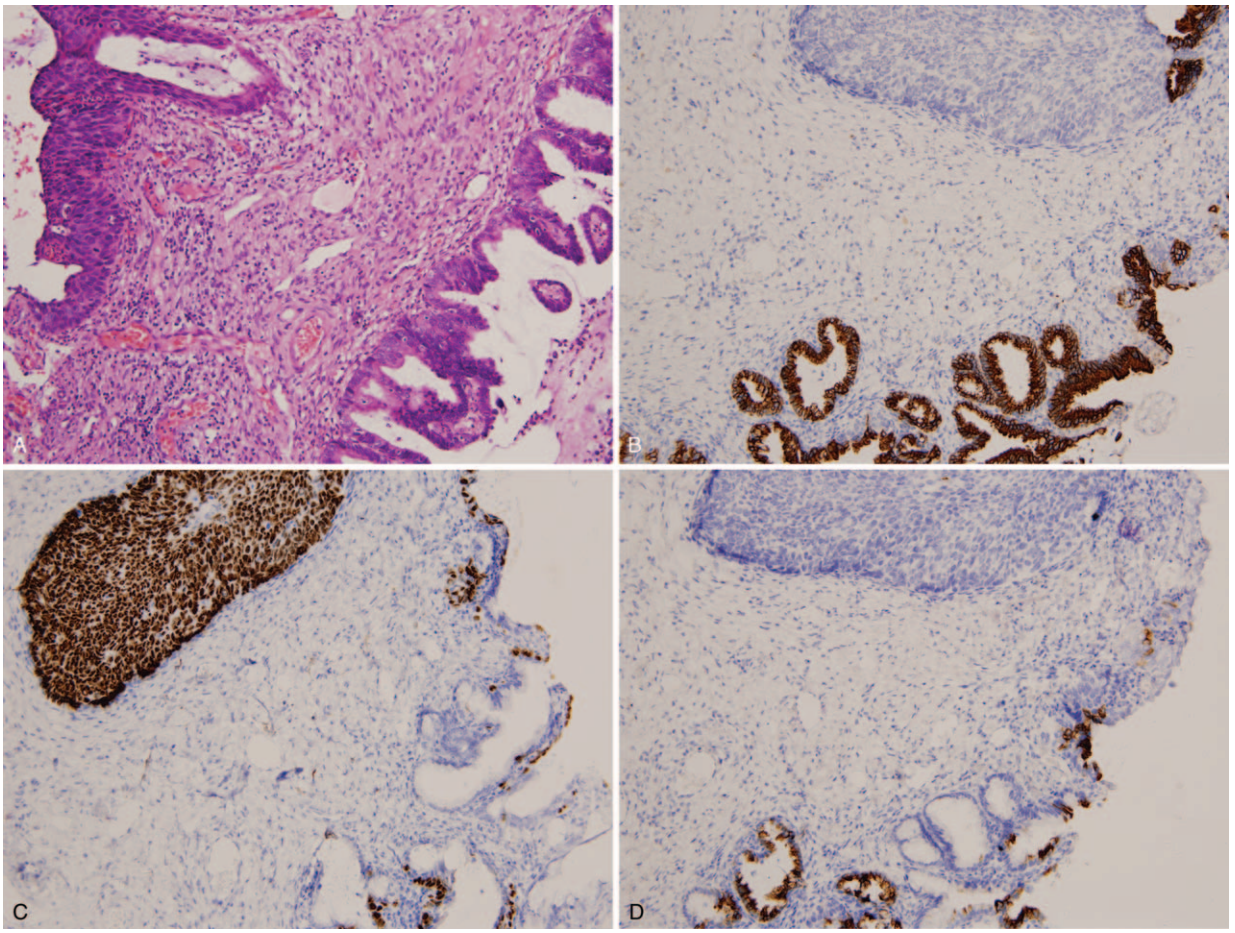

Figure 1. (A) Rare area of histological admixture of adenocarcinoma and squamous cell carcinoma (H&E; 200×); (B) adenocarcinoma immunopositive for MUC5 (IHC; 200×); (C) immunonegative for P63 (IHC; 200×); (D) adenocarcinoma component is immunopositive for MUC2 while the surrounding squamous cell carcinoma is negative (IHC; 200×).

In the literature, expect the 13 patients whose treatment methods were unknown, the remaining 6 patients underwent hysterectomy and pelvic lymph node dissection. Adjuvant chemotherapy and/or radiation therapy were performed on 4 patients.[4] In this study, 23 patients received hysterectomy and 21 patients received pelvic lymph node dissection in addition. Sixteen patients who received adjuvant treatments including chemotherapy and/or radiotherapy.

Ki-Seok Jant reported that the clinical outcome generally depended on tumor stage regardless of histologic subtype.[5] In this study, the patients presented good survival with only 2 patients had disease recurrence and were still alive with disease at time of last follow-up. There were no obvious risk factors in these 2 patients during the preoperative and follow-up period.

According to our study, cervical collision cancer patients classified as FIGO stage IA1-IIB have good prognosis.

The etiology of the collision cancer remains unclear. Different hypotheses have been provided. First, there is a hypothesis which suggests that the two tumor components are two independent processes which is coincidental to present. In another theory, the

Table 3

Summary of previously reported collision tumors of the cervix uteri.

Cases	Age	Diagnosis	Therapy	Stage	Recurrence	Ref.
13	45.6	SCC+AC 7 SCNC+AC 3 ASC+AC 2 MM+SCC 1	NK	I 9 II 4	1	[4]
2	57	SCC+AC 2	HT+PLND	II 2	2	[7]
1	50	ASC+ Hodgkin lymphoma 1	HT+PLND+CT+RT	NK 1	0	[8]
1	60	SCC+ Stromal Sarcoma 1	HT+PLND+CT	I 1	0	[6]
1	36	SCNC+SCC 1	HT+BSO+PLND+CT	Ib2 1	0	[9]
1	32	SCNC+SCC 1	HT+BSO+PLND+CT+RT	NK 1	1	[10]

MM = malignant melanoma, NK = not known.

two components are treated to be of monoclonal origin, which suggests that the tumor arises from a common precursor cell with two diverging developmental pathways.[14–17] Review#1 comment 1: It is reported by Kersemaekers that the different components in collision tumors most likely have the same origin as many genetic alteration are the same in each component.[6] HPV were significantly associated with cervical cancer.[18,19] In our study, 10 patients presented with HPV infection including 8 patients infected with HPV 16. As the same subtype of HPV was tested in both components, it is assumed that the collision cancer was monoclonal origin.

This study is a retrospective review and has several limitations. The sample population is limited. Thus, it will be necessary to analyze patient outcomes using a larger number of cervical collision carcinoma cases to confirm our findings.Review#1 comment2: As no molecular biology signatures was found in collision carcinoma, a careful histopathological evaluation is necessary to accurate diagnosis.

To the best of our knowledge, this was the largest study about cervical collision cancer to date. We described the clinical characteristics and patient outcomes of cervical collision cancer. Our data suggested that cervical collision cancer responded well to the same treatment as the SCC of cervix and was associated with few recurrence and long survival.

Author contributions

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References

[1] Arbyn M, Castellsague X, de Sanjose S, et al. Worldwide burden of cervical cancer in 2008. Ann Oncol 2011;22:2675–86.
[2] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[3] Mathew A, George PS. Trends in incidence and mortality rates of squamous cell carcinoma and adenocarcinoma of cervix—worldwide. Asian Pac J Cancer Prev 2009;10:645–50.
[4] Hui Li , Lei Li , Xiao Tang , et al. Clinical pathology analysis of 13 cases of cervical collision cancer [J]. Chin J Pathol 2014;627–8.
[5] Jang KS, Lee WM, Kim YJ, et al. Collision of three histologically distinct endometrial cancers of the uterus. J Korean Med Sci 2012;27:89–92.
[6] Kersemaekers AM, van de Vijver MJ, Fleuren GJ. Comparison of the genetic alterations in two epithelial collision tumors of the uterine cervix. A report of two cases. Int J Gynecol Pathol 2000;19:225–30.
[7] Small WJr, Mell LK, Anderson P, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys 2008;71:428–34.
[8] Lim K, Small WJr, Portelance L, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. Int J Radiat Oncol Biol Phys 2011;79:348–55.
[9] Lovell MO, Valente PT. Unique collision of hodgkin lymphoma and adenosquamous carcinoma in the uterine cervix: synchronous malignant neoplasms of the cervix. J Low Genit Tract Dis 2003;7:307–10.
[10] Tanveer N, Gupta B, Pathre A, et al. A rare collision tumour of uterus-squamous cell carcinoma and endometrial stromal sarcoma. J Clin Diagn Res 2017;11:ED20–2.
[11] Yazici O, Aksoy S, Ozhamam EU, et al. Squamous cell and neuroendocrine carcinoma of esophagus: collision versus composite tumor: a case report and review of literature. Indian J Cancer 2015;52:603–4.
[12] Mo X, Wei R, Huang M, et al. A case of cervival collision cancer and literature review[J]. Shandong Med J 2013;53:80–2.
[13] Cavalcanti MS, Schultheis AM, Ho C, et al. Mixed mesonephric adenocarcinoma and high-grade neuroendocrine carcinoma of the uterine cervix: case description of a previously unreported entity with insights into its molecular pathogenesis. Int J Gynecol Pathol 2017;36:76–89.
[14] Abeln EC, Smit VT, Wessels JW, et al. Molecular genetic evidence for the conversion hypothesis of the origin of malignant mixed mullerian tumours. J Pathol 1997;183:424–31.
[15] Yajima A, Fukuda M, Noda K. Histopathological findings concerning the morphogenesis of mixed carcinoma of the uterine cervix. Gynecol Oncol 1984;18:157–64.
[16] Dougherty CM, Cotten N. Mixed squamous-cell and adenocarcinoma of the cervix. Combined, adenosquamous, and mucoepidermoid types. Cancer 1964;17:1132–43.
[17] Lauchlan SC, Penner DW. Simultaneous adenocarcinoma in situ and epidermoid carcinoma in situ. Report of two cases. Cancer 1967;20:2250–4.
[18] Grayson W, Rhemtula HA, Taylor LF, et al. Detection of human papillomavirus in large cell neuroendocrine carcinoma of the uterine cervix: a study of 12 cases. J Clin Pathol 2002;55:108–14.
[19] Siriaunkgul S, Utaipat U, Suwiwat S, et al. Prognostic value of HPV18 DNA viral load in patients with early-stage neuroendocrine carcinoma of the uterine cervix. Asian Pac J Cancer Prev 2012;13:3281–5.