Clinical profile and treatment outcome of collision carcinoma in cervix

Pei Shu, MDa, Rui Li, BSb, Dan Xie, MMC, Ying He, MDb, Xin Wang, PHDb, Qingli Li, PHDb,*

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 uterus 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 contact 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 = hysterec- tomy, 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, SONC = 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.1,2,3 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
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 diagnosis 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 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 bleeding (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 (13/24, 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, 58.33%) 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...
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.\(^6\)\(^{–}\)\(^{13}\)}
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. 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. 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

| 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   | 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          | [9]  |
| 1     | 60  | SCC+Stromal Sarcoma 1 | HT+PLND+CT    | I 1   | 0          | [8]  |
| 1     | 36  | SCNC+SCC 1           | HT+BSO+PLND+CT | Ib2 1 | 0          | [10] |
| 1     | 32  | SCNC+SCC 1           | HT+BSO+PLND+CT+RT | NK 1  | 1          | [10] |

MM = malignant melanoma, NK = not known.

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×).
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 Kersemakers that the different components in collision tumors most likely have the same origin as many genetic alteration are the same in each component.\[18\]–\[19\] 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**

Conceptualization: Xin Wang.
Data curation: Rui Li, Dan Xie, Ying He.
Formal analysis: Rui Li.
Investigation: Dan Xie.
Project administration: Qingli Li.
Validation: Bing He, Xin Wang, Qingli Li.
Writing – original draft: Pei Shu, Rui Li.
Writing – review & editing: Pei Shu, Xin Wang.
Xin Wang: 0000-0002-8978-3181.

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