Cervical Carcinosarcoma: Current Understanding on Pathogenesis, Diagnosis, Management and Future Perspectives

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ABSTRACT: Cervical carcinosarcoma (CCS) is a rare aggressive tumor which was referred to as a sarcoma initially with its morbidity less than 1% of all cervical cancers. Four theories have been proposed for the pathogenesis of CCS. The "metaplastic theory," also called "monoclonal theory," has been widely accepted so far. The most common clinical symptom of CCS is abnormal vaginal bleeding. CCS is much less common than the counterparts in uterine corpus and usually confused with uterine carcinosarcoma (UCS) or common cervical cancer. The management for CCS has been mainly extrapolated from studies of UCS or cervical cancers. However, CCS has its special anatomical position and biological behaviors and is usually diagnosed at an early stage than UCS. Currently, there is no consensus on the survival, management and prognosis factors of CCS. We reviewed and summarized the literatures regarding to the epidemiology, clinical presentations, pathogenesis, diagnosis and treatment of CCS for providing clinicians with comprehensive information to diagnose and treat this malignancy.

KEYWORDS: Cervical carcinosarcoma, uterine carcinosarcoma, immunohistochemistry, treatment

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Introduction

Gynecological carcinosarcoma (GCS), also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor (MMMT), is heterogeneous and extremely aggressive malignancy that predominantly appears in the uterine corpus, then in the ovary, uterine cervix, vagina, fallopian tubes and peritoneum.[1] The morbidity (less than 0.005% of all cervical cancers) of cervical carcinosarcoma (CCS) is much less than that of uterine body[2] and CCS commonly occurs in the postmenopausal women. Compared to cervical squamous cell carcinoma and adenocarcinoma, primary CCS has a worse outcome because it is prone to metastasis and recurrence.[3]

CCS, a biphasic neoplasm, which has been regarded as sarcoma previously, is histologically comprises both epithelial and mesenchymal structures.[4] The metaplastic carcinoma theory that the carcinomatous element is the primary force of tumor invasiveness has been widely accepted.[5] CCS is commonly confused with uterine carcinosarcoma, and is easily misdiagnosed as cervical cancers/sarcomas. However, its histological presentations, biologic behavior and outcome is different from these malignancies.[6] Until now, the management for CCS has been mainly extrapolated from studies of uterine carcinosarcoma or cervical sarcomas, but they should not be treated in the similar way.

Most related reports published previously were case reports or case series, and no consensus has been reached on the optimal management, prognostic factors, and survival of CCS.[3] Therefore, we reviewed published literatures to summarize epidemiology, pathogenesis, clinical presentations, diagnosis, treatments, and prognostic factors of CCS with the aim to provide clinicians with accurately diagnosis and therapy.

Method

We reviewed the literature for studies on CCS by using PubMed/EMBASE/Web of Science. We used the keywords included "cervical carcinosarcoma," "carcinosarcoma of the uterine cervix," "cervical malignant mixed Müllerian tumor," "malignant mixed Müllerian tumor of uterine cervix," and "cervical malignant mesodermal mixed tumor" respectively. Previous review articles, papers and case reports were included. Language restrictions were not used. We also searched for clinical trials, and abstracts of scientific meetings. Publications from January 1, 1966 to October 1, 2020 were qualified for inclusion.

Epidemiology

CCS accounts for nearly half of cervical sarcoma, with the recurrence rate less than 1% of all cervical malignancies.[7] In Europe, the incidence of CCS is 0.2 cases per 100,000 population.[8] The age of initial diagnosis of CCS ranges from 12 to 94 and the vast majority of patients occurred in postmenopausal.[3,9-11] Black patients seem to be more likely to suffer from CCS.[3,9]

Pelvic radiotherapy, chemotherapy history and HPV infection in particular 16 type are at high risk of developing CCS.[10,12-14] One patient who received pelvic radiation therapy 12 years ago with the purpose of treating cervical squamous cell

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carcinoma was eventually diagnosed with CCS.[12] Another patient was reported to confirm with CCS after the cessation of cyclophosphamide therapy.[13] CCS also occurred in the lower remaining uterine segment and cervix after subtotal hysterectomy.[15] In addition, some studies have documented the integration of high-risk HPV in both epithelial and mesenchymal components of CCS, although the role of HPV in the evolution of CCS needs further exploration.[10]

Pathogenesis

The pathogenesis of CCS remains unclear and may be associated with the following four theories. The collision theory postulates that tumors stem from two different but synchronous neoplastic cell populations, respectively.[16,17] The combination theory supports both neoplastic cell populations originate from a common stem cell. The composition theory infers that paracrine factors generated from the carcinomatous structure induce proliferative response of mesenchymal components and it has been denied in daily practice as the sarcomatous component shows the histological features of malignancy.[18] However, some recent molecular and immunological findings sustain the metaplastic carcinoma theory that CCS may stem from the carcinomatous elements and then differentiate into sarcoma components.[19-24] The coexistence of CCS and cervical squamous cell carcinoma also support the metaplastic carcinoma theory.[10,14,25]

Clinical Presentations

The initial symptoms of CCS are similar to cervical cancer, mainly including abnormal vaginal spotting/bleeding and watery vaginal discharge. These presentations are easily to be detected by patients in the early stage. Some cases also complain of non-specific symptoms like lower abdominal pain, abdominal swelling, increased abdominal girth, loss of weight and gradual weakness.[3] A polyploid mass in the cervix or even a large necrotic or/and hemorrhagic lump replacing the cervix could be discovered after vaginal exploration. Early metastasis in CCS commonly occurs in vagina, rectum, bladder and bones.[15]

Diagnosis

Clinical manifestations, physical examination especially vaginal exploration, laboratory tests, ultrasound, imaging features and pathology are conducted to diagnose CCS. As no explicit staging system is available for CCS, most cases reported are staged based on the International Federation of Gynecology and Obstetrics (FIGO) surgical staging of cancer of the cervix uteri.[26-28]

The complete blood count, serum biochemical data and tumor biomarkers such as carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 15-3 (CA15-3), carbohydrate antigen 72-4 (CA72-4), are usually unremarkable.[1,29] Notably, the elevated serum level of carbohydrate antigen 125 (CA125) and carcinoembryonic antigen (CEA) could be observed in some cases.[24,29-31] CCS usually presents as a polypoid or bulky mass in cervix on ultrasound.[1] Computed tomography (CT) or magnetic resonance imaging (MRI) is used to detect a heterogeneous abdominopelvic mass and to check whether the mass is confined to the cervix and/or invaded to the vaginal wall.[26,29,31] PET-CT is sometimes available to assure extrauterine metastasis in patients with CCS.[11,32,33]

The gold standard of diagnosing CCS is pathological examination. As the accessibility of the uterine cervix, cervical biopsy examination is easy performed and can bring a definite diagnosis of CCS.[4,34] Grossly, most CCS cases invade mucosal and even full-thickness, in some rare cases, the uterine cervical mucosal were intact. Histologically, CCS is characterized as a biphasic admixture of intimately juxtaposed carcinomatous and sarcomatous components. The malignant epithelial components usually presents with squamous cell carcinoma (SCC), adenocarcinoma, adeno-squamous carcinoma, basaloid carcinoma, of which SCC and adenocarcinoma account for the most.[10,29] The mesenchymal components, either homologous (gynecologic tissue) or heterologous (represented by osteosarcomatous components), predominantly presents as long, spindle cell element.[29] Immunohistochemistry (IHC) displays that the epithelial elements mainly express cytokeratin (CK), broad-spectrum cytokeratin marker (MNF-116), low-molecular-weight cytokeratin marker (CAM 5.2), high-molecular-weight cytokeratin marker (34βE12) and epithelial membrane antigen (EMA), whereas the sarcoma components always express vimentin, desmin, smooth muscle-specific actin (SMA) and muscle-specific actin (MSA). Notably, sarcomatous components can express MNF-116, EMA and epithelial components are immunoreactive for vimentin likewise (Supplementary Figure 1). Meanwhile, IHC is irreplaceable in the classification of heterologous elements.[24] The previous reports showed that the cellular proliferation index (based on Ki-67 immunostaining) was significantly higher in carcinomatous components in contrast with sarcomatous components (mean of 70% and 28% of cells positive, respectively).[35] However, the pathological features of CCS have not been well characterized. Misdiagnosis of CCS sometimes happens in cervical samples because the sarcomatous components are hard to be identified.[9,31] A meta-analysis showed that the accurate diagnosis rate of CCS by preoperative pathology was only around 56%, and CCS was easy to be misdiagnosed as purely epithelial carcinoma.[11] Previous studies identified four molecular subtypes as microsatellite instability, POLE-mutated, copy number low, and copy number high subtypes in gynecologic carcinosarcoma (CS) and linked these genomic instability types with the clinicopathological features of gynecologic CS such as tumor histology, stage, therapy and patient prognosis.[36]

Treatment

There is no evidence-based guideline on optimal treatment approaches for CCS patients given its rarity.[33] Treatment has given priority to surgery. For early-stage CCS patients, surgery combined with adjuvant radiotherapy with or without

chemotherapy, is associated with an improved disease-free survival (DFS) and overall survival(OS).[11] Radiotherapy is commonly recommended to locally advanced-stage CCS patients[11,31,37] while chemotherapy is usually conducted in metastatic CCS patients.[31] Recently, one advanced CCS patient with high TMB, negative for programmed cell death protein 1 expression, microsatellite instability stable, and mutations in POLE received cryoablation followed by pembrolizumab and achieved a complete response and a progression-free survival over 11 months. No treatment-related adverse reactions were reported to this patient. Therefore, cryoablation subsequent with immunotherapy may be an optional choice for TMB-high patients with CCS.[38] It is frustrating that target therapy has not been reported in CCS patients until now and prospective trial regarding to the therapy of CCS has not been found.

Surgery

Surgery including total abdominal hysterectomy, bilateral salpingo-oophorectomy with pelvic lymph node dissection (radical surgery) and excision of cervical mass (cytoreduction), is primarily performed in patients with local CCS.[4,11] Radical surgery is the strongest recommendation for IB stage (Based on the FIGO surgical staging) patients, who account for nearly half of all CCS patients.[11] While cytoreduction is commonly conducted in advanced patients for relieving symptoms or in early-stage patients who is unable to receive radical surgery.[34] Notably, the absence of cervical mucosal involvement lead to tumor-progression in a silent fashion without vaginal bleeding and eventually the increasing volume of the tumor cause unpredictable tumor rupture. Under such emergency circumstance, surgery is immediately needed.[30] Fifty-four patients with CCS were reviewed from published case reports/series and 48 of them have been reported to suffer from surgery. Among these 48 patients, over half of cases who were diagnosed with FIGO stage I mainly received radical surgery (Table 1).

Radiotherapy

Although radiotherapy has been provided in patients of CCS, its impact on survival is uncertain. Pelvic radiation and brachytherapy are carried out for patients with CCS and the former was preferable according to the reported cases.[25,26,31] Of all collected cases (n = 54), 38 patients received radiotherapy at the variable dose ranging from 40 Gy to 65.5 Gy. Significantly, 32 of them accepted both surgery and radiation, which indicated that radiotherapy was adjuvant treatment option (Table 1). In a review conducted by Kimyon Comert G et al, surgery combined with adjuvant radiotherapy was expressively associated with an improved DFS and OS compared with radiotherapy alone in CCS patients.[11]

Chemotherapy

Data on chemotherapy of CCS is finite, mainly from studies of cervical cancer and standard chemotherapy regimens of CCS is still unclear.[25] Cisplatin, doxorubicin, ifosphamide and cyclophosphamide are commonly recommended for metastatic patients with CCS.[31] We collected various chemotherapy regimens conducted on 23 patients of CCS from published reports: Ten patients with FIGO stage I received adjuvant chemotherapy (half of them with platinum-based regimens) following standard surgery and the clinical outcomes of these ten patients were gratifying. Seven patients diagnosed with local advanced stage were treated with the first-line chemotherapy regimens as ifosfamide, cisplatin, adriamycin combined with radiotherapy and their survivals are mixed. One CCS patient with stage IB2 received radical surgery followed by chemotherapy of ifosfamide plus cisplatin. She developed recurrence seven months after surgery and underwent 2 courses of the 2nd line chemotherapy of paclitaxel in combination with carboplatin, then died (Table 1). Obviously, platinum-based chemotherapy regimens were in the majority. However, the effectiveness of chemotherapeutic agents above is hard to evaluate considering lack of prospective or even retrospective study.

Prognostic Factor

The prognosis of CCS is uncertain. Some study showed that the median survival time of CCS patients was only 18 months.[29] One recent research showed two-year DFS and OS of the CCS patients were 49% and 60%, respectively.[11] In early-stage CCS patients, Farley et al also indicated that the 2 year survival rate was around 50%.[15] However, for advanced-stage CCS patients who account for 40-50% in all stages, survival rate cannot be estimated.[29] The prognostic factors of CCS are still indeterminate. There is evidence that the crucial factors revolved prognosis of CCS are the stage, presence of metastasis and extent of invasion.[34] The early tumor stage is an independently positive predictive factor.[11] There were some studies demonstrated homologous carcinosarcoma of the uterus was related to a longer survival compared with the heterologous carcinosarcoma.[39,40] However, homologous and heterologous CCS has a comparable survival.[29] In addition, based on the presented report, neither epithelial nor mesenchymal components of the CCS has an exactly influence on DFS or OS.[11] Compared to cervical SCC and adenocarcinoma, primary CCS has the worst outcome.[3]

Conclusion

CCS is an extremely rare and aggressive tumor commonly occurs in postmenopausal women. HPV infection in particular 16 type, pelvic radiotherapy and chemotherapy history are at high risk of developing CCS. According to the widely accepted "metaplastic theory," CCS may stem from the carcinomatous elements and then differentiate into sarcoma components. The common manifestations such as vaginal bleeding is easy to be noticed, therefore CCS can be detected in the early stage. Pathologically, CCS is characterized as a biphasic admixture of intimately juxtaposed carcinomatous and sarcomatous components. Misdiagnosis of CCS sometimes happens in cervical samples due to the less

Table 1. Published case reports and case series regarding to CCS.

REFERENCE	AGE	CCS TYPE	CLINICAL PRESENTATION	FIGO STAGE	SURGERY	RT AND CT	SURVIVAL (MOS.)	
							DEAD	ALIVE
Rodriguez-Escudero et al[41]	12	Heterologous	Vaginal bleeding	I	H; BSO; LND	RT	NR	NR
Maheshwari et al[31]	60	Homologous	Lower abdominal pain	I	H; BSO	RT 60 Gy	NR	22
Abidi et al[42]	68	NR	NR	I	RH; BSO; PLNDLND	RT	NR	18
Wang et al.[43]	36	Homologous	Vaginal bleeding	I	H; BSO; PLNDLND	CT	NR	NR
Waxman et al[51]	76	NR	Vaginal bleeding; cervical mass	IB	ECM; USO	VS + ADM + CTX	NR	9
Clement et al[34]	45	Heterologous	Vaginal bleeding; cervical mass	IB	H; BSO;PLND	CT; RT	156	NR
	23	Heterologous	Vaginal bleeding	IB	ECM	RT	NR	NR
	66	Homologous	Vaginal bleeding; abnormal pap smear	IB	H; BSO	NR	NR	NR
	61	Homologous	Vaginal bleeding; abnormal pap smear; cervical mass	IB	H; BSO;PLND	NR	NR	54
	70	Homologous	Abnormal pap smear; cervical mass	IB	H; BSO;PLND	NR	NR	NR
	78	Homologous	Cervical mass	IB	H; BSO; PALND	RT	NR	NR
	84	Homologous	Vaginal bleeding; cervical mass	IB	H; BSO;PLND	NR	NR	NR
Gan et al[44]	56	Homologous	Vaginal bleeding	IB	RH; BSO; PLNDLND/PALND	NR	NR	24
Miyazawa and Hernandez[45]	46	Heterologous	Vaginal bleeding	IB1	RH; BSO;PLND	RT	NR	30
Iida et al[29]	61	Heterologous	Vaginal bleeding	IB1	SRH; BSO;PLND	PRT 45Gy	17	NR
Sharma et al[4]	29	Homologous	Abnormal pap smear	IB1	RH; PLNDND	NR	NR	65
	66	Homologous	Vaginal bleeding	IB1	RH; BSO;PLND/ PALND	RT 45 Gy	NR	35
Piura et al[52]	76	NR	Vaginal bleeding	IB1	H; BSO;PLND	RT 50.4 Gy	NR	15

(Continued)

Table 1. (Continued)

REFERENCE	AGE	CCS TYPE	CLINICAL PRESENTATION	FIGO STAGE	SURGERY	RT AND CT	SURVIVAL (MOS.)	
							DEAD	ALIVE
Kadota et al[46]	61	Heterologous	NR	IB1	H; BSO;PLND	TAX + CBP RT 50.4Gy	NR	70
Lopez-Chardi et al[47]	80	Homologous	Vaginal bleeding	IB1	H; BSO	RT	NR	31
Munakata et al[53]	43	Heterologous	Cervical mass	IB1	RH; ND	DDP;RT 40Gy	NR	38
Lin et al[1]	65	Homologous	Vaginal bleeding	IB1	RH; BSO;PLND	None	NR	26
Kimyon Comert et al[11]	67	Homologous	Lower abdominal pain	IB1	RH; BSO;PLND/ PALND	DDP; RT	NR	60
Young et al[6]	53	Homologous	Vaginal bleeding; lower abdominal pain	IB2	RH; BSO;omentectomy	RT 45Gy	NR	NR
Sharma et al[4]	64	Homologous	Vaginal bleeding	IB2	NR	RT 45Gy	28	NR
	25	Homologous	Vaginal bleeding; vaginal discharge	IB2	RH; PLNDND	None	NR	42
Laterza et al[25]	42	Homologous	Vaginal bleeding	IB2	H; BSO;PLND	IFO + DDP	NR	48
Lee et al[48]	47	Heterologous	Vaginal bleeding	IB2	RH; BSO;PLND	CT; T	NR	20
Luo et al[14]	45	Homologous	Vaginal bleeding	IB2	TH; BSO;PLND/ PALND	CT; RT	NR	NR
Kim et al[37]	53	NR	Cervical mass	IB2	RH; BSO;PLND	IFO + DDP TAX + CBP	12	NR
Connor[54]	64	NR	Vaginal bleeding; vaginal discharge	II	NR	PRT + BRT 65.5Gy	2.5	NR
Wang et al[43]	42	Homologous	Vaginal bleeding	II	H; BSO;PLND	RT	NR	82
Meguro et al[28]	63	Homologous	Vaginal bleeding	IIA	RH; BSO;PLND	CT	NR	NR
Kimyon Comert et al[11]	68	Homologous	Abnormal pap smear	IIA1	RH; BSO;PLND/ PALND	DDP; RT	NR	NR
Clement et al[34]	87	Homologous	Abnormal pap smear; cervical mass	IIB	ECM	RT	NR	NR
Laterza et al[25]	74	Homologous	Vaginal bleeding	IIB	RH; BSO;PLND/ PALND	RT 65Gy	11	NR

(Continued)

Table 1. (Continued)

REFERENCE	AGE	CCS TYPE	CLINICAL PRESENTATION	FIGO STAGE	SURGERY	RT AND CT	SURVIVAL (MOS.)	
							DEAD	ALIVE
Gan et al[44]	63	Homologous	Vaginal bleeding;vaginal discharge	IIB	RH; BSO; PLNDLND/PALND	RT	NR	NR
	58	Homologous	Vaginal bleeding	IIB	RH; BSO; PLNDLND/PALND	RT	NR	NR
Semczuk et al[5]	57	Homologous	Vaginal bleeding	IIB	TH; BSO;PLND/ PALND omentectomy	CTX + ADM	NR	7
Gastrell et al[26]	68	Homologous	Vaginal bleeding	IIIB	NR	DDP; RT 45Gy	NR	6
Tseng et al[30]	59	NR	Lower abdominal pain	IIIB	H; BSO;PLND omentectomy	ADM + DDP RT 50.4 Gy	NR	4
Bagué et al[27]	62	Heterologous	NR	IVB	H; BSO	CT; T	NR	39
Sharma et al[4]	64	Homologous	Vaginal bleeding	IVB	NR	IFO; RT 50 Gy	5	NR
Abell and Ramirez[12]	68	NR	Vaginal bleeding	NR	ECM	RT	15	NR
	44	NR	Vaginal discharge	NR	RH; cystectomy; vaginectomy	None	13	NR
	72	NR	Vaginal bleeding	NR	NR	RT	10	NR
	65	NR	Vaginal bleeding	NR	ECM	RT	10	NR
	70	NR	Vaginal discharge	NR	NR	RT	3	NR
	47	NR	Vaginal discharge	NR	ECM	RT	13	NR
Clement et al[34]	71	Homologous	Cervical mass	NR	ECM; PLND	CT; RT	NR	NR
Takeshima et al[49]	84	NR	Cervical mass	NR	H; BSO	CT; RT	NR	NR
Ribeiro-Silva et al[9]	71	Homologous	Vaginal bleeding	NR	H; BSO	CT	NR	12
Wu et al[32]	25	NR	NR	NR	RH	CT; RT	NR	NR
Roma[50]	65	NR	Vaginal bleeding	NR	H; BSO	CT	NR	NR
Ribeiro et al[33]	64	NR	Vaginal bleeding	NR	RH; BSO;LND; omentectomy	TAX + CBP; RT	5	NR

Abbreviations: ADM, adriamycin; CBP, carboplatin; CCS, cervical carcinosarcoma; CT, chemotherapy; CTX, cyclophosphamide; DDP, cisplatin; ECM, excision of cervical mass; FIGO, Federation of Gynecology and Obstetrics; H, hysterectomy; IFO, Ifosfamide; LND, lymph node dissection; NR, not reported; PLND/PALND, pelvic/para-aortic lymph node dissection; RH, radical hysterectomy; RT, radiotherapy; SRH, semi-radical hysterectomy; TAX, paclitaxel; TH, total hysterectomy; USO/BSO, unilateral/bilateral salpingo-oophorectomy; VS, vincristine sulfate.

identification of sarcomatous component. Thus, suspicion of CCS should be raised when sarcomatous component appears. Radical surgery and cytoreduction are primarily performed in patients with local CCS. Radiotherapy at the variable dose ranging from 40 Gy to 65.5 Gy as an adjuvant treatment option after surgery offers a better survival for early-stage CCS patients and platinum-based regimens are most commonly conducted in CCS patients in different stage. Patients can benefit from cryoablation followed by immunotherapy especially when patients with POLE mutation, but further evidence is required to confirm the effectiveness of this strategy. Early stage is the crucial factor to predict a positive survival. Further studies are needed to deeply explore the characteristics and pathogenesis of CCS, and to form a guideline of standard therapy in the future.

Author Contributions

XShu collected data, reviewed the literature and wrote the manuscript. YZhou collected data, wrote and revised the manuscript. GWei collected data and rechecked the manuscript. XChen assisted in drawing. MQiu design and revised the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTAL MATERIAL

Supplemental material for this article is available online.

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