Small Cell Carcinoma of the Uterine Cervix:A Single Institution Experience

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Abstract **Objective** To investigate the clinical characterics, prognositic factors, diagnosis and treatment of small cell carcinoma of cervix. **Methods** Data of fourteen patients with small cell carcinoma of the cervix were studied retrospectively. **Results** The mean age of the patients was 38 years old (range,24-55), the clinical stages at presentation were Ib1 (6), Ib2 (3), IIa (3) and IIb (2). Five (35.7%) tumors were associated with other forms of carcinoma. Neuroendocrine markers immunoreactivity rate was 100% in nine specimens stained. Thirteen patients underwent radical surgery combined with preoperative radiation therapy or chemotherapy,the rate of lymph node involvement was 53.8%. The overall median survival was 40.3 months (range, 1-96months) and overall survival rates were 65% and 43% at 2 and 5 years. **Conclusion** Neoadjuvant chemotherapy and preoperative brachytherapy could be used to enhance the resectability of the large tumors, which maybe helpful to patients with locally advanced disease. More effective therapeutic protocol or other pharmacologic agents should be further investigated in the management of small cell cervical carcinoma.

Key words Small cell carcinoma; Uterine cervix; Neuroendocrine tumor.

Small cell carcinoma of the uterine cervix (SCCC) is rare and accounts for approximately 1~2% of all cervical cancers [1, 2]. SCCC is characterized by frequent and early nodal and distant metastases, which resulted in a poorer prognosis than corresponding squamous cell carcinomas [1-3].Given the aggressive behavior of SCCC, patients with these tumors are thus potential candidates for systemic therapy. However, due to the rarity of these lesions, there are few reports in the literature on the outcome of adjuvant treatment strategies. The aim of this study was to review our experience in fourteen patients (including two patients complicated by pregnancy) diagnosed as SCCC and treated in our institutions between 1994 and 2006.

MATERIALS AND METHODS

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Between July 1990 and August 2006, in the Department of Gynecology, Cancer center of Sun Yat-sen university, the tumor registry section recorded 2637 patients with invasive carcinoma of the uterine cervix, including 14 cases of small-cell carcinoma which accounts for 0.5% of all cervical cancers.

The pathological diagnosis of the tumors were made by senior pathologists of our institution, using pathologic specimens prepared by hematoxylineosin stain, and were based on the criteria highlighted by the 1996 consensus conference [5]. And this criteria includes small, round cells in solid sheets, scant cytoplasm, hyper chromatic nuclei, and absent nucleoli. Numerous mitotic figures and extensive necrosis were also common findings. Specimens of nine patients were stained with antibodies to three neuro-endocrine markers: neuron-specific enolase (NSE), chromagranin(CGR), synaptophysin (SYN) and one epithelial cell marker: cytokeratin (CK). The clinical features of these cases, including ages, symptoms, stages, treatment methods, and prognosis, were investigated. Patients were clinically staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification. The follow-up period

was defined as the time from initial diagnosis to the time of death or last follow-up (August 2006). No patient has been lost to follow-up.

Initial surgery included radical hysterectomy and pelvic lympha-denectomy and bilateral or unilateral salpingo-oophorectomy. Radiation therapy was based on a combination of external beam, using 2Gy daily fractions of megavoltage photons up to 50Gy, and intracavitary low dose rate brachytherapy (iridium insertion). External beam irradiation of para-aortic lymph nodes was performed when needed. The regimen of neo-adjuvant or adjuvant chemotherapy was : CBP (Cyclophosphamide + Bleomycin + Cisplatin),CAP (Cyclophosphamide + Doxorubicin + Cisplatin), IP (Ifosfamide+ Cisplatin), TP(Paclitaxel+ Cisplatin),or TIP(Paclitaxel+ Ifo-sfamide+ Cisplatin). The cycles were repeated every 3 weeks.When necessary,other chemotherapy regimens were used for the salvage treatment to advanced or recurrent disease.

RESULTS

The main clinical characteristics of fourteen patients, treatment modalities and outcome data are listed in Table 1. The median age at diagnosis was 38 years (range 24-55). All patients presented with symptoms of

Table 1 Clinical and pathological characteristics of patients with small cell carcinoma of uterine cervix

NO.	Tumor			Pathology			Treatment strategy	F/U (months)
	age	stage	Size (cm)	Coexist lesion	stromal invovlement	Node Metastases		
1	47	Ib1	3.5	-	<1/2	Y	BT(16GY)-RH	DOD(40)
2	36	Ib1	2	Ac	<1/2	N	RH-adjCT(CAP,2cycles)	DOD(21)
3	30	Ib1	1	Ac	<1/2	Y	RH-adjCT(CBP,2)-RT(50GY)-adjCT(CBP,1)	NED(50)
4	36	Ib1	3.5	-	>1/2	Y	RH-adjCT(TP,2)-RT(50GY)	NED(3)
5	55	Ib1	3.5	Ac	<1/2	N	NeoadjCT(TIP,2)-RH-adjCT(TIP,4)	NED(7)
6	27	Ib1	3	-	>1/2	Y	RH-adjCT(TP,4)-BT(30GY)-RT(50GY)	NED(13)
7	39	Ib2	6	-	>1/2	N	RH-adjCT(TP,4)	DOD(26)
8[a]	34	Ib2	6	-	>1/2	Y	NeoadjCT(IP,3)-RH-adjCT(IP,1)-RT(50GY)	DOD(16)
9[a]	29	Ib2	5	-	<1/2	Y	NeoadjCT(CBP,1)-RH-adjCT(CBP,2)	NED(64)
10	38	IIa	3.5	-	>1/2	Y	RH-adjCT(CBP,2)-RT(50GY)-adjCT(CBP,2)	DOD(23)
11	53	IIa	3.5	-	>1/2	N	RH-adjCT(CBP,4)-BT(30GY)	NED(59)
12	30	IIa	6	Sc	>1/2	Y	BT-RH-adjCT(CBP,1)-RT(50GY)-adjCT(CBP,3)	NED(96)
13	46	IIb	5	Ac	>1/2	N	NeoadjCT(TIP,2)-RH-adjCT(TIP,4)-BT(30GY)-RT(50GY)	AWD(21)
14[b]	48	IIb	3.5	-	NA	NA	CT(TP,1)	DOD(1)

Note: Ac, Adenocarcinoma; Sc, Squamous cell carcinoma; BT, Brachytherapy; RH, Radical hysterectomy and pelvic lymphadenectomy; adjCT, adjuvantchemotherapy; neoadjCT, neoadjuvantchemotherapy; DOD, Died of disease; NED, No evidence of disease; AWD, Alive with disease; C, Cyclophosphamide; A, Doxorubicin; B, Bleomycin; P, Cisplatin; T, Paclitaxel; I, Ifosfamide.

a Patients complicated by pregnancy.

b This patient developed brain metastases after one cycle of chemotherapy

abnormal bleeding or postcoital spotting. Six patients were clinically staged in Ib1, 3 in stage Ib2, 3 in stage I-Ia, and 2 in IIb. None of the patients demonstrated any clinical evidence of abnormal hormone production. Preoperative the diagnosis of small−cell carcinoma was accurately made only in 6 cases (42.9%) with histological examination, seven patients (50.0%) were diagnosed as having squamous cell carcinoma and one (7.1%) as having poorly differentiated carcinosarcoma. In addition to SCCC, adenocarcinoma coexisted in four cases and squamous cell carcinoma in one. Patients with a pure histological pattern had a median survival rate of 38 months, and survive 77 months in those with a mixed histological pattern. Of the thirteen patients who underwent a pelvic lymphadenectomy, 53.8% (7 of 13) had lymph node invision. Especially, immunohistochemical stains were all positive in nine cases stained with antibodies to NSE, SYN, CGR and CK.

Among these 14 cases, one patient (No.14) died due to rapid brain metastasis just after getting one cycle of neoadjuvant chemotherapy, the other thirteen patients underwent radical hysterectomy with or without brachytherapy or neoadjuvant chemotherapy. Given the aggressive behavior of this tumor, an increasing number of women received adjuvant therapy. Nine patients received pre− or post operative radiation therapy, only one patient did not receive adjuvant chemotherapy. Patients who underwent radiotherapy had a median survival of 62 months compared with 30 months in those without radiotherapy.

Three patients had definitely disease recurrence: one case (N0.7) recurred in pelvic sidewall and one (N0.10) recurred in bone and the other one (No.13) had widespread metastasis to lung, liver and spleen.

The overall median survival was 40.3 months (range, 1−96months) and overall survival rates were 65% and 43% at 2 and 5 years.

DISCUSSION

Small cell carcinoma of the cervix was first reported in 1958 and was later described by Albores−Saavedra and colleagues as a well−differentiated carcinoid tumor with features similar to carcinoids of the gastrointestinal tract [3, 4]. Since that time, many terms have been used to describe this aggressive class of morphologically varied tumors. In 1996, a workshop sponsored by the College of American Pathologists and the National Cancer Institute addressed the complicated terminology of neuroendocrine tumors of the cervix [5]. In order to create uniform and reproducible terminology, the members of the committee adopted a classification system that was similar to that for neuroendocrine tumors of the lung. Under this new classification, neuroendocrine tumors were divided into four categories: (1) typical carcinoid tumor, (2)atypical carcinoid tumor,(3) large cell neuroendocrine carcinoma, and (4) small cell carcinoma. SCCC is more common than the carcinoid and large cell types and has a clinical pattern similar to that of small cell (oat) carcinoma of the lung.

It is often difficult [6] to make a preoperative diagnosis of small−cell carcinoma. In our study, only 6 of the 14 patients had an accurate diagnosis of small−cell carcinoma with preoperative histological examination and none of them by cytology. Kim *et al.* [7] reported that histological type could be presumed by cytology in 79% of 18 cases of small cell carcinoma based on the findings, including nuclear molding, nuclear smearing effect, salt and pepper chromatin pattern with minimal cytoplasm, and cell clusters without a typical architectural pattern. And Zhou *et al.* [8] have pointed out, it is often important in clinical practice to consider the differential diagnosis from follicular cervicitis, endometrial cells, adenocarcinoma of the uterine cervix, small−cell type SCC, and lymphoma.

In our series, all nine specimens stained for three neuroendocrine markers were positive. Thus we can immunohistochemically verify the presence of cells with neuroendocrine differentiation. However, Albores−Saavedra *et al.*[5]indicated that not all of the neuroendocrine markers need to be present to make the diagnosis because 60% of small−cell carcinomas are negative for chromogranin A and synaptophysin and 30% for NSE. Ambros *et al.*[9] also indicated that small−cell carcinoma may be diagnosed when tumor cells are positive for neuroendocrine markers such as NSE, chromogranin A, and synaptophysin, and negative for keratin. Likewise, immunohistochemistry may be considered highly

useful in diagnosing such confusing cases.

Many authors have emphasized the poor prognosis of patients with small cell carcinomas. In a large population-based study from Norway, Alfsen *et al.*[10] identified 417 patients with adenocarcinoma, 29 patients with small cell carcinoma, and 59 patients with other non-squamous cell carcinomas of the cervix. Multivariate analysis showed that the most important prognostic variable was the presence of positive lymph nodes. Small cell carcinoma was the only histological subtype that was significantly correlated with outcome, with a 5-year survival rate of only 33% for patients with stage I disease and no survivors among patients with more advanced tumors. Several authors have previously noted a correlation between small tumor size and survival in patients with stage I small cell carcinoma of the cervix [10~13]. Survival is rare for patients who have cancers that are more extensive than stage IB, are larger than 2~4 cm, or involve lymph nodes [11,13~15]. Silva *et al.*[16] also discovered that other histologic cell types admixed with small cell tumor confers a better prognosis. In their series, 34% of patients with small cell NE tumors mixed with squamous cell or adenocarcinoma histology were alive without disease compared with only 8% of those with pure small cell carcinoma. However, in our study, we don´t find significant difference in survival between stage II and I. Two of three stage II patients were survived for 59 and 96 months respectively, and still the longer survival patient had lymph node involvement. And one patient (No.9) who had a tumor mass of 5cm survived for 64 months and no evidence of recurrence. In our series twelve of fourteen tumors size was bigger than 2 cm, the overall survival rate is similar with reports. Patients with a pure histology have a shorter survival month than those with a mixed histology.

Sheets *et al.*[17] studied 14 patients with stage IB or I-IA SCNEC treated with hysterectomy with or without postoperative radiation therapy; 57% of the patients had nodal disease. There were only two survivors, both of whom had small tumors (smaller than 2 cm) with negative nodes. Chan JK *et al.*[19] also stated that only those with small tumors (<2 cm) amenable to surgery and negative margins after hysterectomy are long-term disease-free survivors. In our cohorts, three of six patients of stage Ib2 and IIa with big tumor mass (≥3.5cm) are surviving now, all of whom underwent radical surgery combined with preoperative or postoperative radiation and chemotherapy. So we recommended that preoperative chemotherapy and brachytherapy which can be used to enhance the resectability of the large tumors combined with postoperative radiation or chemotherapy which maybe helpful to locally advanced disease.

Although several case reports and small series have indicated encouraging outcomes in patients treated with a combination of radical hysterectomy or radiation therapy and chemotherapy, the number of patients and follow-up is insufficient to permit determination of whether chemotherapy can improve the outcome of patients with small cell carcinoma of the cervix [7,20]. In our study, one patient (No.14) developed brain metastases just after one cycle of chemotherapy with regimen of paclitaxel and cisplatin, and before treatment we didn´t find evidence of distant metastases, which confirmed the aggressive behavior of SCCC and its chemoresistant nature.

Our study confirmed the aggressive nature of this disease. Although these fourteen patients all were early stage and multimodality treatments had been used, the outcome were less than satisfactory. This suggested that it should be considered as a systemic disease. The aggressiveness and poor prognosis of neuroendocrine cervical cancers have indicated the need for new chemotherapy combinations or other pharmacologic agents. Tangjitgamol S *et al.* [21] found that there was high expression of VEGF in neruoendocrine cervical carcinoma, we might try to incorporate inhibitors of VEGF receptor in the treatment of this disease. Further clinical trials are needed to investigate the target therapeutics.

We recognize the limitations of our study. This is a retrospective analysis of a single institutional experience with a small number of patients and insufficient follow up. The rarity of SCCC limits the ability of single institutions to determine the value of different management approaches and we recommend the need for well-designed multi-institutional group trials.

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