# Clinicopathological characteristics and outcome of patients with small cell neuroendocrine carcinoma of the uterine cervix: case series and literature review

**Y. Wang[1], K. Mei[1], M.F. Xiang[2], J.M. Li[3], R.M. Xie[4]**

*[1]Department of Medical Oncology, [2]Department of Information, [3]Department of Pathology, [4]Department of Gynecology Oncology, Sichuan Cancer Hospital, Chengdu, Sichuan (China)*

**Summary**

*Objective:* To analyze the clinicopathological data of 13 cases of small cell neuroendocrine carcinoma (SCNEC) of the uterine cervix who received treatment at this medical institutions over the past five years with patient survival as the primary endpoint. *Materials and Methods:* The clinicopathologic data of 13 cases were reviewed. Immunohistochemistry was performed using antibodies against synaptophysin and chromogranin A and Ki-67. Survival was analyzed using the Kaplan-Meier method and log-rank tests. *Results:* The median age of these patients was 37 years (range 21-62). Immunohistochemistry showed that the positive rate of synaptophysin and chromogranin A was 100% (13/13) and 69.23% (9/13), respectively. The median survival of patients with early-Stage I-II SCNEC of the uterine cervix (17.5 months) was significantly higher than that of patients with advanced stage SCNEC of the uterine cervix (four months) ($p < 0.05$). There was no local recurrence in all 13 patients. Five patients died of distant metastasis in less than six months. *Conclusion:* SCNEC of the uterine cervix is a highly-malignant disease and early-stage patients showed significantly longer survival compared to late-stage patients. Early diagnosis and prompt combination treatment may improve the outcome of patients with SCNEC of the uterine cervix.

*Key words:* Small cell neuroendocrine carcinoma; Uterine cervix; Immunohistochemistry; Clinical characteristics; Survival.

## Introduction

Neuroendocrine carcinoma (NEC), which arises from peptidergic neurons and neuroendocrine cells, is a type of heterogeneous malignant carcinoma with an incidence about five times higher than that 30 years ago [1]. It occurs in various organs and tissues, such as the digestive tract, lungs, nasopharynx, throat, mediastinum, thymus, breast, and uterus. NECs of the digestive tract account for about 55%-70% of all NECs, followed by NECs in the lungs. Small cell NEC (SCNEC) of the uterine cervix is a rare tumor with a mean annual incidence of 0.06 per 100,000 women [2], accounting for one to six percent of all cervical cancers [3, 4], the most common malignant disease of the female genital tract. SCNEC of the uterine cervix occurs frequently in women of relatively young age. With improvement in clinical diagnosis in recent years, the number of SCNEC of the uterine cervix cases has actually increased. Despite such improvement, the rate of early diagnosis is still very low.

The tumors are characterized by a high incidence of early nodal and distant metastases and are associated with a more dismal prognosis than other subtypes of cervical cancers [5-7]. However, due to its rarity, there have been insufficient reports on SCNEC of the uterine cervix and consequently there is a paucity of knowledge about this disease. Furthermore there are no consensus diagnoses, treatment guidelines, and optimal treatment strategies for this aggressive tumor. Here, the authors retrospectively analyzed the clinicopathologic data of 13 cases of SCNEC of the uterine cervix who received treatment at the present medical institutions over the past five years and the primary endpoint of this analysis was patient survival.

## Materials and Methods

### *Subjects and tumor specimen acquisition*

The authors retrospectively reviewed the clinicopathological data of 13 consecutive cases of SCNEC of the uterine cervix who were treated at the Sichuan Cancer Hospital, Sichuan, China, between January 2006 and December 2010. The study protocol and acquisition of tissue specimens were approved by the local Institutional Review Board. Frozen primary tumor samples were obtained from the Tissue Banks at Sichuan Cancer Hospital and Huaxi Hospital. Human tissue acquisition and use in this study complied with the National Regulations on the Use of Clinical Samples in China. Tissue specimens were obtained from archived tissue samples of these SCNEC patients. SCNEC of the uterine cervix was confirmed pathologically in these patients by two independent and experienced pathologists (W.G.S. and Y.W.). Histopathologic diagnosis was based on morphologic criteria and on immunohistochemical staining for neuron-specific enolase (NSE), synaptophysin, and chromogranin A as previously described [8, 9]. All tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) clinical staging system for cervical cancer, based on physical examination, chest X-ray, intravenous pyelography, cystoscopy, sigmoidoscopy, and abdomino-pelvic computed tomography (CT) scan or magnetic resonance imaging (MRI).

Revised manuscript accepted for publication September 3, 2012

Table 1. — *Clinicopathological data of 13 patients with small cell neuroendocrine carcinoma (SCNEC) of the uterine cervix.*

| Case no. | Age (years) | FIGO Stage | Immunohistochemistry CgA | Syn | Ki-67 | NSE | Therapeutic modality | Survival (month) | Survival status |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 42 | IIIB | + | + | N/A | N/A | radiation + chemotherapy × 3 | 10 | dead |
| 2 | 37 | IIA | +++ | +++ | N/A | ++ | surgery + radiation + chemotherapy × 5 | 46 | dead |
| 3 | 25 | IIIA | -- | + | N/A | + | radiation + interventional chemotherapy × 6 | 53 | alive |
| 4 | 21 | IIA | + | +++ | N/A | + | surgery + chemotherapy × 1 | 49 | alive |
| 5 | 22 | IB | -- | + | > 60% | N/A | surgery + radiation + chemotherapy × 1 | 43 | alive |
| 6 | 31 | IV | +++ | + | N/A | +++ | (surgery + chemotherapy × 2) +chemotherapy × 1 | 3 | dead |
| 7 | 37 | IIIB | +++ | +++ | 80% | ++ | radiation + chemotherapy × 3 | 4 | dead |
| 8 | 43 | IIIB | ++ | +++ | N/A | +++ | radiation + interventional chemotherapy × 1 | 4 | dead |
| 9 | 37 | IIA | + | + | 30% | N/A | surgery + radiation + chemotherapy × 2 | 11 | alive |
| 10 | 39 | IB | -- | ++ | > 90% | N/A | surgery + radiation + chemotherapy × 3 | 19 | alive |
| 11 | 41 | IB | ++ | ++ | 80% | + | surgery | 15 | alive |
| 12 | 35 | IB | -- | + | 80% | N/A | surgery + radiation + chemotherapy × 6 | 15 | alive |
| 13 | 62 | IIB | ++ | +++ | 40% | N/A | surgery + radiation + chemotherapy × 1 | 16 | alive |

CgA: chromogranin A; N/A: not available; FIGO: International Federation of Gynecology and Obstetrics; NSE: neuron-specific enolase; Syn: synaptophysin.

*Treatment*

The chemotherapeutic regimen was comprised mainly of taxol or irinotecan plus platinum (cisplatin or carboplatin) with one to eight cycles. Radical hysterectomy was performed with pelvic lymph node dissection, resection of bilateral fallopian tubes, and bilateral ovarian transposition or resection. Pelvic external radiation with brachytherapy was also carried out where appropriate.

*Immunohistochemistry*

For formalin-fixed and paraffin-embedded tissue specimens, consecutive four-µm thick sections were cut and used for immunohistochemistry. The sections were immunohistochemically stained by the labeled streptavidin-biotin peroxidase method according to the manufacturer's recommendation. The following primary antibodies were used: anti-synaptophysin and chromogranin A and anti-NSE and Ki-67 monoclonal antibodies. The sections were immersed for ten min in 0.3% hydrogen peroxide/methanol to deplete endogenous peroxidase. Then, nonspecific binding sites were blocked with 0.3% normal goat serum for ten min. The primary antibodies were then incubated with the sections overnight at 4°C. After washing with phosphate buffered saline (PBS) (0.01 M, pH 7.4), biotinylated goat anti-mouse IgG was incubated with the tissue sections for ten min at room temperature. After washing with PBS, the sections were sequentially incubated with a streptavidin peroxidase reagent for ten min at room temperature. Finally, the reaction product was visualized by incubating the slides in a solution of 0.3% hydrogen peroxide and 3-amino-9-ethylcarbazole (AEC) chromogen. The sections were counterstained with hematoxylin and eosin (H&E). Negative controls included parallel sections treated without the primary antibodies and adjacent sections from the same block but without the primary antibody, which was replaced by PBS. The density of positive staining was scored using a scale from – to +++ (– for no immunostaining, + for light brown color, ++ for medium brown color, and +++ for dark brown color). In all areas, only malignant cells were scored. The immunoreactions were read by two pathologists (W.G.S. and Y.W.) who were blind to patient data (Figure 1).

*Follow-up*

The patients were followed up by telephone calls, letters, and clinic visits every six months. All patients were advised regarding adjuvant chemotherapy and radiotherapy. The primary endpoint of this retrospective analysis was any cancer-related deaths. All endpoints were calculated from the date of radical hysterectomy to death, or censored at the last follow-up. Survival was defined as the period from the time of diagnosis to the time of death or the final follow-up.

*Statistical analysis*

Survival was evaluated using the Kaplan-Meier method and log-rank tests. The significance level for all analyses was set at less than 0.05. All analyses were carried out using the SPSS 13.0 software. All endpoints were updated in October 2011.

## Results

*Patient demographic and disease characteristics*

Characteristics of the patient population are summarized in Table 1. There were 13 female patients and their median age was 37 years (range 21-62). Four patients were diagnosed with Stage IB, three with Stage IIA, one with Stage IIB, one with Stage IIIA, three with Stage IIIB, and one with Stage IV SCNEC of the uterine cervix. Nine patients received radical hysterectomy with pelvic lymph node dissection, resection of bilateral fallopian tubes, and bilateral ovarian transposition or resection. Twelve cases received chemotherapy including two patients who received interventional chemotherapy. Ten cases underwent pelvic external radiation with brachytherapy. One case of Stage IB SCNEC of the uterine cervix refused adjuvant chemotherapy and radiotherapy.

*Immunohistochemical characteristics of study patients*

Immunohistochemical examination of tissue specimens showed that 100% (13/13) of the patients were positive for synaptophysin and that 69.23% (9/13) were positive for chromogranin A. Seven (100%, 7/7) patients were positive for NSE; immunochemical staining with NSE was not performed in the remaining six cases. Among seven patients whose Ki-67 results were available, five (71.4%) patients had Ki-67 index > 60%. Synaptophysin and chromogranin A were both positive in 69.23% (9/13) of patients. Among four cases with negative chromogranin A, three had Ki-67 index > 60%, and one was positive for NSE (Table 1).

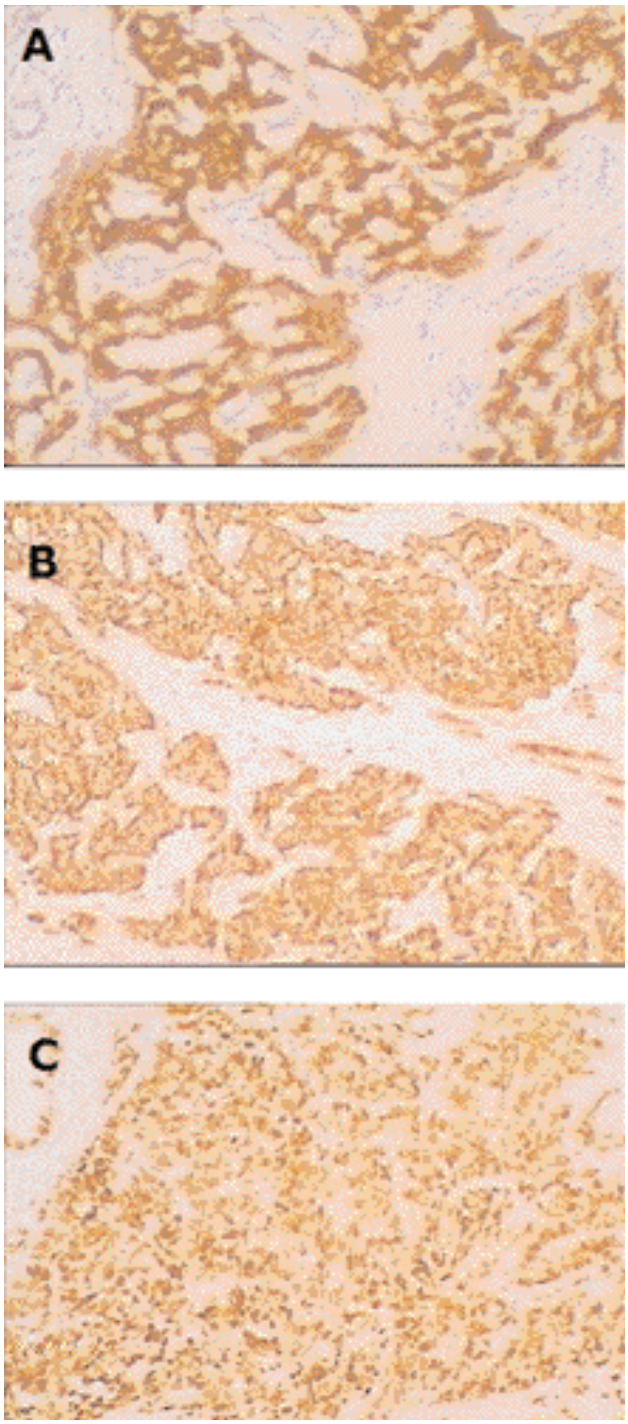


Figure 1. — Immunohistochemistry characteristics of SCNCE of the uterine cervix.
A) synaptophysin (Syn) positive (×100).
B) chromogranin A (CgA ) positive (×100).
C) Ki-67 positive (80%) (×100).

*Patient survival*

The patients were followed up for a mean duration of 15 months (range four to 53). The median survival was 17.5 months (Figure 2). Among the 13 patients, eight

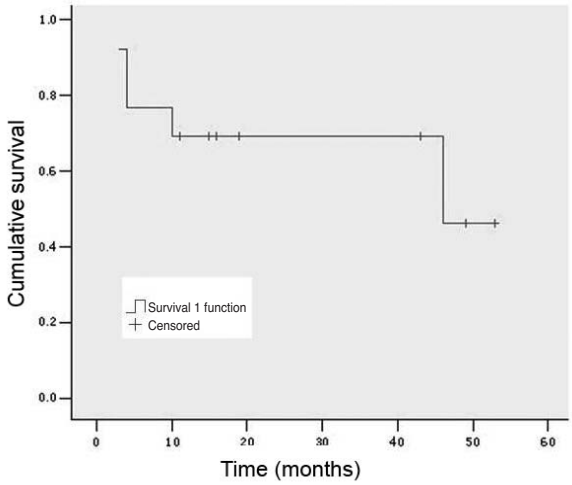


Figure 2. — The survival curve of 13 cases of small cell neuroendocrine carcinoma (SCNEC) of the uterine cervix.

(61.54%) had early stage (Stage I-II) diseases with a median survival of 17.5 months, while five (38.46%) had late stage (Stage III-IV) SCNEC of the uterine cervix with a median survival of four months. There was a significant difference in survival time between patients with early SCNEC and those with late SCNEC ($p = 0.017$). Five patients died within six months after diagnosis of distant metastasis.

## Discussion

Middle-aged and young females were the main population of this study, accounting for 0.395% of cervical carcinoma patients admitted in these hospitals. Common initial symptoms included irregular vaginal bleeding and discharge, which are similar to those seen in cervical cancer patients, while symptoms suggestive of carcinoid syndrome-like spasmodic abdominal pain, diarrhea, and flushing were not found in these patients.

Due to the non-specificity of the symptoms of SCNEC of the uterine cervix, the diagnosis mainly depends on the morphological features of the carcinoma cells under light microscopy and immunohistochemical findings. SCNEC of the uterine cervix is poorly-differentiated and highly-malignant and consists mainly of small or medium-sized cells with significant nuclear atypia, multifocal necrosis, and high mitotic figures. Similar to NEC, it sometimes has an organ structure and expresses neuroendocrine differentiation markers such as synaptophysin and chromogranin A.

SCNEC of the uterine cervix can be classified into 3 grades depending on the proliferation activity and histology. If neurocrine cells account for fewer than 50% of the whole tumor tissue, and are dispersed but appear as a part of the tumor tissue, they are called carcinoma with neuroendocrine differentiation. Patients in this study were confirmed to have SCNEC of the uterine cervix by

histopathology and immunohistochemical staining. All 13 cases were not staged due to the limitation of the pathological diagnosis standard at the time they were treated, however as can be seen in Table 1, the Ki-67 index was higher than 20% in all seven cases who were examined. They can be staged as G3 (G1, G2, and G3 represents low, middle, and high grades, respectively) according to the current standard. It has been acknowledged that immunohistochemical markers such as synaptophysin and chromogranin A and Ki-67 are the most reliable and feasible markers for diagnosing NEC [10, 11] while markers like NSE and others are no longer recommended [12].

The authors consider tumor stage the most important prognostic factor. A unified diagnostic criterion will be beneficial for early diagnosis of this disease. The distant metastasis rate in patients with early-stage disease is low, which is similar to the clinical characteristic of small cell lung cancer. In addition, how to effectively control distant metastasis is also very important. Five of the patients died within six months after diagnosis of distant metastasis. Chemotherapy is an important way to control and eradicate residual and micro-metastatic lesions. Korum *et al*. [13] suggested that survival in patients with early-stage small cell carcinoma of the cervix was better with surgery combined with chemo-radiotherapy. Huang *et al*. [14] showed that radical hysterectomy followed by adjuvant chemotherapy resulted in a higher two-year survival rate compared to radical hysterectomy followed by adjuvant radiotherapy (62.5% vs 16.7%). These findings indicated that the addition of adjuvant chemotherapy tends to be more effective than single treatment in increasing the survival rate [15-17]. Cohen *et al*. [18] showed that the five-year disease-specific survival rate in Stages I-IIA, IIB-IVA, and IVB of the disease was 36.8%, 9.8%, and 0.0%, respectively. They further showed that for Stage II-III patients, adequate chemotherapy is positively correlated with control of metastasis.

No local recurrence occurred in this study after surgery or radiotherapy regardless of the stage of the disease. The authors deduced that these two regional regimens are both effective. In addition, chemotherapy can prevent distant metastasis. These three therapeutic modalities constitute traditional comprehensive therapy; however this model has encountered a bottleneck. The neuroendocrine character of the tumor should be regarded as a target to improve the efficacy of treatment and prognosis. The use of drugs that inhibit the neuroendocrine function of the tumor (such as somatostatin analogues), was supported by the PROMID study [19], which demonstrated that octreotide significantly lengthened the time to tumor progression compared with the placebo in patients with functionally active and inactive metastatic midgut neuroendocrine tumors.

In conclusion, early diagnosis and prompt treatment of SCNEC of the uterine cervix and traditional comprehensive therapy in combination with targeted therapy would bring a new prospect to the treatment of endocrine carcinoma (including carcinoma with neuroendocrine differentiation).

## References


[1] Yao J.C., Hassan M., Phan A., Dagohoy C., Leary C., Mares J.E. *et al.*: "One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States". *J. Clin. Oncol.,* 2008, *26,* 3063.

[2] Chen J., Macdonald O.K., Gaffney D.K.: "Incidence, mortality, and prognostic factors of small cell carcinoma of the cervix". *Obstet. Gynecol.,* 2008, *111,* 1394.

[3] Viswanathan A.N., Deavers M.T., Jhingran A., Ramirez P.T., Levenback C., Eifel P.J.: "Small cell neuroendocrine carcinoma of the cervix: outcome and patterns of recurrence". *Gynecol. Oncol.,* 2004, *93*, 27.

[4] Crowder S., Tuller E.: "Small cell carcinoma of the female genital tract". *Semin. Oncol.,* 2007, *34,* 57.

[5] Appetecchia M., Benevolo M., Mariani L.: "Neuroendocrine small-cell cervical carcinoma". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2001*, 96,* 128.

[6] Stoler M.H., Mills S.E., Gersell D.J., Walker A.N.: "Small cell neuroendocrine carcinoma of the cervix. A human papillomavirus type 18-associated cancer". *Am. J. Surg. Pathol.,* 1991, *15,* 28.

[7] Miller B., Dockter M., El-Torky M., Photopulos G.: "Small cell carcinoma of the cervix: a clinical and flow-cytometric study". *Gynecol. Oncol.,* 1991, *42,* 27.

[8] Albores-Saavedra J., Gersell D., Gilks C.B., Henson D.E., Lindberg G., Santiaqo H. *et al.*: "Terminology of endocrine tumors of the uterine cervix: results of a workshop sponsored by the college of American pathologists and the National Cancer Institute". *Arch. Pathol. Lab. Med.,* 1997, *121*, 34.

[9] McCluggage W.G.: "Immunohistochemistry as a diagnostic aid in cervical pathology". *Pathology,* 2007, *39,* 97.

[10] Slodkowska J., Zych J., Szturmowicz M., Demkow U., Rowinska-Zakrzewska E., Roszkowski-Sliz K. *et al.*: "Neuroendocrine phenotype of non-small cell lung carcinoma: immunohistological evaluation and biochemical study". *Int. J. Biol. Markers*, 2005, *20,* 217.

[11] Rindi G., D'Adda T., Froio E., Fellegara G., Bordi C.: "Prognostic factors in gastrointestinal endocrine tumor". *Endocr. Pathol*., 2007, *18,* 145.

[12] Zhu X.Z., Zheng J.: "Chinese pathologic consensus for standard diagnosis of gastrointestinal and pancreatic neuroendocrine neoplasm". *Chin. J. Pathol. (in Chinese)*, 2011, *40,* 257.

[13] Korcum A.F., Aksu G., Bozcuk H., Pestereli E., Simsek T.: "Small cell carcinoma of the cervix: a case report". *Arch. Gynecol. Obstet.,* 2008, *277*, 367.

[14] Huang C.Y., Chen Y.L., Chu T.C., Cheng W.F., Hsieh C.Y., Lin M.C.: "Prognostic factors in women with early stage small cell carcinoma of the uterine cervix". *Oncol. Res.,* 2009, *18,* 279.

[15] Gersell D.J., Mazoujian G., Mutch D.G., Rudloff M.A.: "Small-cell undifferentiated carcinoma of the cervix: a clinicopathologic, ultrastructural, and immucytochemical study of 15 cases". *Am. J. Surg. Pathol.*, 1988, *12,* 120.

[16] Sheet E.E., Berman M.L., Hrountas C.K., Liao S.Y., DiSaia P.J.: "Surgically treated, early stage neuroendocrine small cell cervical carcinoma". *Obstet. Gynecol.,* 1988, *71,* 10.

[17] Ueda G., Yamasaki M.: "Neuroendocrine carcinoma of the uterus". *Curr. Top. Pathol.,* 1992, *85*, 309.

[18] Cohen J.G., Kapp D.S., Shin J.Y., Urban R., Sherman A.E., Chen L.M. *et al.*: "Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients". *Am. J. Obstet. Gynecol.,* 2010, *203,* 347.

[19] Rinke A., Muller H.H., Schade-Brittinger C., Klose K., Barth P. *et al.*: "Placebo-controlled, double-blind, prospective, randomized study of the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group". *J. Clin. Oncol.*, 2009, *27*, 4656.



Address reprint requests to:
R.M. XIE, M.D.
Department of Gynecology Oncology
Sichuan Cancer Hospital
55, 4th Section, Renmin Road South
Chengdu 610041, Sichuan (China)
e-mail: kawachan@163.com