Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

# Cycles of cisplatin and etoposide affect treatment outcomes in patients with FIGO stage I-II small cell neuroendocrine carcinoma of the cervix

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## HIGHLIGHTS

- Half of stage I-II SCNEC patients experienced disease failure within 3 years after treatment.
- Distant metastasis occurred in >80% of the recurrent patients.
- EP combination therapy for at least 5 cycles improved disease-free survival after radical surgery.
- Postoperative radiation might be unnecessary in patients with mediate- or high-risk factors.

## ARTICLE INFO

*Article history:*
Received 18 July 2017
Received in revised form 17 September 2017
Accepted 19 September 2017
Available online xxxx

*Keywords:*
Small cell neuroendocrine carcinoma of the cervix
Radical surgery
Adjuvant therapy
EP chemotherapy
Disease recurrence

## ABSTRACT

*Objective.* This study sought to explore the outcomes and prognostic factors of patients with small cell neuroendocrine carcinoma of the cervix (SCNEC) and to determine the effects of adjuvant treatment on survival in patients with FIGO stage I-II SCNEC after radical surgery.

*Methods.* A single-institution retrospective analysis was performed in 92 patients who underwent radical surgery for SCNEC. All clinicopathological variables and treatment strategies were reviewed. Kaplan-Meier and Cox regression methods were used for survival analyses.

*Results.* During a median follow-up period of 38 months (23.6–52.4), 43 (46.7%) patients experienced disease recurrence, and distant metastases were documented in 35 (81.4%) patients. The 3-year recurrence-free survival (RFS) for the entire group was 50.1%. The median RFS was 39 months. The multivariate analysis confirmed that lymph node metastasis, positive parametrial extension and cycles of etoposide plus platinum (EP) were independent prognostic factors for disease recurrence. Adjuvant chemotherapy for at least 5 cycles of EP (EP 5+, $n = 39$) was associated with improved 5-year RFS compared with other treatments ($n = 46$) (67.6% vs. 20.9%, $p < 0.001$). Additional radiotherapy or concurrent chemoradiation failed to validate further improved RFS in patients with EP 5+, and this finding was consistent in the subset of patients with high-risk factors (positive lymph nodes or positive parametrium).

*Conclusions.* Half of stage I-II SCNEC patients experienced disease failure within 3 years, and distant metastasis was an outstanding issue. EP regimen for at least 5 cycles improved long-term RFS after radical surgery. Additional radiation might be unnecessary, even in patients with high-risk factors.



## 1. Introduction

Small cell neuroendocrine carcinoma of the cervix (SCNEC) is a rare gynecological malignancy that accounts for 0.9 to 1.5% of carcinomas arising from the cervix [1].However, this entity constitutes the most common cervical neuroendocrine carcinoma (NEC),which was first described by Reagan et al. in 1957 [2]. Histologically, SCNEC shares many similarities with small cell lung cancer. Clinically, SCNEC is characterized by a more aggressive behavior and a worse prognosis than its squamous cell carcinoma (SCC) and adenocarcinoma (AC) counterparts [3–5]. Lymph node involvement is frequently observed and present in 41.6–57% of patients with early-stage disease [6,7]. Moreover, these tumors are prone to hematogenous dissemination at an early stage, resulting in treatment failure and cancer-related death [6].

Given the rarity of SCNEC, data from large, prospective studies are unavailable. Therefore, the current treatment strategy is heavily based

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http://dx.doi.org/10.1016/j.ygyno.2017.09.022
0090-8258/

on experience with small cell lung cancer and data from retrospective studies. Concerning the aggressive nature of this disease, multimodality regimens are recommended for SCNEC patients even at an early stage. The Society of Gynecologic Oncology in 2011 and the Gynecological Cancer InterGroup in 2014 published guidelines based on retrospective reports and expert opinions [8,9].Chemoradiation or systemic chemotherapy is recommended for advanced-stage disease. Early-stage (I–IIa) patients are recommended to receive radical surgery as an initial treatment (tumor size ≤4 cm) or after neoadjuvant chemotherapy (tumor size > 4 cm); adjuvant treatment, including chemotherapy and radiotherapy, is subsequently provided. However, crucial management issues for these patients remain controversial. Thus, SCNEC remains a therapeutic challenge for gynecological oncologists. Herein, we reviewed surgically treated stage I-II patients admitted to our hospital with the aim of determining prognostic factors and an appropriate treatment algorithm based on our experience.

## 2. Patients and methods

### 2.1. Patients and data collection

This was a single-institution retrospective study. All patients diagnosed with SCNEC who underwent radical surgery at the Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center between 2006 and 2016 were recruited. Chart reviews were conducted, and all clinicopathological data were recorded, including age, FIGO stage, histological type, tumor size, depth of myometrial invasion, lymphovascular invasion (LVSI), regional lymph node metastasis, and parametrial involvement. Follow-up data were collected through outpatient clinical records and by telephone. Patients who were lost to follow-up were excluded. Finally, 92 eligible patients were included. This study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center (FUSCC IRB 1708175-14) and was performed in accordance with the approved guidelines.

### 2.2. Pathological assessment

Pathological slides were independently confirmed by two experienced pathologists. Staining for synaptophysin (DAK-SYNAP, 1:100; DAKO), chromogranin (LK2H10 + PHES, 1:100, Maixin Biotech), cytokeratin (AE1/AE3, dilution 1:50; DAKO) and P16 (E6H4, Predilute, Roche) was used to facilitate diagnosis but was not a requirement. The detection of Ewing sarcoma breakpoint region 1 translocation using the locus-specific probe (Vysis EWSR1 Break Apart FISH Probe Kit) was carried out in the differential diagnosis of Ewing sarcoma in some cases. Series involving mixed components with small cell carcinoma were included and termed "Mixed." Imaging examination was used to rule out metastatic small cell carcinoma.

### 2.3. Treatment

All patients underwent radical hysterectomy and pelvic lymphadenectomy. Para-aortic lymphadenectomy was conducted in 17 patients. Eight patients underwent systemic chemotherapy (7) or pelvic radiation (1) prior to surgery. Detailed records of postoperative adjuvant therapy were available for 85 patients. Adjuvant therapies varied and consisted of radiation alone (RT, $n = 1$), concurrent chemoradiation (CCRT, $n = 3$), chemotherapy alone (CT, $n = 27$), radiation plus chemotherapy (RT + CT, $n = 14$), and concurrent chemoradiation plus chemotherapy (CCRT + CT, $n = 37$). It is worth noting that we confined "CCRT" to radiation plus chemotherapy, which served as radio sensitization (DDP30–40 mg/m$^2$ weekly). "CT" refers to those treated with systemic chemotherapy, usually every 3 weeks, whether given with, after, or preceding RT. Several chemotherapeutic agents, such as etoposide (E), cisplatin and its analogs (P), paclitaxel and its analogs (T), cyclophosphamide (C), epirubicin (Epi), doxorubicin (T), and ifosfamide (I), were used in various combinations. In the EP regimen, 100 mg of etoposide and 30 mg of cisplatin were administered intravenously on days 1–3 for 1–8 cycles. The radiotherapy regimen consisted of 45–50 Gy in 25 daily fractions to the pelvis with or without extended para-aortic fields. A schematic of the treatment algorithm is shown in Fig. 1.

### 2.4. Follow-up and statistical analysis

Patients were followed-up with every 3 months during the first 2 years after surgery, every 6 months during the following 3 years, and then annually. The work-up examination included a pelvic examination and palpation of the supraclavicular and inguinal lymph nodes. Sonography and serum neuron-specific enolase measurements were mandatory at every visit. Computed tomography scans of the lungs and abdomen were performed every six months or as indicated. Follow-up and relapse data were mainly obtained from an outpatient clinic and telephone correspondence with patients. Recurrence-free survival (RFS) was defined as the period from the completion of surgery to the date of documented evidence of disease recurrence. Disease recurrence events were defined as one of the following: the first recurrence at a local, regional, or distant site and death from the diseases [10]. The end of the observation period was March 31, 2017, and patients without disease recurrence were censored at their last follow-up visit.

Survival curves were depicted using the Kaplan-Meier method and compared among subgroups using the log-rank test. Multivariate analyses were conducted using Cox proportional hazards modeling. All tests were two-sided, and a $p$ value <0.05 was considered statistically significant unless pair-wise comparisons between the three groups were used ($p < 0.05/2$). All analyses were performed with SPSS 21.0(SPSS Inc.) software.

## 3. Results

### 3.1. Patient characteristics

A total of 112 patients diagnosed with cervical neuroendocrine carcinoma underwent surgery in our center between March 2006 and January 2016. After slide review, patients with atypical carcinoid ($n = 1$) and large cell neuroendocrine ($n = 2$) tumors were excluded from this study. One patient, who was misdiagnosed with endometrial carcinoma before surgery, was confirmed to have SCNEC after surgery and was then excluded for sigmoid colon metastasis (stage IV). Another 16 patients without detailed follow-up information were also excluded from this study. The remaining 92 (82.1%) patients were eligible for investigation (Fig. 1).

Of the 92 patients, the median age of diagnosis was 41 years (range, 24–72). According to the FIGO staging system (2009), 40 patients were classified as stage IB1, 10 as stage IB2, 40 as stage IIA, and 2 as stage IIB. Twenty-nine patients (31.5%) had bulky tumors (>4 cm). Mixed tumors were present in 26 (28.3%) patients, including 2 patients with large cell carcinoma and 24 patients with SCC, AC or adenosquamous carcinoma. All patients underwent pelvic lymphadenectomy, and 46 patients (50.0%) presented with positive pelvic lymph node metastasis. Para-aortic lymphadenectomy was conducted in 17 patients, among which 3 (17.6%) patients showed positive nodes, and these 3 patients also had pelvic lymph node metastasis. Other clinicopathological characteristics of the patients are listed in Table 1.

### 3.2. Treatment outcome

After a median follow-up period of 38 (range, 23.6–52.4) months, tumor recurrence was observed in 43 patients. The median RFS was 39 months in all patients. The 3-year RFS and 5-year RFS were 50.1% and 45.2%, respectively. Detailed recurrence information was available in 40 patients. Among them, 5 patients had local recurrence, distant metastases were observed in 31 patients, and 4 patients experienced both. The initial hematogenous recurrence sites included the liver ($n = 13$),

Please cite this article as: X. Pei, et al., Cycles of cisplatin and etoposide affect treatment outcomes in patients with FIGO stage I-II small cell neuroendocrine carcinoma o..., Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.09.022