The effect of chemotherapy cycles on treatment outcomes in small cell neuroendocrine carcinoma of uterine cervix

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Abstract

Objectives: To investigate the effect of chemotherapy cycles on survival outcomes in small cell neuroendocrine carcinoma of cervix (SCNEC). Methods: Clinical records of 103 biopsy-proven SCNEC were identified from Sun Yat-sen University Cancer Center. The cycles-dependent effect of chemotherapy on survival was estimated by restricted cubic splines (RCS) based cox regression model. Results: Through RCS analysis, we observed an inverse correlation between chemotherapy cycles and progression/death; the risks (hazard ratio [HR]) of progression/death decreased sharply until 5 cycles of chemotherapy. Long-course chemotherapy ([?]5 cycles) was associated with significantly superior PFS ([?]5 vs 1-4: median PFS, 58.6 months vs 25.4 months, P =0.027) and prolonged OS ([?]5 vs 1-4: median OS, 65.1 months vs 37.7 months, P =0.168) than short-course chemotherapy (1-4 cycles). Subgroup analyses suggested that chemotherapy courses had significant interaction with FIGO stage; the survival benefit of long-course chemotherapy was identified in FIGO IIB-IIIC (HRPFS 0.41, 95% CI 0.18-0.92; HROS 0.41, 95% CI 0.17-0.95), rather than FIGO I-IIA (HRPFS 0.67, 95% CI 0.34-1.34; HROS 0.88, 95% CI 0.40-1.97). Additionally, chemotherapy regimen was observed to be relevant to survival outcomes; EP regimen demonstrated obvious prolonged PFS (median PFS: EP vs non-EP, 44.7 months vs 18.0 months) and OS (median OS: EP vs non-EP, 63.3 months vs 41.0 months) than those treated with non-EP regimen. Conclusion: Chemotherapy with [?]5 cycles significantly improved PFS and OS in FIGO stage IIB-IIIC SCNEC, whereas a short course of <5 cycles was adequate for FIGO I-IIA disease.

Introduction

Small cell neuroendocrine carcinoma of the uterine cervix (SCNEC) is a rarely seen tumor that accounting for <3% of all cervical cancers [1-3], with an age-standardized incidence rate (ASR) of 0.1 per 100,000 women[4]. The nature of SCNEC significantly differs from the squamous cell or adenocarcinoma of the cervix, and is characterized by a high incidence of early nodal and distant metastases [5-7], resulting in poor prognosis with 5-year survival rates lower than 30%[2-4, 6-7]. Hence, systemic treatment was essential for the treatment of SCNEC even of early stage, to reduce the risk of distant metastasis. Additionally, resemble to the small cell lung cancer (SCLC), prognosis of SCNEC is significantly associated with the extent of disease. As reported by Zivanovic et al, patients with limited-stage disease (IA-IIA) had significantly longer survival than those with advanced-stage disease (IIB-IV) (median overall survival, 31.2 *vs*6.4 months) [8]. Advanced stage, large tumor size, presence of lymph node metastases was shown to be adverse prognostic factors for patients with SCNEC [9-13]. Thus, systemic treatment intensification was required for the patients with advanced stage or bulky SCNEC.

Nonetheless, the role of chemotherapy in SCNEC was under determined because of the limited evidence in SCNEC owing to the rarity of this disease. Hence, the current treatment option for SCNEC is heavily based on experience from SCLC and data from retrospective studies of small sample sizes. Empirically, concerning the aggressive nature of this disease, multimodality regimens are recommended for SCNEC patients even at an early stage. Clinicians favor to choose radical hysterectomy in combination with systemic

chemotherapy (with or without radiation therapy) for early-stage disease, definitive chemo-radiation therapy for locoregionally advanced disease, and palliative chemotherapy for metastatic disease[1,7,14-15]. However, crucial management issues in terms of chemotherapy regimen and courses for SCNEC remain controversial. Consequently, SCNEC remains a great therapeutic challenge for gynecological oncologists. Here, we then conduct this study by including a relative large-scale well-characterized cohort encompassing early to locally advanced stages of disease from an academic center, aiming to investigate the appropriate chemotherapy algorithm for SCNEC.

Materials and Methods

Patient selection

We identified a total of 119 histopathologically-proven SCNEC cases from Sun Yat-sen University Cancer Center (SYSUCC), diagnosed between January 2010 and December 2018. Eligibility criteria included (1) biopsy-proven SCNEC; (2) age >18 years; and (3) chemotherapy plus radical hysterectomy/chemoradiotherapy. Exclusion criteria included disseminated disease, history of previous or synchronous malignant tumors, pregnancy or lactation, and insufficient data. A total of 103 patients met the inclusion criteria and were considered eligible for the study (**Figure 1**). The institutional ethical review board of SYSUCC approved this retrospective analysis of anonymous data. Requirement for informed consent was waived by the ethical review boards (No.: B2020-231-01).

Pathological evaluation, staging, treatment and follow-up

Detailed information on the diagnosis, treatment, and surveillance for SCNEC were illustrated in **Supplementary Materials (online only**). All patients in each cohort were restaged by two radiation oncologists (FPC and XDH) specialized in gynecological cancer according to the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system [16], with disagreements resolved by consensus.

Statistical analysis

The primary endpoint was progress-free survival (PFS), which was calculated from the initial diagnostic biopsy to date of first relapse regardless of site or a 25% or more increase in size of any pre-existing lesion and/or death from any cause. Secondary endpoint was overall survival (OS), calculated from initial diagnostic biopsy to date of death from any cause, or date of last follow-up visit. Survival analyses were performed using the Kaplan-meier method and compared by the log-rank test. Categorical variables were classified based on clinical findings, and continuous variables were transformed into categorical variables based on median values of our cohort. Because of the complexity of chemotherapy regimens, we classified the multimodal regimens as etoposide plus platinum (EP) and non-EP. Differences of continuous variables were compared using Mann-Whitney U test, and categorical variables were compared using the chi-square or Fisher exact test. The cox proportional hazards regression was performed to calculate hazard ratios (HR) and 95% confidence interval (CI). Multivariable analyses using cox proportional hazards models were performed to evaluate the potential prognostic factors adjusted for age, histology and FIGO stage. The restricted cubic splines (RCS) that estimated from the full cox regression model was used to evaluate the relationships (in HR) between chemotherapy cycles with PFS and OS. All statistical tests were two-sided, and a P -value of <0.05 was considered significant. Statistical analyses were performed in R version 3.4.4 (*http://www.r-project.org/*), and SPSS 23.0 software (SPSS Inc, IL). All end points were updated in January 2021.

Results

Patient characteristics and treatment outcomes

The characteristics of the patients are listed in **Table 1** . Of the 103 patients, FIGO stage I-IIA was diagnosed in 62 (60.2%) patients, and stage IIB-IIIC in 41 (39.8%) patients. All of the enrolled patients have received chemotherapy; EP regimen was carried out in 66 (64.1%) patients, non-EP alone regimens in 37 (35.9%) patient (**Table 1**).

The breakdown of the sites of relapses of these cohorts is detailed in**Table S1 (online only)** . Median PFS and OS of the entire cohort were 30.8 (95% confidence interval [CI], 24.4-37.2) months and 53.5 (95% CI, 25.2-81.8) months, respectively.

Cycle-dependent effect of chemotherapy cycles on survivals

To quantify the cycle-dependent effect on survival outcomes, we entered chemotherapy cycles into the RCS fitted cox regression to allow for nonlinear relationships between chemotherapy course and survivals. The models identified that the risks (HR) of disease progression and death decreased as the cycles increased; 5 cycles of chemotherapy was identified as threshold that consistent for risk discretization to PFS and OS (**Figure 2A and 2B**). Hence, we classified chemotherapy as short-course (1-4 cycles) and long-course ([?]5 cycles) based on the threshold (**Table S2**). Through Kaplan-Meier plots, we observed that patients who received [?]5 cycles of chemotherapy demonstrated significantly superior PFS ([?]5 *vs* 1-4: median PFS, 58.6 months*vs* 25.4 months, P =0.027; **Figure 2C**) and prolonged OS ([?]5 *vs* 1-4: median OS, 65.1 months *vs* 37.7 months, P =0.168; **Figure 2D**) than those treated with 1-4 cycles. After adjustment for potential prognostic covariates (age, histology and FIGO stage) in multivariable analysis, chemotherapy cycles were independently significant for PFS (HR 0.52, 95% CI 0.30-0.88;P =0.015; **Table S3**), and OS (0.57, 0.31-1.00; P=0.050; **Table S3**). These findings indicate that treatment with [?]5 cycles of chemotherapy contribute to survival improvement in patients with SCNEC. Given that heterogeneity in terms of tumor extension and prognosis was obvious among the patients, we then performed subgroup analyses to determine the therapeutic effect of chemotherapy cycles within different FIGO stages.

Therapeutic efficacy of chemotherapy cycles within different FIGO stage

Exploratory subgroup analyses of PFS and OS were generally consistent with the overall findings that [?]5 cycles of chemotherapy was superior to 1-4 cycles (**Figure 3**). An additional analysis by FIGO stage also suggested that significant improvements in PFS and OS were identified in long-course chemotherapy in FIGO stage IIB-IIIC (n=17 for [?]5 cycles, n=24 for 1-4 cycles; HR_{PFS} 0.41, 95% CI 0.18-0.92; HR_{OS}0.41, 95% CI 0.17-0.95), but not entirely significant improvements in FIGO stage I-IIA (n=32 for [?]5 cycles, n=30 for 1-4 cycles; HR_{PFS} 0.67, 95% CI 0.34-1.34; HR_{OS}0.88, 95% CI 0.40-1.97); these results were also confirmed in survival curves (**Figure 4**). Additionally, in multivariate analyses, [?]5 cycles of chemotherapy significantly reduced the risk of disease progress and death, and was independently prognostic for PFS and OS in FIGO stage IIB-IIIC after adjusting for age and histology; nevertheless, such significances were not achieved in FIGO stage I-IIA (**Table S4**). These findings indicated that the survival benefit of long-course chemotherapy in SCNEC can be predicted by FIGO stages; [?]5 cycles of chemotherapy was inclined to achieve favourable survival outcomes in FIGO stage IIB-IIIC, but comparable survivals in FIGO stage I-IIA.

Interaction effect of chemotherapy cycles and regimen

Because of the multiple chemotherapy regimens used in the cohort, we then evaluated the optimal regimen for SCNEC. We observed that patients who received EP regimen had obvious prolonged PFS (median PFS: EP*vs* non-EP, 44.7 months *vs* 18.0 months; **Figure S1A**) and OS (median OS: EP *vs* non-EP, 63.3 months *vs* 41.0 months; **Figure S1B**) than those treated with non-EP regimen, although the statistic significances were not achieved partly owing to the limited sample size. Next, we investigated the interaction between chemotherapy regimens and courses by incorporating them together, and divided the patients into the following four groups: EP with 1-4 cycles (EP 1-4), EP with [?]5 cycles (EP [?]5), non-EP with 1-4 cycles (non-EP 1-4 cycles), and non-EP with [?]5 cycles (non-EP [?]5). Of the whole cohort, we observed significantly different PFS among these four groups, with EP [?]5 obtaining most satisfied survival (P = 0.011, **Figure S2A**); whereas the statistic significance of OS was not achieved (P = 0.160, **Figure S2B**). Then we performed subgroup analyses stratified by FIGO stage; interestingly, we identified that these four groups obtained significances of both PFS (P = 0.026, **Figure S2E**) and OS (P = 0.042, **Figure S2F**) in FIGO stage IIB-IIIC, but neither significant of PFS (P = 0.370, **Figure S2C**) nor OS (P = 0.860, **Figure S2D**) in FIGO stage I-IIA. Hence, we can conclude that EP regimen with [?]5 cycles should be proposed for patients with FIGO IIB-IIIC SCNEC, nonetheless the optimal regimen and course for FIGO stage I-IIA

SCNEC need further investigation.

Discussion

In this retrospective cohort of SCNEC, we observed an inverse correlation between chemotherapy cycles and progression/death; the risks of disease progression and mortality decreased sharply until 5 cycles of chemotherapy. Long-course chemotherapy was associated with significantly superior PFS and OS than short-course chemotherapy. Additionally, FIGO stage was predictive to the therapeutic efficacy of long-course chemotherapy; [?]5 cycles of chemotherapy was superior to <5 cycles of chemotherapy in terms of PFS and OS in FIGO stage IIB-IIIC, whereas such superiority was not observed in FIGO I-IIA. Furthermore, chemotherapy regimen was identified to be relevant to survival outcomes; EP regimen demonstrated obvious prolonged PFS and OS than those treated with non-EP regimen.

SCNEC is one of the most lethal gynecological malignancies that characterized with high mitotic rate, extensive necrosis, frequent lymph-vascular space involvement (LVSI) and strong association with HPV 18 [17-19]. It is highly aggressive with extremely high risk of local and distant failure, even for patients at early stage[14, 19]. In our series, treatment failure was identified in approximately 60% of patients, and the majority presented with hematogenous dissemination to distant organs, including liver, lung, bone marrow and multiple sites; median PFS and OS for the entire cohort were 30.8 (95% CI 24.4-37.2) months and 53.5 (95% CI, 25.2-81.8) months, respectively, which was consistent with previous reports [8, 12, 14]. Therefore, a major challenge in improving the prognosis of SCNEC is to adopt a comprehensive treatment approach to reduce the risk of disease failure. Nonetheless, the optimal treatment strategies, especially the most appropriate chemotherapy regimen and course for patients with SCNEC is under determined as yet [20]. We hence carried out this study to identify the association between chemotherapy intensity and survival outcomes, and aimed to establish a risk-based systemic treatment recommendation for patients with SCNEC.

Foremost, this study represents a critical step toward understanding the cycle-dependent effect of chemotherapy on survival outcomes in SCNEC. The necessity of chemotherapy for improving survival is well recognized for SCNEC on account of the very high risk of hematogenous dissemination[21]. Nonetheless, the optimal chemotherapy regimen and course is under determined owing to the rarity of this disease. In SCLC, a regimen of 4-6 cycles of EP is most commonly recommended because of its superiority in both efficacy and toxicity. Similarly, this regimen was also empirically proposed for SCNEC regardless of tumor extent because of its clinical biological similarity with SCLC. Whereas, there were only a small amount of data focus on this topic and the evidence proving the validity and safety of this regimen was limited. This raises questions whether EP regimen chemotherapy still works in SCNEC, and what's the optimal cycle that possess both satisfied effectiveness and acceptable toxicity. Research into these topics is essential to optimize treatment strategies and individualize treatment plans for SCNEC. Generally, the prognosis of SCNEC is associated with tumor burden, namely FIGO stage. Patients with early staged tumor (FIGO I-IIA) usually demonstrated superior prognosis than those with advanced tumor (FIGO IIB and above). Hence it is reasonable to hypothesize that treatment may be streamlined according to FIGO stage, namely systemic de-intensification for early staged SCNEC, whereas intensification for advanced staged SCNEC to reduce the risk of distant metastasis. In the current study, we observed inverse correlation between chemotherapy cycles with the risks (HR) of disease progression and death; [?]5 cycles was associated with significantly reduced risks of PFS and OS. Nonetheless, not all patients benefited from [?]5 cycles of chemotherapy. Long course chemotherapy with [?]5 cycles mainly showed survival benefit in patients with FIGO stage IIB-IIIC, while a short course of 1-4 cycles was adequate for early staged SCNEC. Hence, we can conclude that chemotherapy was essential for patients with SCNEC, and the intensity of chemotherapy could be modified according to the tumor burden. We proposed a maximum of 4 cycles for those with FIGO stage I-IIA, whereas [?]5 cycles for those with FIGO stage IIB-IIIC was essential.

Additionally, our results support the use of EP chemotherapy regimen as preferred regimen for SCNEC. In our cohort, EP regimen tended to achieve prolonged PFS and OS than non-EP regimen, although the significances were not obtained due to the limited sample size. The combination of cisplatin and etoposide was

initially developed in patients with previously treated SCLC[22], and soon became the most commonly used regimen for patients with SCLC due to the strong evidence showing promising results [23-24]. Additionally, EP regimen was whereafter identified as the first-line chemotherapy for small cell neuroendocrine tumors of other sites such as esophagus[25], ileum [26], and bladder [27] due to the akin natural history to SCLC and their propensity for distant spread. Likewise, EP regimen was also recommended for SCNEC [14, 21] considering evidences showing the superiority of EP regimen over other regimens with better outcome and lower toxicity [28-29]. Chang and colleagues used to report significant survival benefit for patients who treated by vincristine, adriamycin, and cyclophosphamide alternating with EP (VAC/PE) regimen compared to those treated with cisplatin, vinblastine, and bleomycin (PVB) combination (5-year survival VAC/PE*vs* PVB, 68% *vs* 33%, P =0.0078)[30]. Similarly, Zivanovic et al also reported that the patients who received postoperative EP regimen chemotherapy had a significant higher 3-year recurrence-free survival than those who did not receive adjuvant chemotherapy (83% *vs* 0%) for in early stage SCNEC [8]. Hence, EP regimen was firstly proposed as preferred regimen for SCNEC in the latest version of National Comprehensive Cancer Network guidelines (version 1 2021)[21].

Notably, we did not focus on the sequence of chemotherapy in terms of efficacy, since this was beyond the scope of the current study. Additionally, selection bias was obvious in this cohort because induction chemotherapy (IC) was mainly performed in patients with higher tumor burden, whereas adjuvant chemotherapy (ACT) was undertaken in almost all patients. Hence, it is infeasible for the efficacy comparison of IC and ACT in our cohort. Generally, IC was considered to have better tolerated and could eradicate micrometastases earlier, compared with adjuvant sequencing. Nonetheless, IC can also put off the time of radical treatment, which may result in tumor progress. Currently, the role of IC in treatment SCNEC is controversial, since the very small sample sizes of relevant studies make it difficult to draw definitive conclusions [15, 31]. Chang et al. observed a high complete response rate in 6 out of 7 patients that treated with neoadjuvant VAC/PE before hysterectomy; however, microscopic residual tumor was identified in all cases, and additional three courses of ACT were given after surgery [31]. Additionally, Lee et al. reported no survival benefit among 6 patients that received IC[15]. In our cohort, IC alone was only performed in 4 patients, but we still observed inferior survival outcomes in these patients compared with IC+ACT and ACT (median PFS, IC *vs* IC+ACT*vs* IC+ACT: 5.8 *vs* 31.7 *vs* 31.4 months; median OS, 12.4 *vs* 53.5 *vs* 44.3 months; **Figure S3**). Hence, we believe that neoadjuvant sequencing was not adequate for patients with SCNEC, and ACT was essential for the treatment of SCNEC. Other caveats of our study included inherent biases considering the retrospective nature of this study and the patient recruitment from a single institution. Nonetheless, because of the rarity of the disease, it is infeasible to conduct a prospective randomized study in SCNEC. Hence, a solution was to include a consecutive, well-characterized cohort that encompassing early to advanced stages of disease to improve the reliability of our conclusion. Additionally, the conclusions of our study need further validation in external cohort.

In conclusion, our results implied that chemotherapy cycles had inverse correlation with risks of disease progression and death; long-course chemotherapy of [?]5 cycles significantly reduced the risks of PFS and OS in patients with FIGO stage IIB-IIIC, while a short course of 1-4 cycles was enough for early staged SCNEC. We proposed a maximum of 4 cycles for those with FIGO stage I-IIA, but [?]5 cycles for those with FIGO stage IIB-IIIC. Although this study was retrospective in design, with a limited number of patients, it is still one of the largest series reported to date. We hope that our experience contributes to the foundation of knowledge regarding this rare but aggressive tumor.

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Disclosure of interests:

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to Authorship:

LQH, XDH, YSL and FPC took part in the conceptualization, methodology, software, writing- reviewing and editing. YOY and KC were responsible for data curation, writing- original draft preparation. JYL carried out visualization and investigation. YSL, FPC and XPC contributed to the supervision.LS provided support to software and validation.

Details of patient's consent:

We have received informed, written consent from any individual identifiable in any information/images/ /interview transcripts for this material to be published for all patients.

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Table 1. General characteristics**.**

Characteristic	All (n=103)	I-IIA (n=62)	IIB-IIIC (n=41)	*P*-value
Age (years)	Age (years)			0.429
Median	48	47	48	
IQR	41-54	40-53	43-55	
Family history of malignancy, *n* (%)	Family history of malignancy, *n* (%)			0.737
None	89 (86.4)	53 (85.5)	36 (87.8)	
Yes	14 (13.6)	9 (14.5)	5 (12.2)	
Histology, *n* (%)	Histology, *n* (%)			0.858
Pure	82 (79.6)	49 (79.0)	33 (80.5)	

Characteristic	All (n=103)	I-IIA (n=62)	IIB-IIIC (n=41)	*P*-value
Mixed	21 (20.4)	13 (21.0)	8 (19.5)	
Tumor size, *n* (%)				<0.001
<4cm	62 (60.2)	46 (74.2)	16 (39.0)	?¿?
4cm	41 (39.8)	16 (25.8)	25 (61.0)	
Lymph node				<0.001
Negative	71 (68.9)	62 (100)	9 (22.0)	
Positive	32 (31.1)	0 (0)	32 (78.0)	
Chemotherapy regimen, *n* (%)	Chemotherapy regimen, *n* (%)			0.341
EP	66 (64.1)	42 (67.7)	24 (58.5)	
non-EP	37 (35.9)	20 (32.3)	17 (41.5)	
Chemotherapy courses, *n* (%)	Chemotherapy courses, *n* (%)			0.313
1-4	49 (47.6)	32 (51.6)	17 (41.5)	?¿?
5	54 (52.4)	30 (48.4)	24 (58.5)	
Chemotherapy sequencing, *n* (%)	Chemotherapy sequencing, *n* (%)			0.358
IC	4 (3.9)	3 (4.8)	1 (2.4)	
ACT	62 (60.2)	40 (64.5)	22 (53.7)	
IC+ACT	37 (35.9)	19 (30.6)	18 (43.9)	
Treatment modality, *n* (%)	Treatment modality, *n* (%)			0.004
S+CT	39 (37.9)	31 (50.0)	8 (19.5)	
S+RT+CT	52 (50.5)	27 (43.5)	25 (61.0)	
RT+CT	12 (11.7)	4 (6.5)	8 (19.5)	

Abbreviation: IQR: interquartile range; IC: induction chemotherapy; ACT: adjuvant chemotherapy; CT: chemotherapy; RT: radiotherapy; S: Surgery.

Figure legends

Fig 1. Flowchart of patients included in the study.

Fig 2. Cycle-dependent effect of chemotherapy on survival outcomes. A-B: Estimated hazard ratios (HRs) (solid lines) with 95% confidence intervals (dotted line) for the association of chemotherapy cycles with progression-free survival (PFS), and overall survival (OS). A minimal of 5 cycles (indicated by the vertical line) of chemotherapy was identified for reduction of risks disease progress and death. C-D: Long-course chemotherapy with [?]5 cycles outperformed short-course chemotherapy for improving PFS and OS in SCNEC.

Fig 3. Forest plot comparing the effect of chemotherapy cycles on progression-free survival and overall survival by patient subgroup.

Fig 4. Comparisons of survival outcomes between long-course and short-course chemotherapy stratified by FIGO stage .