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The impact of neo/adjuvant treatment choices on prognosis for surgically treated small-cell neuroendocrine carcinoma of the cervix

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Small-cell neuroendocrine carcinoma of the cervix (SCNCC) is a rare and aggressive tumor with a poor prognosis. Surgical resection followed by adjuvant therapy is the standard treatment for early-stage disease but the influence of different neo/adjuvant treatment approaches remains unclear. Retrospectively, we collected patients' characteristics and treatments in two medical centers. Disease status and survival outcomes were renewed through follow-up. Statistics analysis mainly included Kaplan-Meier methods for survival curve estimation, log-rank test for survival curve comparison, and Cox proportional hazards models for independent prognostic factors prediction. Finally, 51 patients treated by radical surgery between January 2010 and April 2020 were enrolled with a median age of 50 years (range: 32-68). 12 (23.5%) patients were at stage IIIC1 according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging systems and the rest were at the early stage. The mean tumor size was 3.6±1.3 cm. Pathological examination found 24 cases with pure SCNCC and 27 cases with admixed SCCC. 29 (56.9%) patients had deep stromal infiltration and 19 (37.3%) patients had lympho-vascular space invasion. 34 (66.7%) patients received neo/adjuvant chemotherapy and pelvic radiation was conducted in 41 (80.39%) patients with a median dose of 46 Gy (range: 40-50.4 Gy). The median follow-up time was 25.0 months. The median disease-free survival (DFS) time was 23.0 months. 27 (52.9%) patients developed distant metastasis and 14 (27.5%) experienced local failure. The median overall survival (OS) was 32.0 months. Univariate and multivariate analysis showed neoadjuvant chemotherapy as negative (HR=2.081, 95% CI 1.030–4.203, p=0.041) and adjuvant chemotherapy (HR=0.409, 95% CI 0.213–0.784, p=0.020) as positive independent prognostic factor for DFS. For OS, only lymph node metastasis was confirmed as an independent prognostic factor in both univariate analysis (HR=1.528, 95% CI 1.011–2.308, p=0.044) and multivariate analysis (HR=1.697, 95% CI 1.041–2.768, p=0.034). In conclusion, for surgically treated SCNCC, adjuvant chemotherapy showed a positive influence on DFS while neoadjuvant chemotherapy harmed DFS. OS was unaffected by either treatment choice.

Key words: small-cell neuroendocrine carcinoma of the cervix; prognostic analysis; retrospective study

Small-cell neuroendocrine carcinoma of the cervix (SCNCC) is a rare pathological type of cervix neoplasm with highly aggressive biological behaviors and poorer prognosis than the most common counterpart with squamous carcinoma [1, 2]. Several different names were used in the past and now it is considered a high-grade malignancy classified as neuroendocrine carcinoma along with carcinoid tumor, atypical carcinoid tumor, and large cell neuroendocrine tumor [3].

Several retrospective studies have demonstrated a gloomy 5-year survival rate of 30–46% for FIGO stage I–II and 0–15% for advanced stages [4–6]. Due to its rarity, efforts have been made to develop prognostic nomograms based on online databases. Age, positive lymph node number, number of resection lymph nodes, chemotherapy, radiotherapy, and surgery were eventually brought into a predictive model for overall survival. The area under curves for OS at 24, 36, and 60 months were above 0.7 which indicated well working efficiency [7].

Despite possible selection bias, surgery remains a very important treatment. A large cohort from Surveillance, Epidemiology and End Results (SEER) databases, showed

that surgery improved median overall survival in both non-metastatic and metastatic groups, which is particularly significant for early-stage patients [8]. For patients with early-stage disease, radical hysterectomy with pelvic lymphadenectomy followed by cisplatin and etoposide chemotherapy or chemoradiation is generally applied [9]. A recently published study in 2023 revealed that surgery improves outcomes of SCNCC patients with locally advanced disease [10].

The lack of high-quality prospective clinical evidence made postoperative treatment options uncertain. Current treatment strategies for SCNCC are mostly based on the standard recommendations for cervical cancer and refer to guidelines for small-cell lung cancer [11, 12]. Sedlis' criteria for squamous cervical cancer and the four-factor model for adenocarcinoma cervical cancer were well accepted worldwide [13, 14]. Patients were classified into high, medium, or low recurrence risk groups according to pathological findings and different postoperative strategies were applied. However, the influence on survival of treatment choices was not generally recognized in this specific clinical setting [15]. Here a renewed analysis of survival for surgically treated SCNCC is conducted in our institutions to shed light on this problem.

Patients and methods

Patients. Patients diagnosed with SCNCC between January 2010 and April 2020 at Zhongnan Hospital of Wuhan University and Central Hospital of Huanggang City were retrospectively reviewed. Those who underwent radical surgery were further scanned. Pathological findings must confirm small cell neuroendocrine carcinoma with or without the presence of a non-SCNCC component. Patients who received inadequate surgical treatment were excluded. Eastern Cooperative Oncology Group (ECOG) performance status was required to be between 0–2, and hematopoietic and organ function had to be at grade 0/1 according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 before anti-tumor treatment initiation.

Data collection and survival follow-up. Archival medical records were reviewed to collect baseline demographic data of enrolled patients. Tumor characteristics, including tumor size, local invasion, myometrial invasion, lymphatic vascular space infiltration (LVSI), and pelvic or para-aortic lymph node metastasis were obtained from primary radiology assessments and postoperative pathological reports. All patients were restaged according to the FIGO 2018 staging system. Neo/adjuvant treatments were also recorded, including the regimens, time, total cycle number, and adverse events of chemotherapy, as well as the treatment technique, prescribed radiation dose, fraction, target volume region, and time of radiotherapy. Other treatments that could affect survival were also inspected and considered in the final analysis. Disease examination results during the post-treatment follow-up period were reviewed by skilled oncologists and radiologists in our hospital information system, and additional disease information was obtained through phone interviews with enrolled patients. Survival outcomes were mainly confirmed through phone interviews.

Statistics. Overall survival (OS) was defined as the time from the beginning of radical surgery to the time of death due to any cause or last follow-up. Disease-free survival (DFS) was defined as the time from the beginning of radical surgery to the time of tumor progression or last follow-up. The Pearson χ^2 test was used to compare the baseline characteristics, and survival analysis was performed using the Kaplan-Meier method and log-rank test. Univariate and multivariate analyses were performed with a Cox proportional hazards model to evaluate potential prognostic factors for OS and DFS. A statistically significant difference was defined as $p<0.05$. All data were processed with SPSS version 21.0.

Ethics statement. This retrospective research was conducted with the approval of Institutional Ethics Review Committees at Zhongnan Hospital of Wuhan University (No. 2023093K) and Huanggang Central Hospital (No. HGYY-KY-2023-010).

Results

Patients' characteristics. In this retrospective study, 51 patients diagnosed with SCNCC were included. All patients underwent Querleu-Morrow classification type C radical hysterectomy and pelvic lymphadenectomy. As summarized in Table 1, the median age of the patients was 50 years (range, 32–68 years). Among them, 27 (52.9%) cases were classified as FIGO 2018 stage IB, comprising 12 (23.5%) cases of IB1, 8 (15.7%) cases of IB2, and 5 (9.8%) cases of IB3. Additionally, 12 (23.5%) cases were at stage IIA, including 10 (19.6%) cases of IIA1 and 2 (3.9%) cases of IIA2. Furthermore, 12 (23.5%) cases presented with stage IIIC1 disease. The mean tumor size was 3.6±1.3 cm. Pathological examination revealed 24 cases with pure SCNCC and 27 cases with admixed SCCC carcinoma (10 mixed with squamous cell carcinomas, 11 mixed with adenocarcinomas, 4 mixed with adenosquamous carcinomas, and 2 with mixed small carcinoids). Deep stromal infiltration (DSI) was observed in 29 (56.9%) patients and 19 (37.3%) patients had LVSI. Pelvic lymph node metastasis (LNM) was detected in 12 (23.5%) patients with mean metastasis numbers of 3.1±3.1 and mean resection numbers of 23.7±9.6. Importantly, none of the enrolled patients exhibited positive surgical margins or parametrial involvement.

Adjuvant chemotherapy. A total of 25.9% (14/51) of patients received neoadjuvant chemotherapy, while 58.8% (30/51) received postoperative adjuvant chemotherapy and 19.6% (10/51) received both. The predominant regimen consisted of paclitaxel or its derivative (docetaxel or paclitaxel-albumin) plus platinum-based drugs (cisplatin, carboplatin, or nedaplatin) with a median cycle of 4 (range 3–5) in 34 patients. Eight patients were administered etoposide plus cisplatin or carboplatin and two patients accepted

PMF (mitomycin C, cisplatin, and 5-fluorouracil) regimens. Notably, 19.6% (10/51) of patients exclusively underwent neo/adjuvant chemotherapy in conjunction with surgery. No statistically significant differences were observed between patients with or without chemotherapy in terms of age (<50 y vs. ≥50 y), tumor size (≤4 cm vs. >4cm), histology (pure vs. mixed), deep stromal invasion (yes vs. no), lymphovascular space invasion (yes vs. no), lymph node metastasis status (yes vs. no), postoperative RT (yes vs. no), and FIGO stage (IB1 vs. ≥IB2) (all p-value >0.05).

Adjuvant radiation. Pelvic radiation was conducted in 80.39% (41/51) patients. External beam radiotherapy was delivered using three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) starting from March 2016. The radiation encompassed the pelvis, with the upper limit at the intervertebral level between L4 and L5, and the lower limit at the inferior border of the obturator. The clinical target volume (CTV) included the primary tumor bed, supra-vaginal portion, para-cervical tissue, and pelvic lymph node regions such as the common iliac, internal and external iliac, obturator, and sacro-anterior. The median radiation dose to the whole pelvis was 46 Gy (range from 40 Gy to 50.4 Gy). Each patient received a daily fraction of 1.8–2.0 Gy within 4–5 weeks (five fractions weekly). Vaginal brachytherapy was implemented in 17 (33.3%) patients' width large-size tumors (tumor size >4 cm) or stage IIA1 and IIA2.The median brachytherapy dose was 18 Gy (range from 12 Gy to 20 Gy). Moreover, 19 (37.3%) patients had weekly concurrent chemotherapy with nedaplatin as the most common regimen. Importantly, all radiotherapy was conducted after the completion of all chemotherapy.

Toxicity

No severe adverse events were reported in patients undergoing postoperative radiotherapy alone. Patients experienced mild to moderate acute grade 1–2 toxicities including anemia, neutrocytopenia, thrombocytopenia, diarrhea, genitourinary issues, and lymphedema during the radiation course. In patients receiving both radiotherapy and chemotherapy, three patients experienced Grade 4 neutrocytopenia, two patients experienced Grade 3 anemia, and one patient had Grade 3–4 diarrhea. Notably, all the Grade 3–4 hematologic and gastrointestinal toxicities were transient and tolerable with appropriate supportive treatment.

Recurrence and disease-free survival (DFS). The median follow-up time was 25.0 months during which treatment failure occurred in 37 patients and the median DFS time was 23.0 months. The 2-year, 3-year, and 5-year DFS rates were 68.6%, 24.9%, and 22.1%, respectively (Figure 1A). Distant metastasis was the most common failure pattern, occurring in 27 (52.9%) patients, among whom 11 (21.6%) had solitary metastasis lesion, and 16 (31.4%) had multiple metastases. Lungs were the most frequent metastasis organ followed by bones, liver, and brain. Local failure occurred in 14 (27.5%) patients with 4 of them simultaneously experiencing metastasis. Among patients with local recurrence only, lesions in 4 (7.8%) patients manifested in the tumor bed or vaginal stump, and 6 (11.8%) had pelvic lymph node recurrence.

Univariate Cox regression analysis (Table 2) revealed that patients receiving adjuvant chemotherapy had significantly better DFS (HR=0.409, 95% CI 0.213–0.784, *p=0.020) (Figure 1B) while those receiving neoadjuvant chemotherapy had worse DFS (HR=2.081, 95% CI 1.030–4.203, *p=0.041) (Figure 1C). A trend of impaired DFS was observed for patients with FIGO stage higher than IB1 (HR=0.494, 95% CI 0.230–1.060, p=0.070) (Figure 1D). Multivariate analysis further confirmed neoadjuvant chemotherapy as a negative prognostic factor and adjuvant chemotherapy as a positive independent prognostic factor. Notably, lymph node metastasis was not identified as a prognostic factor (HR=1.100, 95% CI 0.739–1.636, p=0.639) (Figure 1E), a finding inconsistent with most published studies and potentially attributed to the retrospective nature of the study introducing selection bias.

Adjuvant chemotherapy exhibited a profound influence on DFS. Examining patients with lymph node metastasis, the median DFS for those receiving adjuvant chemotherapy was significantly better than those without adjuvant chemotherapy (18 months vs. 10 months, **p=0.004). This survival advantage extended across patient subgroups, particularly in those with LVSI (43 months vs. 4 months, **p=0.009) and DSI (33 months vs. 8 months, *p=0.015). Furthermore, for patients with a stage higher than IB1, the median DFS in the adjuvant chemotherapy group was also longer than the no adjuvant chemotherapy group (24 months vs. 10 months) while such a difference was not observed in patients of stage IB1.

Overall survival (OS)

A total of 32 deaths occurred and the median OS time for the entire group was 32.0 months (Figure 2A). Patients with LNM had shorter overall survival time compared to those without LNM (21 months vs. 34 months, *p=0.036) (Figure 2B) whereas neo/adjuvant chemotherapy had no impact on OS (Figures 2C, 2D). No statistical difference in OS was found between FIGO stage IB1 and higher-stage patients (Figure 2E).

In contrast to the COX regression results for DFS, lymph node metastasis was confirmed as an independent prognostic factor in both univariate analysis (HR=1.528, 95% CI 1.011–2.308, *p=0.044) and multivariate analysis (HR=1.697, 95% CI 1.041–2.768, *p=0.034). Given the lower p-value in univariate analysis, FIGO stage, pathology type, adjuvant CT, and adjuvant RT were also included in the multivariate COX regression model with lymph node metastasis, but no further significant outcomes were observed (Table 3).

Further analysis was conducted from the perspective of adjuvant chemotherapy. In patients with LNM, median OS was better in the adjuvant chemotherapy group compared

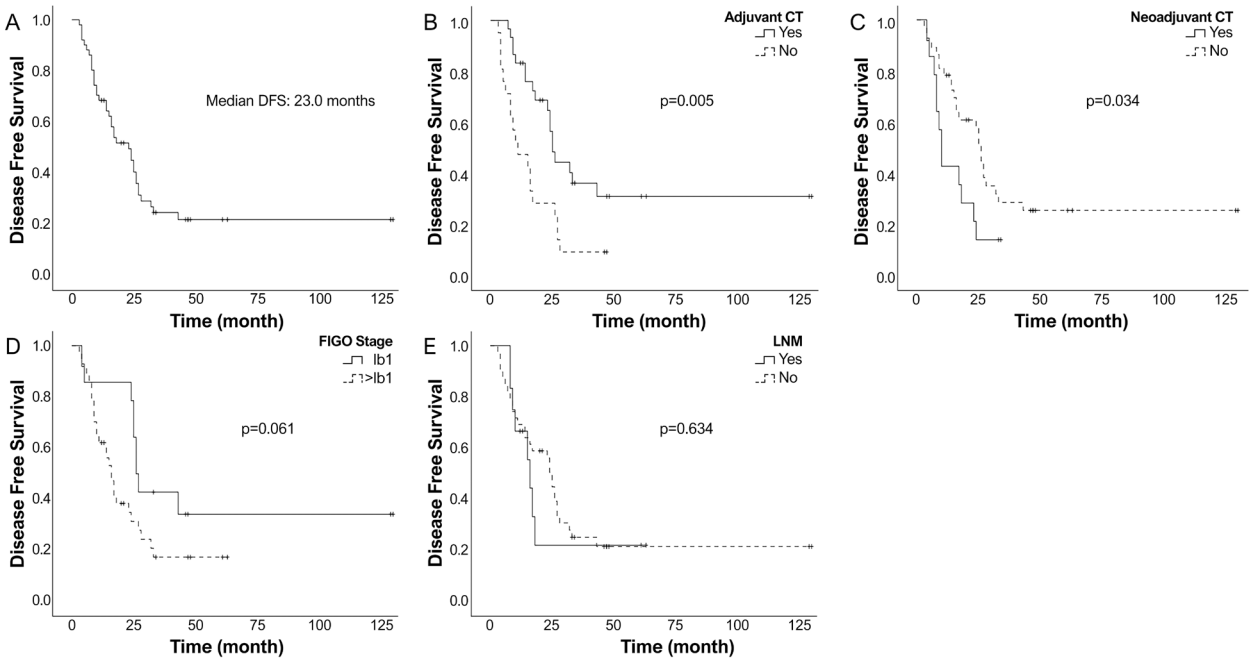

Figure 1. Disease-free survival curves drawn by Kaplan-Meier methods. A) All patients; B) Grouped by adjuvant chemotherapy (CT); C) Grouped by neoadjuvant CT; D) Grouped by FIGO stage; E) Grouped by lymph node metastasis (LNM).

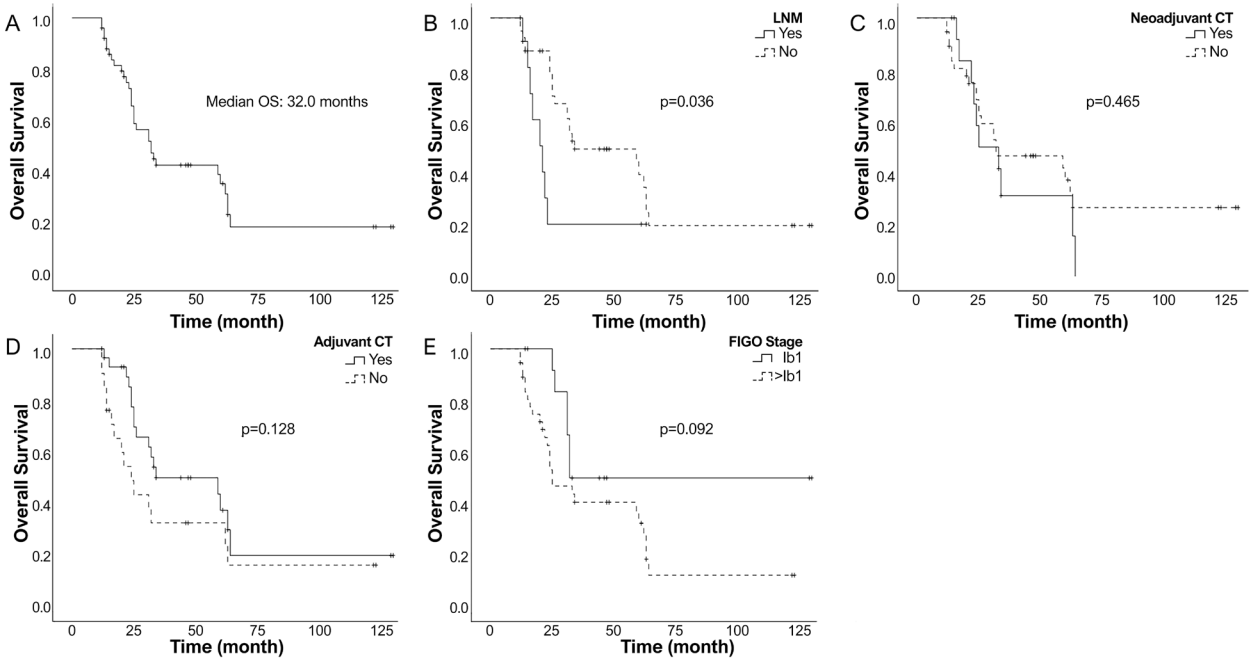

Figure 2. Overall survival curves drawn by Kaplan-Meier methods. A) All patients; B) Grouped by adjuvant chemotherapy (CT); C) Grouped by neoadjuvant CT; D) Grouped by FIGO stage; E) Grouped by lymph node metastasis (LNM).

to the no adjuvant chemotherapy group (23 months vs. 17 months, *p=0.024), and 5-year OS in the adjuvant CT group and non-adjuvant CT group were 40.0% and 0%, respectively (***p<0.001). For patients with LVSI, median OS was not reached in the adjuvant chemotherapy group and 20.0 months in the non-adjuvant chemotherapy group. No significant difference in OS was detected in patients with DSI, larger than 4 cm, or stage higher than IB1.

Discussion

This retrospective cohort study, spanning over a decade and including 51 surgically treated patients with SCNCC sheds light on the complex nature of this rare malignancy. Notably, approximately 25% of patients presented with lymph node metastasis, emphasizing the aggressive nature of the disease. Pathologically, the observed heterogeneity with more than half of the cases displaying admixed cell components, underscores the challenges in treating SCNCC, necessitating a nuanced therapeutic approach.

The primary treatment strategy involved radical hysterectomy and pelvic lymphadenectomy for early-stage diseases. A large-scale study including 1,288 patients in two cohorts (610 in the SEER cohort and 678 in the Chinese cohort) showed that surgery was associated with a better prognosis for locally advanced patients. As the indications for surgery may have expanded, it is essential to establish clearer principles for neo/adjuvant therapies to ensure treatment efficacy. In this group, a substantial proportion of patients (66.7%) received neo/adjuvant chemotherapy, predominantly incorporating paclitaxel and platinum. Concurrently, 80.39% of patients underwent pelvic radiotherapy, employing 3D-CRT and IMRT techniques with a dose of 40–50.4 Gy in regular fractions. The observed severe toxicity, predominantly in patients undergoing combined treatment modalities, underscores the need for careful consideration of the cumulative effects of these interventions.

Despite the comprehensive treatment approach, disease recurrence occurred in 37 patients within an approximate two-year frame. Lung metastasis emerged as the most common treatment failure pattern. The median DFS of 23.0 months and OS of 32.0 months highlight the challenging clinical course of this malignancy. Further analysis with the COX proportional hazards model found adjuvant chemotherapy (median cycles of 4) as a positive independent prognostic factor for DFS. In contrast, neoadjuvant chemotherapy exhibited an adverse effect on DFS, potentially associated with down-staging post-chemotherapy and selection bias. Notably, the impact of lymph node metastasis on OS remained a key independent prognostic factor. Neo/adjuvant chemotherapy and postoperative radiotherapy applied in most patients provided no benefit to OS.

Cervical small cell neuroendocrine carcinoma has similar HPV infection status [16] and gene mutations [17–19] compared to more common cervical epithelial tumors but it has a higher proportion of lymph node metastasis, poorer treatment response, and survival prognosis. A large population-based analysis from NCDB revealed patients with cervical neuroendocrine carcinoma were younger and more often diagnosed with metastatic disease at presentation compared to patients with squamous cancer. Death risk of this rare type was nearly 3 times at an early stage than squamous cancer [5].

The optimal therapeutic strategy for SCNCC remains a subject of ongoing debate. Treatment for small cell neuroendocrine carcinoma of the cervix should be more aggressive and adequate even for early-stage disease [20]. Surgical treatment is a very important therapeutic measure. Patients with stage I–IIA who receive surgical treatment have a higher 5-year survival rate than those who do not receive surgical treatment (38% vs. 24%) [21]. The hazard ratio of death for patients who receive radical concurrent chemoradiotherapy is 4.74 times that of radical surgery [22]. In another retrospective analysis from South Korea, though definitive radiotherapy was more often applied for locally advanced disease, the DFS and OS did not differ from the primary surgery group indicating the potential treatment benefit of radiotherapy [23].

The best treatment choices along with surgery were unclear and the conclusions varied between different researchers. Adjuvant chemotherapy of no less than 4 cycles was the most accepted approach of survival benefit [24–26] whereas few analyses reported the influence of neoadjuvant chemotherapy. A meta-analysis including 2 studies [27, 28] demonstrated a hazard ratio of 2.06 for patients without neoadjuvant chemotherapy indicating a death risk reduction [29]. In our study, shorter PFS was noticed in patients receiving neoadjuvant chemotherapy. This might be the result of a reduction of postoperative treatment because of down-stage after chemotherapy. A selection bias might exist because patients receiving neoadjuvant chemotherapy often had worse disease compared to those who did not. Adjuvant chemoradiation is still a standard recommendation in guidelines while most retrospective research and meta-analysis concluded no influence on DFS or OS for this treatment.

A nomogram model for survival prediction was developed. Combined analysis of clinicopathological features and treatment modalities enrolled FIGO stage, stromal invasion, LVSI, lymph node metastasis, cervical uterine junction invasion, and CgA expression of tumor into a prediction model for recurrence-free survival. The discriminatory power in the training cohort and validation cohort were 0.863 and 0.884, respectively [30]. It still needs further investigation to build a Sedlis' criteria-like model in SCNCC.

This work provided a renewed analysis of the clinical features and prognosis of SCNCC. Considering the rarity, our cohort had a relatively large number of enrolled patients. The follow-up was integrated and the endpoint events for survival analysis were sufficient with a median follow-up time of 2 years. As retrospective research, it had natural limitations including selection bias and uncontrolled comparative factors.

In conclusion, this study contributes a comprehensive analysis of clinical features and prognosis in SCNCC, benefitting from a relatively large cohort. The observed limitations inherent in retrospective research, such as selection bias, underscore the need for ongoing research to elucidate the optimal treatment strategies for this challenging

malignancy. Our findings support the survival benefit of postoperative chemotherapy with at least 4 cycles for surgically treated SCNCC. However, the nuanced impact of neo/adjuvant chemotherapy and the role of adjuvant chemoradiation necessitate further investigation in future research endeavors.

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