International Journal of Women's Health

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Risk of Ovarian Metastasis and Prognosis in Patients with Neuroendocrine Carcinoma of the Uterine Cervix: A Multi-Center Retrospective Cohort Study

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Objective: To determine the risk of ovarian metastasis and prognosis in patients with neuroendocrine carcinoma of the uterine cervix (NECC).

Methods: A retrospective review was conducted of the clinical and pathological information of patients with stage IA2 to IIA2 cervical cancer who underwent radical hysterectomy between 2008 and 2023. Multivariate Cox proportional hazards regression models were used to identify independent prognostic factors for the 5-year overall survival (OS) and disease-free survival (DFS).

Results: The study included 1351 patients from four Chinese medical institutions. Compared to those with squamous carcinoma or adenocarcinoma, patients with NECC had a significantly higher risk of lymph vascular space invasion (LVSI) and more frequently received adjuvant radiotherapy. The overall rates of fallopian tube and ovarian metastases were low (< 1.0%). Furthermore, the ovary had a higher rate of metastasis than the fallopian tube (P< 0.001). Remarkably, none of the 75 patients with NECC exhibited fallopian tube or ovarian metastasis. The 5-year DFS and OS were significantly shorter in patients with NECC than in those with squamous carcinoma (5-year DFS, 64.7% vs 90.1%, P < 0.001; 5-year OS, 75.7% vs 89.6%, P < 0.001) or adenocarcinoma (5-year DFS, 64.7% vs 83.4%, P < 0.001; 5-year OS, 75.7% vs 88.7%, P=0.004). Multivariate analysis identified NECC as an independent risk factor for decreased 5-year DFS (aHR, 6.274; 95% CI, 3.749–10.499) and 5-year OS (aHR, 5.925; 95% CI, 3.097–11.336). Sensitivity assessments yielded consistent results.

Conclusion: NECC is an independent risk factor associated with a worse prognosis. However, the rates of fallopian tube and ovarian metastases are low in NECC patients, suggesting that ovarian preservation may be a safe and feasible option for these patients. Further validation in broader, diverse populations is warranted to generalize these findings.

Keywords: cervical cancer, neuroendocrine carcinoma, prognosis, fallopian tube, ovary

Introduction

According to a recent global analysis, cervical cancer remains a major public health concern. An estimated 661,021 new cases of cervical cancer and 348,189 deaths due to the disease were reported in 2022.[1]

Neuroendocrine neoplasia is an aggressive malignancy derived from neuroendocrine cells. Rarely, it can also occur in other organs such as the female genital tract.[2] Neuroendocrine carcinoma of the uterine cervix (NECC) is a rare disease that accounts for 1.0–1.5% of all cervical cancer.[3–5] Although rare, the cervix is the most common site for neuroendocrine carcinoma of the genital tract. NECC is an aggressive histological variant of the cervical cancer.[6] They mainly include small- and large-cell neuroendocrine carcinomas. The former type is the most common type of NECC. Due to the

Received: 19 September 2025
Accepted: 1 December 2025
Published: 9 December 2025

rarity of this disease, the optimal treatment for NECC remains unclear. Hence, current clinical experience is mostly based on management from small cell lung carcinoma, including surgery, radiotherapy, chemotherapy and immunotherapy.[5,7,8]

The biology of NECC differs from that of squamous cell carcinoma or adenocarcinoma of the cervix with respect to a number of characteristics. For example, NECC may be more likely to develop lymph vascular space invasion (LVSI) and spread to regional lymph nodes. Furthermore, the 5-year overall survival (OS) is significantly lower for patients with NECC (< 45%) than for squamous cell carcinoma and adenocarcinoma (> 65%).[6,9,10] However, the reason for the poor prognosis and treatment strategy of this disease remains unknown.

According to the National Comprehensive Cancer Network (NCCN) guidelines for cervical cancer, fertility-sparing radical trachelectomy is the most validated method for treating tumors ≤2 cm in size.[8] Fertility-sparing surgery is generally not recommended for patients with NECC because of the high risk and paucity of relevant data.[8] In addition, preservation of the fallopian tubes and ovaries in patients with NECC is not recommended because of potential metastasis.[8] Our previous multi-center cohort study has demonstrated that metastasis of some rare sites is related to prognosis in cervical cancer, such as uterine corpus invasion.[11] However, there is still a lack of sufficient evidence regarding the risk of fallopian tube and ovarian metastases in patients with NECC.

Recent molecular studies have begun to unravel the unique genomic landscape of NECC, revealing distinct alterations such as prevalent HER2 and KRAS mutations, in contrast to the TP53 and PIK3CA mutations more commonly found in squamous cell carcinomas.[12–14] While these discoveries hold promise for future targeted therapies, their direct clinical translation, particularly in guiding surgical management such as ovarian preservation, remains limited. Therefore, a thorough understanding of its metastatic patterns and clinical prognosis remains the cornerstone for formulating current treatment strategies.

The objective of this multi-center cohort study was to determine the risk of fallopian tube and ovarian metastasis and prognosis in patients with NECC. Furthermore, we assessed the feasibility of ovarian preservation in patients with NECC.

Methods

Patients

This retrospective study was approved by the Institutional Review Board of the First People's Hospital of Foshan (L2024-70); informed consent from patients was waived due to the retrospective nature of the study. This study was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent revisions.

Medical records and pathological data of patients diagnosed with stage IA2-IIA2 cervical cancer who underwent radical hysterectomy between January 1, 2008, and December 31, 2023, were collected and reviewed. These institutions include the First People's Hospital of Foshan, Fujian Maternity and Child Health Hospital, Anyang Cancer Hospital, and Nanhai District People's Hospital of Foshan. The inclusion criteria were as follows: diagnosis of clinical stage IA2-IIA2 cervical cancer according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system;[15] presence of squamous cell carcinoma, adenocarcinoma, or neuroendocrine carcinoma of the cervix; primary treatment consisting of type B or C (Querleu-Morrow classification) radical hysterectomy and bilateral pelvic lymphadenectomy; and no adjuvant therapy before surgery. Exclusion criteria were preserved ovaries, pregnancy, and other cancers.

The patients were divided into three groups according to their original pathology reports: squamous carcinoma, adenocarcinoma, and neuroendocrine carcinoma. Patients diagnosed with neuroendocrine carcinoma were included, squamous carcinoma was randomly selected at a 1:10 ratio, and adenocarcinoma was included. A total of 1351 patients were included and followed up.

Adjuvant Therapy

The decision to administer adjuvant therapy (radiotherapy with or without chemotherapy) was made on risk-adapted basis. Treatment was recommended for patients with two or more intermediate-risk factors (tumor size > 4.0 cm, stromal invasion depth > 1/2, and LVSI) or any high-risk factors (parametrial involvement [PMI], resection margin involvement [RMI], and lymph node [LN] metastasis) after surgery. The final treatment plan could be influenced by patient and physician preferences.

Follow-Up

Patients were followed up until 2024/6/30 by telephone or through an outpatient information inquiry and examination report system after surgery. Loss to follow-up, mean patient discharge after surgery, and out of touch.

The primary endpoint was the 5-year disease-free survival (DFS), calculated as the number of months from the date of diagnosis to the first evidence of recurrence or death from cervical cancer, whichever occurred first. The secondary endpoint included the following: (1) 5-year OS, calculated as the number of months from the date of diagnosis to death from any cause; and (2) the rates of fallopian tube and ovarian metastasis.

Statistical Analysis

Statistical analyses were performed using SPSS v26.0 (IBM Inc, Chicago, IL, USA) and the Matching package in R (v4.4.0; The R Foundation, Vienna, Austria).

We addressed missing data using multiple imputation. For survival analysis, patients lost to follow-up were censored at the date of their last confirmed follow-up.

Comparisons were made among cervical cancer patients with squamous carcinoma, adenocarcinoma, and neuroendocrine carcinoma (NEC). The chi-squared test was used to compare categorical variables. The Kaplan-Meier method was used to estimate the five-year DFS and OS, and the Log rank test was used to compare the differences. Multivariate forward stepwise Cox proportional hazards regression models were used to identify the independent prognostic factors for OS and DFS. All clinicopathological variables were considered in the multivariate analysis after they were chosen a priori based on their potential impact on survival.

Sensitivity analyses were performed to evaluate the reliability of initial findings. To balance the baseline age, year at diagnosis, stage, tumor size, and surgical technique, a 1:4:4 ratio propensity score matching (PSM) employing near neighbor with a caliper of 0.1, and standard deviations were carried out to quantify the impacts of NEC.[16] A Cox proportional hazards model with previously mentioned factors.

To elucidate the relationship between clinicopathological factors and NEC, subgroup analyses stratified according to stromal invasion depth, LVSI, and adjuvant therapy were performed. The covariates included were identical to those in the techniques section.

Two-sided P-values < 0.05 were considered statistically significant.

Results

Patient Characteristics

The patient selection process is illustrated in Figure S1. Table S1 summarizes the clinical and pathological features of the included patients. Among the 6250 cervical cancer patients with stage IA2-IIA2 included in the multi-center study in China, 75 (1.2%) had neuroendocrine carcinoma. The clinical and pathological characteristics of the 1351 patients with squamous carcinoma, adenocarcinoma, and NEC are shown in Table 1. Compared with squamous carcinoma and adenocarcinoma, NECC has different characteristics in terms of age, stage, surgical approach, stromal invasion depth, and LVSI. Furthermore, patients with NECC had a higher risk of LVSI and adjuvant radiotherapy after balancing the baseline through a 1:4:4 PSM (Table 2).

Fallopian Tube and Ovarian Metastasis

In the included 1351 patients, four and 10 patients had fallopian tube and ovarian metastases, respectively (Table 1). The rates of fallopian tube and ovarian metastases were < 1.0%. Remarkably, no fallopian tube or ovarian metastasis occurred in the 75 patients with NECC.

Although the fallopian tube and ovary were anatomically adjacent, and the fallopian tube was closer to the cervix, the ovary had a higher rate of metastasis than the fallopian tube (0.7% vs 0.3%, $P < 0.001$). Interestingly, the consistency of metastasis was only 13.9% between the two sites (Table S1 and Table 3).

Table 1 Comparison of Squamous Carcinoma or Adenocarcinoma and Neuroendocrine Carcinoma in the Included Patients

Characteristic	Squamous Carcinoma	Adenocarcinoma	NEC	P
Number (%)	750 (55.5%)	526 (38.9%)	75 (5.6%)	
Age, y				**< 0.001**
< 50	348 (46.4)	289 (54.9)	53 (70.7)	
50–59	261 (34.8)	160 (30.4)	15 (20.0)	
≥ 60	141 (18.8)	77 (14.6)	7 (9.3)	
Year at diagnosis				0.735
2008–2018	469 (62.5)	337 (64.1)	45 (60.0)	
2019–2023	281 (37.5)	189 (35.9)	30 (40.0)	
Stage				**< 0.001**
IA2	8 (1.1)	2 (0.4)	0 (0.0)	
IB1	405 (54.0)	351 (66.7)	55 (73.3)	
IB2	88 (11.7)	72 (13.7)	5 (6.7)	
IIA1	193 (25.7)	74 (14.1)	10 (13.3)	
IIA2	56 (7.5)	27 (5.1)	5 (6.7)	
Tumor size, cm				0.593
≤ 2	208 (27.7)	161 (30.6)	23 (30.7)	
2.1–4	398 (53.1)	266 (50.6)	42 (56.0)	
> 4	144 (19.2)	99 (18.8)	10 (13.3)	
Surgical approach				**< 0.001**
Laparotomy	683 (91.1)	328 (62.4)	48 (64.0)	
Laparoscope	67 (8.9)	198 (37.6)	27 (36.0)	
Stromal invasion depth				**< 0.001**
≤ 1/2	262 (34.9)	249 (47.3)	30 (40.0)	
> 1/2	488 (65.1)	277 (52.7)	45 (60.0)	
LVSI				**< 0.001**
No	625 (83.3)	460 (87.5)	50 (66.7)	
Yes	125 (16.7)	66 (12.5)	25 (33.3)	
PMI				0.222
No	742 (98.9)	514 (97.7)	74 (98.7)	
Yes	8 (1.1)	12 (2.3)	1 (1.3)	
RMI				0.140
No	744 (99.2)	516 (98.1)	73 (97.3)	
Yes	6 (0.8)	10 (1.9)	2 (2.7)	
LN metastasis				0.606
No	606 (80.8)	413 (78.5)	60 (80.0)	
Yes	144 (19.2)	113 (21.5)	15 (20.0)	
Fallopian tube metastasis				0.327
No	749 (99.9)	523 (99.4)	75 (100.0)	
Yes	1 (0.1)	3 (0.6)	0 (0.0)	
Ovarian metastasis				0.628
No	745 (99.3)	521 (99.0)	75 (100.0)	
Yes	5 (0.7)	5 (1.0)	0 (0.0)	
Adjuvant radiotherapy				0.600
No	420 (56.0)	280 (53.2)	40 (53.3)	
Yes	330 (44.0)	246 (46.8)	35 (46.7)	

Note: Boldface indicates a statistically significant difference (P < 0.05).

Abbreviations: NEC, neuroendocrine carcinoma; LVSI, lymph vascular space invasion; PMI, parametrial involvement; RMI, resection margin involvement; LN, lymph node.

Table 2 Comparison of Squamous Carcinoma or Adenocarcinoma and Neuroendocrine Carcinoma After 1:4:4 PSM

Characteristic	Squamous Carcinoma	Adenocarcinoma	NEC	P
Number (%)	234 (44.4%)	234 (44.4%)	59 (11.2%)	
Age, y				0.916
< 50	156 (66.7)	157 (67.1)	40 (67.8)	
50–59	58 (24.8)	52 (22.2)	13 (22.0)	
≥ 60	20 (8.5)	25 (10.7)	6 (10.2)	
Year at diagnosis				0.392
2008–2018	196 (83.8)	190 (81.2)	45 (76.3)	
2019–2023	38 (16.2)	44 (18.8)	14 (23.7)	
Stage				0.704
IA2	0 (0.0)	0 (0.0)	0 (0.0)	
IB1	156 (66.7)	163 (69.7)	41 (69.5)	
IB2	31 (13.2)	21 (9.0)	4 (6.8)	
IIA1	37 (15.8)	39 (16.7)	10 (16.9)	
IIA2	10 (4.3)	11 (4.7)	4 (6.8)	
Tumor size, cm				0.826
≤ 2	50 (21.4)	52 (22.2)	13 (22.0)	
2.1–4	143 (61.1)	150 (64.1)	38 (64.4)	
> 4	41 (17.5)	32 (13.7)	8 (13.6)	
Surgical approach				0.728
Laparotomy	200 (85.5)	199 (85.0)	48 (81.4)	
Laparoscope	34 (14.5)	35 (15.0)	11 (18.6)	
Stromal invasion depth				0.055
≤ 1/2	94 (40.2)	112 (47.9)	19 (32.2)	
> 1/2	140 (59.8)	122 (52.1)	40 (67.8)	
LVSI				**< 0.001**
No	200 (85.5)	213 (91.0)	37 (62.7)	
Yes	34 (14.5)	21 (9.0)	22 (37.3)	
PMI				0.967
No	231 (98.7)	231 (98.7)	58 (98.3)	
Yes	3 (1.3)	3 (1.3)	1 (1.7)	
RMI				0.268
No	232 (99.1)	228 (97.4)	57 (96.6)	
Yes	2 (0.9)	6 (2.6)	2 (3.4)	
LN metastasis				0.213
No	197 (84.2)	189 (80.8)	44 (74.6)	
Yes	37 (15.8)	45 (19.2)	15 (25.4)	
Fallopian tube metastasis				0.534
No	234 (100.0)	233 (99.6)	59 (100.0)	
Yes	0 (0.0)	1 (0.4)	0 (0.0)	
Ovarian metastasis				0.881
No	233 (99.6)	233 (99.6)	59 (100.0)	
Yes	1 (0.4)	1 (0.4)	0 (0.0)	
Adjuvant radiotherapy				**0.021**
No	151 (64.5)	124 (53.0)	30 (50.8)	
Yes	83 (35.5)	110 (47.0)	29 (49.2)	

Note: Boldface indicates a statistically significant difference (P < 0.05).

Abbreviations: NEC, neuroendocrine carcinoma; LVSI, lymph vascular space invasion; PMI, parametrial involvement; RMI, resection margin involvement; LN, lymph node.

Table 3 Comparison of Fallopian Tube and Ovarian Metastasis in the Included Patients

Number (%)	Ovarian Metastasis		P
	Negative	Positive	
Fallopian tube metastasis			**< 0.001**
Negative	1338 (99.8)	9 (90.0)	
Positive	3 (0.2)	1 (10)	

Notes: Boldface indicates a statistically significant difference (P < 0.05). The kappa statistic for agreement between the two sites of metastasis was 13.9% (P< 0.001).

Survival Analysis

The median follow-up period of the entire patient population was 36 months. For patients diagnosed with cervical cancer and classified as having squamous carcinoma, adenocarcinoma, or NEC, the median follow-up periods were 38 months, 34 months, and 28 months, respectively. Among patients with cervical squamous carcinoma, 55 (7.3%) exhibited evidence of recurrence or death from cervical cancer and 38 (5.1%) died from cancer. Among the patients with cervical adenocarcinoma, 61 (11.6%) had evidence of recurrence or death from cervical cancer and 37 (7.0%) died of any cause. Among patients with NECC, 21 (28.0%) had evidence of recurrence or death from cervical cancer and 13 (17.3%) died of any cause. Furthermore, among the various anatomical recurrence sites, distant recurrence was more prevalent in adenocarcinoma (45.9%) and NEC (42.9%) (Table S2). A comparative analysis of patients with cervical squamous carcinoma and adenocarcinoma revealed that patients with NEC exhibited significantly shorter 5-year DFS and OS rates (5-year DFS: 64.7% vs 90.1%, P < 0.001; 64.7% vs 83.4%, P < 0.001; 5-year OS: 75.7% vs 89.6%, P < 0.001; 75.7% vs 88.7%, P=0.004; Figure 1A and B). On multivariate analysis controlling for significant prognostic factors in univariate

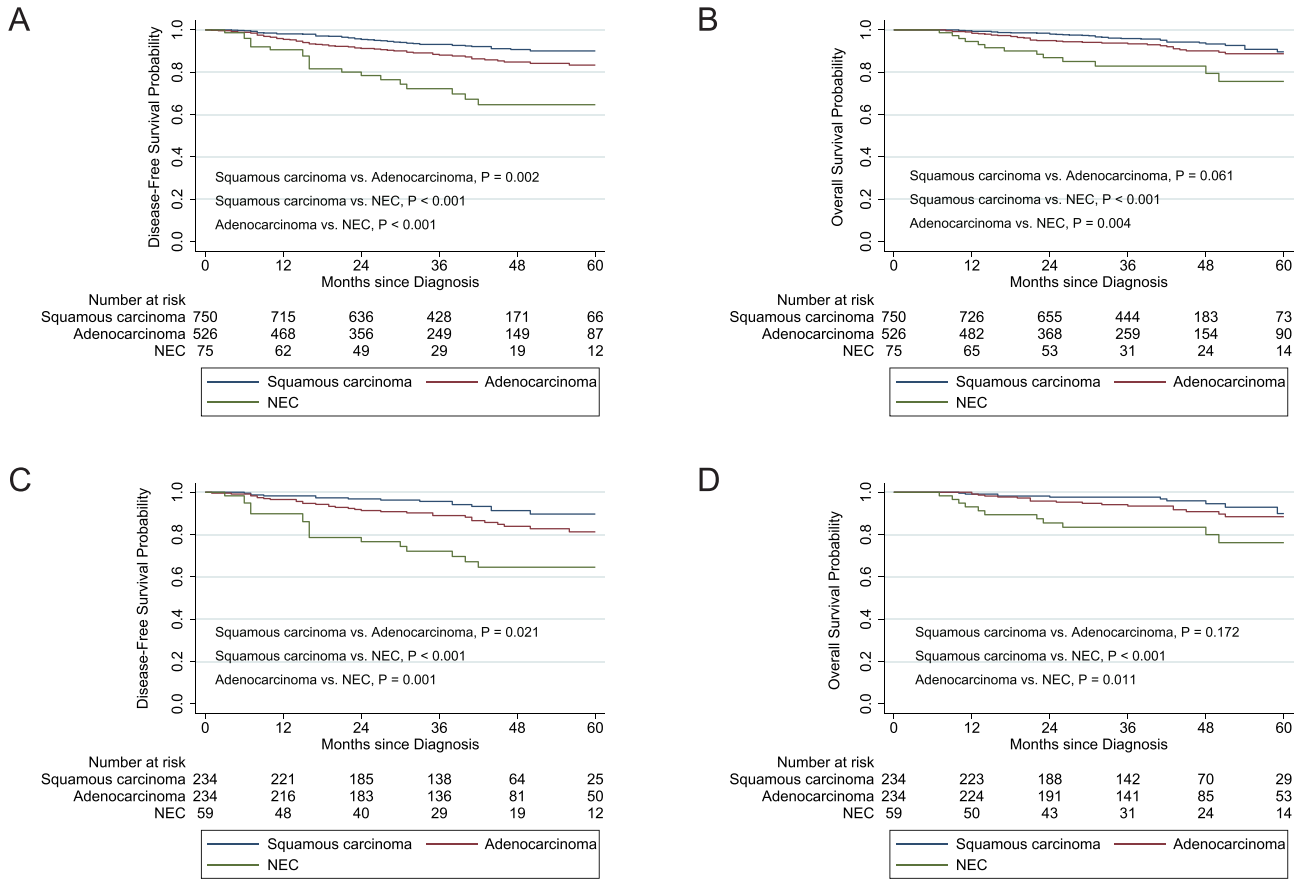

Figure 1 5-year DFS and OS. (**A** and **B**) Primary analysis; (**C** and **D**) propensity score matching.

analysis, NEC was an independent risk factor associated with decreased 5-year DFS (aHR, 6.274; 95% CI, 3.749–10.499, P < 0.001) and 5-year OS (aHR, 5.925; 95% CI, 3.097–11.336; P < 0.001) (Table 4).

Sensitivity Analyses

The consistency of the primary outcomes was reinforced through sensitivity assessments. Following PSM at a 1:4:4 ratio, the study cohort was comprised of 59 NEC cases and 234 squamous carcinoma and adenocarcinoma patients. Post-matching assessments revealed comparable baseline characteristics across groups, with the exception of LVSI prevalence and radiotherapy administration patterns (Table 2). Survival analyses demonstrated substantial disparities, with NEC patients exhibiting markedly reduced 5-year disease-free survival rates compared to both squamous carcinoma (64.6% vs 89.7%, P<0.001) and adenocarcinoma cohorts (64.6% vs 81.3%, P=0.001). Similarly, overall survival outcomes showed significant differences (76.2% vs 89.9%, P<0.001 for squamous carcinoma; 76.2% vs 88.4%, P=0.011 for adenocarcinoma), as illustrated in Figure 1C and D. On multivariate analysis controlling for significant prognostic factors in the univariate analysis, NEC remained an independent risk factor associated with decreased 5-year DFS (aHR, 5.862; 95% CI, 2.917–11.782, P < 0.001) and 5-year OS (aHR, 5.251; 95% CI, 2.202–12.524, P < 0.001) (Table 5).

Table 4 Univariate and Multivariate Analyses of Prognostic Factors for 5-year DFS and OS by Cox Proportional Hazards Regression Models

Prognostic Factor	5-year DFS				5-year OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	aHR (95% CI)	P	HR (95% CI)	P	aHR (95% CI)	P
Age	1.197 (0.963–1.488)	0.105	–	0.449	1.459 (1.120–1.902)	0.005	–	0.113
Year at diagnosis	1.178 (0.823–1.687)	0.371	–	0.969	1.659 (1.057–2.604)	0.028	–	0.198
Stage	1.478 (1.272–1.717)	< 0.001	1.359 (1.154–1.601)	**< 0.001**	1.674 (1.391–2.016)	< 0.001	1.565 (1.279–1.915)	**< 0.001**
Tumor size	1.915 (1.492–2.458)	< 0.001	–	0.067	2.195 (1.600–3.010)	< 0.001	–	0.083
Histologic type								
Squamous carcinoma	1		1		1		1	
Adenocarcinoma	1.789 (1.242–2.578)	0.002	2.155 (1.489–3.118)	**< 0.001**	1.533 (0.974–2.415)	0.065	2.028 (1.283–3.206)	**0.002**
NEC	4.603 (2.782–7.614)	< 0.001	6.274 (3.749–10.499)	**< 0.001**	3.789 (2.016–7.124)	< 0.001	5.925 (3.097–11.336)	**< 0.001**
Surgical approach	1.540 (1.028–2.306)	0.036	–	0.211	1.185 (0.677–2.072)	0.552	–	0.923
Stromal invasion depth	3.315 (2.134–5.150)	< 0.001	2.638 (1.634–4.261)	**< 0.001**	4.841 (2.574–9.105)	< 0.001	3.703 (1.890–7.254)	**< 0.001**
LVSI	1.828 (1.240–2.694)	0.002	–	0.620	2.067 (1.292–3.305)	0.002	–	0.364
PMI	5.221 (2.553–10.675)	< 0.001	2.155 (1.027–4.522)	**0.042**	3.355 (1.230–9.151)	0.018	–	0.481
RMI	2.963 (1.213–7.236)	0.017	–	0.466	3.435 (1.260–9.369)	0.016	–	0.597
LN metastasis	3.796 (2.710–5.316)	< 0.001	2.650 (1.845–3.807)	**< 0.001**	3.883 (2.554–5.904)	< 0.001	2.637 (1.702–4.086)	**< 0.001**
Fallopian tube metastasis	0.050 (0.000–n/a)	0.637	–	0.259	0.049 (0.000–n/a)	0.702	–	0.325
Ovarian metastasis	4.602 (1.701–12.455)	0.003	3.935 (1.444–10.728)	**0.007**	6.968 (2.552–19.023)	< 0.001	5.831 (2.115–16.077)	**0.001**
Adjuvant radiotherapy	1.222 (0.874–1.709)	0.241	0.645 (0.453–0.917)	**0.015**	1.106 (0.727–1.683)	0.639	0.533 (0.345–0.825)	**0.005**

Notes: Boldface in the Multivariate Analysis indicates an independent prognostic factor with statistical significance (P < 0.05). Cox proportional hazards regression models for multivariable analysis. All listed covariates were not found to have multicollinearity.

Abbreviations: PSM, propensity score matching; NEC, neuroendocrine carcinoma; LVSI, lymph vascular space invasion; PMI, parametrial involvement; RMI, resection margin involvement; LN, lymph node; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval.

Table 5 Univariate and Multivariate Analyses of Prognostic Factors for 5-year DFS and OS by Cox Proportional Hazards Regression Models After 1:4:4 PSM

Prognostic Factor	5-year DFS				5-year OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	aHR (95% CI)	P	HR (95% CI)	P	aHR (95% CI)	P
Age	1.417 (1.011–1.987)	0.043	–	0.368	1.565 (1.025–2.389)	0.038	–	0.321
Year at diagnosis	1.186 (0.597–2.354)	0.626	–	0.667	1.941 (0.863–4.362)	0.109	–	0.438
Stage	1.678 (1.347–2.089)	< 0.001	1.261 (0.966–1.647)	0.089	1.881 (1.428–2.477)	< 0.001	1.626 (1.211–2.183)	**0.001**

(*Continued*)

Table 5 (Continued).

Prognostic Factor	5-year DFS				5-year OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	aHR (95% CI)	P	HR (95% CI)	P	aHR (95% CI)	P
Tumor size	2.396 (1.592–3.606)	< 0.001	1.687 (1.030–2.762)	**0.038**	2.896 (1.706–4.914)	< 0.001	–	0.057
Histologic type								
Squamous carcinoma	1		1		1		1	
Adenocarcinoma	2.056 (1.109–3.809)	0.022	2.126 (1.138–3.973)	**0.018**	1.716 (0.791–3.719)	0.172	1.960 (0.881–4.358)	0.099
NEC	5.176 (2.607–10.277)	< 0.001	5.862 (2.917–11.782)	**< 0.001**	4.301 (1.823–10.146)	0.001	5.251 (2.202–12.524)	**< 0.001**
Surgical approach	1.639 (0.853–3.146)	0.138	–	0.096	1.481 (0.619–3.541)	0.378	–	0.679
Stromal invasion depth	3.978 (2.078–7.617)	< 0.001	2.555 (1.276–5.113)	**0.008**	5.489 (2.147–14.036)	< 0.001	3.808 (1.385–10.473)	**0.010**
LVSI	2.208 (1.253–3.889)	0.006	–	0.534	2.517 (1.253–5.056)	0.010	–	0.396
PMI	4.913 (1.540–15.680)	0.007	–	0.183	1.816 (0.249–13.237)	0.556	–	0.685
RMI	1.716 (0.420–7.015)	0.452	–	0.521	2.912 (0.701–12.093)	0.141	–	0.800
LN metastasis	3.666 (2.222–6.049)	< 0.001	2.036 (1.203–3.448)	**0.008**	4.400 (2.341–8.269)	< 0.001	2.674 (1.374–5.204)	**0.004**
Fallopian tube metastasis	0.050 (0.000–n/a)	0.772	–	0.838	0.049 (0.000–n/a)	0.811	–	0.852
Ovarian metastasis	0.049 (0.000–n/a)	0.704	–	0.717	0.049 (0.000–n/a)	0.770	–	0.788
Adjuvant radiotherapy	1.171 (0.716–1.916)	0.530	–	0.053	0.999 (0.527–1.893)	0.998	0.481 (0.247–0.937)	**0.032**

Notes: Boldface in the Multivariate Analysis indicates an independent prognostic factor with statistical significance (P < 0.05). Cox proportional hazards regression models for multivariable analysis. All listed covariates were not found to have multicollinearity.

Abbreviations: PSM, propensity score matching; NEC, neuroendocrine carcinoma; LVSI, lymph vascular space invasion; PMI, parametrial involvement; RMI, resection margin involvement; LN, lymph node; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval.

NEC significantly influenced stromal invasion depth, LVSI, and adjuvant RT. Hence, subgroup analysis was conducted based on these factors. In subgroup multivariate analyses stratified by stromal invasion depth, LVSI, and adjuvant radiotherapy, NEC remained an independent risk factor for decreased 5-year DFS and 5-year OS except for the subgroup with stromal invasion depth ≤ 1/2 (Figure 2A and B).

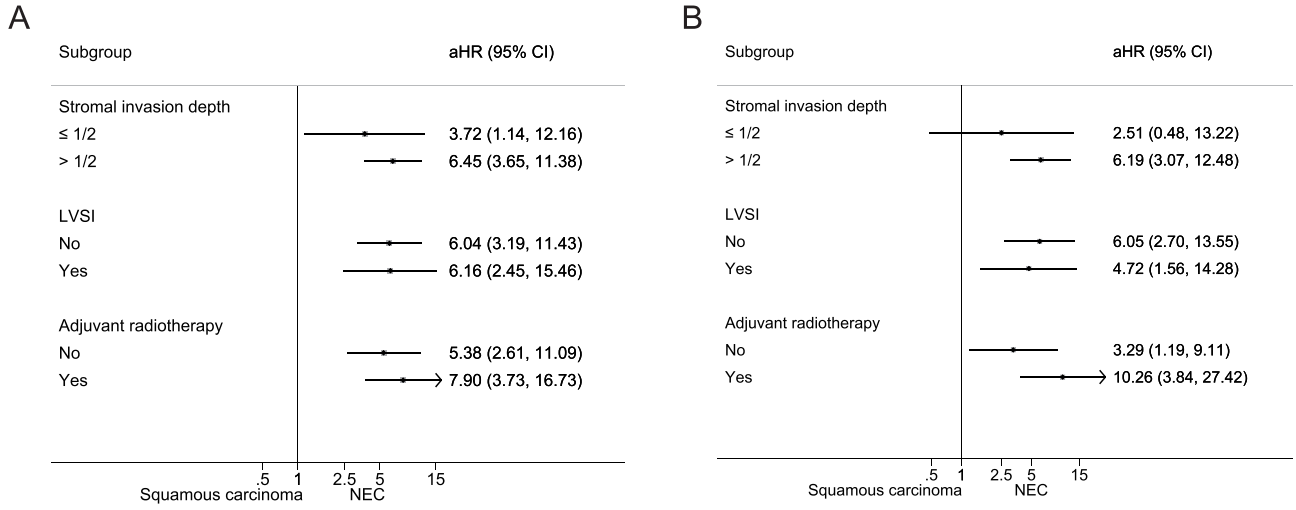

Figure 2 Subgroup analyses. (**A**) Associations between NEC and recurrence or death from cervical cancer; (**B**) associations between NEC and death from any cause, according to stromal (≤1/2 vs >1/2), LVSI (no vs yes) and adjuvant radiotherapy (no vs yes). The included covariates have shown in methods section, included age, year at diagnosis, stage, tumor size, surgical approach, stromal invasion depth, LVSI, PMI, RMI, and LN metastasis, fallopian tube metastasis, ovarian metastasis and adjuvant radiotherapy.

Discussion

This multi-center cohort study aimed to determine the characteristics of tumor metastasis and prognosis in patients with NECC. The incidence of NECC is 1.2% among patients with cervical cancer. Patients with NECC had a higher risk of LVSI and adjuvant radiotherapy than those with squamous carcinoma or adenocarcinoma. The rates of fallopian tube and ovarian metastases were < 1.0%. Furthermore, the ovary has a higher rate of metastasis than the fallopian tube. Remarkably, no fallopian tube or ovarian metastasis occurred in the 75 patients with NECC. Survival analysis revealed markedly poorer 5-year disease-free survival (DFS) and overall survival (OS) rates among cervical cancer patients with NECC than those diagnosed with squamous cell carcinoma or adenocarcinoma. NECC is an independent risk factor associated with a decreased 5-year DFS and OS in patients with cervical cancer.

In the current study, the incidence of NECC was low, which is consistent with previous research reports of 1.0–1.5% of all cervical cancer.[3–5] However, the prognosis is poor, with a 5-year DFS rate of 64.7% and 5-year OS rate of 75.7%. A previous systematic review reports that the 2-year- and 5-year OS rates of 112 patients with NECC were 50% and 34%, respectively.[6] Another previous study with 453 NECC patients revealed that the 5-year progression-free survival and OS were 59% and 71%, respectively, for early stage disease, 28% and 36%, respectively, for locally advanced disease, and 6% and 12%, respectively, for advanced disease.[17] The prognosis reported in these previous studies was worse than that in our study. A possible reason may be that half of the patients in the previous study were in the late stage, and patients in the current study had a disease equal to or earlier than IIA2. Furthermore, many previous studies also revealed that NECC had a poor prognosis, with more than 50% of patients developing metastasis.[9,18–20]

After balancing the baseline of the patients, NECC was found to have a higher rate of LN metastasis than squamous carcinoma or adenocarcinoma. However, no significant differences were observed among the different histological types. A previous study of 535 patients with NECC showed LN metastasis in 16.6%.[18] Another study reported that LN metastasis was observed in 15.2% of patients with NECC.[9] These results are similar to those of the present study. This revealed that LN metastasis may not be the main reason for worse prognosis in patients with NECC. Furthermore, we found that LVSI was the only postoperative pathological factor with a higher rate (37.3%) in NECC. Several previous studies also showed that patients with NECC had a high rate of LVSI (37.3% to 58.8%.[9,21] However, the multivariate analysis in the current study showed that LVSI was not an independent risk factor for survival. Hence, we speculated that early micrometastases could occur in patients with NECC. The distinct clinical behavior of NECC, characterized by a high propensity for LVSI and early distant metastasis as observed in our cohort, may find its origin in its unique molecular landscape. The prevalent HER2 and KRAS mutations reported in NECC, as opposed to the TP53 and PIK3CA mutations common in squamous carcinomas, could drive more aggressive invasion and metastatic pathways.[12–14,22]

In the current study, abdominal and distant recurrences were more common in NECC, accounting for > 70% of all sites of recurrence. A previous study showed that 86.2% and 13.8% of patients with NECC had distant and pelvic recurrence, respectively.[23] Two other studies have also shown that NECC has a higher rate of distant metastasis, and the lungs, liver, and bone are the main sites of recurrence.[9,24] Furthermore, a Japanese multi-center study of 126 patients with small-cell NEC found that distant metastasis was associated with worse outcome.[25] Although current views emphasize the importance of chemotherapy in preventing recurrence after cervical cancer surgery, we found that the rate of adjuvant radiotherapy was higher in patients with NECC and was associated with a better prognosis. Several previous studies have suggested that a multimodal treatment strategy (including surgery, chemotherapy, and radiation) is an important component in the treatment of locally advanced NECC.[21,26]

Cervical cancer rarely causes metastasis to the fallopian tubes and ovaries. Therefore, young women can preserve their ovaries through endocrine function. In the current study, the rates of squamous carcinoma and adenocarcinoma metastasis in the fallopian tubes were 0.1% and 0.6%, respectively, and the rates of squamous carcinoma and adenocarcinoma metastasis in ovaries were 0.7% and 1.0%, respectively. NECC is considered to have a high risk of fallopian tube and ovarian metastasis, and it is often necessary to remove the fallopian tubes and ovaries.[27] However, the rate of NECC in fallopian tubes and ovaries was 0.0%. Although there may be some margin of error due to the relatively limited number of NECC cases, it is speculated that its incidence will not be significantly higher than that of adenocarcinoma. Hence, it is safe and feasible to preserve the ovaries of NEC patients. This finding directly challenges

the prevailing dogma that necessitates oophorectomy. A previous study performed whole exome sequencing of fresh-frozen tissues from 15 NECCs and matched normal tissues. According to these comparative genomics data, NECC may be genetically more similar to common cervical cancer subtypes than to small-cell neuroendocrine carcinomas of the bladder and lung that occur outside the cervical region.[28]

This study aimed to determine the characteristics of tumor metastasis and prognosis in patients with NECC. The sample size of this study was relatively large. High-quality follow-up data and statistical analyses were added to strengthen the data. However, this study has several limitations. First, its retrospective nature may introduce inherent selection biases, despite our efforts to mitigate them through PSM. Second, although our cohort of NECC patients is one of the largest reported, the absolute number remains limited due to the rarity of the disease, which may affect the generalizability of our findings and the statistical power for some subgroup analyses. Third, all patients were recruited from Chinese institutions, and potential regional variations in genetic background, clinical practice, or environmental factors could limit the applicability of our results to other populations. Finally, the median follow-up of 28 months for NECC patients should be considered when interpreting the survival outcomes. While this period is sufficient to capture the definitive pathological status of ovarian and fallopian tube metastases determined at surgery, a longer follow-up could provide a more complete picture of long-term survival and very late recurrences at other sites. However, given the aggressive nature of NECC, wherein the majority of recurrences and survival events typically occur within the first few years, we believe that the current follow-up period robustly supports our primary survival conclusions regarding its poor prognosis.

Conclusions

In conclusion, the incidence of NECC was relatively low. However, NECC is an independent risk factor associated with poor prognosis. Importantly, within our cohort from four Chinese centers, we observed no ovarian metastases among 75 NECC patients. These findings strongly suggest that ovarian preservation may be a safe and feasible option in this specific population. Although the number of NECC cases in our study is limited by the rarity of the disease, our findings provide robust evidence to challenge current practices regarding ovarian preservation. Further multi-national cohort studies are warranted to confirm these findings and to establish definitive, evidence-based guidelines.

Data Sharing Statement

The data associated with this study are provided in the Supplementary Material. Data supporting the findings of this study are available from the corresponding authors, Fangjie He and Shimin Huang, upon reasonable request.

Ethics Approval and Consent to Participate

This retrospective study was approved by the Institutional Review Board of the First People's Hospital of Foshan (L2024-70); informed consent from patients was waived due to the retrospective nature of the study. This study was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent revisions.

Acknowledgments

We would like to thank Editage (www.editage.cn) for English language editing.

Funding

This study was supported by the Joint Funds for the Innovation of Science and Technology, Fujian Province (2023Y9359), Startup Fund for Scientific Research, Fujian Medical University (2023QH1190 and 2023QH1193), and the Fujian Provincial Health Technology Project (2024GGA057). The sponsors were not involved in the study design, collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Disclosure

The authors declare no conflict of interest.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
2. Guadagno E, De Rosa G, Del Basso De Caro M. Neuroendocrine tumours in rare sites: differences in nomenclature and diagnostics-a rare and ubiquitous histotype. *J Clin Pathol*. 2016;69:563–574. doi:10.1136/jclinpath-2015-203551
3. Ganesan R, Hirschowitz L, Dawson P, et al. Neuroendocrine carcinoma of the cervix: review of a series of cases and correlation with outcome. *Int J Surg Pathol*. 2016;24:490–496. doi:10.1177/1066896916643385
4. Gadducci A, Carinelli S, Aletti G. Neuroendrocrine tumors of the uterine cervix: a therapeutic challenge for gynecologic oncologists. *Gynecol Oncol*. 2017;144:637–646. doi:10.1016/j.ygyno.2016.12.003
5. Burzawa J, Gonzales N, Frumovitz M. Challenges in the diagnosis and management of cervical neuroendocrine carcinoma. *Expert Rev Anticancer Ther*. 2015;15:805–810. doi:10.1586/14737140.2015.1047767
6. Tempfer CB, Tischoff I, Dogan A, et al. Neuroendocrine carcinoma of the cervix: a systematic review of the literature. *BMC Cancer*. 2018;18:530. doi:10.1186/s12885-018-4447-x
7. Kloppel G. Neuroendocrine Neoplasms: dichotomy, Origin and Classifications. *Visc Med*. 2017;33:324–330. doi:10.1159/000481390
8. Abu-Rustum NR, Yashar CM, Arend R, et al. NCCN Guidelines® insights: cervical cancer, version 1.2024. *J Natl Compr Canc Netw*. 2023;21 (12):1224–1233. doi:10.6004/jnccn.2023.0062
9. Cohen JG, Kapp DS, Shin JY, et al. Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. *Am J Obstet Gynecol*. 2010;203:347e1–6. doi:10.1016/j.ajog.2010.04.019
10. Lee DY, Chong C, Lee M, et al. Prognostic factors in neuroendocrine cervical carcinoma. *Obstet Gynecol Sci*. 2016;59:116–122. doi:10.5468/ogs.2016.59.2.116
11. He F, Li W, Liu P, et al. Influence of uterine corpus invasion on prognosis in stage IA2-IIB cervical cancer: a multicenter retrospective cohort study. *Gynecol Oncol*. 2020;158:273–281. doi:10.1016/j.ygyno.2020.05.005
12. Chao WR, Lee MY, Lee YJ, et al. Profiling of HER2, KRAS, and PIK3CA mutations in uterine cervical neuroendocrine carcinoma and implications for oncogenic driver targeting therapy. *Cancer Genet*. 2025;296–297:9–14. doi:10.1016/j.cancergen.2025.05.005
13. Voutsadakis IA. PI3KCA mutations in uterine cervix carcinoma. *J Clin Med*. 2021;10(2):220. doi:10.3390/jcm10020220
14. Tornesello ML, Annunziata C, Buonaguro L, Losito S, Greggi S, Buonaguro FM. TP53 and PIK3CA gene mutations in adenocarcinoma, squamous cell carcinoma and high-grade intraepithelial neoplasia of the cervix. *J Transl Med*. 2014;12:255. doi:10.3760/cma.j.cn112141-20230918-00106
15. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet*. 2009;105:107–108. doi:10.1016/j.ijgo.2009.02.009
16. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med*. 2014;33:1242–1258. doi:10.1002/sim.5984
17. Salvo G, Flores Legarreta A, Ramalingam P, et al. Clinicopathologic characteristics, oncologic outcomes, and prognostic factors in neuroendocrine cervical carcinoma: a Neuroendocrine Cervical Tumor Registry study. *Int J Gynecol Cancer*. 2023;33:1359–1369. doi:10.1136/ijgc-2023-004708
18. Yu C, Wu X, Zhang S, et al. Prognostic model for survival in patients with neuroendocrine carcinomas of the cervix: SEER database analysis and a single-center retrospective study. *PLoS One*. 2024;19:e0296446. doi:10.1371/journal.pone.0296446
19. Miyoshi AI, Ueda Y, Kurita T, Kimura T, Yoshino K. Recent advances in the management of small cell carcinoma of the uterine cervix. *Anticancer Res*. 2023;43:1397–1405. doi:10.21873/anticanres.16288
20. Stecklein SR, Jhingran A, Burzawa J, et al. Patterns of recurrence and survival in neuroendocrine cervical cancer. *Gynecol Oncol*. 2016;143:552–557. doi:10.1016/j.ygyno.2016.09.011
21. Zhao D, Sun S, Yang Z, Wang P, Qiu H. The impact of neo/adjuvant treatment choices on prognosis for surgically treated small-cell neuroendocrine carcinoma of the cervix. *Neoplasma*. 2024;71:70–76. doi:10.4149/neo_2023_230802N404
22. Bellone S, Jeong K, Halle MK, et al. Integrated mutational landscape analysis of poorly differentiated high-grade neuroendocrine carcinoma of the uterine cervix. *Proc Natl Acad Sci U S A*. 2024;121(17):e2321898121. doi:10.1073/pnas.2321898121
23. Song XC, Zhang H, Zhong S, et al. Value of surgery combined chemotherapy and radiation therapy in locally advanced neuroendocrine carcinoma of the cervix: a single-center retrospective cohort study. *Zhonghua Fu Chan Ke Za Zhi*. 2024;59:200–209.
24. Park HK. Neuroendocrine carcinomas of the uterine cervix, endometrium, and ovary show higher tendencies for bone, brain, and liver organotrophic metastases. *Curr Oncol*. 2022;29:7461–7469. doi:10.3390/curroncol29100587
25. Ishikawa M, Kasamatsu T, Tsuda H, et al. A multi-center retrospective study of neuroendocrine tumors of the uterine cervix: prognosis according to the new 2018 staging system, comparing outcomes for different chemotherapeutic regimens and histopathological subtypes. *Gynecol Oncol*. 2019;155:444–451. doi:10.1016/j.ygyno.2019.09.018
26. Song XC, Zhang H, Zhong S, et al. Value of postoperative radiotherapy and analysis of prognostic factors in early-stage neuroendocrine carcinoma of cervix. *Zhonghua Fu Chan Ke Za Zhi*. 2023;58:680–690. doi:10.3760/cma.j.cn112141-20230614-00263
27. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: cervical cancer, V.3.2024. Available from: http://www.nccn.org/professionals/physician_gls/PDF/cervicalcancer.pdf. Accessed May 6, 2024.
28. Hillman RT, Cardnell R, Fujimoto J, et al. Comparative genomics of high grade neuroendocrine carcinoma of the cervix. *PLoS One*. 2020;15: e0234505. doi:10.1371/journal.pone.0234505