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Clinical characteristic and prognostic factors in high-grade endometrial neuroendocrine carcinoma

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Abstract

Aim: The aim of the present study was to summarize the clinical characteristics and analyze the independent prognostic factors in patients with high-grade endometrial neuroendocrine carcinoma (ENC).

Methods: Patients diagnosed with ENC, endometrioid adenocarcinoma (EAC), endometrial clear-cell carcinoma (ECC), endometrial serous carcinoma (ESC), endometrioid carcinoma with mucinous features (EMC) from 1987 to 2016 were screened from the National Cancer Institute database (surveillance, epidemiology, and end results [SEER]). Kaplan–Meier were used to assess survival. Univariate and multivariate Cox proportional hazards analysis were done to examine factors affecting survival.

Results: The median survival times of ENC were 11 months, shorter than that of EAC, ECC, ESC, and EMC ($p < 0.01$). There was no significant difference in ages, survival rate, and median survival time between large-cell ENC (LCENC) and small-cell ENC (SCENC), which were all belong to ENC. In a multivariable model, the hazard ratio (HR) of death for women with Federation International of Gynecology and Obstetrics (FIGO) stage I-II of ENC was 0.37 compared to FIGO stage III-IV ($p < 0.01$). The HR of patients who under the surgery was 0.39 compared to the patients who without surgery ($p < 0.01$), and the HR of patients who received chemotherapy was 0.51 compared to the patients who did not received chemotherapy ($p < 0.01$). Radiotherapy did not significantly reduce the mortality risk of patients.

Conclusion: ENC was a kind of devastating endometrial cancers with the poorest prognosis. Surgical treatment and chemotherapy were necessary for improving prognosis of ENC. Early diagnosis favored better prognosis. There was no prognostic difference between with and without radiotherapy.

Key words: high-grade endometrial neuroendocrine carcinoma, large cell, prognosis, small cell, survival rate.

Introduction

Neuroendocrine neoplasm (NEN) is a heterogeneous tumor family, which originates from the neuroendocrine cells of the whole diffuse endocrine system. Most neuroendocrine tumors develop in the lung and stomach pancreas system. Neuroendocrine tumors rarely occur in the genital tract. It was reported neuroendocrine tumors of female genital tract only account for 2% of all gynecological cancers.[1] Neuroendocrine carcinoma originated from endometrium in particular are extremely rare. Endometrial neuroendocrine carcinoma (ENC) accounts for about 0.8% of endometrial carcinoma.[2] In the fifth edition of World Health Organization (WHO) histological classification of female reproductive organ tumors in 2020, classification of gynecologic NENs is based on the distinction between well-differentiated neuroendocrine

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tumors (NET, G1/G2) and poorly differentiated carcinomas neuroendocrine carcinom (NECs, small-/large-cell variants).[3] A category of carcinoma admixed with NEC (combined small-/large-cell NEC) is also included in the current classification, because in the cervix endometrium, and ovary, NECs often occur in association with other neoplasms. ENC are highly endometrial cancers with poor prognosis. The reported median survival time was 17 months (95% confidence interval [CI], 12–23).[2] The clinical manifestations of ENC are usually abnormal uterine bleeding or symptomatic metastasis.[4]

Due to the extremely low incidence of ENC, there are few literatures available, which were mainly retrospective studies with small sample sizes or individual case reports.[4,5] The epidemiological information and accurate recommendations for ENC are still limited, which is not enough for accurate clinical diagnosis and treatment. Therefore, this study collected 171 cases of ENC from SEER (surveillance, epidemiology, and end results) database for 30 years from 1987 to 2016 to summarize and analysis the clinical characteristics of ENC. We found the prognostic factors of ENC, including stage, differentiation, lymph node metastasis, distant metastasis, and treatments. Surgical treatment and chemotherapy were necessary for improving prognosis of ENC. There was no prognostic difference between with and without radiotherapy.

Materials and Methods

Patients and relevant data in this study cohort were collected from SEER database. SEER database contains cancer statistics of 30% of the US population in 14 registered states (website: http://www.seer.cancer.gov [acquired 23 April 2021]).

The diagnostic code of international classification of neoplastic diseases (3rd Edition) (ICD-O-3) was used to diagnose patients with neuroendocrine carcinoma of uterine body. From 1987 to 2016, patients with histologically diagnosed endometrioid adenocarcinoma (EAC) and neuroendocrine carcinoma in SEER database were considered to meet all the following conditions: primary malignant tumor of uterus (ICD-O-3/WHO 2008 website code C54.1), morphology and behavior: carcinoid (8240/3), small-cell neuroendocrine carcinoma (8041/3), large-cell neuroendocrine carcinoma (8013/3), endometrioid carcinoma (8380/3), mucinous adenocarcinoma (8480/3), serous carcinoma (8441/3), clear cell carcinoma (8310/3).

Personal information including demographic, clinicopathological, and treatment parameters was recorded using the case list option. Due to the lack of a unified staging system for neuroendocrine tumors, staging information is based on the tumor node metastasis (TNM) staging system and seer staging system (local, regional, and distant) proposed by the American Joint Committee on cancer (AJCC). According to TNM stage and seer stage, the patients were restaged according to the International Federation of gynecology and Obstetrics (FIGO) staging system. The early stage is FIGO stage I and II, and the late stage is FIGO stage III and IV.

According to the two-level grading system, the low-level (well differentiated and moderately differentiated tumors) is defined as grade 1 and grade 2 in the three-level or four-level grading system, and the high-level is defined as grade 3 or grade 4 (poor and undifferentiated tumors) in the three-level or four-level grading system.

Descriptive statistics are expressed as median (minimum–maximum) for continuous variables and number/percentage for categorical variables. Survival rates of were evaluated using Kaplan–Meier curves, and the comparisons were performed using the log-rank test. The cumulative survival rates were calculated by the life-table method. Multivariate cox proportional hazards regression model was used to calculate the adjusted 95% CI to determine the statistical independence of prognostic variables. SEER * stat software (version 8.3.9; The National Cancer Institute Surveillance Research Pro-gram) was used to collect clinical data. SPSS software SPSS version 25 (IBM SPSS statistics, IBM, Armonk, New York) was used for statistical calculation, and the definition was statistically significant ($p < 0.05$).

Results

Age comparison of endometrial carcinoma with different histological types

A total of 171 patients with ENC, 133 336 patients with EAC 3326 patients with endometrial clear-cell carcinoma (ECC), 6163 patients with endometrial serous carcinoma (ESC), 2072 patients with endometrioid carcinoma with mucinous features (EMC) were included. The mean ages of ENC were younger than that of ECC (65.76 ± 11.33 vs. 69.04 ± 11.67, $p < 0.01$) and ESC (65.76 ± 11.33 vs. 68.82 ± 9.39, $p < 0.01$), and older than that of EAC (65.76 ± 11.33 vs. $62.15 \pm$

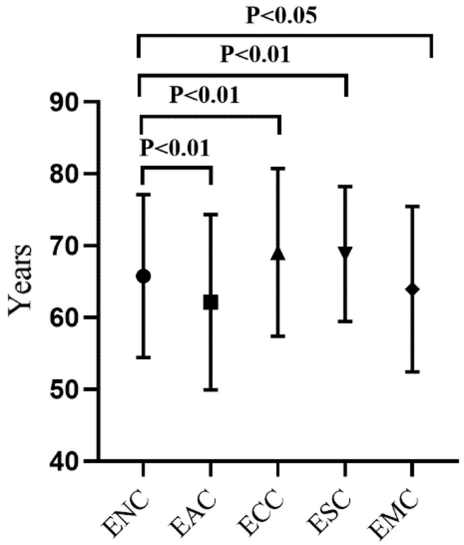

FIGURE 1 Age distribution of different types of endometrial cancers. ENC, endometrial neuroendocrine carcinoma; EAC: endometrioid adenocarcinoma; ECC: endometrial clear-cell carcinoma; ESC: endometrial serous carcinoma; EMC: endometrioid carcinoma with mucinous features

TABLE 1 The mean age of five kinds of endometrial cancers

Histological types	Mean age (years)
ENC	65.76 ± 11.33
EAC	62.15 ± 12.12
ECC	69.04 ± 11.67
ESC	68.82 ± 9.39
EMC	63.95 ± 11.53

Abbreviations: EAC, endometrioid adenocarcinoma; ECC, endometrial clear-cell carcinoma; EMC, endometrioid carcinoma with mucinous features; ENC, endometrial neuroendocrine carcinoma; ESC, endometrial serous carcinoma.

12.12, $p < 0.01$) and EMC (65.76 ± 11.33 vs. 63.95 ± 11.53, $p < 0.05$) (Figure 1, Table 1).

Survival comparison of five histological types of endometrial carcinoma

The median survival times of ENC were 11(95% CI, 7.3–14.7) months, shorter than EAC 220 months (95% CI, 217.1–222.8, $p < 0.01$), ECC 64 months (95% CI, 56.8–71.2, $p < 0.01$), ESC 51 months (95% CI, 47.6–54.4, $p < 0.01$), EMC 209 months (95% CI, 195.0–223.0, $p < 0.01$). The 2-year survival rate 28% (95% CI, 20.16–35.84) and 5-year survival rate 23% (95% CI, 15.16–30.84) of ENC patients were significantly lower than the other endometrial carcinoma (Figure 2, Table 2).

Survival comparison of LCENC and SCENC

There was no significant difference in ages (62.63 ± 11.73 vs 66.57 ± 11.12, $p > 0.05$), survival rate (27 [95% CI: 7.4–46.6] vs. 31 [95% CI: 21.2–40.8]), and median survival time (11 [95% CI: 6–16] vs 12 [95% CI: 4–20], $p > 0.05$) between large-cell endometrial neuroendocrine carcinoma (LCENC) and small-cell endometrial neuroendocrine carcinoma (SCENC), which were all belong to ENC (Figure 3, Table 3).

Clinicopathologic characteristics of ENC

A total of 171 cases of ENC were included in this study. The ratio of grade I-II to grade III-IV was 4/123. According to AJCC staging, there were 58 cases (33.9%) with lymph node metastasis and 77 cases (45%) with tumor distant metastasis at the time of diagnosis, among which 30 cases (17.5%) had lymph node metastasis and tumor distant metastasis. All patients were restaged according to FIGO staging principle based on AJCC and seer staging. There were 37 cases in early stage (FIGO stage I-II) and 125 cases in late stage (FIGO stage III-IV), and 9 cases in unknown stage. Therefore, 77% of the patients were diagnosed as advanced. One hundred and six patients (62%) received surgical treatment. There were 104 patients (60.8%) who received chemotherapy and 45 patients (26.3%) who received radiotherapy (Table 4).

Survival analysis in ENC

One hundred and twenty-three patients were included in the survival analysis excluding patients with unclear histological grade and stage. There were no different between patients with grade III and patients with grade IV (hazard ratio [HR] 1.07, 95% CI 0.67–1.68, $p = 0.078$). The survival rate of ENC was not affected by organizational type of LCENC and SCENC (HR 1.32, 95% CI 0.79–2.22, $p = 0.296$). The cancer-specific survival of patients with ENC who underwent surgery was significantly better than those who did not undergo surgery (HR 0.39, 95% CI 0.25–0.63, $p < 0.01$). Multivariate regression analysis for cancer-specific survival in patients with ENC was also performed, and the detailed results are shown in Table 5 (Figure 4). The hazard ratio for death of stage I-II was 0.37 (95% CI, 0.19–0.72) compared to stage III-IV. Compared to patients without chemotherapy, the hazard ratio for death for women with

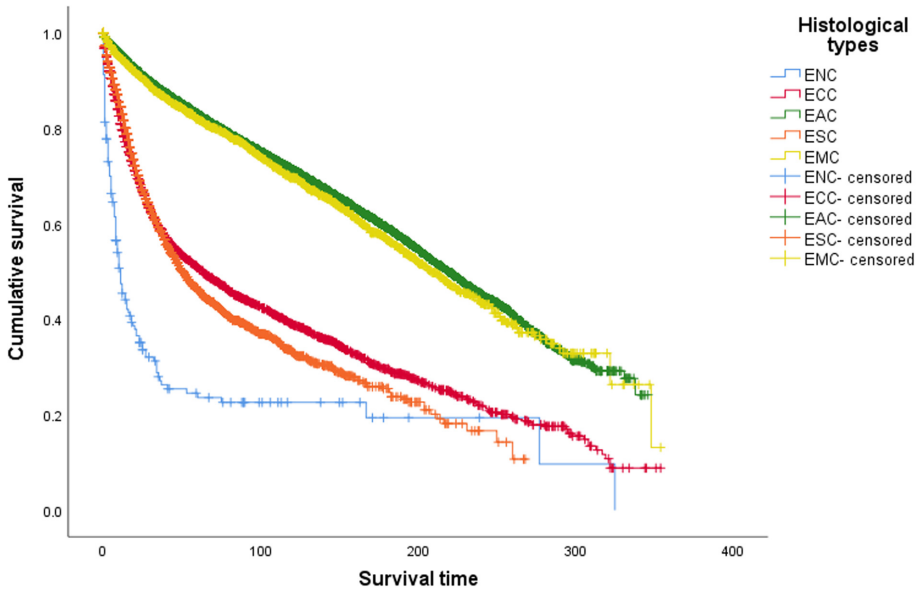

FIGURE 2 Survival curve of different types of endometrial carcinoma

TABLE 2 Comparison of median survival times and survival rates

Histological types	Median survival times (months) (95% CI) (months)	Two-year survival rate (%) (95% CI) (%)	Five-year survival rate (%) (95% CI) (%)
ENC	11 (7.3–14.7)	28 (20.16–35.84)	23 (15.16–30.84)
EAC	220 (217.1–222.8)	89	81
ECC	64 (56.8–71.2)	60 (58.04–61.96)	48 (46.04–49.96)
ESC	51 (47.6–54.4)	59 (57.04–60.96)	43 (41.04–44.96)
EMC	209 (195.0–223.0)	87 (85.04–87.02)	80 (78.04–81.96)

Abbreviation: CI, confidence interval; EAC, endometrioid adenocarcinoma; ECC, endometrial clear-cell carcinoma; EMC, endometrioid carcinoma with mucinous features; ENC, endometrial neuroendocrine carcinoma; ESC, endometrial serous carcinoma.

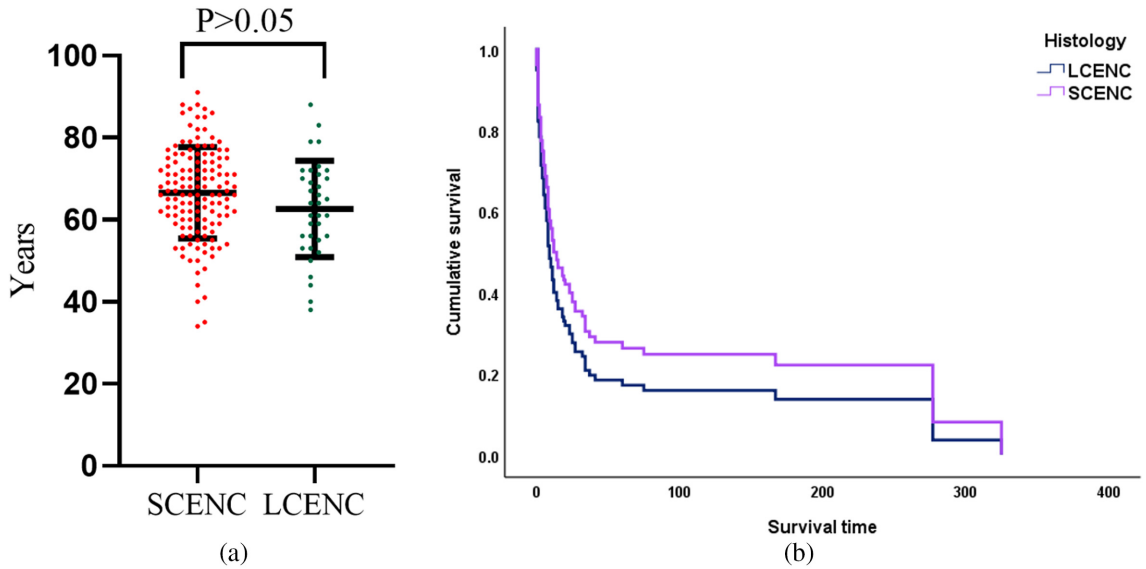

FIGURE 3 (a) Age distribution of different types of SCENC and LCENC; (b) survival curve of different types of SCENC and LCENC. LCENC, large-cell endometrial neuroendocrine carcinoma; SCENC, small-cell endometrial neuroendocrine carcinoma

TABLE 3 The mean age and survival of LCENC and SCENC

Histological types	Mean age (years)	Median survival times (months)	Two-year survival rate (%) (95% CI) (%)	Five-year survival rate (%) (95% CI) (%)
LCENC	62.63 ± 11.73	11 (6–16)	27 (7.4–46.6)	16 (0–35.6)
SCENC	66.57 ± 11.12	12 (4–20)	31 (21.2–40.8)	28 (18.2–37.8)
p	>0.05	>0.05	>0.05	>0.05

Abbreviations: CI: confidence interval; LCENC, large-cell endometrial neuroendocrine carcinoma; SCENC, small-cell endometrial neuroendocrine carcinoma.

TABLE 4 Clinicopathologic characteristics of endometrium neuroendocrine carcinoma patients

Characteristic	*N*	Proportion (%)
Age at diagnosis (years)		
<50	11	6.40%
50–59	36	21.1%
60–69	57	33.3%
70–79	51	29.8%
≥80	16	9.40%
Histological types		
LCENC	35	20.5%
SCENC	136	79.5%
Race		
White	123	71.9%
Black	32	18.7%
Other/unknown	16	9.40%
Year of diagnosis		
1987–1996	14	8.20%
1997–2006	56	32.7%
2007–2016	101	59.1%
Tumor grade		
Grade I	3	1.80%
Grade II	1	0.60%
Grade III	61	35.7%
Grade IV	62	36.2%
Unknown	44	25.7%
SEER stage		
Localized	23	13.5%
Regional	61	35.7%
Distant	77	45.0%
Unknown	10	5.80%
AJCC stage		
T		
T1	37	21.6%
T2	20	11.7%
T3	57	33.3%
T4	8	4.70%
TX	49	28.7%
N		
N0	69	40.4%
N1	58	33.9%
NX	44	25.7%
M		
M0	85	49.7%
M1	77	45.0%
MX	9	5.30%
FIGO stage		
I	24	14.0%
II	13	7.60%
III	45	26.30%
IV	80	46.80%
Unstage	9	5.30%
Surgery performed		
Yes	106	62.0%
No	65	38.0%
Chemotherapy		
Yes	104	60.8%
No/unknown	67	39.2%
Radiotherapy		
Yes	45	26.3%
No/unknown	126	73.7%
Total	171	100%

Abbreviations: AJCC, American Joint Committee on Cancer; FIGO, Federation International of Gynecology and Obstetrics; LCENC, large-cell endometrial neuroendocrine carcinoma; *N*, number; SCENC, small-cell endometrial neuroendocrine carcinoma; SEER, surveillance, epidemiology, and end results.

chemotherapy was 0.51 (95% CI, 0.31–0.81). No surgery was also associated with an increased risk of death. There was no statistical significance in the survival rates of large- and small-cell ENC.

Discussion

Our study showed that ENC was a kind of endometrial epithelial malignant tumor with poor prognosis. Endometrial cancer is diagnosed mainly in postmenopausal women. The average age of ENC is approximately 66 years of age. Ninety percent of women diagnosed with endometrial cancer have abnormal uterine bleeding. Endometrial cancer is often diagnosed in its early stages due to early clinical signs because of abnormal uterine bleeding. However, ENC is a highly aggressive malignant endometrial cancer,

TABLE 5 The results of crude cox regression analysis of ENC

Parameter	HR (95% CI)	*p*-Value
Histological types		
LCENC	1.32 (0.79–2.22)	
SCENC	Referent	0.296
Grade		
III	1.07 (0.67–1.68)	
IV	Referent	0.078
FIGO stage		
I-II	0.37 (0.19–0.72)	
III-IV	Referent	0.004
Surgery		
Yes	0.39 (0.25–0.63)	
No	Referent	0
Chemotherapy		
Yes	0.51 (0.31–0.81)	
No/unknown	Referent	0.005
Radiotherapy		
Yes	0.59 (0.33–1.05)	
No/unknown	Referent	0.072

Abbreviation: CI, confidence interval; ENC, endometrial neuroendocrine carcinoma; HR, hazard ratio; LCENC, large-cell endometrial neuroendocrine carcinoma; SCENC, small-cell endometrial neuroendocrine carcinoma.

which is generally diagnosed at an advanced stage.[2,4] Our data demonstrated that the median survival time of ENC was significantly lower than EAC, ESC, ECC, and EMC. Two-year survival of ENC was only 28% with 5-year survival of only 23%.

ENC includes large-cell and small-cell neuroendocrine carcinoma. The difference between large- and small-cell neuroendocrine carcinoma was mainly manifested in the size of tumor cell volume, nucleocytoplasmic ratio, and nucleolus. LCENC is characterized by large-cell volume, abundant cytoplasm, enlarged nucleus, and common nucleolus. However, SCENC has smaller volume, less cytoplasm, unclear nucleoli, and even no nucleoli. There were few reports about the difference of prognosis between large- and small-cell carcinoma and neuroendocrine carcinoma. Researchers found out previous reports of endometrial NEC surviving >5 years have been of small-cell type, but there are no similar reports in large cell neuroendocrine carcinoma (LCNEC).[5,6] Therefrom, it is concluded that the prognosis of LCENC was worse than SCENC. A retrospective case analysis of 42 cases of ENC published by Matsumoto et al. found the survival rates of pure-type small cell neuroendocrine carcinoma (SCNEC) and mixed-type SCNEC were respectively lower than pure-type LCNEC and mixed-type LCNEC.[7] In our study, the median survival time and survival rate of LCENC were lower than SCENC, but there was no statistical difference. Therefore, whether the histological type affects the prognosis of ENC was need more research to study. However, the incidence rate was contrary in a retrospective study published by Pocrnich et al.[5]

Due to the poor differentiation and high invasiveness, ENC was prone to local or distant metastasis. In this study, 77% (125/162) of the patients were diagnosed as advanced (FIGO III-IV), which was much higher than that of 56%–63% in previous studies.[8–11] There were also research reports 82.4% had lymph-vascular space invasion at the time of diagnosis.[12] There were research reports 82.4% had lymph-vascular space invasion at the time of diagnosis. In our study there were 33.9% (58/171) cases with lymph node metastasis. This is one of the important factors for the very low survival rate of ENC.

At present, there was no unified treatment for ENC. Previous studies have shown that the treatment of NECA is mainly surgery, supplemented by platinum-based chemotherapy or radiotherapy.[10,12,13] These treatments were based on some data of small cell lung cancer, but there was no large-scale study or prospective clinical trial to guide the treatment of ENC. The commonly used chemotherapy regimens of NECA include etoposide and platinum drugs,[14,15] such as etoposide/cisplatin, carboplatin/paclitaxel.[12] Studies have shown that immediate surgery and chemotherapy were preferable to prolong disease-free survival and maintain a good performance status.[16] Our analysis indicated that surgery significantly improved survival rates by multivariate regression analysis for cancer-specific survival. Therefore, surgery should be recommended as the primary treatment modality for neuroendocrine carcinoma of the endometrium with surgical opportunities. The mortality risk ratio of patients with chemotherapy was significantly lower than that of patients without chemotherapy. Therefore, surgery and chemotherapy can markedly improve the prognosis of patients, while radiotherapy did not reduce the risk of death. Due to the lack of access to chemotherapy regimens, it was not clear which chemotherapy regimens patients benefit more.

With the development of targeted therapy, a variety of targeted therapies for small-cell lung tumors and gastrointestinal neuroendocrine tumors were being studied, including angiogenesis inhibitors, mTOR inhibitors, and PARP inhibitors.[17–19] There were more and more studies about targeted therapy in cervical

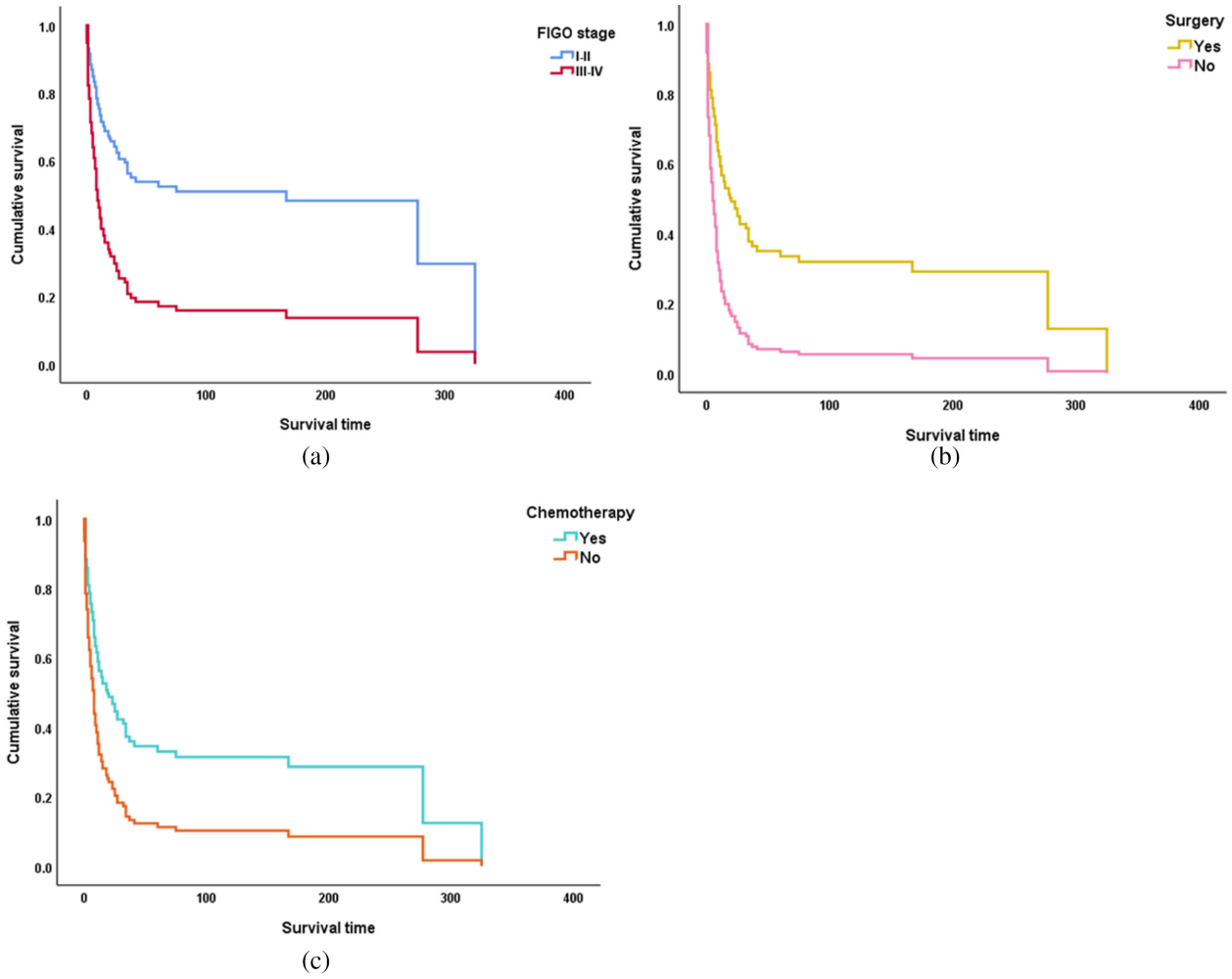

FIGURE 4 (a) Kaplan Meier survival curves of cancer-specific survival for patients with ENC stratified by FIGO stage; (b) Kaplan Meier survival curves of cancer-specific survival of patients with and without surgery for ENC; (c) Kaplan Meier survival curves of cancer-specific survival of patients with and without chemotherapy for ENC

neuroendocrine.[20] However, reports of ENC-targeted therapy were rare. PARP inhibitors were used to two patients of cervical neuroendocrine carcinoma who were detected somatic mutations of BRCA1 and BRCA2.[21] It is known to all patients with a somatic BRCA mutation also show benefit from treatment with PARP inhibitors.[22] Other researchers reported that c-kit mutation was sporadic in cervical neuroendocrine carcinoma. Therefore, c-kit should be selectively applied to patients with cervical neuroendocrine carcinoma.[23] Yasmin a et al. reported a case of cervical neuroendocrine carcinoma with known KRAS mutation receiving trametinib after recurrence. The patient has been taking trametinib for 8 cycles, and there is no sign of disease.[24] Therefore, we speculate that targeted therapy may be an effective way to improve the survival rate of ENC.

The above cases all emphasize the potential benefits of molecular detection in the treatment of patients with ENC of gynecology. However, traditional treatment had limitations for patients with highly invasive ENC. Therefore, gene detection should be recommended for all of ENC. Now, PD-1 inhibitors have been paid more and more attention in tumor therapy. Lenvatinib plus pembrolizumab (an antibody targeting PD-1) showed antitumor activity in patients with advanced recurrent endometrial cancer with a safety profile including endometrial carcinoma.[25] Lenvatinib plus pembrolizumab (an antibody targeting PD-1) showed antitumor activity

in patients with advanced recurrent endometrial cancer with a safety profile.[26] It was reported that the addition of atezolizumab to chemo-therapy in the first-line treatment of extensive-stage small-cell lung cancer resulted in significantly longer overall survival and progression-free survival than chemotherapy alone.[27] We believed that immunosuppressants would also be used in ENC and look forward the prognosis of ENC could be improved.

While SEER database captures cancer statistics of 30% of the US population in 14 registered states, the use of data has important limitations. First, it was a retrospective analysis and selection bias could not be excluded, such as individual patient and physician preferences. Second, the SEER database lacks specific information regarding chemotherapy regimens, disease recurrence, and treatment. we cannot comment on the ideal chemotherapy treatment regimen and treatment of recurrence.

In conclusion, ENC is an extremely rare but aggressive tumor. The prognosis of advanced stage patients is worse. The histological differentiation and grade of ENC may not affect the prognosis. Surgery and chemotherapy can effectively improve the prognosis of patients. There was no prognostic difference between with and without radiotherapy. All of ENC should be recommended gene detection and clinical trial.

Author contributions

Zhifang Zhang contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript. Jing Wang contributed to acquisition of data, drafting of manuscript. Xiaomei Wu contributed to critical revision of the manuscript for important intellectual content, statistical analysis. Yuan Liu contributed to statistical analysis. Xiaowei Xi contributed to conception and design, critical revision of the manuscript for important intellectual content, administrative technical or material support, supervision.

Conflict of interest

None declared.

Data availability statement

The data used for the present article are available in SEER.

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