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Neuroendocrine carcinoma of the endometrium: Disease course, treatment, and outcomes☆

Kathryn Schlechtweg [a], Ling Chen [a], Caryn M. St. Clair [a, c, d], Ana I. Tergas [a, b, c, d], Fady Khoury-Collado [a, c, d], June Y. Hou [a, c, d], Alexander Melamed [a, c, d], Alfred I. Neugut [a, b, c, d], Dawn L. Hershman [a, b, c, d], Jason D. Wright [a, c, d, *]

[a] Columbia University Vagelos College of Physicians and Surgeons, United States of America
[b] Joseph L. Mailman School of Public Health, Columbia University, United States of America
[c] Herbert Irving Comprehensive Cancer Center, United States of America
[d] New York-Presbyterian Hospital, Columbia University Irving Medical Center, United States of America

HIGHLIGHTS

- Neuroendocrine carcinoma of the endometrium is a rare and aggressive uterine carcinoma.
- Compared to patients with poorly differentiated endometrioid tumors, patients with neuroendocrine carcinomas present with later stage disease.
- Survival for neuroendocrince carcinomas is inferior to that of high grade endometrioid carcinomas.

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ABSTRACT

Objective: Neuroendocrine carcinoma of the endometrium (NECE) is a rare malignancy. We examined the natural history and outcomes of women with NECE compared to patients with poorly differentiated endometrioid endometrial cancer (EC).

Methods: The National Cancer Database (NCDB) was used to identify women with NECE and women with poorly differentiated EC from 2004 to 2015. Clinical, demographic, and treatment characteristics were compared between groups. Kaplan-Meier survival curves and multivariable Cox proportional hazard regression models were used to identify associations between tumor histology and survival.

Results: A total of 28,291 women with EC and 364 women with NECE were identified. Patients with NECE were more often non-white and presented with later stage disease compared to patients with EC. Women with NECE were more likely to receive adjuvant chemotherapy (60.2% vs. 29.6%), but were less likely to receive radiation (28.0% vs. 47.6%) ($P < 0.001$ for both). Median survival was 17 months (95% CI, 12–23) for NECE and 144 months (95% CI, 140–148) for EC. 5-year survival was 38.3% (95% CI, 32.7–43.8%) for NECE vs. 68.8% (95% CI, 68.2–69.4%) for EC. In a multivariable model, the hazard ratio for death for women with NECE compared to EC was 2.32 (95% CI, 1.88–2.88). Similar findings were noted when the analysis was limited to women with stage I (HR = 1.62; 95% CI, 1.01–2.61), and stage III (HR = 2.57; 95% CI, 1.88–3.53) neoplasms.

Conclusions: NECE is a rare and aggressive uterine carcinoma. Compared to patients with poorly differentiated EC, patients with NECE present with later stage disease and have decreased survival.

1. Introduction

Neuroendocrine carcinomas of the endometrium (NECE) are rare tumors accounting for just 0.8% of endometrial carcinomas [1]. NECE falls under neuroendocrine tumors (NETs) which represent a spectrum of tumors all arising from the neuroendocrine cell system with prognosis determined by histology and site of origin [2]. NETs are subdivided into well-differentiated low-grade tumors, including carcinoid and atypical carcinoid, and poorly-differentiated high-grade tumors, including small cell carcinoma

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* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, 161 Fort Washington Ave, 8th Floor, New York, NY 10032, United States of America.
E-mail address: jw2459@columbia.edu (J.D. Wright).

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(SCC) and large cell carcinoma (LCC) which together are neuroendocrine carcinomas (NECs) [2,6–9]. Histologically, poorly-differentiated NECs (SCC and LCC) have a high mitotic rate, nuclear atypia, frequent lymphovascular space invasion, and necrosis. In the gynecologic tract, these tumors most commonly arise in the cervix and follow an aggressive clinical course [2,3].

NECE are generally considered aggressive tumors and often present with advanced-stage disease [12,13]. Their presenting symptoms are usually abnormal uterine bleeding or symptomatic metastases [2,11,12]. Histologically, NECE is often in admixture with other endometrial malignancies, most commonly endometrioid carcinoma [4,10,12,14,15]. While the literature on NECE is limited, prior reports have suggested that prognosis is poor with most patients recurring within two years of diagnosis [2,5,10]. The mean overall survival has been reported as 22 and 12 months for stage I–II and stage III–IV disease, respectively [5].

Given the paucity of data describing the outcomes of women with NECE, we performed an analysis to examine the natural history and outcomes of women with neuroendocrine carcinomas of the endometrium. Specifically, we compared the clinical and demographic characteristics and survival of women with NECE to women with poorly differentiated endometrioid adenocarcinomas.

2. Methods

2.1. Data source and patient selection

The National Cancer Database (NCDB) was used for analysis. The NCDB is a registry developed and sponsored by the American College of Surgeons and American Cancer Society [23,24]. The NCDB captures all patients with newly diagnosed invasive cancers from over 1500 Commission on Cancer (CoC) affiliated hospitals across the United States. NCDB collects data on patient characteristics, cancer staging and tumor histological characteristics, first course of treatment, and outcomes. Incident tumor cases are compiled by trained registrars and the data is audited regularly to confirm accuracy [23,24].

We identified all women with stage I–IV neuroendocrine carcinoma of the endometrium (NECE) and endometrioid endometrial carcinoma (EC) from 2004 to 2015. We excluded all patients without histological confirmation, those who received neoadjuvant therapies, and those who did not undergo hysterectomy. We limited our cohort of women with endometrioid adenocarcinoma to those with poorly differentiate EC (Fig. 1).

2.2. Clinical and demographic characteristics

Demographic data in this analysis included age at diagnosis (<50, 50–59, 60–69, 70–79, ≥80 years), race (white, black, Hispanic, other, or unknown), insurance status (uninsured, private, Medicaid, Medicare, or other government/unknown), median household income for the patient's zip code (<$38,000, $38,000–$47,999, $48,000–$62,999, ≥$63,000, or unknown), education which was measured as percent of adults in the patient's zip code who did not graduate from high school (≥21%, 13–20%, 7–12.9%, <7%, or unknown), location (metropolitan, urban, rural, unknown), comorbidity (0, 1, ≥2) and year of diagnosis (2004–2015). Tumor stage (IA–IVB or unknown) and grade (well, moderate, poorly, or unknown) were recorded for each patient. Hospital data included region (Northeast, Midwest, South, or West).

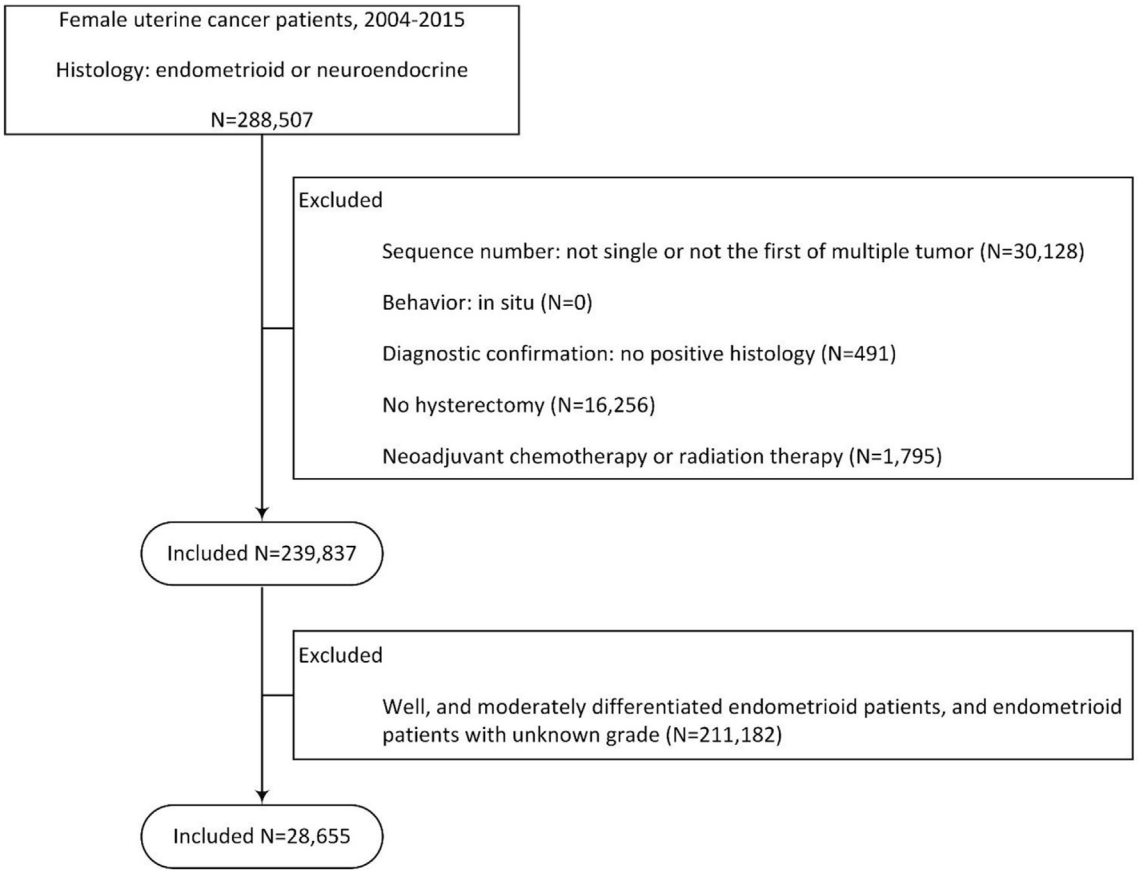

Fig. 1. Flowchart of cohort selection.

Table 1
Demographic, clinical and treatment characteristics comparing NECE and EC.

	Endometrioid adencocaricnoma		Neuroendocrine carcinoma		*P*-value
	N	(%)	N	(%)	
All	28,291	(98.7)	364	(1.3)	
Age					0.62
<50	2695	(9.5)	41	(11.3)	
50–59	7389	(26.1)	88	(24.2)	
60–69	9417	(33.3)	114	(31.3)	
70–79	5916	(20.9)	82	(22.5)	
≥80	2874	(10.2)	39	(10.7)	
Race					0.02
White	22,300	(78.8)	265	(72.8)	
Black	3038	(10.7)	50	(13.7)	
Hispanic	1492	(5.3)	29	(8.0)	
Other	1118	(4.0)	18	(4.9)	
Unknown	343	(1.2)	*	*	
Year					0.01
2004	2061	(7.3)	22	(6.0)	
2005	2173	(7.7)	24	(6.6)	
2006	2306	(8.2)	17	(4.7)	
2007	2278	(8.1)	19	(5.2)	
2008	2414	(8.5)	32	(8.8)	
2009	2385	(8.4)	34	(9.3)	
2010	2531	(8.9)	41	(11.3)	
2011	2766	(9.8)	30	(8.2)	
2012	2399	(8.5)	36	(9.9)	
2013	2391	(8.5)	27	(7.4)	
2014	2339	(8.3)	36	(9.9)	
2015	2248	(7.9)	46	(12.6)	
Insurance status					0.21
Private	12,704	(44.9)	146	(40.1)	
Medicare	12,239	(43.3)	165	(45.3)	
Medicaid	1497	(5.3)	20	(5.5)	
Uninsured	1124	(4.0)	21	(5.8)	
Other government/ unknown	727	(2.6)	12	(3.3)	
Income					0.91
<$38,000	4958	(17.5)	62	(17.0)	
$38,000–$47,999	6501	(23.0)	86	(23.6)	
$48,000–$62,999	7557	(26.7)	101	(27.7)	
$63,000+	8996	(31.8)	113	(31.0)	
Unknown	279	(1.0)	*	*	
Education					0.89
≥21%	4799	(17.0)	62	(17.0)	
13–20%	7201	(25.5)	92	(25.3)	
7.0–12.9%	9300	(32.9)	126	(34.6)	
<7%	6726	(23.8)	82	(22.5)	
Unknown	265	(0.9)	*	*	
Location					0.79
Metropolitan	22,619	(80.0)	294	(80.8)	
Urban	4254	(15.0)	49	(13.5)	
Rural	537	(1.9)	*	*	
Unknown	881	(3.1)	13	(3.6)	
Comorbidity					0.52
0	21,208	(75.0)	282	(77.5)	
1	5717	(20.2)	65	(17.9)	
≥2	1366	(4.8)	17	(4.7)	
Hospital type					0.51
Academic/research	11,960	(42.3)	162	(44.5)	
Community cancer	1414	(5.0)	13	(3.6)	
Comprehensive community cancer	11,725	(41.4)	145	(39.8)	
Integrated network cancer	3192	(11.3)	44	(12.1)	
Hospital region					0.98
Northeast	6544	(23.1)	84	(23.1)	
Midwest	7457	(26.4)	95	(26.1)	
South	9515	(33.6)	126	(34.6)	
West	4775	(16.9)	59	(16.2)	
Stage					<0.001
IA	9278	(32.8)	35	(9.6)	
IB	5465	(19.3)	24	(6.6)	
I NOS	845	(3.0)	*	*	
II	2270	(8.0)	22	(6.0)	
IIIA	903	(3.2)	19	(5.2)	
IIIB	450	(1.6)	*	*	
IIIC	3883	(13.7)	85	(23.4)	
III NOS	313	(1.1)	*	*	
IVA	278	(1.0)	11	(3.0)	
IVB	1539	(5.4)	67	(18.4)	
IV NOS	195	(0.7)	10	(2.7)	
Unknown	2872	(10.2)	72	(19.8)	
Grade					<0.001
Well	–	–	*	*	
Moderate	–	–	*	*	
Poorly	28,291	(100.0)	301	(82.7)	
Unknown	–	–	50	(13.7)	
Chemotherapy					<0.001
No	18,871	(66.7)	134	(36.8)	
Yes	8385	(29.6)	219	(60.2)	
Unknown	1035	(3.7)	11	(3.0)	
Radiation					<0.001
No	14,550	(51.4)	260	(71.4)	
Yes	13,470	(47.6)	102	(28.0)	
Unknown	271	(1.0)	*	*	

* Cell size < 10.

Additionally, hospitals were classified by CoC criteria as academic/research centers, community cancer center, comprehensive community cancer center, or integrated network cancer center [25]. Treatment patterns included chemotherapy and radiation.

2.3. Statistical analysis

Clinical and demographic characteristics of women with NECE and EC were compared using Chi-square tests. Kaplan-Meier survival curves were generated to compare survival between women with NECE and EC and compared using log-rank tests. Marginal Cox proportional hazard regression models were developed to analyze the associations between overall survival and histology while adjusting for clinical and demographic differences and hospital level clustering. The model included age, race, year of diagnosis, insurance, income, location, comorbidity, facility type and region, stage, histology, chemotherapy and radiation. Similar models were fitted among stage I and stage III tumors. A separate model limited to women with NECE was also developed. All hypothesis tests were two-sided. To examine differences in outcomes among women with various histologic subtypes of NECE, we performed a stratified analysis to analyze women with small cell and large cell

Table 2
Five-year survival rate by stage, comparing NECE and EC.

	EC, % (95% CI)	NECE, % (95% CI)
Overall	68.8% (68.2%–69.4%)	38.3% (32.7%–43.8%)
Stage		
IA	85.4% (84.5%–86.2%)	76.4% (56.5%–88.0%)
IB	72.7% (71.2%–74.1%)	65.0% (40.3%–81.5%)
I NOS	83.5% (80.4%–86.2%)	83.3% (27.3%–97.5%)
II	67.1% (64.9%–69.2%)	37.5% (15.4%–59.8%)
IIIA	58.2% (53.6%–62.4%)	16.1% (1.0%–48.3%)
IIIB	46.4% (40.7%–51.9%)	45.0% (10.8%–75.1%)
IIIC	53.1% (51.3%–54.9%)	34.2% (22.9%–45.8%)
III NOS	61.6% (55.0%–67.6%)	33.3% (0.9%–77.4%)
IVA	28.8% (23.0%–35.0%)	0.0% (0.0%–0.0%)
IVB	27.7% (25.2%–30.3%)	15.4% (6.9%–27.0%)
IV NOS	27.5% (20.6%–35.0%)	12.0% (0.7%–40.8%)
Unknown	63.4% (61.6%–65.2%)	42.2% (30.4%–53.5%)

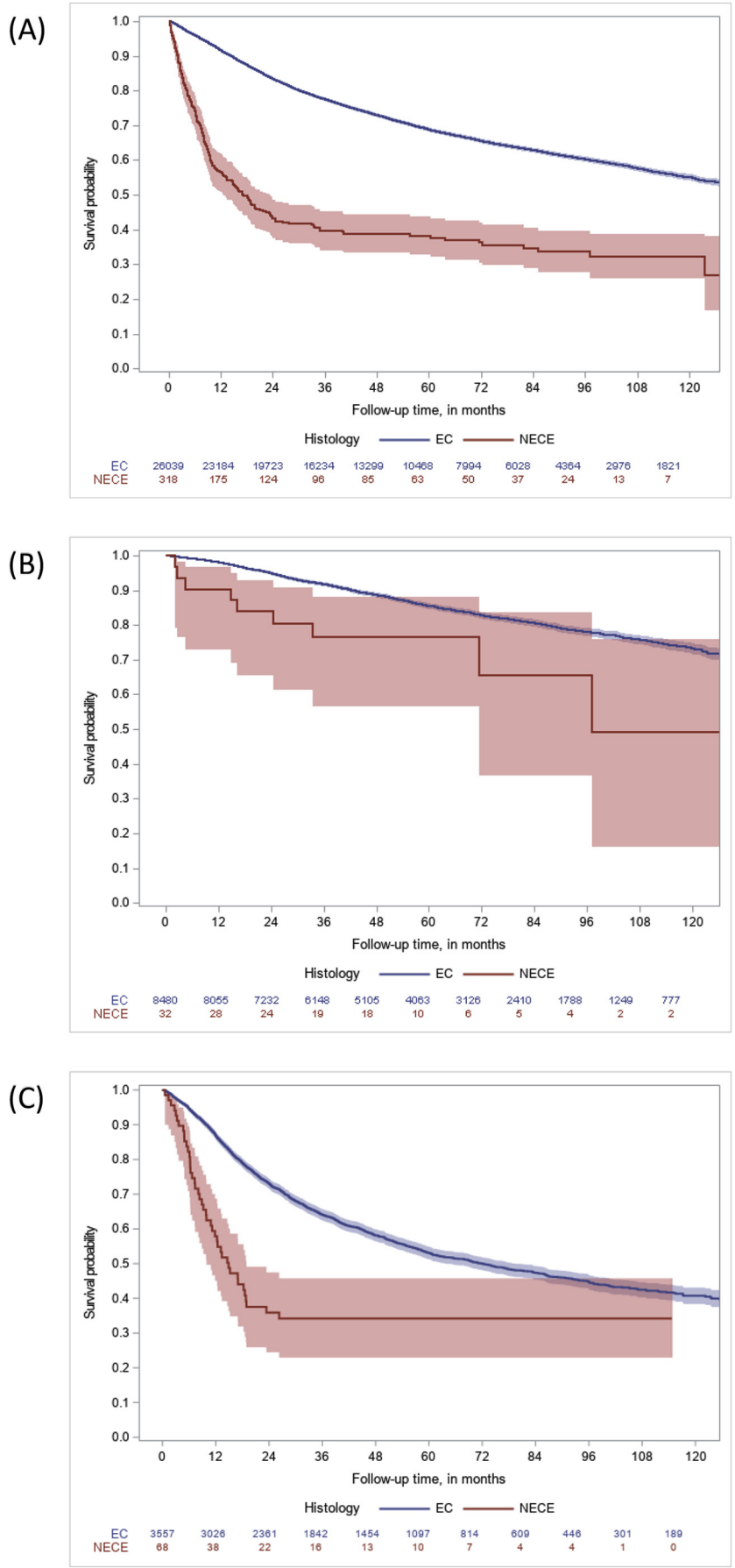

Fig. 2. Kaplan-Meier curves comparing NECE and EC. (A) Overall (P-value < 0.001); (B) stage IA (P-value = 0.02); (C) stage IIIC (P-value < 0.001). Shade represented 95% CI.

Table 3
Multivariable model for predictors of all-cause mortality among the overall cohort, and stratified by stage.

	Overall aHR	Stage I aHR	Stage III aHR
Age			
<50	Referent	Referent	Referent
50–59	1.14 (1.03–1.26)*	1.14 (0.92–1.41)	1.23 (1.02–1.49)*
60–69	1.49 (1.34–1.65)*	1.73 (1.40–2.14)*	1.51 (1.25–1.82)*
70–79	2.09 (1.88–2.34)*	2.74 (2.18–3.45)*	2.03 (1.65–2.49)*
≥80	3.49 (3.09–3.94)*	5.28 (4.17–6.70)*	2.80 (2.23–3.50)*
Race			
White	Referent	Referent	Referent
Black	1.34 (1.24–1.45)*	1.49 (1.31–1.68)*	1.23 (1.08–1.40)*
Hispanic	0.86 (0.76–0.97)*	0.92 (0.75–1.14)	0.72 (0.58–0.89)*
Other	0.94 (0.81–1.08)	0.96 (0.76–1.20)	0.86 (0.66–1.13)
Unknown	0.94 (0.74–1.19)	0.71 (0.48–1.05)	0.95 (0.57–1.57)
Year			
2004	Referent	Referent	Referent
2005	1.06 (0.96–1.17)	1.08 (0.93–1.25)	1.14 (0.91–1.42)
2006	0.99 (0.90–1.09)	0.97 (0.83–1.14)	0.89 (0.72–1.11)
2007	1.01 (0.92–1.12)	1.00 (0.86–1.17)	0.94 (0.74–1.18)
2008	1.01 (0.91–1.12)	1.03 (0.86–1.22)	0.99 (0.79–1.23)
2009	0.91 (0.82–1.01)	0.77 (0.64–0.92)*	1.02 (0.81–1.28)
2010	0.95 (0.85–1.07)	1.00 (0.84–1.18)	0.97 (0.79–1.21)
2011	0.99 (0.89–1.11)	1.03 (0.86–1.23)	0.94 (0.76–1.16)
2012	1.00 (0.88–1.12)	1.03 (0.85–1.25)	1.02 (0.81–1.27)
2013	1.06 (0.94–1.20)	1.19 (0.98–1.44)	1.04 (0.83–1.30)
2014	1.04 (0.91–1.19)	1.11 (0.87–1.41)	1.06 (0.83–1.36)
Insurance status			
Private	Referent	Referent	Referent
Medicare	1.27 (1.20–1.35)*	1.38 (1.24–1.53)*	1.18 (1.05–1.33)*
Medicaid	1.36 (1.22–1.52)*	1.61 (1.32–1.96)*	1.32 (1.09–1.61)*
Uninsured	1.29 (1.13–1.47)*	1.32 (1.01–1.72)*	1.39 (1.12–1.72)*
Other government/unknown	1.15 (1.004–1.32)*	1.31 (1.04–1.65)*	0.98 (0.71–1.34)
Income			
<$38,000	Referent	Referent	Referent
$38,000–$47,999	0.99 (0.92–1.06)	0.95 (0.86–1.06)	0.95 (0.82–1.09)
$48,000–$62,999	0.99 (0.92–1.07)	0.91 (0.81–1.01)	0.98 (0.85–1.12)
$63,000+	0.87 (0.80–0.93)*	0.79 (0.70–0.89)*	0.88 (0.76–1.01)
Unknown	2.09 (1.69–2.59)*	2.02 (1.38–2.95)*	3.27 (2.19–4.87)*
Location			
Metropolitan	Referent	Referent	Referent
Rural	0.99 (0.86–1.15)	1.04 (0.82–1.34)	1.02 (0.75–1.39)
Unknown	0.98 (0.85–1.13)	0.95 (0.75–1.20)	0.80 (0.58–1.09)
Urban	1.02 (0.94–1.10)	1.03 (0.93–1.14)	1.04 (0.91–1.19)
Comorbidity			
0	Referent	Referent	Referent
1	1.24 (1.17–1.31)*	1.23 (1.13–1.35)*	1.12 (1.01–1.26)*
≥2	1.66 (1.53–1.81)*	1.80 (1.57–2.06)*	1.78 (1.50–2.13)*
Hospital type			
Academic/research	Referent	Referent	Referent
Community cancer	1.05 (0.94–1.18)	1.20 (1.02–1.41)*	1.00 (0.83–1.20)
Comprehensive community cancer	1.06 (0.999–1.13)	1.10 (1.01–1.19)*	1.07 (0.96–1.18)
Integrated network cancer	1.02 (0.92–1.13)	1.09 (0.95–1.25)	1.09 (0.92–1.28)
Hospital region			
Northeast	Referent	Referent	Referent
Midwest	1.07 (0.98–1.17)	1.01 (0.91–1.12)	1.08 (0.94–1.25)
South	1.06 (0.98–1.16)	1.00 (0.89–1.11)	1.08 (0.94–1.24)
West	1.05 (0.96–1.16)	0.98 (0.87–1.12)	1.11 (0.95–1.29)
Stage			
IA	Referent	Referent	–
IB	1.90 (1.77–2.03)*	1.79 (1.66–1.93)*	–
I NOS	1.16 (0.99–1.36)	1.17 (0.99–1.39)	–
II	2.42 (2.21–2.65)*	–	–
IIIA	3.73 (3.26–4.26)*	–	Referent
IIIB	5.53 (4.74–6.45)*	–	1.53 (1.27–1.85)*
IIIC	4.61 (4.25–5.00)*	–	1.27 (1.11–1.46)*
III NOS	3.52 (2.94–4.21)*	–	0.93 (0.75–1.14)
IVA	9.55 (7.90–11.56)*	–	–
IVB	9.77 (8.78–10.87)*	–	–
IV NOS	8.81 (7.03–11.03)*	–	–
Unknown	2.76 (2.55–2.99)*	–	–
Histology			
Endometrioid	Referent	Referent	Referent
Neuroendocrine	2.32 (1.88–2.88)*	1.62 (1.01–2.61)*	2.57 (1.88–3.53)*
Chemotherapy			
No	Referent	Referent	Referent
Yes	0.80 (0.74–0.85)*	0.93 (0.82–1.06)	0.68 (0.62–0.76)*
Unknown	0.73 (0.64–0.84)*	0.68 (0.55–0.85)*	0.61 (0.48–0.77)*

Table 3 (*continued*)

	Overall aHR	Stage I aHR	Stage III aHR
Radiation			
No	Referent	Referent	Referent
Yes	0.77 (0.73–0.80)*	0.89 (0.83–0.97)*	0.63 (0.58–0.69)*
Unknown	0.76 (0.60–0.97)*	0.74 (0.50–1.09)	1.11 (0.76–1.61)

Marginal Cox proportional model was fitted including age, race, year, insurance status, income, location, comorbidity, hospital type and region, stage, histology, chemotherapy and radiation, accounting for hospital level of clustering. Separate models were fitted for stage I and stage III tumors.

* *P*-value < 0.05.

neuroendocrine tumors. A *P*-value of <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

3. Results

A total of 28,655 women including 28,291 (98.7%) diagnosed with poorly differentiated EC and 364 (1.3%) with NECE were identified (Table 1). Patients with NECE were more often black (13.7% NECE vs. 10.7% EC), Hispanic (8.0% NECE vs. 5.3% EC) ($P = 0.02$), and present with stage III or IV disease (55.7% NECE vs. 26.7% EC) ($P < 0.001$). Women with NECE were less likely to receive a diagnosis prior to 2008 (22.5% NECE vs. 31.3% EC) ($P = 0.01$) and present with stage I disease (18.4% NECE vs. 55.1% EC) ($P < 0.001$).

Treatment patterns differed between the NECE and EC groups (Table 1). Patients with NECE were more likely to receive adjuvant chemotherapy than those with EC (60.2% NECE vs. 29.6% EC) ($P < 0.001$). Additionally, patients with NECE were less likely to receive adjuvant radiotherapy than those with EC (28.0% NECE vs. 47.6% EC) ($P < 0.001$) (Table 1). Among women with stage I tumors, 48.8% of NECE received chemotherapy compared to 13.0% of those with EC.

The median follow-up time for the cohort was 49 months. Median survival in women with NECE was 17 months (95% CI, 12–23 months) compared to 144 months (95% CI, 140–148 months) for women with EC (Table 2). In women with NECE, five-year survival was 38.3% (95% CI, 32.7%–43.8%) while five-year survival in women with EC was 68.8% (95% CI, 68.2%–69.4%). In a series of Kaplan-Meier analyses, survival was worse for NECE patients compared to EC patients overall ($P < 0.001$), for stage IA disease ($P = 0.02$), and for stage IIIC disease ($P < 0.001$, Fig. 2).

The risk of death for women with NECE was higher than that of women with EC (Table 3). For all stages, the hazard ratio for death for patient with NECE was 2.32 (95% CI, 1.88–2.88) compared to those EC. Compared to women with EC, the hazard ratio for death for women with stage I NECE was 1.62 (95% CI, 1.01–2.61) and 2.57 (95% CI, 1.88–3.53) for those with stage III disease. Advanced stage disease, advanced age, greater comorbidity and non-private insurance were also associated with an increased risk of death.

In models that were restricted to women with NECE, several factors were identified as independent predictors of death (Table 4). Risk of death was significantly increased in patient with NECE diagnosed at 80 years of age or older with hazard ratio of death 2.41 (95% CI, 1.17–4.99). All patients with NECE who presented with stage II disease or higher had increased risk of death compared to those presenting with stage I disease. Patient with NECE who were treated with adjuvant chemotherapy had decreased risk of death seen in a hazard ratio of death of 0.36 (95% CI, 0.23–0.56) compared to patients who did not receive adjuvant chemotherapy. In an analysis of just women with small cell (N = 135) and large cell (N = 56) NECE there was no difference in survival in either an unadjusted model (HR = 0.85; 95% CI, 0.57–1.26) or after adjustment for the other clinical and demographic characteristics (HR = 0.91; 95% CI, 0.49-1.69).

4. Discussion

Our data demonstrate that NECE has a distinctive natural history and follows an aggressive clinical course. Survival for women with NECE is worse than the survival of women with poorly differentiated EC. The decreased survival associated with NECE was noted for women with both early and advanced stage disease. Additionally, for women with NECE, chemotherapy reduced their risk of death while radiotherapy did not.

Given the rarity of NECE, the literature consists of only case reports and small-case series, the largest of which includes 25 patients [12,13]. Prior studies reported mean survival of approximately 22 months for stage I–II disease and approximately 12 months for stage III-IV tumors respectively [5]. Few long term survivors have been reported in the literature with an overall survival between 2 and 11 years [5,10–13,16–19]. The cohort of long term survivors in the literature had consisted of mostly stage I disease until a recent study by Pocrnich and colleagues reported on a cohort of 25 patients with NECE. They had 10 long-term survivors, of whom 6 had stage III or IV disease [13]. Seven patients in their cohort attained 5-year survival of whom 3 had stage I disease and 4 had stage III disease. These patients received surgical resection, radiotherapy, and chemotherapy [13]. Our data confirm that survival for women with NECE is poor overall. For all women with NECE, five-year survival was 38.3% and median survival was 17 months from diagnosis.

Patients with NECE tumors are at increased risk for metastatic disease at the time of diagnosis. Several reports in the literature report similar findings, with 56% presenting with stage III or IV [12,13]. These tumors likely are highly proliferative with early spread outside of the endometrium which may hinder early detection. We noted similar findings, 31% of women in our study were diagnosed with stage III neoplasms while 21% had stage IV tumors.

Treatment strategies for NECE are not standardized. Prior series describe a variety of treatments including surgical resection, radiotherapy, and platinum-based chemotherapy [5,10–13,16–19]. These treatment options are based in part on small cell lung cancer data, but no large studies or prospective clinical trials have been performed to guide treatment of NECE. Extrapolating from other tumor sites, chemotherapy for NECE often consists of etoposide and a platinum analog. In our cohort, all patients underwent surgical resection and 60% received chemotherapy while 28% underwent radiotherapy. Additionally, patients with NECE were more likely to receive chemotherapy and less likely to receive radiotherapy than patients with EC. Our data demonstrated a significantly decreased risk of death when patient with NECE were treated with chemotherapy, but no decreased risk of death was found for radiotherapy.

Given the poor prognosis for patients with neuroendocrine tumors, targeted therapeutic approaches have been described for these tumors at other sites. Recent studies of neuroendocrine cervical cell lines and neuroendocrine carcinoma of the cervix (NECC) case studies have identified potential targeted therapies including PD-1, PI3K, and MEK inhibitors [20–22]. Specifically, cell growth was significantly inhibited when a PI3K inhibitor was combined

Table 4
Multivariable model for predictors of all-cause mortality among women with NECE.

	aHR
Age	
<50	Referent
50–59	1.43 (0.70–2.91)
60–69	1.22 (0.65–2.29)
70–79	1.35 (0.66–2.77)
≥80	2.41 (1.17–4.99)*
Race	
White	Referent
Black	1.16 (0.67–2.00)
Hispanic	0.78 (0.41–1.50)
Other	0.94 (0.40–2.25)
Unknown	0.90 (0.18–4.43)
Year	
2004	Referent
2005	1.47 (0.64–3.36)
2006	0.84 (0.28–2.49)
2007	2.37 (0.94–5.97)
2008	2.26 (0.96–5.30)
2009	1.06 (0.43–2.62)
2010	1.77 (0.78–4.04)
2011	1.62 (0.66–3.95)
2012	1.94 (0.88–4.28)
2013	2.44 (0.97–6.14)
2014	1.85 (0.76–4.45)
Insurance status	
Private	Referent
Medicare	1.13 (0.72–1.77)
Medicaid	1.12 (0.40–3.14)
Uninsured	1.37 (0.63–3.01)
Other government/unknown	1.10 (0.33–3.72)
Income	
<$38,000	Referent
$38,000–$47,999	1.44 (0.77–2.69)
$48,000–$62,999	1.61 (0.89–2.93)
$63,000+	1.25 (0.65–2.41)
Unknown	7.04 (1.15–43.04)*
Location	
Metropolitan	Referent
Rural	1.12 (0.30–4.10)
Unknown	0.34 (0.07–1.56)
Urban	0.99 (0.57–1.73)
Comorbidity	
0	Referent
1	1.24 (0.79–1.95)
≥2	1.19 (0.58–2.42)
Hospital type	
Academic/research	Referent
Community cancer	1.21 (0.52–2.81)
Comprehensive community cancer	1.02 (0.70–1.49)
Integrated network cancer	0.75 (0.41–1.37)
Hospital region	
Northeast	Referent
Midwest	0.93 (0.51–1.71)
South	1.05 (0.59–1.87)
West	0.90 (0.51–1.59)
Stage	
IA	Referent
IB	2.69 (0.98–7.35)
I NOS	0.58 (0.15–2.31)
II	5.00 (1.84–13.55)*
IIIA	4.74 (1.64–13.73)*
IIIB	8.46 (2.39–29.92)*
IIIC	7.16 (3.02–16.98)*
III NOS	16.39 (5.08–52.87)*
IVA	18.92 (7.41–48.33)*
IVB	14.94 (6.29–35.48)*
IV NOS	10.04 (3.51–28.67)*
Unknown	5.14 (2.04–12.99)*
Chemotherapy	
No	Referent
Yes	0.36 (0.23–0.56)*
Unknown	0.33 (0.08–1.39)
Radiation	
No	Referent
Yes	0.78 (0.53–1.15)
Unknown	2.67 (0.79–9.04)

Marginal Cox proportional model was fitted among women with NECE. The model included age, race, year, insurance status, income, location, comorbidity, hospital type and region, stage, chemotherapy and radiation, accounting for hospital level of clustering.

* P-value < 0.05.

with etoposide and cisplatin [20]. Paraghamian and co-workers reported a case of NECC treated with nivolimumab, a PD-1 inhibitor, that resulted in a “complete response” [21]. Another report described a patient with a NECC with a KRAS mutation that was treated with trametininb, a MEK inhibitor, and the patient is currently living disease free [22]. Additionally, multiple targeted therapies are being studied for pulmonary small cell tumors including angiogenesis inhibitors, mTOR inhibitors, and PARP inhibitors [25–29]. Afibercept, a VEGF inhibitor, when combined with topotecan improved survival in patients with recurrent small cell lung cancer [25]. Given that small cell lung cancer highly expresses PARP1, PARP inhibitors seem to be another possible strategy currently under investigation [28]. Given rarity of NECE, it is unlikely that trials of these targeted therapies will be performed in women with neuroendocrine uterine tumors.

While the use of a large, nationwide dataset allowed us to include a large sample of women with NECE, the use of administrative data has important limitations. The data set lacks specific information regarding chemotherapy regimens, radiation protocols, and disease recurrence and treatment. Additionally, the NCDB only captures 70% of newly diagnosed cancers in the US which could hinder its generalizability. Given the rarity of NECE and the commonly admixed histology it is possible that patients’ in this cohort were misclassified as there was no central pathology review. Finally, the data cannot capture individual patient and physician preferences.

In this study, we demonstrated that NECE is a rare and aggressive histological subtype of uterine cancer with poor survival. Survival is inferior for NECE compared to women with EC at all stages of disease. Most treatment strategies for NECE are based upon case reports and small-cohort case series that utilize multimodal therapy based on pulmonary SCC treatment. Further studies are needed to prospectively analyze the natural history, treatment regimens, and survival of women with NECE.

Author contributions

Kathryn Schlechtweg — study conception, analysis of data, manuscript preparation, and final approval of manuscript.

Ling Chen — study conception, analysis of data, manuscript preparation, and final approval of manuscript.

Caryn M. St. Clair — analysis of data, manuscript preparation, and final approval of manuscript.

Fady Khoury Collado — analysis of data, manuscript preparation, and final approval of manuscript.

June Y. Hou — analysis of data, manuscript preparation, and final approval of manuscript.

Alexander Melamed — analysis of data, manuscript preparation, and final approval of manuscript.

Ana I. Tergas — analysis of data, manuscript preparation, and final approval of manuscript.

Jason D. Wright — study conception, analysis of data, manuscript preparation, and final approval of manuscript.

Declaration of competing interest

Dr. Wright has served as a consultant for Tesaro and Clovis Oncology and received research funding from Merck. Dr. Neugut has served as a consultant to Pfizer, Teva, Otsuka, Hospira, and United Biosource Corporation. He is on the scientific advisory board

of EHE, Intl. No other authors have any conflicts of interest or disclosures.

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