GYNECOLOGY

Clinicopathologic features, incidence, and survival trends of gynecologic neuroendocrine tumors: a SEER database analysis

Jennifer Gibbs, DO; Shirley Mei, MD; Katherine Economos, MD; Yi-Chun Lee, MD; Margaux J. Kanis, MD

BACKGROUND: Primary gynecologic neuroendocrine tumors are uncommon malignant neoplasms associated with poor prognosis. Clinically, these tumors present a significant challenge because of the lack of standardized management guidelines.

OBJECTIVE: The objective of this study is to evaluate the clinicopathologic features, incidence, and survival trends in gynecologic neuroendocrine tumors.

MATERIALS AND METHODS: The Surveillance, Epidemiology and End Results (SEER) cancer registry was queried for women diagnosed with primary gynecologic neuroendocrine tumors from 1987 to 2012. Data regarding stage, grade, presence of extrauterine disease, receipt of adjuvant radiation, surgical intervention, incidence, and overall survival were extracted. Patients were classified as having early-stage disease (International Federation of Gynecology and Obstetrics Stage I/II) or advanced-stage disease (Stage III/IV). Extrauterine disease was defined as either regional or distant metastasis. χ^2 Tests, Pearson correlation, and Kaplan—Meier curves were used for statistical analysis.

RESULTS: In all, 559 cases of gynecologic neuroendocrine tumors were identified during the study period: 242 cervical, 160 ovarian, 118 uterine, and 39 vulvar/vaginal. The majority of patients in all subsets of gynecologic neuroendocrine tumors presented with poorly differentiated tumors, extrauterine disease spread, and advanced-stage disease. Poorly differentiated tumors represented 65.0% of cervical tumors, 45.3% of ovarian tumors, and 57.4% of uterine tumors. Extrauterine disease at the time of diagnosis was present in the case of 66.9% of cervical tumors, 83.5% of ovarian tumors, and 83.6% of uterine tumors. The overall incidence of gynecologic neuroendocrine tumors increased 4-fold during the study period, from 0.3 in 1987 to 1.30 per million in 2012. The study period was divided into two 13-year periods (1987—1999 and 2000—2012) for time trend mean survival analysis. We observed no significant change in overall survival across all gynecologic neuroendocrine tumor subtypes. The mean survival time of cervical neuroendocrine tumors was 74.3 vs 45.4 months ($P = .31$), ovarian neuroendocrine tumors 47.8 vs 41.2 months ($P = .56$), and uterine neuroendocrine tumors 42.9 vs 47.7 months ($P = .44$) for each time period, respectively.

CONCLUSION: Neuroendocrine tumors of the gynecologic tract are uncommon aggressive malignancies. These poorly differentiated tumors present at advanced stage, with a high incidence of extrauterine disease. Despite 25 years of advances in cancer therapy, we observed no improvement in overall survival.

Key words: cervical cancer, gynecologic neuroendocrine tumors, ovarian cancer, uterine cancer

Primary gynecologic neuroendocrine tumors (gNET) are uncommon, representing approximately 2% of all gynecological malignancies. The most common site is the cervix, followed by the ovaries and uterus.[1–3] The histological classification of gNET is derived from small cell carcinoma of the lungs and consists of 4 categories: typical carcinoid, atypical carcinoid, small cell neuroendocrine carcinoma, and large cell neuroendocrine carcinoma. Prognosis is based largely on histologic subtype. Typical and atypical carcinoid tumors are well differentiated and follow an indolent course. However, most gNET are small cell carcinomas, and a smaller portion are large cell carcinomas, which are classified as high-grade tumors that behave aggressively.[1–3] Although well and poorly differentiated tumors exhibit dramatically different clinical courses, they are grouped together because of the expression of neuroendocrine makers detected by immunohistochemistry, specifically synaptophysin and chromogranin.[4,5]

In recent years, there has been an increase in the reported incidence of neuroendocrine tumors across all organ sites, including gNET.[2,6,7] This upward trend is likely due to an improvement in diagnosis, as opposed to a true increase.[1,2] Despite this, there is a lack of standardized management guidelines for gNET because of its overall rarity. At present, treatment is extrapolated from small cell carcinoma of the lung and focuses on a multimodal therapeutic approach including surgery, chemotherapy, and radiation.[1,8] The objective of this study is to evaluate the incidence and survival trends in gNET.

Materials and Methods

This study was approved by the Institutional Review Board at SUNY (State University of New York) Downstate Medical Center. Patients were identified using the Surveillance, Epidemiology and End Results (SEER) cancer registry database. We identified women with gNET from 1987 to 2012 using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes of C53.9 (malignant neoplasm of the cervix uteri), C54.1 (malignant neoplasm of the corpus uterus), C56.9 (malignant

Cite this article as: Gibbs J, Mei S, Economos K, et al. Clinicopathologic features, incidence, and survival trends of gynecologic neuroendocrine tumors: a SEER database analysis. Am J Obstet Gynecol 2019;221:53.e1-6.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2019.02.052

AJOG at a Glance

Why was this study conducted?

This study was conducted to investigate the clinicopathologic features, incidence, and survival trends in gynecologic neuroendocrine tumors.

Key findings

Gynecologic neuroendocrine tumors represent an aggressive form of malignancy. Although these tumors are uncommon, their incidence is on the rise, without any signs of improvement in overall survival.

What does this add to what is known?

To our knowledge, this is the largest single review of gynecologic neuroendocrine tumors. Here we present 25 years of retrospective data that demonstrate an increasing incidence of these tumors with no change in overall survival. The present study illustrates the need for prospective data to better guide management of these challenging tumors.

neoplasm of the ovary), C57.0 (malignant neoplasm of the fallopian tube), C52.0 (malignant neoplasm of the vagina), and C51.9 (malignant neoplasm of the vulva). We then limited our study to include only patients with high-grade neuroendocrine tumors (small cell or large cell carcinoma), code C7A.1. Exclusion criteria included benign or in situ neoplasms. Patient characteristics including year of diagnosis, age, race/ethnicity, stage, grade, surgery, receipt of radiation therapy, and survival were obtained. Race was classified into white, black, and other. Patients were classified as having either early-stage disease (International Federation of Gynecology and Obstetrics [FIGO] stage I/II) or advanced-stage disease (FIGO stage III/IV). Data for staging were available only from 2004 to 2012 for gNET. Type of surgery included all therapeutic excisions, but those done for diagnostic purposes only were excluded. The χ^2 and t tests were used to compare frequency distribution among categorical and numerical variables, respectively. Kaplan–Meier curves were used to analyze survival outcomes. The study period was divided into two 13-year periods (1987–1999 and 2000–2012) for time trend mean survival analysis. Pearson correlation tests were used to analyze trends in gNET. Statistical significance was defined as $P < .05$. Analyses were performed using SPSS, Version 22.0. (IBM Corp., Armonk, NY).

Results

A total of 559 cases of gNET were identified using the SEER database from 1987 to 2012; these comprised 242 cervical NET (cNET), 160 ovarian NET (oNET), and 118 uterine NET (uNET). The remaining 39 patients had NET of the vulva, vagina, or an unspecified gynecological site. We observed a 4-fold increase in the incidence of all gNET during the study period, from 0.3 per million in 1987 to 1.30 per million in 2012. Notably, the majority of tumors were diagnosed after 1999. Only 59 (24.4%) cNET, 24 (15.0%) oNET, and 14 (11.9%) uNET were diagnosed prior to 2000. The current study will focus on the 3 most common forms of gNET.

Cervical NET

A total of 242 patients with cNET were identified. The mean age at diagnosis was 48.1 years (range, 21–89 years). The majority of patients (77.7%) were white. Of the patients, 56% presented with advanced-stage disease. Distant metastasic disease was present in 37.5% of patients at the time of diagnosis. In all, 54.6% and 24.4% of patients with cNET received surgery and radiation, respectively. A total of 65% presented with poorly differentiated tumors (Table 1). During the study period, we observed an increased incidence of cNET from 0.3 per million in 1987 to 0.5 per million in 2012 ($R = 0.87$; $P \leq .01$) (Figure 1). The mean survival time of cNET was 74.3 vs 45.4 months for each of the time periods, respectively ($P = .31$). However, there were 3 years within the 1987–1999 cohort (1987, 1988, and 1996) with significantly longer OS (163.0 months) compared to the median OS of all other years (median, 39.1 months), which likely skewed data toward improved survival (Table 2). When extracting these 3 outliers, the median OS for the cohort was 54.0 months.

Ovarian NET

A total of 160 patients with oNET were identified. The mean age at diagnosis was 61.4 years (range, 20–95 years). The majority of patients were white (83.1%) and presented with advanced-stage disease (72.5%). Distant metastasis was present in 73.3% of patients at the time of diagnosis, with 83.5% of patient presenting with extrauterine disease, defined as both regional and distant metastatic spread. Of the patients with oNET, 70.9% and 4.4% underwent surgery and radiation, respectively. A total of 45.3% presented with poorly differentiated tumors (Table 1). During the study period, we observed an increased incidence of oNET from 0 per million in 1987 to 0.38 per million in 2012 ($R = 0.86$, $P \leq 0.01$) (Figure 1). The mean survival time for oNET was 47.8 vs 41.2 months, for each of the time periods ($P = .56$). Similarly to cNET, the trend toward decreased OS in the 1987–1999 cohort is attributed to an outlier within the dataset. Specifically, the year 1991 demonstrated dramatically greater OS (199.0 months) compared to all other years. When excluding this year, the median OS for the cohort was 30.9 years.

Uterine NET

A total of 118 patients with uNET were identified. The mean age at diagnosis was 64.8 years (range, 30–97 years). The majority of patients (77.1%) were white and presented with advanced-stage disease (82.1%). Distant metastasis was present in 49.1% of patients at the time of diagnosis, and 83.6% of all patients presented with extrauterine disease. In all, 69.2% and 22.9% of patients with uNET underwent surgery and radiation, respectively. Of the patients, 57.4% presented with poorly differentiated tumors

TABLE 1
Patient demographics and characteristics

	cNET		oNET		uNET	
	n	%	n	%	n	%
Total Number	242		160		118	
Mean age (range)	48.1 (21–89)		61.4 (20–95)		64.8 (930–97)	
Race						
White	188	77.7%	133	83.1%	91	77.1%
Black	26	10.7%	14	8.8%	11	9.3%
Other	28	11.6%	13	8.1%	16	13.6%
Ethnicity						
Hispanic	40	16.5%	16	10.0%	21	17.8%
Non-Hispanic	202	83.5%	144	90.0%	97	82.2%
Stage[a]						
Early (I/II)	106	43.7%	44	27.5%	21	17.9%
Advanced (III/IV)	136	56.3%	116	72.5%	97	82.1%
Grade						
Moderately Differentiated	7	3.8%	19	17.9%	3	3.0%
Poorly Differentiated	121	66.5%	48	45.3%	58	57.4%
Undifferentiated	54	29.7%	39	36.8%	40	39.6%
Summary staging						
Local	78	33.2%	26	16.6%	19	16.4%
Regional	69	29.4%	16	10.2%	40	34.5%
Distant	88	37.5%	115	73.3%	57	49.1%
Surgery						
Yes	130	54.6%	112	70.9%	81	69.2%
No	108	45.4%	46	29.1%	36	30.8%
Radiation						
Yes	59	24.4%	7	4.4%	27	22.9%
No	183	75.6%	153	95.6%	91	77.1%

cNET, cervical neuroendocrine tumors; *gNET*, gynecologic neuroendocrine tumors; *oNET*, ovarian neuroendocrine tumors; *uNET*, uterine neuroendocrine tumors.

[a] Data for staging only available between 2004 and 2012

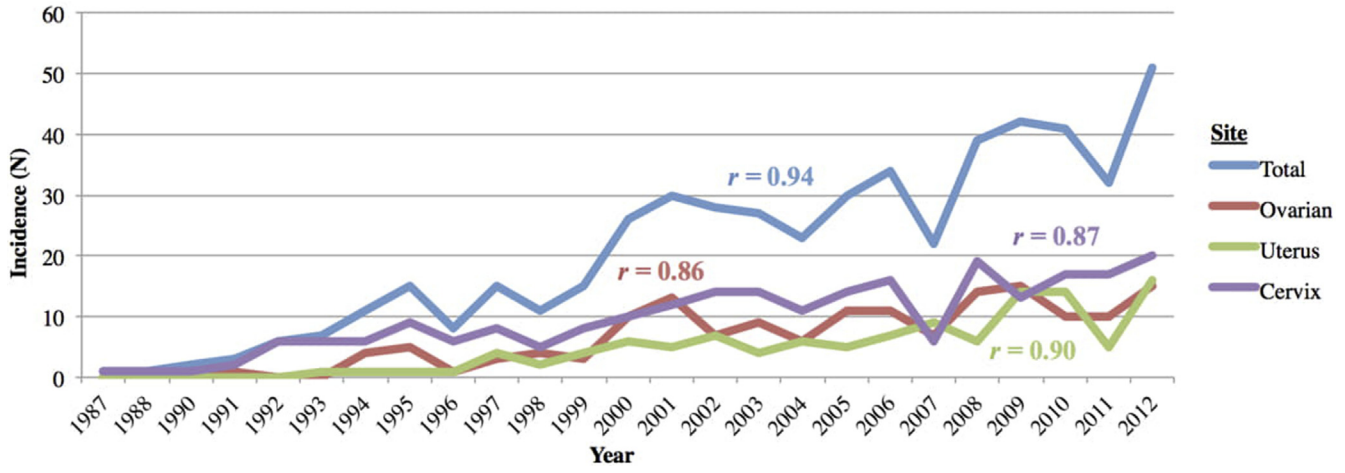
Gibbs et al. Incidence and survival trends in gNET. Am J Obstet Gynecol 2019.

(Table 1). During the study period, we observed an increase incidence of uNET from 0 per million in 1987 to 0.41 per million in 2012 ($R = 0.90$; $P \leq .01$) (Figure 1). The mean survival time uNET was 42.9 vs 47.7 months, for each time period ($P = .44$).

Comment

gNET are rare malignant neoplasms associated with a poor prognosis. Corresponding to recently published data, we observed a 4-fold increase in gNET during the study period. Many authors propose that this is due to the development of a standardized classification system and improved diagnostic recognition rather than a true increase in incidence.[1,2,9,10] Small and large cell gNET are often mixed with other histological types, most commonly squamous cell carcinoma or adenocarcinoma. Prior to clarification of terminology in 1997, these tumors with mixed components were often misclassified. By current standards, unless the neuroendocrine histology is present only as isolated tumors cells, the primary classification should be neuroendocrine, as this is most likely to determine the clinical outcome.[11] This may account for the underrepresentation of gNET prior to 1997. Fitting with this explanation, we observed an increased incidence in each subtype of gNET (Figure 1).

FIGURE 1
Trends in the incidence of gynecologic neuroendocrine tumors (gNET) from 1987 to 2012



Gibbs et al. Incidence and survival trends in gNET. Am J Obstet Gynecol 2019.

The study time frame was divided into two 13-year periods (1987−1999 and 2000−2012) to analyze trends in mean survival time. We observed no statistically significant difference in overall survival (OS) between the two study periods. However, we did detect a trend toward decreased mean survival in cNET and oNET between the 2 time periods. There are several plausible explanations for these findings. uNET were more likely to be treated with any modality compared to cNET and oNET. Of the uNET patients, 92.1% received underwent surgery, radiation, or both, compared to 79.0% of cNET and 75.3% of oNET patients. When examining survival trends in cNET and oNET, careful interpretation must be used. In the cNET cohort, there were 3 years (1987, 1988, and 1996) with significantly longer OS (163.0 months) compared to the median OS of all other years (median, 39.1 months), which likely skewed data toward improved survival in the 1987−1999 cohort (Table 2). When removing these 3 outliers, the median OS for the cohort was 54.0 months, which was just marginally greater than that observed in the 2000−2012 cohort. Similarly, 1 year in the oNET cohort (1999) demonstrated dramatically longer OS (199.0 months) compared to all other years. When excluding this year, the median OS for the 1987−2012 cohort was 30.9 years. The significantly longer OS among these outliers may be explained by inappropriate classification, as most outliers were noted prior to the clarification of terminology to define neuroendocrine tumors in 1997.

In the present study, the majority of patients across all subtypes were non-Hispanic white, corresponding to published literature on NET. In a recent large SEER database analysis of all NETs, this group represented 79.2% of affected patients.[12] By definition, small and large cell carcinoma are high grade, but they may exist as moderately, poorly, or undifferentiated tumors, consistent with our findings. Recent studies of gastrointestinal NET have led to further classification, staging, and grading systems: specifically, a grading system based on Ki67 proliferation, which has guided new biological and targeted therapies, showing promising results in preliminary studies.[6,7] Perhaps this could be applied to gNET.

There are limited data regarding the clinicopathologic features and management oNET and uNET. At present, there are no prospective studies to guide management, and the literature is based on small studies and case reports with findings mirroring those of cNET.[1,2,13] Current therapies are extrapolated from cNET, which is based on data arising from pulmonary literature, focusing on the use of multimodality therapy including surgery, chemotherapy, and radiation.[14−16] In the current study, the majority of patients with oNET and uNET underwent surgical management; however, few received radiation therapy (Table 1). These findings are likely in part attributable to the low rate of radiation use to treat more common ovarian carcinoma histologies. However, literature on NET at other sites support positive responses and decreased recurrence with the use of radiation, suggesting that this treatment modality should be further explored across gNET, including oNET.[17]

The most extensively studied type of gNET is cNET. In this setting, concurrent etoposide/cisplatin chemotherapy and radiation has yielded initial response rates as high as 50−79%.[15,18] A study of cervical large cell NET showed improved survival with platinum as a single agent and when given in combination with etoposide.[19] However, recurrence and progression frequently occur, leading to a lower OS at all stages compared to that for squamous cell carcinoma of the cervix.[20,21] A recent SEER database analysis

TABLE 2
Incidence and median overall survival (OS) of patients with gynecologic neuroendocrine tumors by year

	oNET		uNET		cNET	
Year	n	Median OS (mo)	n	Median OS (mo)	n	Median OS (mo)
1987	0	n/a	0	n/a	1	209.0
1988	0	n/a	0	n/a	1	172.0
1989	0	n/a	0	n/a	0	n/a
1990	1	2.0	0	n/a	1	45.0
1991	1	199.0	0	n/a	2	13.0
1992	0	n/a	0	n/a	6	87.3
1993	0	n/a	1	1.0	6	86.3
1994	4	61.7	1	15.0	6	13.0
1995	5	46.4	1	6.0	9	76.6
1996	1	13.0	1	2.0	6	108.0
1997	3	34.3	4	8.0	8	77.0
1998	4	3.8	2	90.5	5	75.0
1999	3	55.3	4	83.5	8	13.3
2000	10	42.7	6	38.5	10	36.5
2001	13	36.2	5	63.2	12	24.2
2002	7	60.0	7	11.3	14	45.1
2003	9	50.4	4	37.8	14	10.4
2004	6	8.5	6	37.0	11	48.3
2005	11	24.5	5	64.6	14	56.4
2006	11	16.1	7	36.0	16	31.7
2007	7	18.1	9	27.1	6	26.2
2008	14	21.2	6	22.7	19	15.5
2009	15	26.4	14	17.3	13	27.2
2010	10	11.4	14	11.4	17	17.6
2011	10	14.9	5	4.4	17	16.1
2012	15	6.9	16	8.4	20	8.1
Totals	160	52.8	118	54.6	242	65.4

cNET, cervical neuroendocrine tumors; *oNET,* ovarian neuroendocrine tumors; *OS,* overall survival; *n/a,* no data available; *uNET,* uterine neuroendocrine tumors.
Gibbs et al. Incidence and survival trends in gNET. Am J Obstet Gynecol 2019.

demonstrated equally poor outcomes in cNET patients undergoing surgery alone and those undergoing primary radiotherapy. The 5-year OS of the entire cohort (stage I–IV) was 51%, declining to a dismal 9% in stage IV disease.[20] Because of differences in methodology, this review featured a larger number of patients than the current study, as we excluded patients with incomplete survival data. However, like the present study, this report demonstrates the aggressive nature of these tumors and stresses that single-modality treatment is inadequate.

In addition, data suggest that there is a promising future in the incorporation of targeted therapeutics in the treatment of gNET. Frumovitz et al observed a statistically significant PFS benefit in patients with recurrent small-cell carcinoma of the cervix who received a combination of topotecan, paclitaxel, and bevacizumab compared to those who received other regimens, the majority of which did not contain bevacizumab.[22] Similarly, a recent report of cNET reported a complete response to immunotherapy with nivolumab even in the absence of PD-L1 tumor expression, again highlighting the potential role of targeted therapy in these aggressive tumors.[23]

The major limitation of our study is its retrospective nature. Furthermore, the SEER database encompasses only

approximately 28% of the United States population and does not include information on chemotherapy use. Despite these limitations, this is the largest study to date to examine the clinicopathologic features of gNET.

In conclusion, high-grade neuroendocrine tumors of the gynecologic tract are rare and aggressive tumors. Despite 25 years of advances in cancer therapy, we have seen no improvement in survival. Prospective studies are needed to define optimal treatment strategies and to explore targeted therapy options. ■

References

1. Gardner GJ, Reidy-Lagunes D, Gehrig PA. Neuroendocrine tumors of the gynecologic tract: a Society of Gynecologic Oncology (SGO) clinical document. Gynecol Oncol 2011;122:190–8.

2. Rouzbahman M, Clarke B. Neuroendocrine tumors of the gynecologic tract: select topics. Semin Diagn Pathol 2013;30:224–33.

3. Patibandla JR, Fehniger JE, Levine DA, Jelinic P. Small cell cancers of the female genital tract: molecular and clinical aspects. Gynecol Oncol 2018;149:420–7.

4. Travis WD, Rush W, Flieder DB, et al. Survival analysis of 200 pulonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol 1998;22:934.

5. Arasmura H, Kameya T, Matsuno Y, et al. Neuroendorcine neoplasms of the lung: a prognostic spectrum. J Clin Oncol 2006;24:70–6.

6. Uri I, Grozinsky-Glasberg S. Current treatment strategies for patients with advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Clin Diabetes Endocrinol 2018;4:16.

7. Zhong Q, Chen QY, Xie JW, et al. Incidence trend and conditional survival estimates of gastroenteropancreatic neuroendocrine tumors: a large population-based study. Cancer Med 2018;7:3521-33.

8. Reed NS, Gomez-Garcia E, Gallardo-Rincon D, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for carcinoid tumors of the ovary. Int J Gynecol Cancer 2014;24(9 Suppl 3):S35–41.

9. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 2017;3:1335–42.

10. Landoni L, Marchegiani G, Pollini T, et al. The evolution of surgical strategies for pancreatic neuroendocrine tumors (Pan-NETs): time-trend and outcome analysis from 587 consecutive resections at a high-volume institution. Ann Surg 2019;269:725–32.

11. Albores-Saavedrea J, Gersell D, Gilks CB, et al. Terminology of endocrine tumors of the uterine cervix: results of a workshop sponsored by the College of American Pathologists and the National Cancer Institute. Arch Pathol Lab Med 1997;121:34–9.

12. Sarshekeh AM, Gu D, Shou S, Bo Z, Shen C, Darari A. J Clin Oncol 2018;36(suppl15):e16175.

13. Gadducci A, Carinelli S, Aletti G. Neuroendrocrine tumors of the uterine cervix: a therapeutic challenge for gynecologic oncologists. Gynecol Oncol 2017;144:637–46.

14. Boruta II DM, Schorge JO, Duska LA, Crum CP, Castrillon DH, Sheets EE. Multimodality therapy in early-stage neuroendocrine carcinoma of the uterine cervix. Gynecol Oncol 2001;81:82–7.

15. Dowell JE. Small cell lung cancer: are we making progress? Am J Med Sci 2010;339:68–76.

16. Cohen JG, Kapp DS, Shin JY, Urban R, Sherman AE, Chen LM, Osann K, Chan JK. Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. Am J Obstet Gynecol 2010;4:347.

17. Bischof M, Debus J, Herfarth K, et al. Surgery and chemotherapy for small cell lung cancer in stage I-II with or without radiotherapy. Strahlenther Onkol 2007;183:679–84.

18. McCann GA, Boutsicaris CE, Preston MM, et al. Neuroendocrine carcinoma of the uterine cervix: the role of multimodality therapy in early-stage disease. Gynecol Oncol 2013;129:135–9.

19. Embry JR, Kelly MG, Post MD, Spillman MA. Large cell neuroendocrine carcinoma of the cervix: prognostic factors and survival advantage with platinum chemotherapy. Gynecol Oncol 2011;120:444–8.

20. Hou WH, Schultheiss TE, Wong JY, Wakabayashi MT, Chen YJ. Surgery versus radiation treatment for high-grade neuroendocrine cancer of uterine cervix: a Surveillance Epidemiology and End Results database analysis. Int J Gynecol Cancer 2018;28:188–93.

21. Margolis B, Tergas A, Che L, et al. Natural history and outcome of neuroendocrine carcinoma of the cervix. Gynecol Oncol 2016;141:247–54.

22. Frumovitz M, Munsell MF, Burzawa JK, Byers LA, Ramalingam P, Brown J. Combination therpay with topotecan, paclitaxel and bevacizumab improves progression-free survival in recurrent small cell neuroendocrine carcinoma of the cervix. Gynecol Oncol 2017;144:46–50.

23. Paraghamian SE, Longoria TX, Eskander RN. Metastatic small cell neuroendocrine carcinoma of the cervix treated with PD-1 inhibitor nivolumab: a case report. Gynecol Oncol Res Pract 2017;4:3.

Author and article information

From the Division of Gynecologic Oncology (Drs Gibbs, Mei, Lee, and Kanis), SUNY Downstate Medical Center, Brooklyn, NY; Division of Gynecologic Oncology (Dr Economos), New York—Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY.

Received Nov. 13, 2018; revised Feb. 24, 2019; accepted Feb. 27, 2019.

The authors report no conflict of interest.

Corresponding author: Jennifer Gibbs, DO. Jennifer.Gibbs@downstate.edu