Research Report

Small cell neuroendocrine carcinoma of the cervix: Analysis of prognostic factors and patterns of metastasis

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ABSTRACT

Objectives: To describe characteristics and outcomes of patients with small cell neuroendocrine carcinoma of the cervix (SCNCC) and determine the staging system most predictive of outcome—the two-tier (limited-stage [LS] vs. extensive-stage [ES]) or International Federation of Gynecology and Obstetrics (FIGO) staging system.
Methods: Patients with SCNCC evaluated at our institution from 1/1/1990–6/30/2021 were included. Medical records were reviewed for variables of interest. Appropriate statistical tests were performed to determine associations. Survival curves were created using the Kaplan-Meier method. Concordance probability estimates (CPEs) were calculated to evaluate the prediction probability of the staging systems.
Results: Of 63 patients, 41 had LS and 22 ES SCNCC. Patients with ES disease were significantly older than those with LS disease (median, 54 and 37 years, respectively; p < 0.001). Smoking status, race, and history of HPV were not associated with stage or outcomes. Forty-eight patients had metastatic disease (24 [50%] at initial diagnosis). The most common first sites of metastasis were lung (n = 20/48, 42%), lymph nodes (n = 19/48, 40%), and liver (n = 13/48, 27%). Nine patients had brain metastasis (8 symptomatic at recurrence; 1 asymptomatic at initial diagnosis). Both staging systems were associated with progression-free and overall survival. Adjusted CPE found the FIGO staging system was more predictive of outcomes than the two-tier staging system.
Conclusions: Providers should have a low threshold to obtain brain imaging for patients with SCNCC, especially in the presence of visceral metastases. FIGO staging should be used to classify SCNCC. Further research is necessary to understand prognostic factors of this rare disease.

1. Introduction

Extrapulmonary small cell neuroendocrine carcinoma is rare, but the cervix is one of the most common primary sites (Galanis et al., 1997). Small cell neuroendocrine carcinomas comprise only 2% of cervical cancers, but they are more likely to present at an advanced stage and have significantly worse outcomes compared to other histologies (Margolis et al., 2016). The hazard ratio (HR) for death is 2.96 times higher for early-stage small cell neuroendocrine carcinoma of the cervix (SCNCC) (stage IA-IIA) compared to the same stage of squamous cell cervical carcinoma (Margolis et al., 2016). Even when disease is limited to the cervix, the 5-year overall survival (OS) rate is 31–51% (Salvo

et al., 2019; Zivanovic et al., 2009). Recent studies suggest that SCNCC is human papillomavirus (HPV)-driven, but a causative relationship has not been established, as with squamous cell carcinoma and adenocarcinoma (Castle et al., 2018).

Given its rarity, optimal treatment of SCNCC is challenging and not clearly defined. Previously described treatment paradigms have included a combination of surgery, radiation therapy (RT), and chemotherapy, depending upon the extent of disease. In small cell lung cancer (SCLC), a two-tier system of limited-stage (LS) versus extensive-stage (ES) disease is widely used to stratify patients and has shown correlation with outcomes (Zelen, 1973). LS is defined as disease limited to the ipsilateral hemithorax and regional lymph nodes and can be encompassed in one RT field; disease spread beyond this is considered ES (Micke et al., 2002). However, the definitions of LS and ES have not been clearly delineated for SCNCC. Historically, cervical cancer has been clinically staged, only recently allowing for the incorporation of imaging and/or pathologic findings (Bhatla et al., 2019; Corrigendum, 2019). The traditional TNM staging system is dependent on pathologic staging, which requires surgical resection for confirmation. As with SCLC, the majority of patients with SCNCC present with locally advanced or metastatic disease and are not appropriate candidates for surgical resection. A simple two-tier system may carry better prognostic value, but the optimal staging strategy is unclear.

The objectives of our study were to describe the characteristics and outcomes of patients with SCNCC in a single-institution cohort and to determine if a two-tier staging system (LS vs. ES), similar to the one used in SCLC, is a better predictor of prognosis compared to the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system (Bhatla et al., 2019).

2. Methods

2.1. Case selection

After Institutional Review Board approval, we performed a retrospective review of an institutional database of patients seen and treated for SCNCC at our institution between 1/1/1990 and 6/30/2021. Patients with SCNCC were included if they were evaluated at our institution and underwent pathology review confirming small cell neuroendocrine histology. Patients were excluded if their pathology was not reviewed or if their pathology was reviewed but they were not seen or treated at our institution. Due to the rarity of SCNCC, patients who presented to our institution after first-line therapy at an outside institution were included if they had adequate records of prior treatments. Sensitivity analysis including only patients treated at our institution from diagnosis was performed (see *Statistical analysis)*. Patients with inadequate records of diagnosis and therapy were also excluded.

2.2. Data collection

Electronic medical records were reviewed for clinical data, including age at diagnosis, race, ethnicity, smoking status, cancer therapies (surgery, RT, chemotherapy), pathology, history of HPV (based on review of pathology [e.g., HPV RNA in situ hybridization, cervical cancer screening results], and/or clinical documentation [including patient report]), FIGO stage, outcomes (recurrence/death date), imaging, and sites of metastasis. Patient records were reviewed, and disease was classified according to the two-tier staging system (LS vs. ES). In the literature, LS SCNCC has been defined as disease that can be encompassed within a single RT port. ES has been defined as disease that cannot be encompassed in a single RT port (Zelen, 1973; Micke et al., Sep 2002). We determined LS or ES based on imaging and medical records.

Pelvic external-beam RT for cervical cancer typically covers gross disease (if present), parametria, uterosacral ligaments, and vaginal margins. For patients without suspected nodal metastasis, the external

iliac, internal iliac, obturator, presacral, and sometimes common iliac nodal beds should also be included. Extended-field pelvic and/or *para-aortic* RT is recommended up to the level of the nodal involvement. If the lower third of the vagina is involved, bilateral groins should also be treated. In our study, LS disease was confined to the pelvis, could be encompassed in one RT field, and did not require extended fields to treat all initial disease. ES disease had spread beyond the pelvis and/or required extended fields for treatment. ES disease could include distant metastases and/or malignant pericardial or pleural effusions. FIGO stage was assigned based on 2018 FIGO guidelines published by Bhatla et al. (Bhatla et al., 2019; Corrigendum, 2019).

2.3. Statistical analysis

Associations between stage groups (two-tier and FIGO stage) and continuous variables were compared using the Wilcoxon rank-sum test; categorical clinical variables were compared using the two-tailed Fisher exact test. Progression-free survival (PFS) and OS curves were created using the Kaplan-Meier method. PFS and OS were defined from the date of diagnosis until the date of first progression/recurrence/death or last follow-up. P values were generated by applying the log-rank test for categorical variables and Wald test based on Cox proportional hazards model for continuous variables. HRs with 95% confidence intervals (95% CI) based on the Cox model are also reported. A p value < 0.05 was considered significant. To investigate bias for patients referred to our center at recurrence versus time of initial diagnosis, we performed sensitivity analyses for PFS and OS among patients seen at our center at diagnosis.

In order to compare the two staging systems, a concordance probability estimate (CPE) was used to evaluate their prediction probability on PFS and OS outcomes separately (Gonen and Heller, 2005; Olawaiye et al., 2021). CPE is based on the Cox proportional hazards model; it measures the model's ability to discriminate between patients for their predicted outcome. The CPE is the chance that given two randomly selected patients, the patient who survives longer has a higher predicted survival probability based on the model. CPE can range from perfect concordance (1.0) to perfect discordance (0.0). A value of 0.5 indicates that for two randomly selected patients there is a 50% chance the patient with the higher predicted probability will have longer survival (i.e., the prediction performance of the model is no better than a coin flip).

To avoid overfitting and ensure an unbiased estimated CPE, we used 200 bootstrap samples. Specifically, a model was built on a bootstrap sample (training set) and then evaluated on the original data (test set) without modification. Two indices were calculated based on the training and test sets. The difference between the two indices was the optimism of the fit. This process was repeated 200 times. The final optimism estimate was calculated as the mean of the 200 differences. The difference between the original CPE and the final optimism is the unbiased measure of the concordance probability (Harrell et al., 1996). All statistical analyses were performed using R version 3.6.3 (https://cran.r-project.org/).

3. Results

3.1. Demographics

Sixty-three patients with SCNCC were identified - 41 with LS and 22 with ES disease. The 4 patients (6%) diagnosed with stage II (all IIB) disease were combined with patients with stage III disease. The NCCN (National Comprehensive Care Network) guidelines separate SCNCC into three distinct groups for treatment recommendations: disease confined to the cervix, locally advanced disease, and metastatic disease (Network, 2022). Stage II and III are both considered locally advanced and were combined for descriptive and survival statistical analysis due to the same treatment approach and the limited number of patients with stage II disease. Patients with ES disease were significantly older than

Table 1
Clinical factors by limited/extensive stage groups.

Characteristic	Overall N = 63	Limited n = 41	Extensive n = 22	p
Median age at diagnosis, years (range)	40 (22–85)	37 (22–75)	54 (25–85)	**0.001**
	n (%)	n (%)	n (%)	
Smoker				>0.99
No	40 (66%)	26 (67%)	14 (64%)	
Yes	21 (34%)	13 (33%)	8 (36%)	
Missing	2	2	0	
Self-identified race				0.54
Non-White*	16 (25%)	9 (22%)	7 (32%)	
Asian	*8 (50%)*	*6 (67%)*	*2 (29%)*	
Black	*4 (25%)*	*1 (11%)*	*3 (43%)*	
Native American	*1 (6%)*	*0*	*1 (14%)*	
Not specified	*3 (19%)*	*2 (22%)*	*1 (14%)*	
White	47 (75%)	32 (78%)	15 (68%)	
Stage				**<0.001**
I	26 (41%)	26 (63%)	0 (0%)	
II/III	20 (32%)	15 (37%)	5 (23%)	
IV	17 (27%)	0 (0%)	17 (77%)	
History of HPV†				0.52
No	33 (66%)	21 (62%)	12 (75%)	
Yes	17 (34%)	13 (38%)	4 (25%)	
Missing	13	7	6	
Primary surgery				**<0.001**
No	29 (46%)	9 (22%)	20 (91%)	
Yes	34 (54%)	32 (78%)	2 (9%)	
Primary RT				**0.002**
No	23 (38%)	9 (23%)	14 (67%)	
Yes	37 (62%)	30 (77%)	7 (33%)	
Missing	3	2	1	
Chemotherapy‡				0.061
No	24 (38%)	12 (29%)	12 (55%)	
Yes	39 (62%)	29 (71%)	10 (45%)	
Type of upfront chemotherapy				0.546
Cisplatin and etoposide	34 (87%)	26 (90%)	8 (80%)	
Cisplatin and irinotecan	2 (5%)	1 (3%)	1 (10%)	
Cisplatin alone	3 (8%)	2 (7%)	1 (10%)	

HPV, human papillomavirus; RT, radiation therapy; ISH, in situ hybridization.
* P-value for race was determined by comparing White vs Non-White; patients who self-identified as Black, Asian, Native American, or non-White not specified were combined due to limited numbers for statistical analysis.
† History of HPV was determined based on review of pathology (e.g., HPV RNA ISH, cervical cancer screening results), and/or clinical documentation (including patient report).
‡ Chemotherapy as a part of first-line therapy at initial diagnosis.

those with LS disease (median age of 54 and 37 years, respectively; p < 0.001). Smoking status, race, and history of HPV were not associated with stage (Table 1).

3.2. Treatment

Forty-six patients (73%) presented to our institution at diagnosis, prior to receiving any treatment. Of those who presented after first-line treatment (n = 17, 27%), 3 (18%) presented at the time of first recurrence and 14 (82%) presented at subsequent recurrence. Compared to patients with LS disease, those with ES disease were less likely to have undergone primary surgical management and radiation (p < 0.001 and p = 0.002, respectively). Of 39 patients (62%) who underwent chemotherapy at initial diagnosis, 14 (36%) were treated with chemotherapy alone and 25 (64%) with chemotherapy and concurrent RT. The majority of patients who underwent chemotherapy were treated with cisplatin and etoposide (n = 34, 87%); 3 were treated with cisplatin alone (8%) and 2 (5%) with cisplatin and irinotecan (Table 1). Patients with LS and ES disease received a similar number of chemotherapy cycles (median, 4 cycles: range, 1–6). No patients received prophylactic cranial irradiation. Of the patients who underwent RT as first-line treatment (n = 37), 19 (51%) had RT after primary surgery and 18

(49%) had definitive RT.

3.3. Metastatic disease

Forty-eight patients (76%) had metastatic disease—24 (50%) at initial diagnosis and 24 (50%) at recurrence. The most common first site of metastasis was the lung (n = 20, 42%); other first sites of metastasis included the lymph nodes (n = 19, 40%), liver (n = 13, 27%), peritoneum (n = 10, 21%), bone (n = 8, 17%), and brain (n = 4, 8%) (Table 2). Nine (24%) of the 38 patients who underwent brain imaging had brain metastases—1 (11%) at initial diagnosis and 8 (89%) at recurrence. Four patients had brain metastasis at the time of first diagnosis of metastatic disease, and 5 developed brain metastases following a previous diagnosis of metastatic disease at other sites. Indications for brain imaging were headaches (n = 3), ataxia (n = 2), visual changes (n = 2), and seizure (n = 1). One patient had asymptomatic brain metastasis identified during the initial staging workup.

Seven (78%) of the 9 patients with brain metastasis had lung metastases. Brain metastasis was diagnosed after lung metastasis in 4 (57%) of these 7 patients, with a median of 12.4 months (range, 6.3–23.0 months) between the diagnosis of lung and brain metastasis. Two patients had brain and lung metastases diagnosed at the same time. One patient had lung metastasis diagnosed 2.3 months after brain metastasis. Brain metastases were treated with RT alone in 6 patients, neurosurgery followed by RT in 2 patients, and treatment was not recorded for 1 patient. After local treatment of brain metastases, 6 patients were treated with systemic antineoplastic treatment, of whom 2 also received bevacizumab.

3.4. Survival

Of the 58 patients with available outcomes data, 45 (78%) experienced a recurrence or progression of disease. The median follow-up time for progression-free survivors (n = 12) was 65.2 months (range, 5.5–281.1 months); there was one death without progression. On univariate analysis, both staging systems (FIGO and two-tier) were associated with PFS (p < 0.001 for both; Table 3). On sensitivity analysis, restricted to only patients who presented to our institution at the time of initial diagnosis (n = 42), the median PFS and significant variables were the same (Supplementary Table 1).

OS was evaluated for the entire cohort (n = 63); there were 37 deaths (59%). Median follow-up for survivors (n = 26) was 45 months (range, 1.9–281.1 months; Table 4). On univariate analysis, age was associated with OS (p = 0.043). Both staging systems were associated with OS. On bivariate analysis with age, the two-tier system was still associated with OS (p < 0.001). Median OS from diagnosis of metastasis was 12 months (95% CI: 9.1–17.1). Among the 9 patients with brain metastases (5

Table 2
Description of metastatic disease.

Characteristic	Overall N = 48	At diagnosis n = 24	At recurrence n = 24
First site of metastasis*			
Lung	20 (42%)	10 (42%)	10 (42%)
Lymph nodes	19 (40%)	15 (63%)	4 (17%)
Liver	13 (27%)	9 (38%)	4 (17%)
Peritoneum	10 (21%)	2 (8%)	8 (33%)
Bone	8 (17%)	6 (25%)	2 (8%)
Brain	4 (8%)	1 (4%)	3 (13%)
Breast	1 (2%)	1 (4%)	0
Any brain imaging			
No	25 (40%)		
Yes	38 (60%)		
Brain metastasis			
No	29 (76%)		
Yes	9 (24%)	1 (11%)	8 (89%)

*24 patients had multiple sites at diagnosis of first metastatic disease.

Table 3

Univariate progression-free survival analysis.

Variable	N	Progression #	Median PFS, mo (95 %CI)	1-y PFS (95% CI)	5-y PFS (95% CI)	HR (95% CI)	p
All	**58**	**46**	**11.2 (6.6–15.1)**	**45.5% (32.2–57.8%)**	**17.4% (8.7–28.7%)**		
Age						1.02 (1–1.04)	0.064
Smoker							0.265
No	38	30	12 (6.7–16.7)	49.4% (32.7–64.1%)	17.6% (7.1–32%)	—	
Yes	18	15	7.1 (5.7–12.5)	35.9% (14.8–57.7%)	12% (2–31.6%)	1.43 (0.76–2.66)	
Race							0.304
White	42	32	12 (6.5–16.3)	49.2% (33.3–63.2%)	21.6% (10.5–35.3%)	—	
Non-White	16	14	9.4 (4.2–15)	35.2% (13.3–58.2%)	7% (0.5–27.1%)	1.39(0.74–2.62)	
HPV							0.939
No	28	23	11.4 (6.6–16.3)	46.4% (27.6–63.3%)	17.1% (5.9–33.3%)	—	
Yes	17	13	12.2 (4.5–40.9)	52.9% (27.6–73%)	22.1% (6.1–44.1%)	0.97 (0.49–1.92)	
FIGO stage							**<0.001**
I	23	15	15.4 (12.2-NE)	73.9% (50.9–87.3%)	33.8% (15.6–53.1%)	—	
II/III	20	16	10.8 (5.8–17)	45.9% (22.7–66.4%)	11.5% (1.9–30.5%)	1.87 (0.92–3.8)	
IV	15	15	4.2 (1.4–4.9)	Not Reached	Not Reached	16.33 (6.19–43.08)	
Two-tier							**<0.001**
Limited	38	28	15.2 (12–24.4)	65.1% (47.5–78%)	23.1% (10.9–38%)	—	
Extensive	20	18	4.7 (2.5–7.1)	6.7% (0.5–25.1%)	6.7% (0.5–25.1%)	3.93 (2.06–7.5)	

P value was obtained by applying the log-rank test for categorical variables and Wald test based on Cox proportional hazards model for continuous variables.

Table 4

Overall survival analysis.

Variable	N	Progression #	Median OS, mo (95% CI)	1-y OS (95% CI)	5-y OS (95% CI)	HR (95% CI)	p
Univariate							
All	63	37	30.9 (19–52.3)	79.5% (66.6–87.8%)	27.1% (15.1–40.6%)		
Age						1.02 (1–1.05)	**0.043**
Smoker							0.56
No	40	26	30.6 (14.6–52.3)	73.8% (56.7–85%)	24.3% (10.9–40.6%)	—	
Yes	21	10	30.9 (16.3-NE)	89.3% (63.2–97.2%)	29% (8.1–54.3%)	0.81 (0.39–1.67)	
Race							0.976
White	47	27	30.6 (15.2–52.3)	79.4% (64.1–88.7%)	30% (15.9–45.6%)	—	
Non-White	16	10	35.2 (10.9–52.8)	79.8% (49.4–93%)	19.3% (3.2–45.7%)	1.01 (0.49–2.09)	
HPV							0.11
No	33	23	24.1 (12–52.3)	71.3% (52–83.9%)	21.3% (8.3–38.1%)	—	
Yes	17	7	Not Reached	87.8% (59.5–96.8%)	50.7% (22.7–73.2%)	0.51 (0.22–1.18)	
FIGO stage							**<0.001**
I	26	9	Not Reached	100%	55.5% (31–74.4%)	—	
II/III	20	14	32.5 (16.3–52.8)	89.2% (63.1–97.2%)	14.3% (2.5–36%)	2.44 (1.06–5.66)	
IV	17	14	7.2 (3.2–14.6)	31.9% (10.3–56.2%)	Not Reached	15.58 (5.98–40.57)	
Two-tier							**<0.001**
Limited	41	20	52.3 (30.9-NE)	94.7% (80.6–98.7%)	37% (19.9–54.2%)	—	
Extensive	22	17	9.1 (5.5–19)	48.9% (25.3–68.9%)	6.1% (0.4–24.2%)	4.4 (2.24–8.62)	
Bivariate							
Age						1.01 (0.98–1.03)	0.53
Two-tier							**<0.001**
Limited						—	
Extensive						4.03 (1.95–8.32)	

OS, overall survival; CI, confidence interval; HR, hazard ratio; HPV, human papillomavirus; NE, not estimable; FIGO, International Federation of Gynecology and Obstetrics.

P value was obtained by applying the log-rank test for categorical variables and Wald test based on Cox proportional hazards model for continuous variables.

deaths and 4 survivors), the median OS from diagnosis of brain metastasis was 7.8 months (95% CI: 0.99-NE). Smoking status, race, and history of HPV were not associated with PFS or OS (Tables 3 and 4). On sensitivity analysis, restricted to only patients presenting to our institution at time of initial diagnosis (n = 46), the median OS and significant variables were the same (Supplementary Table 2).

Adjusted CPE for PFS found FIGO staging was more predictive for PFS than two-tier staging (adjusted CPE, 0.693 [95% CI: 0.633–0.753], and 0.627 [95% CI: 0.575–0.679], respectively). Adjusted CPE for OS found FIGO staging was also more predictive for OS than two-tier staging (adjusted CPE, 0.709 [95% CI: 0.651–0.767] and 0.637 [95% CI: 0.585–0.688], respectively; Fig. 1).

4. Discussion

We sought to determine whether the two-tier staging system of LS versus ES disease was more predictive of outcomes compared to the traditional FIGO staging system for SCNCC. Survival analysis showed that both the FIGO staging system and the two-tier staging system were associated with survival outcomes of interest; however, the FIGO system was more predictive when applying adjusted CPE (Fig. 1).

The two-tier staging system used for SCNCC was adapted from the Veterans Administration Lung Study Group (VALG) system for SCLC, which was established in 1957 for use in randomized trials in patients with inoperable lung cancer (Zelen, 1973; Micke et al., 2002). The system was extended to extrapulmonary small cell carcinoma and classifies patients into those with LS versus ES disease based on whether their tumors can be treated within a single RT field or not. Prior studies identified clinical stage as the most important prognostic factor in SCNCC (Ishikawa et al., 2019; Cohen et al., 2010; Chan et al., 2003). Prior to 2018, all FIGO cervical cancer staging was clinical and did not include modern imaging or pathologic findings (Bhatla et al., 2019). Treatment modalities may differ depending on which staging system is used, ultimately effecting clinical outcomes.

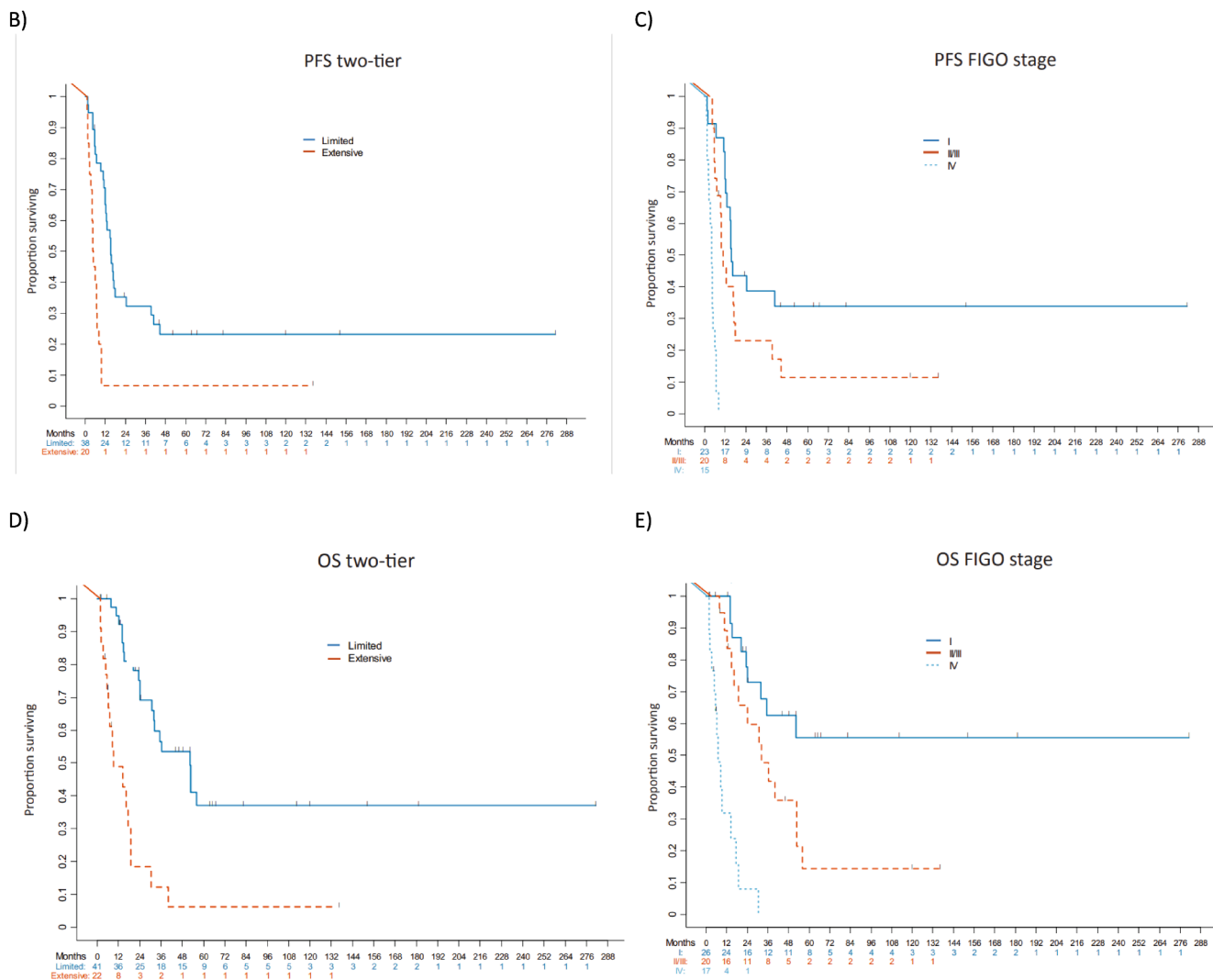| Stage System	Adjusted CPE (95%CI)
OS	
Two-tier	0.627 (0.575-0.679)
FIGO stage	0.693 (0.633-0.753)
PFS	
Two-tier	0.637 (0.585-0.688)
FIGO stage	0.709 (0.651-0.767)

Fig. 1. A) Concordance probability estimate (CPE) to evaluate the prediction probability of two-tier and FIGO stage on progression-free survival (PFS) and overall survival (OS). **B-E)** PFS and OS curves created using the Kaplan-Meier method. CPE, concordance probability estimate; CI, confidence interval; OS, overall survival; FIGO, 2018 International Federation of Gynecology and Obstetrics; PFS, progression-free survival.

Recent literature in SCLC has recommended moving away from the VALG criteria, especially given advances in imaging and radiation over the last 60 years (Micke et al., 2002; Carter et al., 2014). In SCNCC, a 2019 paper by Ishikawa et al. found that each component of the 2018 FIGO staging system was predictive of prognosis, with increasing risk of death with increasing tumor size, lymph node positivity, and distant metastasis (Zivanovic et al., 2009; Ishikawa et al., 2019). In this study, CPE was used as a quantitative statistic to compare FIGO and two-tier staging. CPE values were between 0.6 and 0.7, demonstrating the limitations of predicting outcomes in SCNCC. The CPE 95% CIs for PFS and OS with FIGO staging did not include the CPE values for two-tier staging; therefore, we were able to establish FIGO staging as more predictive of outcomes than two-tier staging in SCNCC (Fig. 1).

In addition to stage, a 2003 paper by Chan et al., which reported on

34 patients with SCNCC, demonstrated smoking was an independent risk factor for survival on multivariate analysis (Chan et al., 2003). This finding was not reflected in our cohort; smoking status, race, and history of HPV were not associated with outcomes in our study. The presence of distant metastasis is one of the most influential factors on prognosis of SCNCC (Zivanovic et al., 2009; Ishikawa et al., 2019). Forty-eight patients in our study developed documented metastases during their disease course, with a median OS of 12.2 months (95% CI: 9.1–17.1) after diagnosis of metastatic disease.

The most common first site of metastatic disease in our cohort was the lung (42%) (Table 2). Sixty percent of patients (n = 38) had brain imaging during their disease course, and 9 were diagnosed with brain metastases (24%). Brain metastasis in SCNCC is not well described, and brain imaging is typically performed for neurologic symptoms (e.g.,

seizures, headaches) or to complete staging in the presence of visceral metastases (Viswanathan et al., 2004). In a case series of 40 patients with neuroendocrine cervical cancer (small and large cell), 8 patients had brain metastasis; half of the patients with brain metastasis did not have liver or lung metastasis (Stecklein et al., 2016). In our cohort, brain metastasis typically occurred following disease spread to the lungs. Similar to prior studies, only 1 patient (3%) developed brain metastasis without disease spread to the liver, lung, or other sites (Viswanathan et al., 2004; Stecklein et al., 2016). It is reasonable to consider brain imaging after diagnosis of visceral metastases, especially lung metastasis, as early detection of brain metastasis leads to better outcomes. Eight of the 9 patients with brain metastases had brain imaging performed in the setting of new neurologic symptoms. Providers should have a low threshold to order brain imaging, including at diagnosis, and especially in the presence of neurologic symptoms.

A complete staging workup for SCLC includes brain imaging; up to 15% of patients with SCLC have brain metastasis at diagnosis, 5–8% of whom are asymptomatic at presentation (Hardy et al., 1990). In SCLC, including those with LS disease, prophylactic cranial irradiation has been shown to decrease the incidence of brain metastasis and prolong survival, with limited neurotoxicity (Meert et al., 2001). In SCNCC, however, there is no definitive data to support routine brain imaging at initial diagnosis in the absence of visceral metastasis or neurological symptoms. Prophylactic cranial irradiation is not recommended at initial diagnosis of SCNCC (Naidoo et al., 2013).

Due to the rarity of SCNCC, we included patients diagnosed as early as 1990 in our cohort; there have been changes to treatment and staging over time, which limits the validity of our results. While our sample size is limited, it is still one of the largest cohorts of SCNCC evaluated at a single institution. Our institution is a tertiary referral center, so the effect of referral bias must be acknowledged, as our cohort is likely enriched for patients with poor prognosis. A quarter of our patients presented after first-line treatment at an outside institution. To determine the implications of this, we performed a sensitivity analysis for PFS and OS to include only those patients who presented to our institution at the time of initial diagnosis. The results were the same as those for the entire cohort.

In addition to changes in staging and treatment of cervical cancers over time, SCNCC is now recognized as an HPV-driven cancer (Schultheis et al., 2022). With our historical cohort, we did not have adequate data to determine associations with HPV status and outcomes. There are recent and ongoing studies of targeted therapies for HPV-driven tumors, which may lead to improved outcomes in SCNCC (Jazaeri et al., 2019). Beyond cervical cancer, immunotherapy is being studied in extrapulmonary small cell neuroendocrine carcinomas as a whole (Clinicaltrials.gov ID: NCT05058651).

Continued research on SCNCC is necessary to better understand prognostic factors of this rare, deadly disease; development of improved treatments leading to better outcomes are possible. Based on our results, the FIGO staging system should be used for SCNCC rather than the two-tier system. In addition, providers should have a low threshold to obtain brain imaging, especially at diagnosis of visceral metastasis. Given the rarity of this tumor, the international Neuroendocrine Cervical Tumor Registry (NeCTuR) (necervix.com) was developed to initiate and execute meaningful clinical trials for patients with SCNCC.(Salvo et al., 2019) Studies like ours, which report on clinical experience with rare cancers, are necessary to add to the global experience of this disease. Through international collaboration, advances in the treatment of SCNCC can be expedited.

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CRediT authorship contribution statement

Sushmita Gordhandas: Data curation, Formal analysis, Writing – review & editing, Writing – original draft. **Brooke A. Schlappe:** Conceptualization, Data curation, Formal analysis, Writing – review & editing, Methodology, Writing – original draft. **Qin Zhou:** Formal analysis, Writing – review & editing, Methodology. **Alexia Iasonos:** Formal analysis, Writing – review & editing, Methodology. **Mario M. Leitao:** Formal analysis, Writing – review & editing, Methodology. **Kay J. Park:** Formal analysis, Writing – review & editing, Methodology. **Louise de Brot:** Formal analysis, Writing – review & editing. **Kaled M. Alektiar:** Formal analysis, Writing – review & editing. **Paul J. Sabbatini:** Formal analysis, Writing – review & editing. **Carol A. Aghajanian:** Conceptualization, Formal analysis, Writing – review & editing, Methodology. **Claire Friedman:** Formal analysis, Writing – review & editing. **Oliver Zivanovic:** Conceptualization, Data curation, Formal analysis, Writing – review & editing, Methodology, Supervision, Writing – original draft. **Roisin E O'Cearbhaill:** Conceptualization, Data curation, Formal analysis, Writing – review & editing, Methodology, Supervision, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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