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Patterns of Recurrence and Survival in Neuroendocrine Cervical Cancer

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Abstract

Objective—To analyze patterns of recurrence and survival and identify prognostic factors in women with neuroendocrine cervical cancer (NECC).

Methods—We reviewed patients with International Federation of Gynecology and Obstetrics stage I–IVA NECC who were enrolled in the Neuroendocrine Cervical Tumor Registry and treated with curative intent. Event-free survival (EFS) and overall survival (OS) according to disease and treatment characteristics were analyzed using the Kaplan-Meier method.

Results—Among 40 patients with NECC, 25 (62%) had small cell NECC, eight (20%) had large cell NECC, and seven (18%) had unspecified neuroendocrine histology. With a median follow-up of 21.5 months, 32 patients (80%) experienced progression, and 28 (70%) died. For all patients, the 5-year EFS rate was 20%, and the 5-year OS rate was 27%. Patients with large cell NECC had significantly better median EFS (median not reached vs. 10.0 months, $p=0.02$) and showed a trend towards better median OS (153 months vs. 21 months, $p=0.08$) than patients with other histologic types. In patients with early-stage clinically node-negative disease, chemoradiation was associated with significantly better median EFS than surgery (median not reached vs. 18.0 months, $p=0.04$).

Conclusions—Patients with large cell NECC have better outcomes than patients with other subtypes of NECC. In early-stage node-negative NECC, chemoradiation yields better EFS than surgery. Most patients with NECC, even those with no evidence of nodal disease at diagnosis, rapidly develop widespread hematogenous metastases and die of their disease.

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Conflicts of Interest

The authors have no conflicts of interest.

Keywords

Cervical cancer; Neuroendocrine; Small cell; Large cell

Introduction

Neuroendocrine cervical cancers (NECCs) are rare, accounting for approximately 1% of all cervical cancers diagnosed in the United States each year. While squamous cell carcinomas and adenocarcinomas, which account for 95% of all cervical cancers, are curable even at relatively advanced stages, NECC typically has a rapidly progressive course and leads to widespread hematogenous metastases despite aggressive local and systemic therapies.

NECCs are morphologically indistinguishable from neuroendocrine cancers arising in other organs. Small cell neuroendocrine carcinoma (SCNECC) and large cell neuroendocrine carcinoma (LCNECC) are the most common morphologic types of NECC found in the cervix, although well-differentiated carcinoid-type NECCs are also seen, albeit rarely. NECCs typically express markers of neuroendocrine differentiation (synaptophysin, chromogranin A, and CD56), and immunohistochemical analysis, while not required for diagnosis, is commonly employed to support a diagnosis of NECC. The molecular pathogenesis of NECCs remains poorly understood.

Since NECC is exceedingly rare, there are no randomized prospective data to guide its treatment. Most treatment of NECC has been based on small case series using regimens that show activity in other, more common neuroendocrine cancers, especially small cell lung cancer [1–7]. To better understand the natural history of NECC and to identify prognostic factors, we performed a retrospective analysis of a cohort of women with immunohistochemically proven NECC.

Methods

We reviewed the records of women enrolled in an Institutional Review Board–approved registry, the Neuroendocrine Cervical Tumor Registry (NeCTuR), maintained at The University of Texas MD Anderson Cancer Center. At the time of our analysis, 56 patients were enrolled in the retrospective arm of the registry. Patients either voluntarily consented to participation or, in the case of deceased patients, were enrolled by means of a research study waiver. For this study, we included patients with International Federation of Gynecology and Obstetrics (FIGO) stage I–IVA invasive NECC who were treated with curative intent and whose tumors demonstrated immunohistochemical evidence of neuroendocrine differentiation (i.e., expressed synaptophysin, chromogranin A, or CD56). Four patients were excluded from analysis because their records lacked details of diagnosis, treatment, or follow-up; four patients were excluded because their tumors lacked immunohistochemical evidence of neuroendocrine differentiation; and eight patients were excluded because they had evidence of distant metastatic disease at diagnosis. The remaining 40 patients formed the final study population. Patient, tumor, and treatment data were abstracted from clinical records. Recurrence and survival data were obtained from a chart review of clinic records,

including follow-up physical examination notes, radiology and pathology reports, and tumor and death registry records.

Event-free survival (EFS), defined as the time from diagnosis to first recurrence, and overall survival (OS), defined as the time from diagnosis to death from any cause, were analyzed according to disease and treatment characteristics using the Kaplan-Meier method. All statistical analyses were done in SPSS (version 23); all tests were two-sided unless otherwise specified. Graphs were generated in GraphPad (version 6.07).

Results

Patient, Tumor, and Treatment Characteristics

The median age at diagnosis was 37 years (range 24–77 years). Thirty-two patients (80%) were white, four (10%) were black, and one (3%) was Asian. Race was unknown or unrecorded for three patients (7%). Four patients (10%) were Hispanic or Latino, although Hispanic or Latino ethnicity status was unknown in eight patients (20%).

Patient, tumor, and treatment characteristics are detailed in Table 1. Most patients presented with FIGO stage I disease. Twenty-five patients (62%) had SCNECC, while eight patients (20%) had LCNECC. The tumors of seven patients (18%) did not have a discrete morphologic classification but exhibited neuroendocrine differentiation on immunohistochemical analysis; these cases are hereafter referred to as NECC not otherwise specified (NECCNOS). The neuroendocrine differentiation markers synaptophysin, chromogranin A, and CD56 were expressed in 90%, 65%, and 35% of patients, respectively. Immunohistochemical profile was not associated with morphologic subtype.

All 40 patients were treated with intent to cure. Twenty-one patients (53%) received definitive radiotherapy as the primary local treatment, and 18 of them (86%) received concurrent chemotherapy. Seven patients (18%) underwent hysterectomy as the primary local treatment. Twelve patients (30%) received a combination of hysterectomy and radiotherapy as the primary local treatment; nine of them underwent surgery followed by radiation (n=2) or chemoradiation (n=7), and three of them underwent chemoradiation followed by surgery for either residual disease (n=1) or technical difficulty with brachytherapy (n=2).

Among the 19 patients who underwent hysterectomy, 10 (53%) underwent surgery at an outside facility, and nine (47%) had surgery at MD Anderson Cancer Center. Among the 33 patients who received radiotherapy as part of their definitive local therapy, 11 (33%) were treated at an outside facility, and 22 (67%) received radiotherapy at MD Anderson.

Among the 16 patients who underwent surgery as the sole form of local therapy (n=7) or had surgery before radiation or chemoradiation (n=9), only one had radiologic evidence of nodal metastasis at diagnosis. Lymphadenectomy was performed in 14 (88%) of these 16 patients. Of these 14 patients, three had pathologically positive pelvic nodes, and one patient (the patient with radiologic evidence of pelvic nodal disease before surgery) had pathologically positive pelvic and para-aortic nodes. Among the 24 patients who underwent definitive

radiation or chemoradiation as the sole (n=21) or initial (n=3) local therapy modality, 16 patients (67%) had radiologic evidence of nodal metastasis at diagnosis. Twelve patients (50%) had disease localized to the pelvic lymph nodes, while four (17%) had evidence of paraaortic disease. In total, seventeen of the 40 patients (43%) had radiologic evidence of nodal disease before the initiation of any therapy.

Survival

With a median follow-up of 21.5 months (range 5–183 months), 32 of 40 patients (80%) had experienced disease progression, and 28 of 40 patients (70%) had died. Rates of recurrence by FIGO stage, histologic type, and extent of disease at diagnosis are detailed in Table 2. For patients who experienced recurrence, the median time from diagnosis to first recurrence was 9.0 months (range 5–34 months). More than 85% of recurrences had occurred by 18 months, and 94% of recurrences had occurred by 24 months. The distribution and cumulative frequency of recurrences over time are shown in Figure 1. The 5-year EFS rate was 20%, and the 5-year OS rate was 27%. Patients with FIGO stage IB1 disease had a trend toward better median EFS (21.0 months vs. 9.0 months, $p=0.09$) and significantly better median OS (41.0 months vs. 17.0 months, $p=0.05$) than patients with higher-stage disease. Patients with evidence of metastatic pelvic or para-aortic nodal disease at diagnosis had significantly poorer median EFS (9.0 months vs. 18.0 months, $p=0.01$) and median OS (16 months vs. 38 months, $p=0.02$) than patients with no evidence of nodal disease at diagnosis. Interestingly, patients with LCNECC had a significantly better median EFS than patients with SCNECC or NECCNOS (median survival not reached for LCNECC vs. 10.0 months for the other subtypes, $p=0.02$, Figure 2A) and a trend toward better median OS than patients with SCNECC or NECCNOS (153 months vs. 21 months, $p=0.08$, Figure 2B).

Effects of Treatment on Recurrence and Survival

The efficacy of surgery and chemoradiation for early-stage node-negative NECC have not been directly compared. Surgery is generally considered to be the standard of care for patients with low-volume (< 4 cm) clinically node-negative squamous cell carcinoma and adenocarcinoma, and most patients with NECC who meet this criteria are treated primarily with surgery, though definitive radiation or chemoradiation is an acceptable alternative. In our cohort, patients with early-stage (FIGO I–IIA) NECC without radiologic evidence of pelvic or para-aortic nodal metastases at diagnosis (n=14), definitive chemoradiation (n=7) was associated with significantly better median EFS than definitive surgery without adjuvant radiation (n=7) (median not reached vs. 18.0 months, $p=0.04$, Figure 3A) and showed a trend toward better median OS than surgery (153 months vs. 38 months, $p=0.11$, Figure 3B). Also, the surgery group had a higher rate of pelvic recurrence (four of seven patients, 57%) than the chemoradiation group (zero of seven patients, $p=0.07$). There was no difference in the distribution of SCNECC, LCNECC, and NECCNOS or the frequency of adjuvant chemotherapy between the surgery and chemoradiation groups. Despite its better outcomes, the chemoradiation group had more patients with disease more advanced than FIGO stage IB1 (four of seven patients, 57%) than the surgery group did (one of seven patients, 14%).

Among all 16 patients treated primarily with surgery, the addition of radiotherapy did not appear to improve outcomes; those who received adjuvant radiotherapy (n=9) had a median

EFS of 9.0 months, whereas patients who received surgery alone (n=7) had a median EFS of 18.0 months (p=0.49). Similarly, median OS among patients treated primarily with surgery did not significantly differ between patients treated with adjuvant radiotherapy (23.0 months) and those not treated with adjuvant radiotherapy (38.0 months, p=0.38). There was no difference in the rate of pelvic recurrence in patients treated primarily with surgery who received adjuvant radiation therapy compared to patients who did not receive radiation therapy (four of nine patients (44%) vs. four of seven patients (57%), respectively, p=0.61).

Of the 33 patients who received definitive radiation therapy, 28 (85%) received concurrent chemotherapy; concurrent chemotherapy was significantly associated with better EFS (11.0 vs. 8.0 months, p=0.03) and OS (22.0 vs. 15.0 months, p=0.05) than radiation therapy alone. There was no obvious difference in radiation fields or age (a surrogate of comorbidity) between definitive radiation therapy recipients who received concurrent chemotherapy and those who did not receive concurrent chemotherapy.

Among patients who received definitive local therapy (surgery, radiation, or chemoradiation), the addition of adjuvant chemotherapy did not significantly improve median EFS (17 months vs. 11 months, p=0.46) but did show a trend toward median OS (38.0 months vs. 18 months, p=0.10) compared with no adjuvant chemotherapy.

Patterns of Recurrence

The most common sites of first recurrence were the lung (12 patients, 38%) and liver (11 patients, 34%), and these remained the most common sites of recurrence at any time (15 patients each, 47%). Other common sites of metastasis included the peritoneum (eight patients, 25%), brain (eight patients, 25%), and bone (seven patients, 22%). Four of the eight patients who developed brain metastasis did not have liver or lung metastases, although only one patient (3%) developed brain metastasis in the absence of any other clinically apparent metastatic disease. Among the 33 patients who received definitive radiation therapy, seven patients (21%) had in-field recurrences, and two patients had marginal recurrences just above the superior border of the radiation field.

Discussion

Our study of patients with NECC confirms the aggressive nature of this disease. Most patients develop widespread hematogenous metastases and die of their disease, despite aggressive local and systemic therapy. Early-stage disease and lack of lymph node metastasis are known favorable prognostic factors. We show that LCNECC has better outcomes than SCNECC. Moreover, our finding that chemoradiation yields significantly better EFS and numerically superior OS than surgery in patients with early-stage node-negative NECC challenges the current standard of care for this patient population.

NECCs represent a rare and highly aggressive subtype of cervical cancer. Unlike squamous cell carcinoma and adenocarcinoma, which are often highly curable with aggressive locoregional therapy, NECCs usually have poor outcomes, even when diagnosed at an early stage. Most patients in our study had a rapidly progressive course and died of their disease, even after showing encouraging initial responses to therapy. Almost 80% of all recurrences

occurred within 1 year of diagnosis, and recurrences after 2 years were uncommon, representing approximately 5% of all recurrences.

Given the rarity of NECCs, there are no prospective data and only limited retrospective data to guide treatment. The Gynecologic Cancer Intergroup (GCIg) and Society of Gynecologic Oncology (SGO) have issued recommendations for treating NECCs based on the available literature [8, 9], but there remains debate about the optimal local and systemic treatment of these malignancies. According to the GCIg and SGO guidelines, patients with early-stage (FIGO I–IIA) disease should undergo radical hysterectomy with lymphadenectomy followed by either chemotherapy with cisplatin and etoposide or concurrent chemoradiation with EP. Given the high risk of distant recurrence associated with NECC, some have suggested the use of neoadjuvant chemotherapy before definitive local therapy, and the SGO guidelines suggest consideration of neoadjuvant chemotherapy if tumors are >4 cm at diagnosis [8]. Experience with neoadjuvant chemotherapy for NECC is limited and has shown mixed results. One study demonstrated remarkable clinical remissions in six of seven patients receiving vincristine, doxorubicin, and cyclophosphamide alternating with cisplatin and etoposide, although all patients had residual microscopic tumor present at surgery [2]. Another study did not demonstrate any benefit from neoadjuvant chemotherapy [5]. Drawing from the limited-stage small cell lung cancer experience, Takada et al. demonstrated that patients receiving concurrent chemoradiation had better survival than patients who received neoadjuvant chemotherapy followed by radiation therapy [10]. Several meta-analyses have demonstrated that the interval between the initiation of chemotherapy and the completion of radiation therapy in patients with limited-stage small cell lung cancer predicts survival, confirming the importance of early initiation of radiation therapy [11–14]. Our limited experience has not shown promise for neoadjuvant chemotherapy for NECC, and our standard is to initiate chemoradiation in patients who are not expected to undergo surgery.

There are no prospective data comparing surgery followed by chemotherapy and definitive chemoradiation in patients with early-stage resectable NECC. The current SGO guidelines state that radical hysterectomy with lymphadenectomy should be the standard of care for patients with FIGO stage I–IIA NECC. In our study, among patients with FIGO stage I–IIA disease without evidence of nodal metastases, those treated with definitive chemoradiation had better EFS and showed trends toward better OS and lower risk of pelvic recurrence than those treated with definitive surgery. Since hematogenous dissemination of NECC occurs early in the natural history of this disease and is the major driver of outcome, we speculate that the early introduction of systemic therapy with chemoradiation would halt metastatic progression of early-stage disease. While there are rare patients who truly have localized node-negative disease, many clinically node-negative cases likely have occult nodal metastasis at the time of diagnosis, so early introduction of systemic therapy seems prudent. We are re-evaluating the role of surgery in the treatment of NECC and considering the possibility that chemoradiation should be employed in all cases of NECC, even cases diagnosed at the earliest stage. Although radically different from the guidelines currently proposed by SGO and GCIg, this paradigm is well established in the treatment of limited-stage small cell lung cancer, where chemoradiation, rather than surgery, is almost always employed as primary treatment for early-stage clinically node-negative disease [15].

In patients treated with up-front surgery, the literature does not support the use of adjuvant radiation therapy [5, 16]. This pattern emerged in our study as well, as patients who were treated with radiation following surgery did not have better EFS, OS, or a decreased risk of pelvic recurrence than patients treated with surgery alone.

Although adjuvant chemotherapy is commonly employed in patients with NECC, the published data on the efficacy of adjuvant chemotherapy in these patients show mixed results and efficacy appears to depend on clinical stage [3, 4, 6]. Cisplatin and etoposide is the most common adjuvant chemotherapy regimen for NECC reported in the literature, although this regimen is again based on the experience with small cell lung cancer. In patients with extensive-stage small cell lung cancer, cisplatin and etoposide has remained the standard of care for more than 30 years, as other regimens, including three-drug combinations, alternating combinations (e.g., vincristine, doxorubicin, and cyclophosphamide alternating with cisplatin and etoposide, and escalated dose regimens have failed to significantly improve outcomes [17]. While the combination of cisplatin and etoposide has not been prospectively tested in NECC, it is the regimen recommended by the SGO for treatment-naïve patients with NECC [8]. Despite aggressive systemic therapy, most patients in our cohort experienced recurrence and died. While our study suggested a trend toward improved survival with the addition of chemotherapy after definitive local therapy (surgery, radiation, or chemoradiation), this difference was not statistically significant. The small nature of our study, coupled with the heterogeneity of the agents used and sequencing with local therapy, limits any conclusions about the effect of systemic therapy.

In our study, patients with LCNECC had better EFS and OS than patients with SCNECC or NECCNOS. Like NECC in general, the histogenesis and pathobiology of LCNECC is poorly understood, and LCNECC tends to be treated the same way SCNECC is treated. We have anecdotally observed better outcomes in LCNECC, and the current analysis confirms that LCNECC is a more favorable histologic type than SCNECC.

While prophylactic cranial irradiation is part of the standard recommended treatment for small cell lung cancer, it does not appear that prophylactic cranial irradiation is warranted in NECC. Although eight patients (25%) in our cohort developed brain metastases, seven of those eight had extensive extracranial metastatic disease identified before or concurrent with the brain metastases. It appears that isolated brain metastasis is quite uncommon in NECC and that whole-brain radiation therapy can be offered if brain metastases arise. A recent study examining multiple extrapulmonary small cell cancers, in which the cervix was among the most common primary sites, suggested that prophylactic cranial irradiation is not warranted in these cancers [18].

As a small retrospective analysis, our study has many limitations. Despite these limitations, we have a well-selected cohort of patients with NECC diagnosed using modern pathologic and immunohistochemical techniques, and our study confirms the aggressive nature of this rare disease. Importantly, we demonstrate that LCNECC is a more favorable histologic type than SCNECC or NECCNOS and that patients with early-stage LCNECC treated with aggressive locoregional and systemic therapy have a reasonable likelihood of long-term survival. Our findings support published guidelines that prophylactic cranial irradiation is

unnecessary but call into question whether surgery should be undertaken for any patient with LCNECC or SCNECC, regardless of stage. Abandoning radical surgery for early-stage disease would be a major change from current practice but would more closely mirror the approach to small cell lung cancer. Continued research on the cause, diagnosis, classification, and treatment of these rare but deadly cancers is desperately needed. To this end, we have established NeCTuR [19] and advertised it on multiple social media platforms in the hopes that we concentrate women with NECC to initiate and execute meaningful clinical trials that will improve outcomes in this disease.

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Highlights

- Neuroendocrine cervical cancer (NECC) is a rare and deadly disease.
- Large cell NECC is a favorable histologic subtype of NECC.
- Chemoradiation yields better survival than surgery in early-stage NECC.
- Prophylactic cranial irradiation (PCI) is not indicated in NECC.

Figure 1. Temporal distribution of first recurrence from time of diagnosis. Gray bars indicate number of events within each 1-month bin. The black line depicts cumulative recurrence rate (as a percentage of all recurrences) over time.

Figure 2.

(A) Event-free survival and (B) overall survival Kaplan-Meier plots for all patients by histologic type. Numbers at risk at 0, 5, and 10 years noted in parentheses. P denotes log-rank test.

Figure 3.

(A) Event-free survival and (B) overall survival Kaplan-Meier plots for patients with clinically node-negative FIGO stage I-IIA NECC by primary local treatment modality. Numbers at risk at 0, 5, and 10 years noted in parentheses. P denotes log-rank test.

Table 1

Patient, tumor, and treatment characteristics.

Variable	No. (%) ^I
Median Age (Range)	37 Years (24–77 Years)
Race	
White	32 (80%)
Black	4 (10%)
Asian	1 (3%)
Unknown	3 (7%)
Ethnicity	
Not Hispanic or Latino	28 (70%)
Hispanic or Latino	4 (10%)
Unknown	8 (20%)
FIGO ² Stage	
IB1	15 (37%)
IB2	16 (40%)
IIA2	2 (5%)
IIB	2 (5%)
IIIB	4 (10%)
IVA	1 (3%)
Histology	
Small Cell	25 (62%)
Large Cell	8 (20%)
Neuroendocrine, NOS ³	7 (18%)
Extent of Disease at Diagnosis	
No Evidence of Metastatic Disease	23 (57%)
Pelvic or Para-Aortic Nodal Disease	17 (43%)
Local and Systemic Treatment	
Radiation	21 (52%)
No Chemotherapy	3 (14%)
Neoadjuvant	0 (0%)
Neoadjuvant + Concurrent	3 (14%)
Concurrent	9 (43%)
Concurrent + Adjuvant	6 (29%)
Adjuvant	0 (0%)
Surgery	7 (18%)
No Chemotherapy	4 (57%)
Neoadjuvant	1 (14%)
Neoadjuvant + Adjuvant	0 (0%)

Variable	No. (%) ^I
Adjuvant	2 (29%)
Surgery + Radiation	9 (23%)
No Chemotherapy	0 (0%)
Neoadjuvant	1 (11%)
Neoadjuvant + Concurrent	1 (11%)
Concurrent	2 (22%)
Concurrent + Adjuvant	4 (44%)
Adjuvant	1 (11%)
Radiation + Surgery	3 (8%)
No Chemotherapy	0 (0%)
Neoadjuvant	0 (0%)
Neoadjuvant + Concurrent	1 (33%)
Concurrent	1 (33%)
Concurrent + Adjuvant	1 (33%)
Adjuvant	0 (0%)

^IExcept where otherwise indicated.

²International Federation of Gynecology and Obstetrics.

³Not otherwise specified.

Table 2

Risk of recurrence by FIGO stage, histologic type, and extent of disease at diagnosis.

Variable	No. (%)
FIGO ¹ Stage	Recurrence
IB1	11/15 (73%)
IB2	13/16 (81%)
IIA2	1/2 (50%)
IIB	2/2 (100%)
IIIB	4/4 (100%)
IVA	1/1 (100%)
Histology	
Small Cell	23/25 (92%)
Large Cell	3/8 (38%)
Neuroendocrine, NOS ²	6/7 (86%)
Extent of Disease at Diagnosis	
No Evidence of Metastatic Disease	16/23 (70%)
Pelvic or Para-Aortic Nodal Disease	16/17 (94%)

¹International Federation of Gynecology and Obstetrics.

²Not otherwise specified.