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Patterns of recurrence and survival in neuroendocrine cervical cancer

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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.

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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 toward 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.

1. 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

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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 treatments of NECC have 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.

2. 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, they were enrolled by means of a research study waiver. For this study, we included patients with International Federation of Gynecology and Obstetrics (FIGO) stages 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).

3. Results

3.1. 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

Table 1
Patient, tumor, and treatment characteristics.

Variable	No. (%)[a]
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[b] 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[c]	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%)
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%)

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