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Original Article

PRIMARY NEUROENDOCRINE CARCINOMA OF THE CERVIX: RETROSPECTIVE ANALYSIS

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ABSTRACT

Objective: Neuroendocrine carcinoma of the cervix is a rare variant of cervical carcinoma with a poorer prognosis. There is no standard treatment for this variant of cervical carcinoma. Due to the rarity of this malignancy, the management of NECC is difficult and associated with uncertainty. An interdisciplinary approach is necessary because most studies investigating the treatment of neuroendocrine tumors have been performed in patients with tumors in organs other than the cervix, mostly the lung and pancreas.

Methods: A retrospective analysis of 32 patients diagnosed by biopsy with neuroendocrine carcinoma of the cervix was done. This study was carried out at Adyar Cancer Institute Chennai. All stage I patients underwent surgery followed by chemotherapy. All stage II and III patients underwent chemoradiotherapy. All stage IV patients underwent palliative chemotherapy. Disease-free survival and overall survival were seen.

Results: Overall, while the mean survival time decreases as the disease progresses from Stage I to Stage IV, the variability (SD) is highest in the early stages (I and II) and relatively lower in the advanced stages (III and IV), though the differences in survival times between the stages were not statistically significant.

Conclusion: We found that NECC is a rare form of cervical cancer with a poor prognosis. Due to the small number of cases and the retrospective nature of this analysis, conclusions are limited, but multimodality treatment with radical surgery and adjuvant or neoadjuvant chemotherapy with etoposide and cisplatin is the mainstay of treatment for early-stage disease while combined chemoradiotherapy and chemotherapy are appropriate for women with locally advanced or recurrent NECC.

Keywords: Neuroendocrine carcinoma, NECC, Small cell neuroendocrine carcinoma, Cervical cancer, Chemotherapy

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INTRODUCTION

Neuroendocrine neoplasia (NENs) are aggressive malignancies derived from neuroendocrine cells. The term neuroendocrine refers to the fact that the tumor cells originate from the embryonic neuroectoderm and display an immunohistochemical profile consistent with endocrine glandular cells. They may or may not secrete peptide hormones. In humans, NENs are typically located in the gastrointestinal tract, the pancreas, and the lungs and are subdivided into well-differentiated NENs and poorly differentiated NENs. Well-differentiated NENs include neuroendocrine tumors (NET) G1 (also known as typical carcinoid), NET G2 (also known as atypical carcinoid), and NET G3. Poorly differentiated neuroendocrine carcinomas (NECs) include small-cell NEC and large-cell NEC [1].

NENs may also occur in other organs, such as the female genital tract. Neuroendocrine carcinoma of the cervix (NECC) is an aggressive histological variant of cervical cancer accounting for about 1–1.5% of all cervical cancers. Small cell NEC is the most common type of NECC, whereas well-differentiated NETs, especially NET G1 (typical carcinoid) and NET G2 (atypical carcinoid), are very rare at this location. The grading of NECC is similar to NEN of other location like the lung or the digestive system [2]. Due to the rarity of this malignancy, the management of NECC is difficult and associated with uncertainty. An interdisciplinary approach is necessary because most studies investigating the treatment of neuroendocrine tumors have been performed in patients with tumors in organs other than the cervix, mostly the lung and pancreas. Specifically, neuroendocrine tumors mainly occur in the lungs, and thus, treatment schedules for neuroendocrine tumors originating in other organs are similar to those used in small-cell lung cancer. The biology of NECC is different from that of squamous cell carcinoma or adenocarcinoma of the cervix in terms of many characteristics. For example, NECC is more likely to invade the lymphovascular space and spread to the regional lymph node basin at the time of diagnosis. Also, local and distant relapses occur more often in NECC, and the 5 y overall survival is significantly poorer with around 30% compared to>65% for squamous cell carcinoma and adenocarcinoma of the cervix. Thus, the aggressive nature of NECC resembles that of small-cell lung cancer, which, at the time of initial diagnosis, is rarely localized and mostly locally advanced or metastasized [3, 4].

Positive immunohistochemical staining for neuroendocrine markers like synaptophysin (SYN), chromogranin (CHG), CD56 (N-CAM), and neuron-specific enolase (NSE) is diagnostic for NECC. For establishing the diagnosis, positive staining of at least two neuroendocrine markers is recommended [5, 6]. SYN and CD56 are the most sensitive markers. In some cases of small cell NECC, however, expression of neuroendocrine markers may be negative. Differential diagnosis of NECC includes metastasis of extracervical NEC (e. g. lung or gastro-enteropancreatic NEC) and extracervical NEC with local wide tumor spread (e. g. urinary bladder, rectum, or Merkel cell carcinoma of the skin). NECC must be distinguished from lymphomas, poorly differentiated squamous cell carcinomas, and sarcomas or melanomas with morphological small cell-like features. Furthermore, large cell NECC may be positive for p63, a marker strongly expressed in squamous cell carcinomas. In this case, however, positive immunohistochemical staining for neuroendocrine markers excludes the diagnosis of squamous cell carcinoma. While isolated neuroendocrine cells may occur in squamous cell carcinomas and adenocarcinomas, these tumors should not be interpreted as NECs if they lack the morphological features of NECs. Studies show prevalence of HPV infection in women diagnosed with neuroendocrine carcinoma of cervix [7].

MATERIALS AND METHODS

Patient selection

Patients diagnosed with neuroendocrine carcinoma of the cervix from January 2011 to December 2015 at Adyar Cancer Institute, Chennai Tamil Nadu, were retrospectively included in this study.

The number of cases during the study period determined the sample size. The total number of patients included in the study was 32. The staging was done as per the FIGO staging system for cervical carcinoma.

There were 6 patients with Stage I, 11 patients with Stage II, 7 patients with stage III, and 8 patients with stage IV NECC.

Treatment

Two Stage Ia patients underwent Total abdominal hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection followed by adjuvant chemotherapy.

Four stage IB2 patients and all stage II, III patients received definitive chemoradiation EBRT 50.4 Gy in 28 fractions with weekly cisplatin (dose 40 mg/m^2) followed by 3 fractions of weekly intracavitary brachytherapy with 7Gy per fraction. All patients received adjuvant chemotherapy.

The adjuvant chemotherapy regimen was either cisplatin etoposide or Carboplatin Etoposide.

All stage IV patients received palliative chemotherapy with Cisplatin etoposide or carboplatin etoposide.

Dose: Carboplatin AUC 5 IV on day 1, Etoposide 100 mg/m^2 IV on Days 1 to 3 with intervals of three weeks.

Dose: Cisplatin 25 mg/m^2 IV on days 1 to 3, Etoposide 100 mg/m^2 on days 1 to 3 with intervals of three weeks.

Outcome

The primary outcome was to assess overall survival. Overall survival was defined as the length of time from diagnosis of disease till the patient is alive or last follow-up.

The secondary outcome was to study the response of chemoradiation in early-stage disease and the response of palliative chemotherapy in the advanced stage.

Statistical analysis

Descriptive analyses were presented as numbers and percentages. Survival time was compared across disease stages using one-way ANOVA. A p-value of<0.05 was considered statistically significant. IBM SPSS Version 22 was used to calculate the p-value.

RESULTS

Most of the patients were in the age group 51-60 y, ranging from 32 y to 79 y. The median age of the patients was 50 y. Most of the patients were non-smokers. Per vaginal postmenopausal discharge was seen in 19 patients; per vaginal bleeding was seen in 11 patients and other presenting complaints were seen in 2 patients. Most patients have poorly differentiated carcinoma, a type of cancer that is less well-defined and often associated with more aggressive and advanced stages of the disease, which on IHC confirmed as small cell carcinoma in 60 percent of patients. A smaller proportion of patients have small cell carcinoma, which is known for its rapid growth and high potential for metastasis, while large cell carcinoma accounts for few of the cases.

Table 1: Distribution according to staging of the disease

Staging of the disease	Frequency (No)	Percentage (%)
I	6	18.75
II	11	34.3
III	7	21.8
IV	8	25
Total	32	100.0

The distribution of cases in table 1 reveals that the most common stages of neuroendocrine carcinoma are IIA2 (21.6%), followed by IIIB, IV, and IVB (10.8% each). Stages IB, IB2, and IIB account for 8.1% of cases each. In contrast, the early stages (I, II, and III) are less frequent, contributing between 2.7% and 5.4% of the total cases. This pattern suggests a higher prevalence of more advanced stages, such as IIA2, IIIB, IV, and IVB, indicating that a significant proportion of cases are diagnosed at later stages. Overall, the data points to a trend of neuroendocrine carcinoma being more commonly detected in its advanced stages.

Table 2: Distribution according to response to treatment

Response to treatment (%)	Frequency (No)	Percentage
Complete response	12	36.4
Partial response	14	42.4
Stable disease	0	0.0
Progression of disease	3	9.1
No response	3	9.1
Total	32	100.0

As shown in table 2, among the 32 patients, 12 (36%) achieved complete response, 14 (42%) had partial response, 3 (9%) experienced progression of disease, and 3 (9%) showed no response. None of the patients had stable disease.

Table 3: Survival (months) in relation to the disease stage

Staging of the disease	Frequency (No.)	Mean±SD [Survival in months]	F Value	P value
I	6	27.67±18.64	1.862	0.164, Not
II	11	19.80±12.61		Significant
III	7	23.00±5.35		
IV	8	12.00±5.66		
Total	32			

One-way ANOVA was applied. P value<0.05 was considered as statistically significant.

The table 3, shows the mean survival times in relation to the staging of the disease.

In Stage I, the mean survival was the longest at 27.67±18.64 mo, with considerable variability in survival times. Stage II had a mean survival of 19.80±12.61 mo, indicating moderate variability. In Stage III, the mean survival was 23.00±5.35 mo, with less variability compared to earlier stages. Stage IV had the shortest mean survival of 12.00±5.66 mo, with relatively low variation.

Overall, while the mean survival time decreases as the disease progresses from Stage I to Stage IV, the variability (SD) is highest in the early stages (I and II) and relatively lower in the advanced stages (III and IV), though the differences in survival times between the stages were not statistically significant.

DISCUSSION

NECC is an aggressive histological variant of cervical cancer, accounting for 1.4% of all cervical cancers. The management of NECC is difficult and is associated with uncertainty. We found that NECC is a rare variant of cervical cancer, with small-cell NECC being the most common histological subtype [8, 9]. As per previous literature, this tumor carries a poor prognosis with a mean overall survival of 40 mo and a 5 y overall survival rate of 34%. Multimodality treatment with radical surgery and adjuvant or neoadjuvant chemotherapy with etoposide and cisplatin is the mainstay of treatment for early-stage disease, while combined radiochemotherapy and chemotherapy are appropriate for women with locally advanced or recurrent NECC. Many chemotherapy regimens have been described in the treatment of patients with NECC, but cisplatin/carboplatin and etoposide alone or in combination with other drugs have been described in more than two-thirds of the published studies [10-12]. Novel therapeutics such as immune checkpoint inhibitors and targeted therapies may be beneficial, but evidence for their efficacy is lacking. Although there is no standard of care regarding the choice of chemotherapy for women with NECC, we found that cisplatin/carboplatin and etoposide were the most used regimen in the primary treatment and may thus be regarded as an informal standard. Of note, this combination was described in 30/40 studies. The exact dosage and therapy duration of this scheme, however, varied considerably in the published Tempfer *et al.* BMC Cancer (2018) 18:530 Page 11 of 16 studies. For example, Baykal *et al.* used cisplatin 80 mg/m^2 on day 1 together with etoposide 120 mg/m^2 on days 1, 2, and 3 in a 21 d cycle. Intaraphet *et al.* used cisplatin 75 mg/m^2 and etoposide 100 mg/m^2 every 3 w. Hoskins *et al.* used etoposide (40 mg/m^2/d) and cisplatin (25 mg/m^2/d) over 5 consecutive days starting on days 1, 15, 29, and 43 and combined this scheme with locoregional irradiation started on day 15 [13-15]. In women with recurrent NECC, cisplatin/etoposide alone or in combination with other cytotoxic drugs was also the most used cytotoxic regimen described in 5/8 studies. Of note, women with recurrent disease who had already been treated with cisplatin/carboplatin and etoposide in the primary setting might benefit from a triplet regimen consisting of topotecan, paclitaxel, and bevacizumab. In the largest series of women with recurrent NECC, Frumovitz *et al.* found that the combination of topotecan, paclitaxel, and bevacizumab was superior to platinum-based regimens with or without a taxane [16-18]. Thus, in women who already had received cisplatin/carboplatin and etoposide in the primary treatment, topotecan, paclitaxel, and bevacizumab might be an appropriate choice. Women with NECC have a poor prognosis, irrespective of the treatments used. Even with aggressive treatment schemes involving radical surgery, chemotherapy and radiotherapy, the mean 5 y overall survival rate was only 34% in our pooled analysis of the published data [19, 20]. Therefore, new treatment concepts are warranted for this subgroup of cervical cancer patients. Targeted therapies and immune checkpoint inhibitors might be such new treatment options for NECC. In two case reports, nivolumab led to durable remissions in patients with recurrent disease as did the MEK-inhibitor trametinib in a woman with recurrent small cell NECC and a KRAS mutated tumor [21, 22]. Clearly, this is not a broad evidence base. On the other hand, NECC is a very rare disease and in view of a reasonable alternative, these novel agents might be used in women with recurrent NECC and progression after conventional chemotherapy regimens such as cisplatin/etoposide or topotecan, paclitaxel, and bevacizumab. When comparing these regimens to those usually used for small-cell lung cancer, platinum compounds, etoposide, topotecan and anthracyclines are familiar drugs, whereas paclitaxel or bevacizumab is rarely used in small-cell lung cancer [23].

CONCLUSION

We found that NECC is a rare form of cervical cancer with a poor prognosis. Due to the small sample size and the retrospective nature of this analysis, conclusions are limited, but multimodality treatment with radical surgery and adjuvant or neoadjuvant chemotherapy with etoposide and cisplatin is the mainstay of treatment for early-stage disease while combined chemoradiotherapy and chemotherapy are appropriate for women with locally advanced or recurrent NECC. Considering the or prognosis of women with NECC despite aggressive treatment, novel therapeutics such as immune checkpoint inhibitors and targeted agents should be incorporated into the management even without controlled evidence.

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AUTHORS CONTRIBUTIONS

This work was carried out in collaboration with authors. Author Dr Prateek Tiwari and Dr Shreena Patidar were the principal investigators of the study and were involved in the design, clinical treatment protocol, conduct, and analysis of the study and author Dr V Pal contributed in applying Histological and Anatomical concepts, report wrote, reviewed, and edited the manuscript.

CONFLICTS OF INTERESTS

The authors declare that they have no conflict of interest.

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