

## Neuroendocrine Carcinoma of The Uterine Cervix: Clinicopathological Profile and Outcomes from a Tertiary Referral Center in Indonesia

Anita Permatasari\*, Birgitta Maria Dewayani, Anglita Yantisetiasti

Universitas Padjadjaran, Indonesia

Email: [anita22003@mail.unpad.ac.id](mailto:anita22003@mail.unpad.ac.id)\*

### ABSTRACT

Neuroendocrine carcinoma of the cervix (NECC) is a rare and highly aggressive malignancy with a poor prognosis. Data on its clinicopathological profile and outcomes from Indonesia are extremely limited. This study aims to characterize the clinicopathological features and survival outcomes of NECC patients at a tertiary referral center in Indonesia. A retrospective study was conducted on 55 NECC cases diagnosed between 2019 and 2025. Data on age, FIGO stage, histologic subtype, lymphovascular invasion (LVI), and metastatic status were collected. Overall survival (OS) was analyzed using the Kaplan-Meier method. The median age at diagnosis was 46 years. Most patients (54.5%) presented with locally advanced disease (FIGO II-III), and 25.5% had distant metastases at diagnosis. The small cell subtype was predominant (74.5%). LVI was present in 43.6% of cases. The median OS was 14.5 months, with 1-year and 2-year survival rates of 52% and 42%, respectively. NECC in Indonesia is predominantly diagnosed at advanced stages, leading to poor survival outcomes. These findings underscore the aggressive nature of this tumor and highlight the critical need for early detection, accurate pathological diagnosis, and improved treatment strategies.

**Keywords:** neuroendocrine carcinoma, uterine cervix, clinicopathological profiles, outcomes, tertiary hospital.

### INTRODUCTION

Cervical cancer is one of the most common gynecological malignancies worldwide, particularly in developing countries (Salvo et al., 2023). The majority are squamous cell carcinomas and adenocarcinomas, while neuroendocrine carcinoma of the cervix (NECC) accounts for only 1–1.5% of cases. Despite its rarity, NECC is clinically important due to its aggressive nature, early metastasis, and poor prognosis (Winer et al., 2021).

(Salvo et al., 2023). Most NECCs are considered part of the HPV-driven oncogenesis pathway, particularly associated with high-risk HPV type (Castle et al., 2018). However, compared with squamous cell carcinoma and adenocarcinoma of the cervix, NECC carries significantly worse survival rates, with five-year survival often reported at only 30–50% in early stages and less than 15% in advanced disease (Salvo et al., 2023; Zhang et al., 2023).

In Indonesia, where cervical cancer remains a significant public health problem, data on NECC are extremely limited (Kementerian Kesehatan Republik Indonesia, 2024). The clinicopathological profile, stage distribution, and outcomes of patients with NECC have not been comprehensively described. This data scarcity creates significant gaps in understanding the disease behavior, optimal management strategies, and prognostic factors specific to the Indonesian population. Furthermore, the aggressive nature of

NECC and its rarity make it challenging for clinicians to recognize and appropriately manage, often leading to delayed diagnosis and suboptimal treatment outcomes.

The urgency of this research stems from several critical factors. First, NECC's aggressive biological behavior and poor prognosis require immediate attention from the medical community to improve patient outcomes. Second, the lack of comprehensive data from Indonesia limits evidence-based clinical decision-making and treatment planning. Third, early recognition and accurate pathological diagnosis are crucial for appropriate staging and treatment selection, but these require better understanding of disease patterns in the local population. Fourth, the rarity of NECC necessitates systematic data collection and analysis to generate meaningful insights for clinical practice. Finally, establishing baseline data is essential for future comparative studies and collaborative research efforts.

Previous international studies have provided valuable insights into NECC characteristics and outcomes. However, most research has been conducted in Western populations or other Asian countries with different healthcare systems and population characteristics. Studies from Taiwan, Korea, and Thailand have reported varying clinicopathological features and survival outcomes, but no comprehensive analysis has been conducted specifically for the Indonesian population. The existing literature gap includes limited data on disease presentation patterns, histopathological characteristics, stage distribution, and survival outcomes in Indonesian patients. Additionally, there is insufficient information about the optimal diagnostic approach and treatment strategies suitable for resource-limited settings like Indonesia.

This study represents the first comprehensive analysis of NECC clinicopathological features and survival outcomes from a major Indonesian tertiary referral center. The novelty includes the relatively large sample size for such a rare tumor in the Indonesian context, systematic evaluation of histopathological characteristics including immunohistochemical profiles, and detailed survival analysis using standardized methodology (Gadducci et al., 2019). Furthermore, this research provides crucial baseline data that can serve as a reference for future studies and clinical practice guidelines in Indonesia and similar resource-limited settings.

The primary objective of this study is to characterize the clinicopathological features and survival outcomes of patients with NECC diagnosed at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. Secondary objectives include evaluating stage distribution patterns, identifying prognostic factors, and providing baseline data for future research. The benefits of this research include improved understanding of NECC behavior in the Indonesian population, enhanced awareness among pathologists and clinicians for accurate diagnosis, contribution to evidence-based treatment guidelines, and establishment of a foundation for future collaborative research efforts. To our knowledge, this represents one of the

largest single-institution series of NECC from Indonesia, providing valuable baseline data to guide future clinical and research efforts.

## **METHOD**

This was a retrospective study of patients diagnosed with neuroendocrine carcinoma of the cervix (NECC) at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, between January 2019 and June 2025. A total of 55 consecutive cases were included. The diagnosis of NECC was established based on histopathological examination and supported by immunohistochemistry (IHC).

Data were retrieved from pathology archives and medical records. The parameters collected included age at diagnosis, clinical presentation, FIGO stage (2018 International Federation of Gynecology and Obstetrics classification), histologic subtype (small cell, large cell, or admixed), lymphovascular invasion (LVI), regional lymph node status, and presence of distant metastasis at diagnosis. As part of the diagnostic work-up, neuroendocrine markers (synaptophysin, chromogranin, or INSM1) were applied in all cases to confirm the diagnosis. Ki-67 proliferative index was routinely assessed, while cytokeratin and p16 were evaluated in a subset of cases.

Follow-up data were available for all patients. Overall survival (OS) was defined as the interval between the date of diagnosis and the date of death (event) or last follow-up (censored). Patients who died during follow-up were classified as events, while those alive at the last contact were treated as censored observations. Survival estimates were calculated using the Kaplan–Meier method.

This retrospective study is part of a larger study entitled “Association between Poly (ADP-Ribose) Polymerase 1 and Phosphorylated AKT Expression to FIGO Staging in Neuroendocrine Carcinoma of The Uterine Cervix.” The Ethical Committee of Padjadjaran University granted ethical approval for this study approval number 365/UN6KEP/EC/2025.

## **RESULTS AND DISCUSSION**

### **Patient characteristics**

A total of 55 patients with NECC were identified between 2019 and 2025. Patients’ ages ranged from 24 to 82 years, with a median of 46 years (mean  $44.5 \pm 11.5$  years). According to the 2018 FIGO classification, most cases were diagnosed at locally advanced stages (II–III, 54.5%), while 14 patients (25.5%) had distant metastatic disease (IVB) at diagnosis. Early-stage disease (I) accounted for 18.2% of cases, and one patient (1.8%) was classified as stage IVA (Table 1).

### **Histopathology**

Histologically, small cell NECC was the predominant subtype (41/55, 74.5%), followed by large cell NECC (8/55, 14.5%) and mixed variants (6/55, 10.9%). Lymphovascular invasion (LVI) was observed in 24 cases (43.6%). Regional lymph node metastasis was documented in 12 cases (21.8%). Metastases at diagnosis were identified in 15 patients (27.3%), most commonly in the lungs, followed by bone, liver, and isolated sites such as brain, pancreas, and mammary lymph node (Table 1).

#### Immunohistochemistry

All cases were confirmed with neuroendocrine markers (synaptophysin and chromogranin, or INSM1). The Ki-67 proliferative index exceeded 20% in all cases. Cytokeratin was performed in 28 cases and was positive in 22, while p16 was performed in 14 cases and was positive in 7. Representative histopathological and immunohistochemical features of NECC in Figure 1.

#### Survival analysis

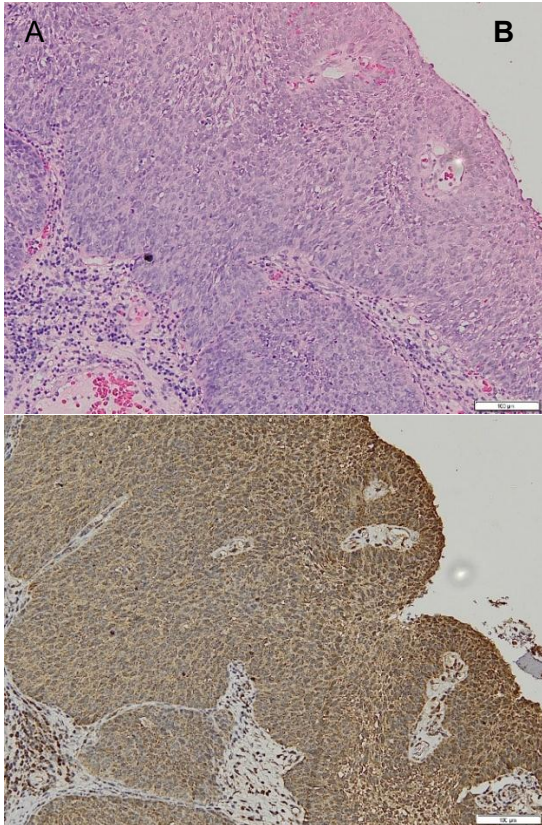
At the last follow-up, 25 patients (45.5%) had events (death), while 30 patients (54.5%) were censored (alive at last contact). Kaplan–Meier analysis demonstrated a median overall survival (OS) of 14.5 months, with estimated 1-year OS of 52% and 2-year OS of 42% (Figure 1). The survival curve showed the steepest decline within the first two years after diagnosis.

**Table 1.** Patient characteristics and Histopathological Findings

Variable	n = 55 n (%)
<b>Age (Mean ± Standard deviation)</b>	44,1 ± 10,2
<b>FIGO Stage</b>	
IB2	5 (9.1%)
IB3	5 (9.1%)
IIA	3 (5.5%)
IIA2	1 (1.8%)
IIB	7 (12.7%)
IIIB	13 (23.6%)
IIIC1	6 (10.9%)
IVA	1 (1.8%)
IVB	14 (25.5%)
<b>Lymphovascular invasion</b>	
Present	24 (43.6%)
Absent	31 (56.4%)
<b>Regional lymph node involvement</b>	
Positive	12 (21.8%)
Negative	43 (78.2%)
<b>Distant Metastasis</b>	
Positive	15 (27.3%)
Negative	40 (72.7%)
<b>Histologic subtype</b>	

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Variable	n = 55
	n (%)
Small cell	41 (74.5%)
Large cell	8 (14.5%)
Mixed neuroendocrine non neuroendocrine	6 (10.9%)



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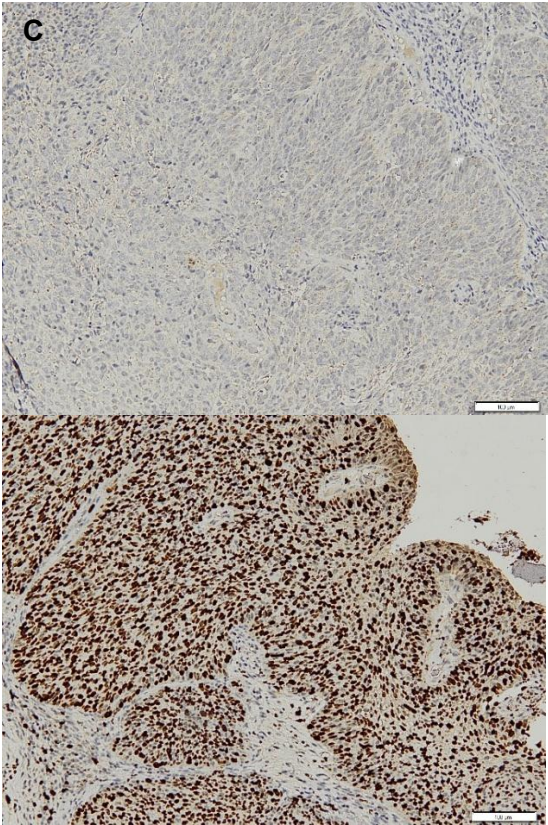


Figure 1. Part of ectocervix with neuroendocrine carcinoma mimicking squamous cell carcinoma. (100x magnifications) A. Haematoxylin-Eosin staining; B. Chromogranin expressed positive; C. Synaptophysin expressed negative; D. Ki67 proliferation index expressed positive more than 20%.

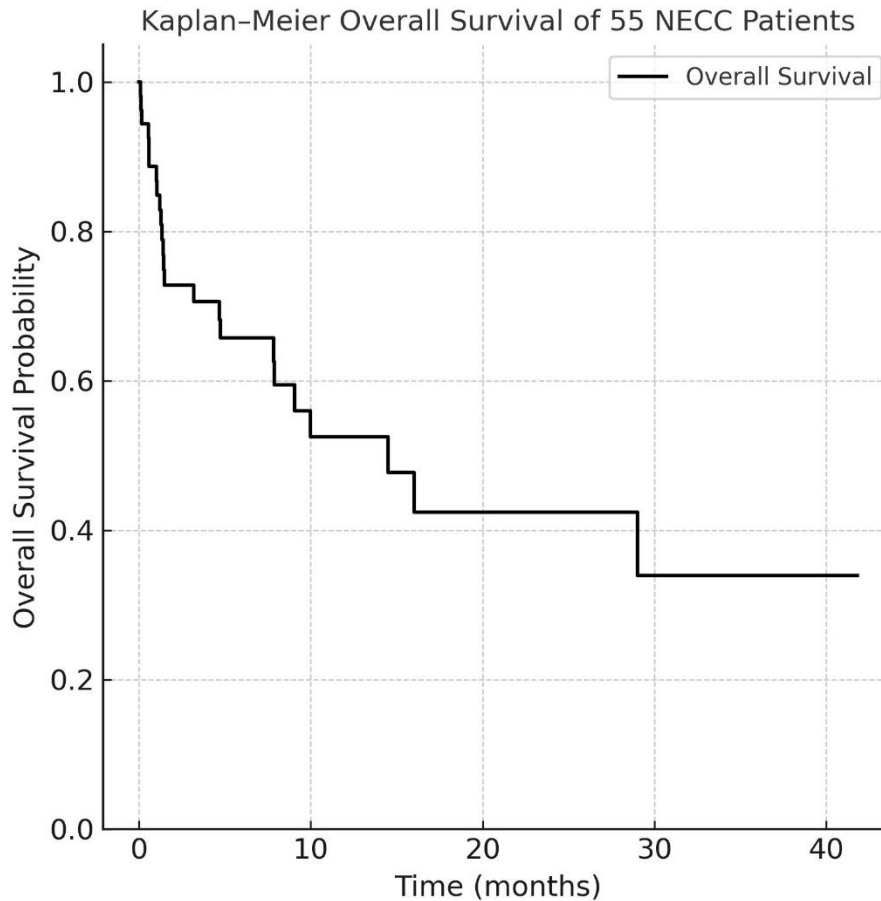


Figure 2. Kaplan–Meier overall survival curve of 55 patients with neuroendocrine carcinoma of the cervix. The median overall survival was 14.5 months, with 1-year and 2-year survival rates of 52% and 42%, respectively.

## Discussion

This study describes the clinicopathological profile and survival outcomes of 55 patients with NECC. Most patients presented at locally advanced or distant metastatic stages, with the small cell subtype being predominant. Lymphovascular invasion and nodal metastasis were frequent, and the median overall survival was only 14.5 months.

In our study, the small cell subtype was the predominant histologic variant (74.5%), consistent with previous reports in which small cell NECC accounts for the majority of cases (Isabel Alvarado-Cabrero et al., 2020; Tempfer et al., 2018).

Our results are consistent with previous reports from other regions. Frumovitz et al. reported a 5-year survival of less than 15% in advanced-stage disease, while Wang et al. from Taiwan demonstrated a median survival of approximately 16 months for small cell NECC.<sup>7</sup> Similarly, our 1- and 2-year survival rates of 52% and 42% align with international data, underscoring the universally poor prognosis of this tumor regardless of geographical setting (Salvo et al., 2023; Lee et al., 2016; Intaraphet et al., 2014; Li et al., 2020).

The predominance of advanced-stage disease at diagnosis may reflect delayed detection and the aggressive natural course of NECC. The high frequency of early metastasis, particularly to the lungs, suggests that comprehensive staging and systemic evaluation should be considered at presentation. Accurate recognition of neuroendocrine morphology by the pathologist is critical, as NECC carries a markedly worse prognosis compared to conventional squamous or adenocarcinomas of the cervix.

The main strengths of this study are the relatively large sample size for such a rare tumor and the inclusion of survival analysis, which provides valuable baseline data from a tertiary referral center in Indonesia. However, limitations include its retrospective design, incomplete immunohistochemical profiling (CK and p16 performed only in a subset), variable follow-up durations, and the lack of detailed treatment analysis.

This study highlights the aggressive nature of NECC and the importance of accurate pathological recognition of its neuroendocrine morphology. Greater awareness among pathologists is essential, as distinguishing NECC from conventional cervical carcinomas carries critical prognostic implications. In resource-limited settings, improving access to diagnostic immunohistochemistry and minimizing loss to follow-up are also crucial. Collaborative efforts across centers are needed to build larger study and establish standardized management approaches for this rare malignancy.

## CONCLUSION

This study provides baseline clinicopathological and survival data of neuroendocrine carcinoma of the cervix from an Indonesian tertiary center, showing that most patients presented at advanced stages with poor overall survival. Accurate pathological recognition of neuroendocrine morphology, supported by access to diagnostic immunohistochemistry and improved follow-up, is essential to optimize patient outcomes and guide future collaborative efforts. Future research should focus on establishing standardized diagnostic protocols, developing comprehensive treatment guidelines suitable for resource-limited settings, and conducting multi-institutional collaborative studies to better understand prognostic factors and optimize therapeutic strategies for Indonesian patients with NECC.

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