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Large Cell Neuroendocrine Carcinoma of the Cervix Responding to Etoposide–Cisplatin Chemotherapy, Enabling Radical Hysterectomy: An Evidence-Based Case Report

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ABSTRACT

Large Cell Neuroendocrine Carcinoma (LCNEC) of the cervix is a rare and highly aggressive malignancy with limited standardized therapeutic protocols. A 29-year-old woman presented with vaginal discharge and bleeding. Imaging and biopsy confirmed stage IIB LCNEC of the cervix. She received cisplatin–etoposide chemotherapy followed by radical hysterectomy. On follow-up, she demonstrated complete remission. A systematic review of multiple databases was conducted, and relevant data were extracted from the included studies. Seven studies met the criteria for qualitative analysis. Histological and immunohistochemical confirmation remains essential for diagnosis. Our review suggests that multimodal therapy combining radical hysterectomy with cisplatin-etoposide chemotherapy offers the most promising disease control in LCNEC, although long-term prognosis remains guarded. We conclude that LCNEC requires prompt diagnosis and aggressive combined chemotherapeutic–surgical management. This case highlights the responsiveness of LCNEC to cisplatin-etoposide and underscores the need for standardized treatment guidelines.

Keywords: Large-cell, Neuroendocrine, Carcinoma of cervix, Surgery, Chemotherapy

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1. Introduction

Cervical cancer remains a major global health concern, particularly affecting women in low-resource settings. While squamous cell carcinoma is the most common histological subtype, rare variants such as Neuroendocrine Carcinomas (NECs) represent a small yet clinically significant category due to their aggressive behavior and poor prognosis **(1)**.

Cervical Neuroendocrine Carcinoma (NECC) is an uncommon and highly aggressive form of cervical cancer, accounting for approximately 1-1.5% of all cases. Among its subtypes, small cell neuroendocrine carcinoma is the most prevalent. Well-differentiated neuroendocrine tumors NET G1 (typical carcinoid) and NET G2 (atypical carcinoid) are exceedingly rare in the cervix. The grading of NECC parallels that of Neuroendocrine Neoplasms (NENs) found in other organs, including the lung and gastrointestinal tract. Due to its rarity, NECC poses significant challenges in diagnosis and management, often leading to uncertainty in clinical decision-making **(2-4)**.

Large Cell Neuroendocrine Carcinoma (LCNEC) of the cervix is an exceptionally rare subtype, representing less than 0.1% of cervical cancers. Because of the limited number of reported cases, no standardized treatment guidelines currently exist. This case report describes a young woman with stage IIB LCNEC who showed a favourable response to etoposide-cisplatin chemotherapy followed by radical hysterectomy, demonstrating the potential effectiveness of multimodal therapy in managing this aggressive malignancy.

2. Case Presentation

A 29-year-old P2002 woman referred from Kertosono Public Hospital, Nganjuk, to our center with a preliminary diagnosis of small cell neuroendocrine

carcinoma based on cervical biopsy. She presented to the obstetrics and gynecology outpatient clinic with complaints of vaginal bleeding and whitish vaginal discharge for the past three months. On physical examination, vaginal discharge was noted, although no active bleeding was present. Tumor infiltration involved the proximal one-third of the vaginal wall. The cervix appeared friable and irregular, with a palpable exophytic mass measuring approximately 3 cm. The uterus was anteflexed and normal in size, and both adnexa were non palpable. Rectovaginal examination revealed smooth rectal mucosa without nodularity. The cervix was partially to completely fixed (CFS 75-100%), indicating progressive local extension.

Abdominal ultrasonography (Figure 1) demonstrated a solid cervical mass measuring approximately 3.41×3.90×5.45 cm, highly suggestive of malignancy. No metastases were detected in the liver or para-aortic, iliac, or inguinal lymph nodes. Initial biopsy showed poorly differentiated cervical carcinoma. Subsequent immunohistochemical analysis confirmed large cell neuroendocrine carcinoma of the cervix. A thoracic X-ray and CT scan (Figure 2) were performed for staging and revealed no evidence of distant metastasis. The final diagnosis was stage IIB cervical large cell neuroendocrine carcinoma.

The patient subsequently received six cycles of Etoposide-cisplatin (EP) chemotherapy, which she tolerated well. Following completion of chemotherapy, she underwent radical hys- terectomy with pelvic lymph node dissection and bilateral ovarian transposition. At her most recent follow-up visit, the patient was in good clinical condition. Physical examination and pelvic ultrasonography showed no evidence of residual or recurrent disease.

Method

a. Search Strategy and Eligibility Criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to structure this systematic

A comprehensive search was conducted in PubMed, Science Direct, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to May 6, 2025. The following search terms were applied: ("Cervix") AND ("Cancer" OR "Carcinoma") AND ("Cis- platin" AND "Etoposide").

b. Eligibility Criteria

Studies were screened according to the following inclusion criteria:

1) **Study Type**: Case report, original research article, systematic review, or meta-analysis.

2) **Content**: Published studies describing chemotherapeutic management using cisplatin and etoposide for neuroendocrine carcinoma of the cervix.

Exclusion Criteria Included

Studies with inaccessible full texts. Figure 5 illustrates the complete PRISMA flow diagram used for study selection.

c. Data Extraction

From each eligible publication, the following data were extracted:

- Author and year of publication
- Patient characteristics
- Details of clinical management
- Treatment outcomes.

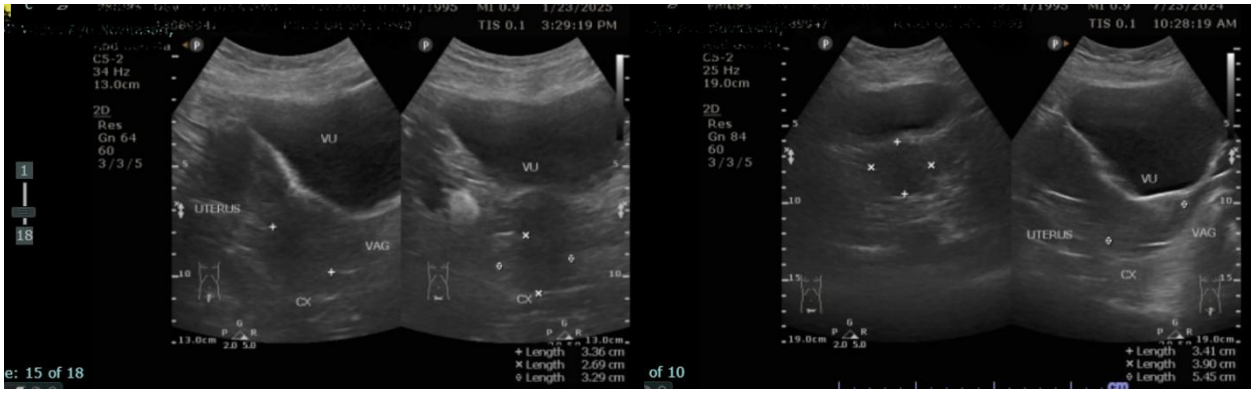


Figure 1. Abdominal ultrasonography

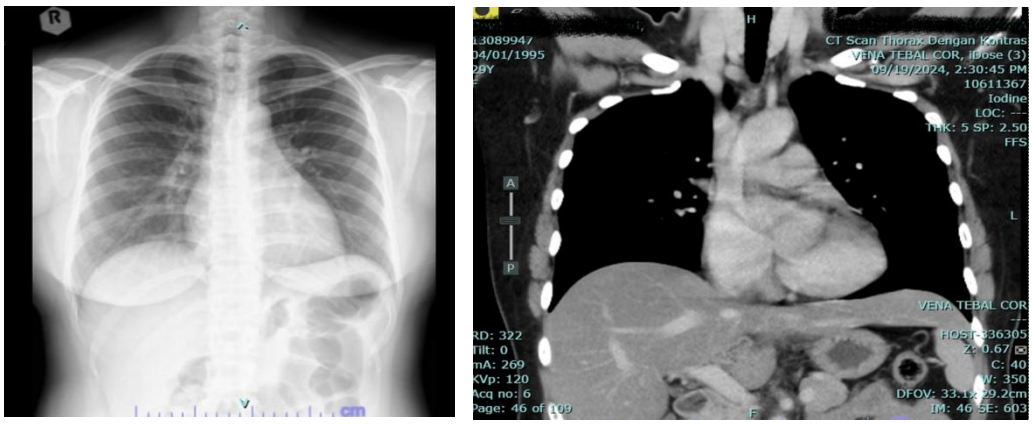


Figure 2. **Thorax x-ray and CT scan**

Table 1. **Study characteristics and results**

Author (Year)	Number of patients	Patient's characteristics	Management	Outcome	Level of evidence
Faridzi et al., (2025)(2)	1	Stage IB2 neuroendocrine carcinoma of the cervix with ovarian metastasis (small-cell type)	Primary debulking surgery and followed by cisplatin (75 mg/m2, day 1) + etoposide (100 mg/m2, days 1–3), every 21 days ×6 cycles.	Favorable response; at 12-month follow-up, patient remained disease-free on exam and ultrasound	5
PJacomina, et al., (2021)(1)	1	Stage IIIC1r cervical cancer with stage IV pelvic organ prolapse (small cell type)	Manual reduction with vaginal pessary; concurrent cisplatin (60 mg/m2, day 1) + etoposide (100 mg/m2,days 1–3), every 21 days × 4 cycles(3 during RT, 1 after); IMRT + brachytherapy.	Tolerated therapy well; at 1-year follow-up, patient had no evidence of disease or prolapse recurrence	5
Lee, et al., (2019)(5)	1	Stage IB2 cervical cancer with pancreatic metastasis (small-cell type)	Six cycles of cisplatin-based concurrent chemo-radiation therapy (CCRT)	PET/CT showed widespread metastases (lymph nodes, pancreas, breasts, adrenals, peritoneum); patient receiving palliative cisplatin–etoposide	5
Nakao, et al., (2020)(6)	1	Stage IVB small-cell carcinoma of the cervix (pT2bN1M1)	six cycles of EP (etoposide 100 mg/m², days 1–3; cisplatin 80 mg/m², day 1);	Partial response after EP; recurrence at 3 months; subsequent TC + Bev achieved remission; patient alive at 24 months without recurrence	5
Bajaj, et al., (2018)(7)	1	Stage IVB small-cell carcinoma of the cervix	Concurrent chemoradiotherapy (EP regimen + EBRT + brachytherapy); cisplatin 50 mg/m² (day 1, q3w) + etoposide 100 mg/m² (days 1-3, q3w)	Complete response; brain MRI negative for metastasis; no prophylactic cranial	5

				irradiation; patient disease-free at report	
Siu, et al., (2025)(8)	1	Stage IIIC1 large-cell carcinoma of the cervix	Open type C2 radical hysterectomy (Querleu–Morrow), bilateral salpingo-oophorectomy, pelvic + para-aortic lymphadenectomy; concurrent cisplatin–etoposide × 4 cycles + radiotherapy.	At 4-month follow-up, patient remained in remission; tumor markers stable.	5
Tempfer, et al., (2018)(3)	3,538	Neuroendocrine carcinoma of the cervix	Across 48 trials: surgery + chemotherapy most common; radiotherapy/CCRT also used; 24/40 studies employed cisplatin/carboplatin + etoposide	Poor prognosis overall; mean recurrence-free survival 16 months; mean overall survival 40 months	

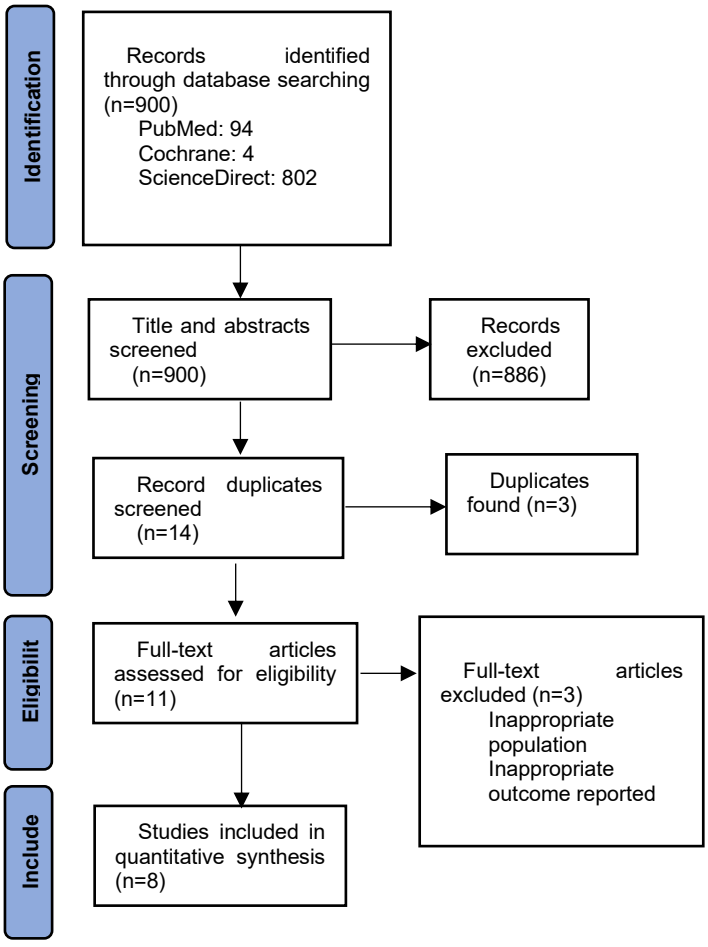


Figure 5. Diagram flow of literature search strategy for this meta-analysis

3. Discussion

The initial search identified 900 studies across all databases. After screening titles and abstracts, 886 studies were excluded. Three duplicate records were removed. An additional three articles were excluded due to their irrelevance to the review topic. Ultimately, seven studies met the inclusion criteria for qualitative analysis. These consisted of one systematic review and seven case reports, encompassing a total of 3,544

patients. The summarized findings of all included studies are presented in Table 1.

This case illustrates a diagnosis of Large Cell Neuroendocrine Carcinoma (LCNEC) of the cervix in a young woman without evidence of distant metastases. Cervical neuroendocrine carcinoma is a rare and highly aggressive subtype of cervical cancer, typically affecting younger women compared with other cervical malignancies. Primary gynaecologic neuroendocrine neoplasms are uncommon, accounting for approximately 2% of all female reproductive tract tumors. The cervix is the most frequent site for poorly differentiated neuroendocrine carcinoma, as demonstrated in our patient. Crane et al. reported that over 50% of gynecologic neuroendocrine tumors arise in the cervix, followed by 24% in the uterine corpus **(9)**.

Clinical Presentation

The clinical manifestations of cervical NEC resemble those of other cervical cancers, including abnormal vaginal bleeding, pelvic pain, and leukorrhoea. Some patients may exhibit systemic symptoms related to neuroendocrine activity, such as hypo- glycemia, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), or hypercalcemia. On pelvic examination, cervical NEC often appears as an erosive, ulcerative, or cauliflower-like mass **(2)**.

The World Health Organization (WHO) Classifies Cervical Neuroendocrine Tumors Into

Low-grade: typical carcinoid and atypical carcinoid

High-grade: Small Cell Neuroendocrine Carcinoma (SCNEC), Large Cell Neuroendocrine Carcinoma (LCNEC). Tempfer et al., reported that among NECC cases, 80.4% were small cell, 12% were large cell, and 7.6% belonged to other subtypes. In our patient, histopathological evaluation confirmed LCNEC, an exceptionally rare entity representing only 0.087% of invasive cervical cancers. LCNECs are characterized by large cells with coarse chromatin, prominent nucleoli, high mitotic activity, and neuroendocrine differentiation.

Histologically, LCNECs exhibit trabecular and organoid growth patterns with extensive necrosis and typically show strong positivity for neuroendocrine markers such as chromogranin A, CD56, and synaptophysin. Immunohistochemical (IHC) staining is essential for confirming neuroendocrine differentiation. Markers including P40, CEA, CD56, synaptophysin, chromogranin A, and P16 are particularly important for distinguishing neuroendocrine carcinomas from other cervical neoplasms, and all of these markers were notably positive in our patient. The diagnosis of LCNEC relies on a combination of clinical, cytological, histological, and immunohistochemical findings, with neuroendocrine marker positivity being a key requirement for confirmation. LCNEC may also occur concurrently with small-cell carcinoma or other cervical malignancies **(4,8,10)**. Despite the availability of surgical intervention, radiation therapy, and chemotherapy, the overall prognosis of LCNEC remains poor, with survival typically limited to 6-18 months after diagnosis. No comparable studies have evaluated treatment modalities surgery, chemotherapy, or radiotherapy at equivalent stages of disease progression. Surgery is considered a viable option in the early stages of LCNEC. Radical Hysterectomy With Pelvic Lymphadenectomy (RHPL) is the standard treatment for early-stage cervical cancer, including neuroendocrine carcinomas, although less radical procedures may be sufficient for selected patients **(2,8)**. RHPL has demonstrated favorable long-term outcomes with minimal morbidity; however, factors such as advanced stage, non-squamous histology, and lymph node involvement negatively influence prognosis. Minimally invasive radical hysterectomy is considered safe; however, evidence from the LACC trial indicates it is associated with higher recurrence and mortality rates compared with open surgery. This finding has led to a reevaluation of surgical approaches in cervical cancer management, with open radical hysterectomy now recommended as the standard of care for stage IA2-IB1 cervical cancer. Given the tendency of LCNEC to disseminate systemically at an early stage, surgery alone is often insufficient. A multimodal approach combining major surgery with chemotherapy either neoadjuvant or adjuvant with or without radiotherapy, offers greater therapeutic benefit. Although no universally accepted chemotherapeutic regimen exists for Neuroendocrine Cervical Carcinoma (NECC), the most commonly used protocol includes cisplatin or carboplatin combined with etoposide. Platinum-based therapy appears to outperform taxane-platinum combinations; nevertheless, its effectiveness in achieving long-term remission remains limited. The patient underwent six cycles of Etoposide/cisplatin (EP) chemotherapy. Following completion of systemic treatment, she underwent radical hysterectomy with pelvic lymph node dissection and bilateral ovarian transposition (Figure 3). The gross surgical specimens obtained fol lowing radical hysterectomy are shown in Figure 4. At her most recent follow-up visit, the patient was in good health, with no evidence of residual malignancy on physical examination or pelvic ultrasonography.

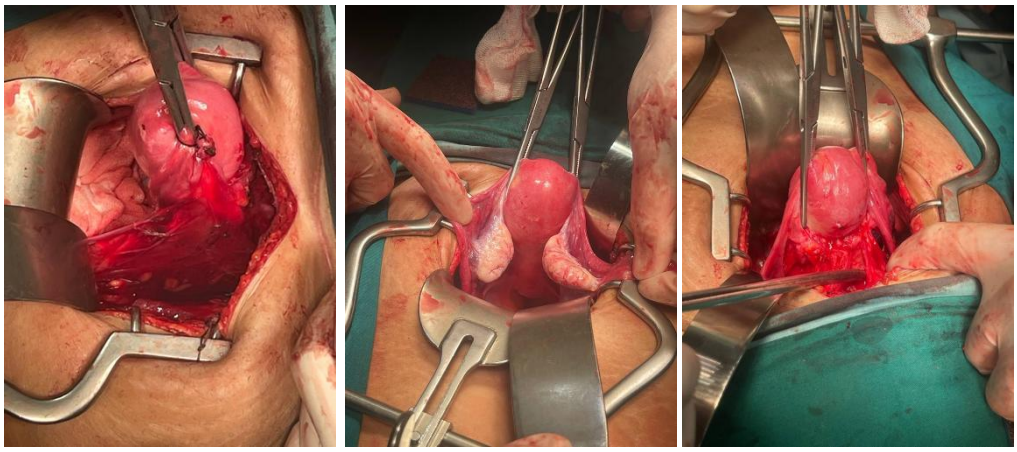


Figure 3. **Intra-operative view of radical hysterectomy**



Figure 4. **Post-operative view following radical hysterectomy**

Evidence From Literature

Wang et al. evaluated 179 patients with locally advanced Small Cell Cervical Carcinoma (SCCC) treated for FIGO stages I-IV. Among patients with stage IIB-IVB disease (n=56), receiving≥5 cycles of EP chemotherapy were associated with a significantly improved:

- 5-year Failure-Free Survival (FFS): 42.9% vs. 11.8%, (P=0.041)
- Cancer-Specific Survival (CSS): 45.6% vs. 17.1%, (P=0.035)

Concurrent Chemoradiotherapy (CCRT) using EP demonstrated superior outcomes compared with chemotherapy alone. Poor prognosis was associated with advanced stage, para-aortic or distant metastases, and inadequate treatment cycles. Although overall outcomes remain poor, early-stage patients receiving multimodal therapy show improved survival, with mean disease-free survival of 16 months and an overall survival of 40 months. Across published data, the average 5-year overall survival was only 34%, underscoring the aggressive nature of LCNEC.

The absence of standardized treatment protocols highlights the urgent need for focused research, as current strategies are frequently derived from small-cell neuroendocrine carcinoma or pulmonary neuroendocrine tumors **(6,8).**

4. Conclusion

The rarity of Large Cell Neuroendocrine Carcinoma of the Cervix (LCNEC) leads to limited clinical experience and contributes to frequent misdiagnosis. Effective management requires prompt recognition and histological confirmation using neuroendocrine markers. In our case, treatment with cisplatin-etoposide followed by surgical hysterectomy resulted in clinical remission and the absence of detectable residual disease. Current evidence suggests improved outcomes with multimodal therapy; however, the lack of standardized treatment guidelines and the overall poor long-term prognosis underscore the urgent need for larger prospective studies and collaborative research to optimize management strategies for this rare malignancy.

5. Declarations

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Ethical Considerations

This case report was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from the patient for the use of clinical information and photographs in this publication. All identifying details have been removed to ensure patient anonymity. Ethical approval was not required for this case report, in accordance with institutional policies for single-case descriptions without experimental intervention.

Authors' Contributions

Mona Nulanda: Conceptualization, case management, data acquisition, literature review, manuscript drafting, preparation of figures and clinical documentation. Hari Nugroho: Clinical evaluation, data interpretation, critical manuscript revision. Brahmana Askandar Tjokroprawiro: Validation of clinical and surgical management, methodological guidance, final review and approval of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

Fund or Financial Support

The authors declare that no external funding was received for this work.

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