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Case Report

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Small Cell Neuroendocrine Carcinoma of the Cervix: A Case Report and Literature Review

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Abstract

Neuroendocrine tumors (NETs) are neoplasms that arise from neuroendocrine cells. They predominantly affect the pancreas and digestive tract; however, NETs have been described in other locations such as the lung and, less commonly, the female genital tract. Cervical cancer is the eighth most common cancer worldwide, with 662,301 new cases diagnosed annually. Squamous cell carcinoma is the most frequent histological type. Cervical NETs are extremely rare, accounting for only 0.9 to 1.5% of malignant cervical tumors. Small cell neuroendocrine carcinomas of the cervix are the most common subtype. In this article, we report the case of a 66-year-old woman and discuss the clinical, diagnostic, particularly histological and immunohistochemical, and therapeutic aspects of these extremely rare tumors.

Keywords: *Neuroendocrine carcinoma, Cervical cancer, Small cell cancer, Chemotherapy, Surgery.*

Introduction

Cervical cancer ranks eighth in terms of cancer frequency worldwide, with 662,301 new cases diagnosed annually. Squamous cell carcinoma is the most common histological type [1]. Neuroendocrine tumors (NETs) arise from neuroendocrine cells and predominantly affect the pancreas and digestive tract. However, NETs have been described in other locations such as the lung and, less commonly, the female genital tract. Neuroendocrine tumors of the cervix account for 0.9 to 1.5% of cervical tumors [2].

Observation

A 66-year-old widowed woman, G5P4, with no significant medical history and a family history of endometrial cancer, presented with a several-week history of foul-smelling brown vaginal discharge. Gynecological examination revealed a large, irregular, polypoid, cauliflower-like cervix that bled on contact. A biopsy was performed.

Pathological examination of five tissue fragments revealed exclusively cellular proliferation arranged in trabeculae and sheets, composed of small to medium-sized cells with scant cytoplasm and large, hyperchromatic nuclei. The reactive stroma was fibrous and showed little inflammation with areas of tumor necrosis. These findings suggested a carcinoma, but the exact nature remained to be determined by immunohistochemistry (Figure 1).

Supplementary immunohistochemical studies were performed (Figure 2), including cytokeratin, P40, CD45, chromogranin A, synaptophysin, CD56, and Ki-67. The results are summarized in Table 1. A diagnosis of small cell neuroendocrine carcinoma of the cervix was therefore retained.

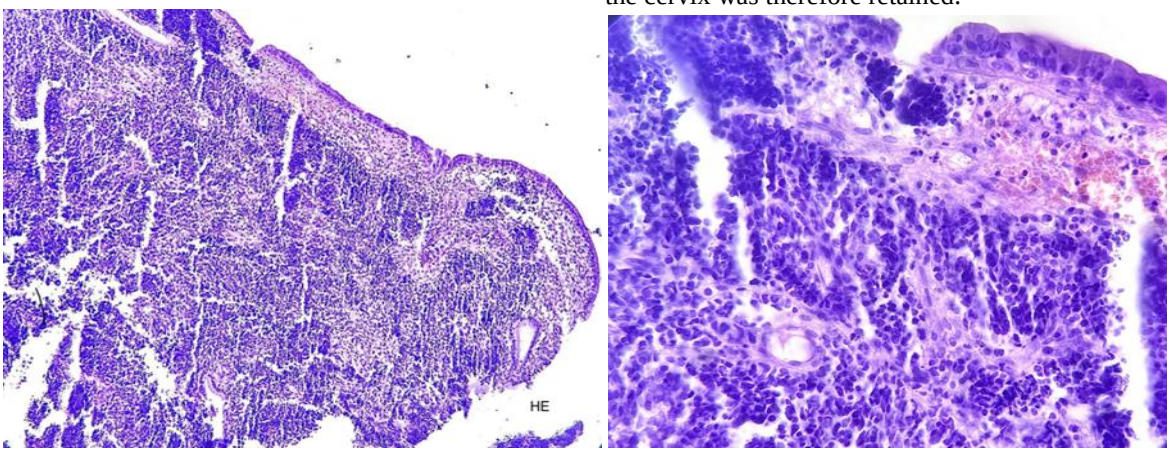

Figure 1: Histological aspect of the cervical biopsy (*Photo credit: Dr M.A. LAGHOUATI*)

Table 1: Immunohistochemistry staining results.

Antibodies	Staining
Cytokeratin	Positive staining on all tumor elements
P40	Negative staining
CD45	Negative staining on tumor cells Positive staining on inflammatory elements
ChromogranineA	Heterogeneous and focal positive staining of tumor elements
Synaptophysin	Diffuse positive staining of tumor elements
CD56	Heterogeneous and focal positive staining of tumor elements
Ki67	Nuclear positivity on 100% of tumor cells

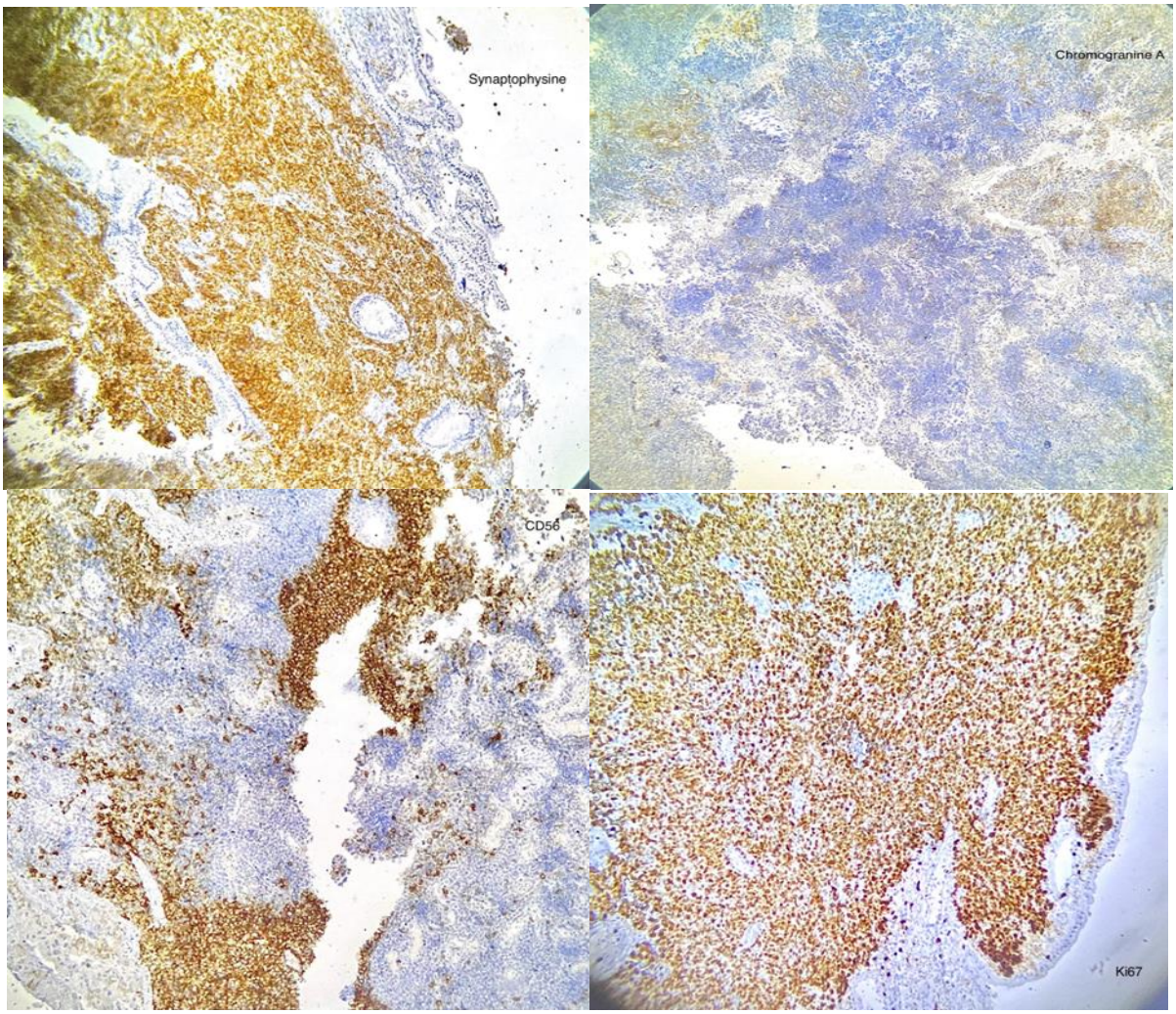

Figure 2: Immunohistochemical staining (*Photo credit: Dr M. LAGHOUATI*)

A pelvic MRI was performed to evaluate the spread of the tumor locally and regionally, revealing an aggressive cervical tumor, infiltrating both the endo- and exocervix on its right side. On T2-weighted images, the lesion was hyperintense, with hyperintensity on diffusion-weighted imaging and reduced apparent diffusion coefficient (ADC) and hypointensity on T1-weighted images. It showed marked enhancement after contrast administration. The tumor measured 50 x 43 mm across and extended 42 mm in height. It had spread into the uterine isthmus, the posterior and right lateral parts of the vaginal fornix, the right parametrium, and infiltrated more than the upper two-thirds of the vaginal wall. This tumor was classified as stage IIB according to the FIGO staging system.

A further work-up was performed, including a chest-abdomen-pelvis CT scan, which was normal.

A multidisciplinary team meeting was held to discuss the case, and it was decided to initiate first-line chemotherapy, followed by a re-evaluation for a complete surgical procedure, namely a radical hysterectomy with bilateral salpingo-oophorectomy, based on the response to chemotherapy. The patient was therefore started on cisplatin-etoposide chemotherapy. A follow-up pelvic MRI after three cycles of chemotherapy showed an objective response of 28% according to RECIST 1.1. After a reassessment of the case, it was decided to proceed with concurrent chemoradiotherapy, with the possibility of surgery to be reevaluated after completion of chemoradiotherapy.

Discussion

Cervical cancer is the 8th most frequent cancer worldwide, with approximately 662,301 new cases each year. The most common histological type is squamous cell carcinoma [1]. Neuroendocrine tumors (NETs) are tumors that develop from neuroendocrine cells, with a primary location in the pancreas and the digestive tract. NETs can also develop in other areas, including the lungs, and are rarely found in the female genital tract. Contrary to previous beliefs, it is increasingly evident that NETs represent a heterogeneous group of tumors. Certain clinical and pathological features are specific to the tumor's organ of origin, while others are shared across neuroendocrine tumors, regardless of their location. Depending on the affected organ, different classification systems have been developed [2–3].

Neuroendocrine tumors of the cervix represent 0.9 to 1.5% of cervical tumors [2]. The histological subtypes of small cell, large cell, and others account for 80.4%, 12.0%, and 7.6% of cases, respectively [4]. Small cell neuroendocrine carcinomas were first identified in 1957, though their actual incidence is likely underestimated due to descriptions under various terms such as carcinoid tumor, argyrophilic cell carcinoma, apudoma, oat cell carcinoma, neuroendocrine carcinoma, atypical carcinoid, undifferentiated small cell carcinoma, or intermediate cell carcinoma [5-7].

Over the past two decades, the incidence of small cell neuroendocrine carcinomas has increased, unlike cervical squamous cell carcinomas. This is partly due to the adoption of consistent terminology, which has enabled retrospective studies to document several distinctive features of these tumors [7, 8]. These tumors tend to occur at a median age of 42 years (20–87) [7, 9], which appears younger than for cervical squamous cell carcinomas. Our patient is 66 years old, which is uncommon. Clinical symptoms are nonspecific, with the most frequently observed signs being metrorrhagia and leukorrhea, as seen in our patient, who presented leukorrhea as the initial symptom.

The diagnosis of small cell neuroendocrine carcinoma is often made at a more advanced stage than cervical squamous cell carcinoma; the latter's incidence is decreasing, and it is increasingly detected early thanks to screening smears, which are not effective for small cell neuroendocrine carcinoma [10]. Small cell neuroendocrine carcinomas of the cervix also present more frequent lymphatic and vascular invasion at diagnosis than squamous cell carcinoma [2, 11]. Our patient was diagnosed at stage IIB and did not show lymph node infiltration at diagnosis, aligning with the results of a 2014 study in which half of the patients were diagnosed at stage IIB without lymph node infiltration [9].

Histologically, neuroendocrine neoplasms (NENs) are aggressive malignant tumors derived from neuroendocrine cells. The term "neuroendocrine" indicates that the tumor cells originate from the embryonic neuroectoderm and exhibit an immunohistochemical profile consistent with endocrine glandular cells [2]. They may or may not secrete peptide hormones. In humans, NENs are generally located in the gastrointestinal tract, pancreas, and lungs and are subdivided into well-differentiated NENs and poorly differentiated NENs [13]. Well-differentiated NENs include grade 1 neuroendocrine tumors (NET G1, also known as typical carcinoids), NET G2 (also known as atypical carcinoids), and NET G3. Poorly differentiated neuroendocrine carcinomas (NECs) include small-cell NECs and large-cell NECs (Table 1).

Table 1: Grading of neuroendocrine neoplasias of the cervix.

Classification/Grade	Mitotic Index[a]	Ki-67 Index[b]
Well-differentiated NEN		
NET G1	**< 2/10**	**≤ 2**
NET G2	**2-20**	**3-20**
NET G3[c]	**> 20**	**> 20**
Poorly differentiated NEN		
NEC G3	**> 20**	**> 20**
Small cell carcinoma Large cell carcinoma		

According to Kim et al. [13]. NEN neuroendocrine neoplasia, NET neuroendocrine tumor, NEC neuroendocrine carcinoma; a: Mitotic index: based on the evaluation of mitoses in 50 high-power fields (HPF; 0.2 mm2 each) in areas of higher density; expressed as mitoses per 10 high-power fields (mitoses/2 mm2); b: Ki-67 proliferation index: based on the evaluation of ≥500 tumor cells in areas of higher nuclear labeling (so-called hotspots); c: NET G3 is defined as NET with Ki-67 proliferation index/mitotic index > 20 and without morphological features of small cell NEC or large cell NEC.

In rare cases, NENs can also occur in other organs, such as the female genital tract [3]. Neuroendocrine carcinoma of the cervix (NECC) is an aggressive histological variant of cervical cancer. Small cell NEC is the most common type of NECC, while well-differentiated NETs, particularly NET G1 (typical carcinoid) and NET G2 (atypical carcinoid), are very rare at this site [12, 14]. The grading of NECC is similar to that of NENs in other locations, such as the lungs or digestive system (Table 1).

Immunohistochemical analysis is essential to confirm the diagnosis; antibodies such as synaptophysin (SYN), chromogranin (CHG), CD56 (N-CAM), and neuron-specific enolase (NSE) are necessary to diagnose NECC [12]. To establish the diagnosis, positive staining for at least two neuroendocrine markers is recommended. SYN and CD56 are the most sensitive markers [14].

However, in some cases of small-cell NECC, neuroendocrine marker expression may be negative. The differential diagnosis of NECC includes metastases from extracervical NECs (e.g., lung or gastro-entero-pancreatic NEC) and extracervical NECs with extensive local tumor spread (e.g., urinary bladder, rectum, or Merkel cell carcinoma of the skin) [4]. In our patient's case, immunostaining was performed, showing positivity for synaptophysin, CD56, and chromogranin. With a Ki-67 of

100%, the diagnosis of neuroendocrine carcinoma was confirmed.

As with cervical squamous cell carcinoma, high-risk HPV DNA has been detected in the majority of small and large cell NECCs [15]. In a recent meta-analysis, Castle et al. [16] analyzed HPV infection data from 403 cases of small cell NECC and 45 cases of large cell NECC. They found that 85% and 88% of cases, respectively, were positive for HPV, with HPV18 and HPV16 being the main subtypes. The authors conclude that HPV infection is the underlying cause of most NECC cases and that most, if not all, cases could thus be prevented through prophylactic HPV vaccination.

Due to the high propensity for regional and metastatic spread, initial assessment should include abdominopelvic imaging, preferably magnetic resonance imaging (MRI) [12]. In an analysis of data from the Surveillance Epidemiology and End Results (SEER) program over a 15-year period (1983 to 1998), McCusker et al. found a lymph node involvement rate of 57% for small cell neuroendocrine carcinomas compared to 18% for squamous cell carcinomas [7]. For the latter, recent imaging techniques have improved lymph node staging, notably with positron emission tomography (PET), which has shown superior performance for both pelvic (67% vs. 20%) and para-aortic (21% vs. 7%) lymph node detection. PET-CT is considered a standard examination for staging squamous cell carcinomas of the cervix beyond stage IB2, and some authors recommend it for earlier-stage tumors as well [17].

For small-cell neuroendocrine carcinomas of the cervix, PET-CT may also be indicated for localized tumors: 20% of stage IB1 tumors involve pelvic lymph nodes, and this rate exceeds 50% for stages above IB2 [7, 18]. Furthermore, extrapelvic metastases are present at diagnosis in nearly 25% of cases, mainly in the lungs, bones, and supraclavicular area, even in the absence of pelvic adenopathy [7, 12, 19, 20]. Brain imaging is only necessary if there are warning signs or evidence of lung metastases [12, 17, 21].

The rarity of small cell neuroendocrine carcinomas of the cervix has resulted in limited evidence from randomized clinical studies. The few prospective series, involving a small number of patients, do not provide sufficient data to establish a standard treatment [22,23]. As a result, treatment for these tumors generally follows guidelines for more common cervical cancers, with adaptations based on the unique biological traits of neuroendocrine tumors and clinical experience from treating neuroendocrine tumors of the lung [24].

For stage I-IIA localized tumors, according to FIGO classification, local treatment of the primary tumor does not seem to prevent distant metastases, and overall survival does not exceed three years. Several studies have shown disappointing outcomes for localized tumors treated only with local methods (surgery with or without radiotherapy), with 5-year progression-free survival rates between 0% and 36% [24, 25]. Relapses are primarily visceral (67 to 90% of cases) and lymphatic (34% of cases).

Retrospective studies have compared local treatment alone through surgery to local treatment combined with adjuvant chemotherapy. Zivanovic et al. found a 3-year recurrence-free survival rate of 83% for patients who received chemotherapy based on cisplatin and etoposide, compared to 0% for those undergoing local treatment alone [26]. Analysis of a larger Japanese series of 52 patients also demonstrated the benefit of chemotherapy in terms of both progression-free survival and overall survival [18]. Finally, in the series by Cohen et al., there was indeed a survival benefit with adjuvant chemotherapy (47.8% vs. 38.7%), but this difference did not reach statistical significance [27].

Neoadjuvant chemotherapy results in a partial tumor response in 69.4% of cases and a complete response in 15.3%, with a direct impact of the tumor residue on survival. Indeed, the presence of a tumor residue greater than 2 cm after chemotherapy is predictive of a 3-year overall survival rate of 21%, whereas this survival rate is 58% if the residue is less than 2 cm [28]. A large study has demonstrated that in stages IIB-IV, neoadjuvant treatment comprising at least 5 cycles of Cisplatin-Etoposide (PE) was correlated with longer disease-free survival (DFS) and overall survival (OS) at 5 years compared to other treatment modalities: DFS: 42.9% vs. 11.8%, p = 0.04; OS: 45.6% vs. 17.1%, p = 0.03. Moreover, concurrent chemoradiotherapy with at least 5 cycles of PE was associated with even better 5-year DFS (62.5% vs. 13.1%, p = 0.02) and 5-year OS (75.0% vs. 16.9%, p = 0.01) [29].

Thus, chemotherapy plays a role in both neoadjuvant and adjuvant settings, as well as in combination with radiotherapy. The most commonly used treatment regimens include cisplatin and etoposide (PE), vincristine, doxorubicin, and cyclophosphamide (VAC), cisplatin, vincristine or vinblastine, and bleomycin (PVB), cisplatin, doxorubicin, and etoposide (PAE), cisplatin and 5-fluorouracil (P-FU), carboplatin and etoposide (CE), carboplatin and paclitaxel (CP), and cisplatin and irinotecan (PI) [23, 26, 30-34] (Table 2).

Table 2: Chemotherapy regimens used for small cell neuroendocrine carcinoma of the uterine cervix.

Author ref	Setting	CT regimen
Boruta [30]	Adjuvant CT after surgery (N=34)	PE (N:15); VAC (N:7); VAC/PE (N:2); other (N:10)
Chang [23]	Adjuvant CT after surgery (N:23)	VAC/PE (N: 14); PVB (N: 8); others (N: 1)
Viswanathan [31]	NACT to RT (N: 8) CT/RT (n. 2) Adjuvant CT after surgery (N: 4)	PAE (N: 7); PE (N: 1) P (N: 1); P-FU (N: 1) PAE (N: 4)
Zivanovic [26]	Adjuvant CT after surgery or CT/RT (N: 6)	PE (N: 5); CE (N: 1)
Nagao [34][a]	Adjuvant CT after surgery (N: 9) Adjuvant CT/RT after surgery (N:7)	PI (N: 8); CP (n: 1) Nedaplatin (N: 6); P (N: 1)
Dongol [33]	NACT to surgery (N: 3) Adjuvant CT after surgery (N: 4)	PE (N: 1); PVB (N: 1); carboplatin-based CT (N: 1)[b] PE (N: 2); PVB (N: 1); CP (N: 1)

ref.: reference; CT: chemotherapy; PE: cisplatin and etoposide; VAC: vincristine, doxorubicin and cyclophosphamide; PVB: cisplatin, vincristine or vinblastine and bleomycin; NACT: neo-adjuvant chemotherapy; RT: radiotherapy; PAE: cisplatin, doxorubicin and etoposide; P: cisplatin; P-FU: cisplatin and 5-fluorouracil; CE: carboplatin and etoposide; CP: carboplatin and paclitaxel; PI: cisplatin and irinotecan.
a Of the 23 patients, 11 patients had small cell carcinoma and 12 had large-cell neuroendocrine carcinoma of the uterine cervix.
b Arterial chemoembolization with carboplatin, vincristine and mitomycin (one case).

The Society of Gynecologic Oncology has issued recommendations to facilitate the management of these particular tumors. A proposed decision-making algorithm is presented in Figure 3, established based on the recommendations of Gardner et al. and the findings of Wang et al. [12, 35].

Across various studies, 5-year overall survival rates, regardless of treatment approaches and considering prognostic factors such as tumor size, lymph node involvement, and lymphovascular space invasion, ranged from 14% to 67% across all stages [25, 28, 30]. When analyzed by stage, the 5-year overall survival was between 30% and 60% for early stages and between 0% and 17% for advanced stages [28, 30, 32, 36]. In the SEER study, the 5-year overall survival for small cell neuroendocrine carcinoma (SCNEC) was lower than that for squamous cell carcinoma (35.7% vs. 60.5%; hazard ratio [HR] = 0.55; 95% confidence interval [CI] = 0.43-0.69) and adenocarcinoma (35.7% vs. 69.7%; HR = 0.48; 95% CI = 0.37-0.61) [37].

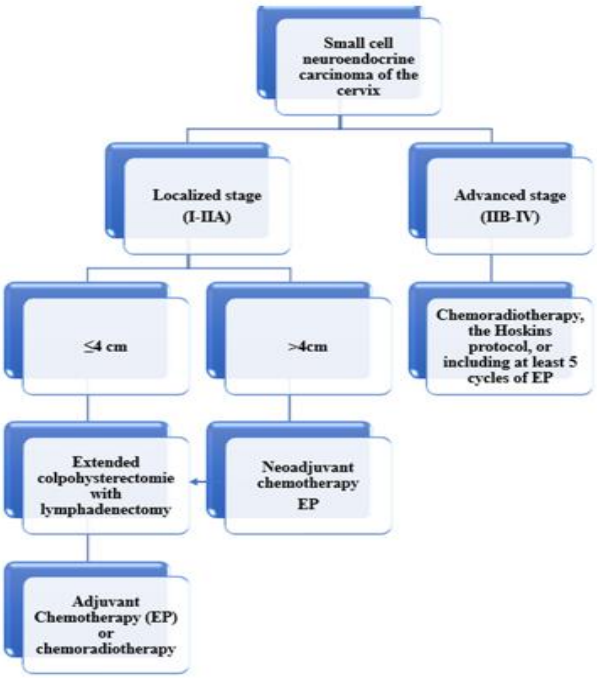

Figure 3: Therapeutic algorithm for the management of small cell neuroendocrine tumors of the uterine cervix.

Conclusion

Small cell neuroendocrine carcinoma of the cervix differs from squamous cell carcinoma or adenocarcinoma of the cervix in several ways: it is a tumor that is more likely to invade lymphatic and vascular spaces and to spread to regional lymph nodes at the time of diagnosis; its prognosis is poorer as local and distant recurrences occur more frequently; and the overall 5-year survival rate is significantly lower. At the time of initial diagnosis, it is rarely localized and is most often locally advanced or metastatic.

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