**Key Points:**

1. Neuroendocrine cancer of the uterine cervix is a rare and aggressive disease.
2. Treatment for neuroendocrine cervical cancer is usually more intensive than that for most other types of cervical cancer, and therapy often utilizes multiple different modalities such as surgery, chemotherapy and radiation.
3. There are several differences between neuroendocrine and other types of cervical cancer, in prognosis, diagnosis and treatment.
4. Because of the rare nature of this disease, clinical trials for neuroendocrine cancer of the cervix are lacking. Social media and other innovative techniques may be useful to identify patients with this rare tumor. Patients may benefit from receiving care from centers with expertise in treating this disease.

**What is neuroendocrine cervical cancer?**

Neuroendocrine tumors (NETs) are neoplasms that are composed of cells which have features of both the endocrine (hormonal) as well as the nervous system [1]. They can be classified as benign or malignant (cancer). These tumors can originate from many different sites in the body, including the uterine cervix. The following discussion will be limited to malignant neuroendocrine carcinoma (NEC) of the cervix.

The cervix is the narrow, lower segment of the uterus (womb) that connects with the upper vagina. Tumors can arise from the outer (ectocervical) or inner (endocervical) portion of the cervix. Approximately 12,000 women in the United States will be diagnosed with cervical cancer in 2012 [2]. That means that approximately 1 in 147 women will develop cervical cancer in their lifetime [3].

There are multiple different types of cervical cancer, named after the appearance of the cells under the microscope. The most common type is squamous cell cancer, accounting for 70% of all cervical cancers. The second most common is adenocarcinoma, which accounts for 20-25% of all cervical cancer [4]. Neuroendocrine tumors account for only 2% of all cervical cancers [5]. Therefore, approximately 250 women are diagnosed annually with NEC of the cervix in the United States.

Four subtypes of NEC have been delineated:
- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma
- Typical carcinoid tumor
- Atypical carcinoid tumor

Of these four types, carcinoid tumors, although malignant, are considered to be well differentiated and therefore have a more indolent course and favorable prognosis [1]. Poorly differentiated, or high grade, NEC includes small cell neuroendocrine carcinoma (SCNEC) and large cell neuroendocrine carcinoma (LCNEC). Of the four subtypes, SCNEC is most common and LCNEC second most common of NEC arising from the cervix [6].
Since these two subtypes represent the majority of NEC of the cervix as well as the most aggressive phenotypes, the remaining discussion below will be limited to these two subtypes. In fact, small cell and large cell subtypes behave and are therefore treated similarly, and will be grouped together in the following statements.

**Who gets neuroendocrine carcinoma of the cervix?**

Because NEC of the cervix is uncommon, the etiology and predisposing risk factors are poorly understood. In one study, when compared to women with the more common squamous cell carcinoma of the cervix, women were slightly younger at the time of diagnosis. The mean age at diagnosis was 49 years-old (compared to 52 years-old). There was also a higher proportion of Asian women with NEC of the cervix, when compared to women with squamous cell carcinoma of the cervix [7].

While the Human Papilloma Virus (HPV) and smoking are now well-known risk factors for developing most other kinds of cervical cancer, less is known about the role they play in development NEC of the cervix. Several studies have demonstrated a relationship between HPV infection and NEC of the cervix [8]. However, unlike HPV-associated squamous and adenocarcinoma (SA) of the cervix which have a preinvasive lesion that can often be detected by routine screening methods prior to growth of an actual cancer, no such preinvasive phase appears to exist for NEC.

**What are the symptoms of neuroendocrine carcinoma of the cervix?**

In general, the symptoms of neuroendocrine cancer do not appear to differ significantly from those of other types of cervical cancer [9]. Like other cancers of the uterine cervix, the symptoms of NEC of the cervix typically depend on the extent of the spread of disease (stage of disease). However, because of the aggressive nature of these tumors, patients more frequently have advanced disease at the time of initial diagnosis.

Similar to other cervical cancers, symptoms may include vaginal discharge, abnormal vaginal bleeding including postcoital bleeding (bleeding after intercourse), and pelvic pain. More advanced disease can include symptoms of weight loss, abdominal bloating, or symptoms specific to metastatic disease (liver, adrenals, bone, bone marrow, and the brain) [10]. Occasionally, like neuroendocrine tumors of the lung, small cell cancer of the cervix can present with paraneoplastic syndromes affecting the endocrine (hormonal) and/or nervous systems such as hypercalcemia (elevated blood calcium levels), neurologic disorders, Cushing’s syndrome, and SIADH [11].

**How is neuroendocrine carcinoma of the cervix diagnosed?**

Symptoms such as those listed above often prompt a medical evaluation leading to the diagnosis. Sometimes, routine gynecologic pelvic exam may reveal a cervical mass. Biopsy should be performed of any cervical mass to determine a more definitive
diagnosis. Occasionally, early disease may be detected by routine screening Pap smear. Although Pap smear may detect the disease, the efficacy of it as a screening modality is unknown, and it likely performs worse than it does for other cervical cancers. Some women with NEC of the cervix have had normal annual Pap smears leading up to the time they were diagnosed with cancer.

As mentioned above, more advanced disease may be associated with different symptoms leading to different routes of diagnosis. Ultimately, biopsy of a tumor in the cervix or other metastatic tumor will be obtained and analyzed by a pathologist. Under the microscope, neuroendocrine cancers of the cervix appear identical to those originating in the lung. Special immunohistochemical stains will be performed to confirm the diagnosis. These tumors can be mixed (have other components), but a tumor with any NEC component no matter how small, should be treated as so. Of note, sometimes the neuroendocrine component of the cancer may be missed on a tissue biopsy and will not be made until more tissue is obtained, such as at the time of surgery.

Once a tissue diagnosis has been made, further investigation will be made to determine the extent of spread of disease, or the stage of disease. Two different staging systems have been used to describe this disease. The FIGO system is the one used to describe all cervical cancers, while the two-tiered system used to describe small cell carcinomas of the lung is also used (see tables with staging). Although cervical cancer is typically staged clinically (based on exam with limited imaging such as a chest X-ray), when there is a known diagnosis of NEC of the cervix prior to starting treatment, more extensive workup is recommended. Given the aggressive nature of the disease and the propensity for early metastases (spread of disease beyond the cervix), additional imaging of the chest and abdominopelvic cavities is recommended. This can be accomplished with CT imaging. PET/CT imaging may also be considered, although trials are lacking to prove its superiority over routine CT scan in this disease. More dedicated imaging may be required based on symptomatology or findings on initial imaging such as a bone scan or brain imaging. Equally important to imaging, referral to a gynecologic oncologist for a thorough pelvic exam is essential to help to determine if surgical resection is appropriate.

**How is neuroendocrine carcinoma of the cervix treated?**

Once the stage of disease has been determined, a treatment plan is formulated. As mentioned above, because cervical cancer is clinically staged, some of the findings on the initial workup are not included in the official stage, but do alter treatment recommendations. Because the disease is so rare, there are no completed prospective trials to date establishing the standard of care for the treatment of this disease. While treatment plans are often extrapolated from treatment of more common types of cervical cancers, given the aggressive nature of this particular disease, a multimodal approach to treatment is more often employed. In 2011, the Society of Gynecologic Oncology issued a clinical document summarizing available literature on NET of the
female reproductive tract [12]. The treatment algorithms below are based on that document [13]. Additionally, there is extensive data for treatment of high-grade lung and extrapulmonary NEC provided by the North American Neuroendocrine Tumor Society (NANETS) and their published consensus guidelines [14]. Knowledge gained from treatment of NEC affecting other sites of origin has been extrapolated to the treatment of cervical NEC.

For early stage disease that is confined to the cervix and has not spread to the lymph nodes or other organs, the initial treatment depends on tumor size and involvement of local tissue.

For tumors less than 4cm in size that do not appear to locally invade other pelvic structures based on physical exam, initial treatment frequently includes surgery in the form of radical hysterectomy and removal of appropriate lymph nodes. Ideally, this should be performed by a gynecologic oncologist. Pathological information from surgery will dictate additional care, although usually further therapy is recommended, even if the tumor has been completely resected with negative margins. Usually chemotherapy with a combination of cisplatin and etoposide (EP) is recommended. Frequently this is given at the same time a radiation therapy, and additional chemotherapy is given following completion of chemoradiation. An acceptable alternative approach for initial treatment of women in this category may be with chemoradiotherapy followed by chemotherapy alone, without surgery.

For early stage disease with bulky tumors (>4cm), chemoradiation is recommended. There is limited data about the use of neoadjuvant chemotherapy then proceeding with surgery, followed by more chemotherapy with consideration for radiotherapy as well.

For locally advanced disease including those with lymph node metastasis, the recommended approach includes a combination of chemotherapy and radiation.

When disease has spread to other organs beyond the pelvis and lymph nodes, chemotherapy is the recommended treatment. This can include the two drugs mentioned above, cisplatin and etoposide. Another regimen that has been used effectively and was borrowed from treatment of lung cancer is VAC/PE (vincristine, adriamycin and cyclophosphamide, alternating with cisplatin and etoposide).

Unlike NEC of the lung, given the uncommon incidence of spread NEC of the cervix to the brain, prophylactic cranial irradiation (PCI) is not recommended at this time.

For patients without evidence of disease at the completion of their primary treatment, frequent routine follow-up with their physician is recommended. They may choose to perform imaging such as a CT or PET/CT scan at regular intervals, and imaging is recommended for any patient with symptoms that might indicate recurrence.
What is the prognosis?

Like most cancer, the prognosis depends on the stage of disease at the time of diagnosis. In one study of women with NEC of the cervix, 71% of patients were diagnosed with early stage disease (stage I-IIA), 24% were diagnosed with locally advanced disease (stage IIB-IVA), and 4% with diagnosed with distant metastatic disease (stage IVB) [9].

When looking at patients diagnosed at all stages, five year survival for NEC of the cervix is worse than that for other more common types of cervical cancer (36 vs 60-70%) [15]. In the same study mentioned above, 5-year survival was 37% for those with I-IIA disease versus 9% for those with more advanced disease. In another series, survival for stage I was 42%, stage II 19%, stage III 10% and stage IV 23% [7].

It appears that prognosis for small cell neuroendocrine carcinoma originating from the cervix is better than when originating in the lung. As noted above, while the five year survival for patients with early stage NEC of the cervix ranges from 19- 42%, the survival for limited stage lung cancer is about 10%. Similarly, the survival for those with extensive stage disease of the cervix is about 10-23%, while the comparable survival rates for disease starting in the lung is 1-2% [16].

What clinical trials are available?

Due to the rarity of the disease, clinical trials are not widely available for women that are specific to neuroendocrine carcinoma of the cervix.

The original trial at M. D. Anderson opened a Phase II study of weekly Taxol and bevacizumab for women with recurrent disease. Unfortunately, the trial was unable to accrue sufficient patients in a timely manner and was closed. Since then, by building a reputation as a center of excellence in this disease, through social media, and by word of mouth, we have seen the volume of patients with high grade neuroendocrine cancer of the cervix presenting to our center increase and we now have the ability to open trials, enroll patients, and complete them in a timely manner.

We currently have ongoing trials to treat patients with neuroendocrine cancers that although not specific to site of origin allow for patients with cervical cancer. https://clinicaltrials.gov/ct2/show/NCT04701307?term=carl+gay&draw=2&ranc=4

The Gynecologic Oncology Group (GOG) as well as the Gynecologic Cancer Intergroup (GCIG) have both created subcommittees for rare tumors of the female reproductive tract. These committees were created in effort to increase national and international collaboration amongst physicians treating these cancers in order to improve clinical trial design and enrollment. However, as of now, those groups do not have any trials open for women with cervical neuroendocrine carcinoma.
References:


