

“Neuroendocrine Tumor of the Uterine Cervix: A Therapeutic Challenge for Gynecologic Oncologists” (2017), by Angiolo Gadducci, Silvestro Carinelli, and Giovanni Aletti

In 2017, Angiolo Gadducci, Silvestro Carinelli, and Giovanni Aletti published, “Neuroendocrine Tumor of the Uterine Cervix: A Therapeutic Challenge for Gynecologic Oncologists,” hereafter, “Neuroendocrine Tumor” in the journal, *Gynecologic Oncology*. The authors conducted a systematic review of existing literature that documented the symptoms, diagnosis, staging, treatment, and outcomes of women diagnosed with neuroendocrine tumors, or cervical NETs, which are tumors with cells similar to cells from both the hormonal and the nervous system. Based on high mortality rates and the rarity of cervical NET diagnoses, the authors conclude that cervical NETs present a challenge for physicians in terms of devising novel ideas for treatment. By compiling the treatment methods and resulting outcomes of different studies, the authors presented evidence that there is a need for new forms of treatment to reduce the number of women dying from cervical NETs each year.

The type of tumor cells that the authors discuss differ from other types of tumor cells. NET cells originate from disruptions of the embryonic neuroectoderm, a structured formed by embryos during development, which eventually becomes the nervous system. The NET cells typically are similar to cells found in certain endocrine glands in the human body, such as pancreatic cells, pituitary gland cells, or ovary cells. Endocrine glands produce hormones, and due to their similar structures, NETs also produce hormones. While glandular cells release hormones such as insulin or estrogen, NETs can either release no hormones, or release a variety of hormones in the location of the body where the tumor is, impacting the organs in the location of the tumor. Cancer is an abnormal growth of cells, which proliferate in an uncontrolled manner and tend to metastasize, or spread and grow in other parts of the body.

When cancer cells metastasize, there is a higher rate of complications and death. Scientists typically find NETs in the lungs, intestinal tract, and pancreas, and only 0.9 to 1.5 percent of cervical cancers are cervical NETs. Some scientists refer to common forms of cervical cancer as adenocarcinomas, cancers from cells that line internal organs, or squamous cell carcinomas from the cells that line the cervix, which have a more favorable outcome than cervical NETs. That is due to the neuroendocrine type that has a high rate of metastasis in its earliest stages, something not typical of other forms of cervical cancer. For many people, neuroendocrine tumors do not cause any symptoms until they metastasize to the liver, making them hard to diagnose in the early stages.

The three authors worked in Italy at the time of the article's publication. As of 2022, Gadducci still works in the Department of Clinical and Experimental Medicine, Division of Obstetrics and Gynecology at the University of Pisa in Pisa, Italy. Carinelli worked in the Department of Pathology and Laboratory Medicine at the European Institute of Oncology in Milan, Italy. Aletti also worked at the European Institute of Oncology but in the Department of Gynecologic Surgery in Milan, Italy. The three authors combined their expertise to evaluate neuroendocrine tumors of the cervix in 2016.

“Neuroendocrine Tumor” has seven parts. The “Introduction” presents background knowledge of NETs, including those found on the cervix and other organ systems in the human body. The authors describe the profile of women who develop cervical NETs and the incidence rates in the section “Eti-

ology and Pathogenesis.” The next section, “Classification and Pathologic Features,” distinguishes the difference in classification, treatment, and prognosis between two different types of cervical NETs. Sections titled “Symptoms, Diagnosis, and Staging” and “Prognosis,” describe the symptoms and mortality statistics associated with cervical NETs. In “Therapy,” the authors propose medication and radiation recommendations to treat cervical NETs. The authors conclude the article by stating that cervical NETs are not well-studied and are deadlier than typical cervical tumors in the “Conclusion” section.

In the “Introduction,” the authors outline the science behind neuroendocrine tumors. All NETs have certain characteristics shared by all types of neuroendocrine tumors, regardless of the location or origin for the tumors in the body. That means a NET in the lung will share similar characteristics to one found in the cervix. They also mention that most scientists evaluate, or grade, NETs based on how aggressive the tumor is, assigning a tumor either a low-grade NET or a high-grade NET. Low-grade NETs are typically slow-growing but can still be aggressive in their infiltration into other bodily tissues through metastasis. Scientists usually find them in people who have genetic diseases predisposing them to develop NETs. High-grade NETs are much more common, less differentiated, and very aggressive in the human body. That means that the tumor cells are very similar to the body's cells, making it harder for medications such as chemotherapy drugs to treat and destroy the cancer without also harming healthy bodily tissues. The authors state that because cervical NETs are rare, there are no clear recommendations on how to treat the tumors. Most of the studies on NETs focus on NETs in more common areas of the body, such as the intestines and lungs. Physicians tend to treat cervical NETs in the same way as they treat intestinal or lung NETs, due to a lack of references specifically on cervical NETs in the literature.

In the “Introduction,” the authors mention that their article is a systematic review designed to develop a more effective diagnosis and treatment plans for patients with cervical NETs. A systematic review answers focused research questions by using a clearly formulated question that uses systematic and reproducible methods to identify, select, and critically appraise all relevant research and to collect and analyze data from various review studies. The sources that the authors identify include information about treatment for cervical NETs and review how physicians have classified cervical NETs over time into low-grade and high-grade cervical NETs. The authors look at how cervical NETs progressed in diagnosed women and assess the overall prognosis for those women. They look at the different treatments in the scientific and medical literature to determine which therapeutic approach to treat cervical NETs worked the best.

The “Etiology and Pathogenesis” section describes the incidence rates for women diagnosed with cervical NETs. Cervical NETs account for roughly one hundred to 200 cervical NET diagnoses per year in the United States. The National Cancer Institute Surveillance, Epidemiology, and End Results, or SEER, database reports that between 1977 and 2003, cervical NETs accounted for an incidence rate of about 0.06 per 100,000 women in the US. Compared to a combined 7.8 per 100,000 women diagnosed with the more common forms of cervical cancer, which are squamous cell carcinoma and adenocarcinoma. A study published in the National Cancer Database revealed that women diagnosed with cervical NETs were typically white, young, and more often diagnosed with metastatic disease, one invades and grows in other parts of the body, than the other forms of cervical cancers. Due to rapid growth and early metastases through woman's bodies, cervical NETs were deadlier than other cervical cancers.

In the same section, there is a discussion of the relationship between cervical NETs and Human Papillomavirus, or HPV. In the 1980s, researcher Harald zur Hausen working at the German Cancer Research Center in Heidelberg, Germany discovered HPV while working with cervical cancer tumor samples. According to the Centers for Disease Control and Prevention, or CDC, HPV transmitted by body fluids and sexual activity is the most common sexually-transmitted disease, and can cause cervical cancer in women. As of 2022, scientists can explain that various strains of HPV can cause a myriad of other cancers, including vulvar, anal, penile, and cancers of the head and neck. High-grade cervical NETs are associated with HPV as opposed to low-grade cervical NETs, which arise from the neuroendocrine cells in the inner lining of the uterine cervix. The lining of the uterine cervix has two different types of cells, an outer layer of cells called squamous epithelial cells and an inner single layer of cervical epithelium cells called reserve cells. In the review almost every

case of high-grade cervical NET tumor samples, scientists' detected HPV DNA strains HPV18 and HPV16 associated with non-NET cervical cancers, meaning that HPV may cause high-grade NETs. HPV may not cause all cervical tumors. Exceptions are cervical NETs, which are either low-grade or caused by a hereditary cancer syndrome that causes NETs to form throughout the body.

In "Classification and Pathologic Features," the authors explain the differences between low-grade and high-grade cervical NETs. Microscopic analysis distinguishes low-grade and high-grade NETs by tumor cell types. The authors state that cervical low-grade NETs are extremely rare and show some features of NETs in different sites including expressing cell markers revealed by antibodies to those markers they are not HPV related like high-grade cervical NETs. Biopsies of the tumors are important because low-grade and high-grade NETs are difficult to distinguish with the naked eye. While low-grade NETs are less common, they are aggressive tumor types that can metastasize or spread throughout the body even in its earliest stages.

The authors discuss women's experiences with cervical NETs in the next section, "Symptoms, Diagnosis, and Staging." In the authors' sources, women mention that the most common symptoms they experienced when physicians diagnose them with cervical NETs were abnormal vaginal bleeding and bleeding following sex. Women also report abdominal pain as well as pain or difficulty associated with urination. When physicians examine women during a pelvic exam, the lesions associated with cervical NETs are often large, with diameters of around 0.5 to eleven centimeters, and resemble a barrel in shape. With Pap smears used to diagnose cervical NETs physicians insert a cotton swab into a woman's vagina, swabbing the cervix, then viewing the cells under a microscope for any cellular changes. Physicians diagnose cervical NETs and other forms of cervical cancers with Pap smears. The authors state that staging of cervical NETs is difficult. Other NETs like GI tract and pancreas have staging systems in place, but since cervical NETs are so rare, it is difficult to have a large enough population. They stage cervical NETs as low-grade or high-grade when viewing the cervical cell samples under a microscope.

The next section, "Prognosis," is a forecast of the likely outcome of a disease, often measured by how likely a patient is to die from their disease. A prognosis of low-grade cervical NETs is difficult to determine because low-grade cervical NETs are so rare. Women with high-grade cervical NETs are more likely to die even in the early stages due to metastases and evidence of HPV18 infection.

The authors discuss different treatment methods in the "Therapy" section. Studies identified many different therapies, sometimes combined therapies, that included chemotherapy, or drugs that kill cancer cells, brachytherapy, or the insertion of radiographic materials directly into the cervix, external pelvic radiation, and surgery. Surgery normally involved a complete removal of all of the reproductive structures and surrounding lymph nodes, or lymph glands, the key part of immune systems that fights infections. In one study, the authors found that twelve out of fourteen women treated with surgery and radiation died from their cervical NETs between eight and thirty-one months following the initiation of treatment. Another study, found that out of thirty-one women treated with chemotherapy and radiation together, had a three-year survival rate of sixty percent, with or without active disease. That meant that two out of every five women had already died from their cervical NETs less than three years after treatment. Many of the women in that study experienced severe side effects, including severe vomiting, diarrhea, and compromised immune system, or low white blood cell counts.

The authors make final recommendations in "Conclusions" based on their systematic review. Women with cervical NETs are more likely to have metastatic involvement of pelvic lymph nodes. If they are in remission, their cancer often recurs within a few years, especially when compared to the more common types of cervical cancers. Cancer of any kind that spreads to the lymph nodes can then spread to the rest of the body via the lymphatic system, which links to all of the organ systems. All categories of cervical NETs present a significant therapeutic challenge for physicians because there are no treatment guidelines available. The most effective form of treatment found in their review was a combination of two different chemotherapy drugs, which physicians derived from treatment models used to combat lung NETs. The authors make additional therapeutic recommendations based on the staging of the patient's disease between high-grade and low-grade NETs and conclude the need for novel therapeutic approaches due to the high death rates associated with cervical NETs.

In "Neuroendocrine Tumor," Gadducci, Carinelli, and Aletti summarize the knowledge associated with cervical NETs as of 2017 and compiled the therapeutic indications which physicians had attempted at that point. The authors' note that HPV causes a vast majority of cervical NETs and encourage physicians to recommend the HPV vaccine to their patients to prevent a cervical NET diagnosis. As of 2021, physicians have yet to release any widespread therapeutic indications to treat cervical NETs.

Sources

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