Cervical neuroendocrine tumors.
A literature review

Abstract
Neuroendocrine cervical tumors represent rare but very aggressive malignancies, accounting for almost 0.4% of all cervical neoplasia. Four types of cervical neuroendocrine tumors have been described: small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, typical and atypical carcinoid tumors. Due to their rarity standard therapeutic protocols are hard to be established. We present a literature review regarding pathogenesis, the role of surgery and the most important prognostic factors for this rare gynecological malignancy.

Keywords: neuroendocrine, cervical tumors, radiotherapy, prognostic factors

Introduction
Cervical cancer is the third most common female cancer and the fourth leading cause of cancer death in women worldwide. About 530 000 new cases and approximately 275 000 deaths occurred in 2008(1). Squamous cell carcinoma (81.1%) and adenocarcinoma (10.6%) are the two most common histological subtypes. Neuroendocrine tumors represent a small fraction (0.4%) of cervical cancers. The distinction of squamous, glandular and neuroendocrine carcinoma of the cervix is clinically significant for at least two reasons. First, a poorly differentiated carcinoma of glandular origin, even with early invasion, is likely to have a worse prognosis than a similar squamous tumor. Second, neuroendocrine carcinomas are more aggressive than their squamous counterparts and are managed with different protocols.

Neuroendocrine tumors are commonly found in the gastrointestinal system and the lungs. Rarely are they encountered in the uterine cervix. According to the classification adopted by the College of American Pathologists and the National Cancer Institute in 1997, cervical neuroendocrine tumors are categorized into four subtypes: small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, typical and atypical carcinoid tumors. This terminology, identical to that used for the classification of pulmonary neuroendocrine tumors, has been incorporated into the latest World Health Organization Classification of Tumors of the Female Genital Tract.

Small cell neuroendocrine carcinoma
Small cell carcinoma is a neuroendocrine tumor most frequently (95%) found in the lung. Extrapulmonary small cell carcinoma (EPSCC) has an incidence of 0.1% to 0.4% in the US. It has been reported in almost every organ. The gynecologic tract is one of site where extrapulmonary small cell carcinoma occur more frequently, representing up to 2% of all gynecologic malignancies. Reported gynecologic sites include the cervix, but also the endometrium, ovary, fallopian tube, vagina and vulva.

Irrespective of the organ of origin, small cell carcinomas display similar morphological features. EPSCC has an aggressive clinical behavior whether in pure form or in conjunction with other histologic type of cancer. Small cell carcinoma of the cervix, first described by Albores-Saavedra et al. in 1972, is the most common and aggressive subtype of cervical neuroendocrine tumours, although it is a very rare disease (0.5% to 5% of all uterine cervical cancers). Its high degree of aggressiveness and early distant metastatic conduct to a poor prognosis. There are less than 20 cases of atypical carcinoid reported in literature.

The origin of neuroendocrine tumors is controversial. It was assumed that these tumors arise from neuroendocrine cells in the Amine Precursor Up-take and Decarboxilation (APUD) system. To date, it is thought that the origin is either a totipotent stem cell capable of differentiating into a variety of cell types, or it arises as a late-stage phenomenon in the genetic progression of carcinomas.

The role of human papillomaviruses (HPV) in the etiology of cervical cancer is well established. HPV genotypes are broadly classified into high-risk (HPV 16, 18, 31) and low-risk types (HPV 6, 11, 40). High-risk HPV can be detected in >90% of cervical cancers.

Small cell carcinoma of the cervix is defined as malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders with common nuclear molding, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. Architectural patterns shared with other neuroendocrine tumors include nesting, trabeculae, peripheral palisading, and rosette formation and sheet-like growth is also common. Numerous mitotic figures and extensive necrosis...
are common features. They are by definition of high histologic grade. Lymph-vascular space involvement is frequently observed, and neurosecretory granules can be seen upon ultrastructural examination. Small cell carcinoma often coexists with squamous cell carcinoma or adenocarcinoma (up to 64% present a mixed histology)(4).

**Large cell neuroendocrine carcinoma**

Large cell neuroendocrine carcinoma is characterized by cells of large size, polygonal shape and low nuclear-cytoplasmic ratio, mitotic activity in excess and immunohistochemical or ultrastructural evidence of neuroendocrine differentiation(5). The usual presenting symptom of cervical neuroendocrine tumors is vaginal bleeding, and a clinically detectable cervical mass is present in most cases.

Neuroendocrine tumors may have the ability to synthesize and secrete biologically active substances that can cause distinct clinical syndromes. The term ‘paraneoplastic syndromes’ is used to denote syndromes secondary to substances secreted from tumors not related to their specific organ. Such syndromes are mainly associated with hormonal and neurological symptoms. Small cell carcinoma of lung is the most frequent cause of paraneoplastic syndromes (Cushing’s syndrome, Carcinoïd syndrome and hypoglycaemia), however rare in neuroendocrine carcinoma of the uterine cervix(14).

Pathologically, the diagnosis is supported by the identification of neuroendocrine granules on electron microscopy, as well as by immunoperoxidase studies that are positive for a variety of neuroendocrine proteins, such as calcitonin, insulin, glucagon, somatostatin, gastrin and adrenocorticotropic hormone(15).

Neuroendocrine immunohistochemical markers are frequently used to support the diagnosis. Chromogranin A, synaptophysin and neuron-specific enolase are the most frequently used markers for immunohistochemical detection of neuroendocrine differentiation even though neither the uterine cervix workgroup(4) nor the current World Health Organization classification consider their assessment required(16).

The neuroendocrine carcinoma is more likely to develop in the endocervical canal and hence will require endocervical curettage in addition to biopsying the cervix for obtaining an adequate specimen for pathology. Immunohistochemical analysis reveal the presence of neuroendocrine hormones and polypeptide hormones within the cells, and this can differentiate from other morphologically similar entities like basaloid squamous cell carcinoma, embryonal rhabdomyosarcoma, lymphoma, and undifferentiated carcinoma arising from the lower uterine segment. A small cell neuroendocrine carcinoma must be differentiated from poorly differentiated squamous cell carcinoma with neuroendocrine features. Even though neuroendocrine carcinoma of the cervix are staged as any other cervical cancer, they don’t follow the locoregional pattern of spread of cervical cancer. Even in stage IB1 tumors, there is 40% pelvic lymph node involvement and 60% lymphovascular invasion and this correlates with its aggressiveness and poor prognosis(17).

The first entity to exclude in the differential diagnosis of small cell carcinoma of the cervix is metastatic small cell carcinoma from other sites, in particular the lung(18).

**The epidemiological and clinical features**

Because of the rarity of cervical neuroendocrine tumors, the epidemiological and clinical features are mainly based on the analysis of retrospective studies. In addition to case series up to 30 cases from a single center, three larger retrospective population-based studies have been published to date, including 179(19), 185(20) and 290(10) patients, respectively. In these reports the mean age of diagnosis was between 45 and 50 years. Also patients with neuroendocrine carcinoma of the cervix were more likely to be diagnosed at advanced stage than those with squamous carcinoma and adenocarcinoma, with a significant higher involvement of the pelvic and extra-pelvic lymph nodes. They develop earlier distant metastases and have a worse prognosis compared with other histological types.

Boruta et al. showed that lymph node involvement was a prognostic factor among patients with early stage small cell carcinoma treated by radical surgery and adjuvant chemotherapy(21), although lymph node status was not found as an independent prognostic factor in recent large series multivariate analyses(10,19).

The rate of lymph node involvement by FIGO stage is 27.5% in stage I small cell carcinoma, higher than 10.9% in squamous cell carcinoma report, the rate of lymph node metastases in stage IB1 was 20% and in stage > IB2, at least half had lymph node metastases(22).

Small cell carcinoma has a poor prognosis, with recurrence-free and overall survival ranging from 8.5 to 20 months and 11 to 57.7 months, respectively. In the large series, the median overall survival for patients with small cell carcinoma of the cervix was between 22 and 24.8 months compared to 10 years for those with squamous carcinoma(10,19,23).

Hematogenous spread is common in cervical neuroendocrine carcinoma with liver, bone, lung and brain being the most frequent metastatic sites(22). Relapses occur early with 80% occurring within the first year from diagnosis(5). Distant sites of recurrence are more common than local failure(24). Walker et al. reported that 75% of patients die within 1 year. FIGO stage is the most important prognostic factor in cervical neuroendocrine tumors. The 5-year overall survival rates are 31-51% for early stage (I-II) and 0-6.5% for late stage (III-IV) disease(25).

Smoking, large tumor size, pure small cell histology, deep cervical invasion and positive margins have been linked to worse clinical outcome in various studies(26,27).

The treatment in cervical neuroendocrine tumors patients is based on treatment strategies for patients with other histologic types of cervical carcinoma and pulmonary small cell carcinoma.
Standardization of treatment for patients with this disease would require controlled prospective clinical trials, which are unfortunately challenging to perform due to the rarity of the disease.

Surgery has been suggested to have a beneficial role in early stage disease. The 5-year disease specific survival for stage I-IIA patients who received radical hysterectomy was 38.2% compared to 23.8% for those who did not undergo surgery.

In multivariate analysis, early-stage disease (I-IIA), use of any chemotherapy and radical hysterectomy were independent prognostic factors for improved survival[28].

Thoracic radiation in conjunction with chemotherapy has demonstrated improved outcomes in patients with limited stage pulmonary small cell carcinoma[6].

The benefit of radiotherapy for small cell carcinoma of the cervix is more controversial. 5-year overall survival for stage IB2-IIIA patients who received adjuvant radiotherapy after radical hysterectomy with pelvic lymphadenectomy was observed to be similar compared to those who did not receive radiation[29].

Concurrent chemoradiation therapy has been also tested in patients with cervical neuroendocrine tumors. In a clinical trial using four cycles of cisplatin plus etoposide along with pelvic radiotherapy in stage IB-IIIB, the rate of distant and pelvic failure were 28% and 13% after long-term follow-up[29].

In stage IA-IB, 100% of patients who did not receive adjuvant chemoradiotherapy as part of their initial treatment developed recurrent disease as compared to 33.3% of patients who did receive adjuvant chemoradiotherapy[30]. Also in advanced disease, chemotherapy treatment has been found to be associated with improved survival[19,28]. Neoadjuvant treatment regimens have also been proposed, but few reports are available to date[31]. In advanced disease chemotherapeutic agent of choice for small cell carcinoma is etoposide.

In contrast to small cell carcinoma whose aggressive behavior and resistance to therapy have been well-established, cervical large small cell carcinoma was often under-recognized and misdiagnosed as poorly differentiated squamo-or adenomatous cell carcinoma until 1997 when Gilks et al. reported 12 cervical large cell carcinoma cases. Since then, about 70 cases have been reported. Prognosis of this population remains poor despite multimodal treatments. The majority of patients die within 2 to 3 years of diagnosis[15].

The management algorithm proposed by Chan may be helpful in treating neuroendocrine tumors of the cervix. Radical hysterectomy with lymphadenectomy followed by etoposide/platinum chemotherapy in tumors less than 4 cm and neoadjuvant chemotherapy with cisplatin and etoposide followed by locoregional treatment (radical surgery/ radiotherapy) in tumors larger than 4 cm and confined to pelvis may give the best results[26,32].

There has been a paradigm shift in the preventive aspect of this disease over the last few years. Siriaunkgul et al. reported that 75% of the cases of cervical neuroendocrine were positive for HPV 18 and 30% were positive for HPV 16, both of which are high-risk HPV variants. Thus, it was hypothesized that vaccination against HPV 16 and 18 may represent a preventive measure. Although the Korean Society of Obstetrics and Gynecology and the National Cancer Center recommend the Pap smear to women over age 30, the effectiveness of the Pap smear for diagnosis of small cell carcinoma is relatively low as in adenocarcinoma. Therefore, it could be helpful for elevating the sensitivity of Pap smear to HPV testing[33, 34]. Over the last few years, studies were conducted on the CD117 marker (c-kit proto-oncogene, a tyrosine kinase) which is overexpressed in the majority of small cell lung carcinoma cases and has set a foundation for targeted therapy. As for the expression of CD117 in cervical small cell carcinomathese results are inconclusive[33].

Molecular targeted treatments are not yet available clinically for patients with cervical neuroendocrine tumors. Their genomic characterization may lead to the identification of molecular targets that could be exploited for the treatment of subgroups of the disease.

Conclusions

Neuroendocrine tumors of the cervix are rare and very aggressive tumors. The behavior of this rare malignancy is different from that of squamous cell carcinomas, with a high propensity for nodal and distant metastases. Patients should have close follow-up after primary therapy. Patients with cervical neuroendocrine tumors have the poorest prognosis in both early and advanced cancer stage compared with adenocarcinoma and squamous carcinoma. Due to the rarity of these tumors, it is difficult to gather sufficient information in order to assess the evidence-based data regarding its therapeutic and prognostic aspects.
References


