Neuroendocrine carcinoma of the cervix: Review of classification and current developments in diagnosis and management

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Abstract: Neuroendocrine carcinoma of the female reproductive tract are a heterogeneous group of rare neoplasms posing both diagnostic and therapeutic challenges. The recent classification by WHO includes neuroendocrine carcinomas (NECs) and neuroendocrine tumours (NETs). NECs are the poorly differentiated small cell carcinoma (SCNEC) and large cell neuroendocrine carcinoma (LCNEC), while well-differentiated NETs include typical carcinoids (TC) and atypical carcinoids (AC). Majority of these tumours have an aggressive clinical course and published data is supportive of multi-modal therapeutic strategies. Etoposide/platinum based chemotherapy is commonly advocated. Histopathological categorisation and diagnosis are paramount to guide therapy. Well-differentiated carcinoid and atypical carcinoid tumours should be managed similar to gastroenteropancreatic neuroendocrine tumours. This review discusses the current classification, clinic-pathologic characteristics and advances in the diagnostic evaluation and the treatment options of neuroendocrine carcinoma of the cervix.

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Keywords: High grade neuroendocrine tumours, well-differentiated neuroendocrine tumours, carcinoid tumours.

Introduction

Neuroendocrine tumours (NETs) include a spectrum of malignancies that arise from diffuse neuroendocrine cell system.[1] These tumours comprise approximately 2% of all gynaecological tumours. While the most common site is the cervix, it may arise from vagina, vulva, uterus and ovary.[2,3] The clinical features are usually non-specific and depend on the site of origin. The rare occurrence of these tumours provides limited data to guide diagnostic and therapeutic decision making. The recent decade has witnessed an increase in the incidence of neuroendocrine tumours, probably related to improvements in diagnostic recognition and utilisation of the standardised classification criteria of these tumours.[1] This review discusses the current classification, clinic-pathologic characteristics and advances in the diagnostic evaluation and the treatment options of neuroendocrine carcinoma of the cervix.

Methods

A MEDLINE search on all studies with 'Neuroendocrine tumours' of the gynaecologic tract was done. In view of rarity of these tumours, the search was not limited to systematic review or meta-analysis. All the reviews, case series and case reports available in the literature were searched for the review.

Classification of neuroendocrine tumours

According to the 2000 edition of the World Health Organisation (WHO) a rational approach to the nomenclature and classification of pulmonary NETs was given which include well differentiated endocrine tumours (WDET), well differentiated endocrine carcinomas (WDEC), and poorly differentiated endocrine carcinomas (PDEC).[4] This was followed by a revised version of the 2010 WHO classification that categorises them into neuroendocrine carcinomas (NECs) and neuroendocrine tumours (NETs). NECs include poorly differentiated small cell carcinoma (SCNEC) and large cell neuroendocrine carcinoma (LCNEC), while well differentiated NETs include typical carcinoids (TC) and atypical carcinoids (AC).[5] NETs are further subdivided by their Ki67 index which is the cellular marker for proliferation into G1 and G2 tumours. Tumours with a Ki67 index of <2% are classified as G1 and those with 3-20% are classified as G2. The division of NETs into G1/G2 based on Ki67 index was validated and a cut off of 3% is considered appropriate to predict metastasis or recurrence. This classification of neuroendocrine tumours for the pulmonary has been incorporated into the World Health Organisation Classification of tumours of the Female Genital Tract 2010.[6] The recent 2014 WHO

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classification of NETs proposes the nomenclature for these tumours as Low Grade Neuroendocrine tumours which includes Typical carcinoid (TC) and Atypical carcinoid (AC) and High grade neuroendocrine carcinoma which include small cell carcinoma (SCCA) and large cell neuroendocrine carcinoma (LCCA). However, the Ki-67 index is not included in the 2014 WHO diagnostic criteria for cervical NETs as further studies are required to validate the correlation between Ki-67 index and clinical outcomes in cervical NETs.[7] From histological perspectives it is identified that some cancers display a combination of NE and non-NE features, usually either glandular or squamous components.[8,9] Accordingly, two terms are widely accepted i.e. mixed exocrine-endocrine carcinoma (MEEC) and (adeno) carcinoma with (focal) NE differentiation which are included in the classification. The WHO diagnostic criteria of mixed exocrine-endocrine tumour takes into account at least two major diagnostic parameters i.e. an extension of at least 30 % for each component and the recognition of structural NE features such as well-differentiated organoid or solid/diffuse growth patterns.[10,11] The classification of the neuroendocrine tumours is shown in Table 1.

Table 1: WHO classification of neuroendocrine tumours of female reproductive organs. (Table created by author from the literature review)

WHO 2000*	WHO 2010**	WHO 2014***
Well-differentiated neuroendocrine tumours (WDET)	**Well-differentiated neuroendocrine tumours (NETs)** ==> Typical carcinoid (TC) ==> Atypical carcinoid (AC) +/- : **NET** G1 (Ki67 index of <2%) G2 (Ki67 index 3—20%)	**Low grade Neuroendocrine tumours** ==> Typical carcinoid (TC) ==> Atypical carcinoid (AC)
Well-differentiated neuroendocrine carcinoma (WDEC)		
Poorly differentiated endocrine carcinoma / Small cell carcinoma (PDEC)	**Poorly differentiated neuroendocrine carcinomas (NECs)** ==> Small cell carcinoma (SCCA) ==> Large cell neuroendocrine carcinoma (LCCA)	**High grade neuroendocrine carcinoma** ==> Small cell carcinoma (SCCA) ==> Large cell neuroendocrine carcinoma (LCCA)
Mixed exocrine and endocrine carcinoma (MEEC)	**Tumours with both combination of NE and non-NE features** ==> MEEC ==> (adeno) Carcinoma with (focal) NE differentiation	**Adenocarcinoma admixed with neuroendocrine carcinoma**

* Colgan *et al* (2014)
** Eichon *et al* (2001) & Dias *et al* (2015)
*** Volante *et al* (2006) & Solcia *et al* (2000)

High grade neuroendocrine carcinomas: Small cell carcinoma (SCNEC) and large cell neuroendocrine carcinoma (LCNEC)

Clinical characteristics

Majority of the neuroendocrine carcinomas of the cervix are small cell carcinomas. They account for 1-6% of cervical carcinomas. The median age of diagnosis is 21 to 87 years.[12] These tumours are characteristically aggressive with high mitotic rate, extensive necrosis,

frequent lympho-vascular space involvement (LVSI) with extra-pelvic recurrences for bone, supraclavicular lymph nodes and lung.[13] They are strongly associated with HPV-18, although HPV-16 positive tumours have been demonstrated.[14] The clinical presentation is nonspecific with vaginal bleeding. A small proportion of patients present with abnormal pap smear or clinically visible cervical mass.[13] Paraneoplastic manifestations such as hypercalcemia, hypoglycaemia, carcinoid syndrome and Cushing's syndrome can be demonstrated, related to ectopic hormone production.[15] The prognosis is worse off compared to poorly differentiated squamous cell carcinoma of the cervix. Stage for stage women small cell tumours have 1.84 times greater risk of death compared to patients with squamous cell carcinomas.[16]

Large cell neuroendocrine carcinoma of the cervix are aggressive tumours that have similar outcome as small cell carcinoma of the cervix. These tumours are associated with high rate of recurrence and distant metastasis even at early stage.[17]

Histopathological and Immunocytochemistry

The small cell carcinomas consist of small cells with scanty cytoplasm, ill-defined borders with nuclear moulding. They have finely granular nuclear chromatin, and absent or inconspicuous nucleoli (Figure 1). The common features include numerous mitotic figures and extensive necrosis.[18] Lymph-vascular space involvement is frequently observed, and neurosecretory granules can be seen on ultrastructural examination.[19] It is estimated from a case series that 11-64% of these cases present with admixed histology due to co-existence with squamous cell carcinoma and adenocarcinoma.[17] The frequently used markers for immunohistochemical detection of neuroendocrine differentiation include positivity of at least one of the neuroendocrine markers such as Chromogranin A (CgA), synaptophysin (SYN) and neuronspecific enolase (NSE)[20,21] (Figures 2 & 3). However, expression of these neuroendocrine markers may be focal and accompanying crush artifacts in biopsy specimens pose challenges in the interpretation of these markers.[20] Although immunohistochemistry supports the diagnosis of small cell carcinoma, both the current World Health Organisation (WHO) classification and Uterine Cervix Working Group do not consider immunohistochemistry as a mandate for assessment of these tumours.[21]

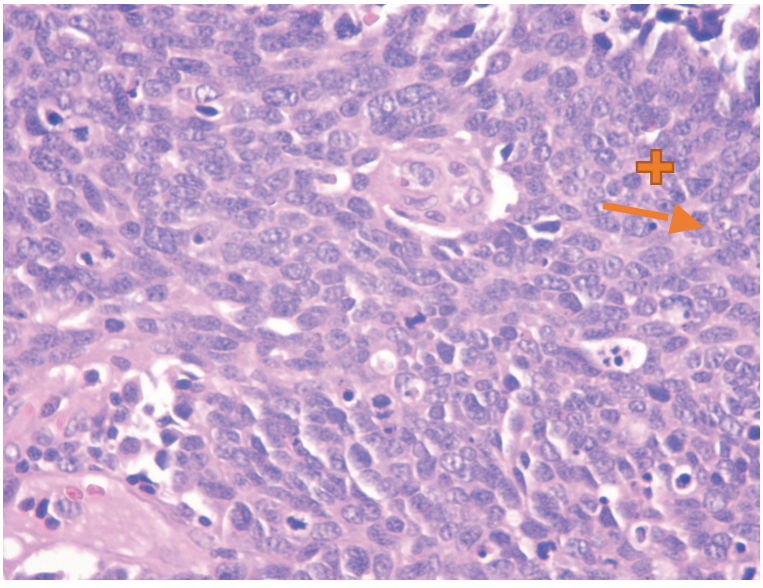

Figure 1: Small Cell carcinoma: Cells with scanty cytoplasm, ill-defined borders, nuclear moulding, finely granular nuclei with inconspicuous nucleoli and brisk mitosis (400X magnification).

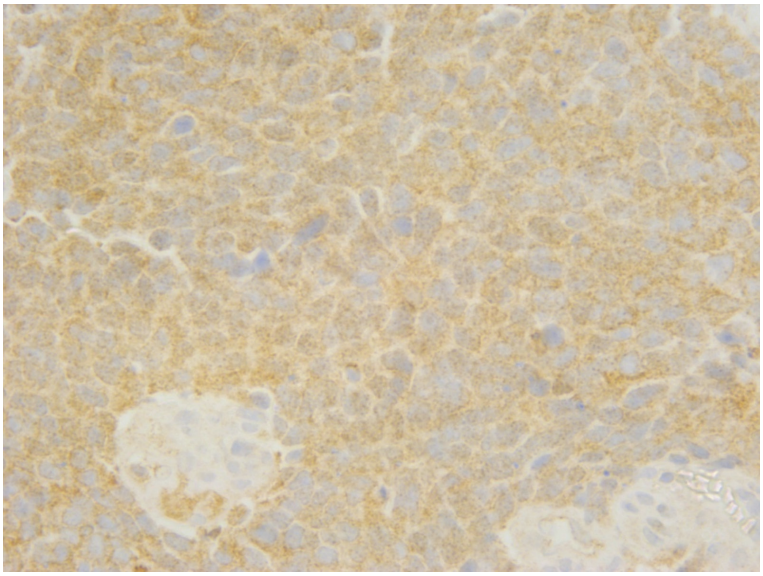

Figure 2: Small cell carcinoma: Immunohistochemistry study showing positivity for neuronspecific enolase (400X magnification).

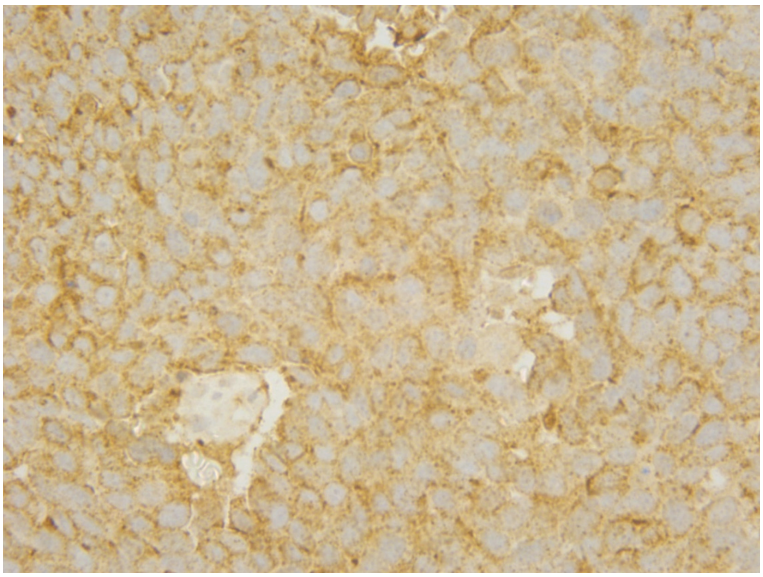

Figure 3: Small cell carcinoma: Immunohistochemistry study shows positivity for Chromogranin (400X magnification).

The large cell carcinoma tumour cells have abundant cytoplasm with large vesicular high grade nuclei and prominent nucleoli. They comprise of tumour cells that have abundant cytoplasm, large-vesicular high grade nuclei with prominent nucleoli. The tumour cells are organised as sheet-like, insular or trabecular patterns. There is frequent mitotic activity seen with more than 10 mitoses/10 HPF and geographic necrosis.[22] Unlike small cell carcinomas, positive immunohistochemistry is essential for diagnosis in large cell carcinomas.[24]

Diagnosis

The most common presenting symptom is the presence of vaginal bleeding and a cervical mass on examination. An abnormal pap smear can be a presenting feature[23,24,25]. Although diagnosis can be established on cervical biopsy, the limited tissue obtained in the biopsy may fail to demonstrate the neuroendocrine component that may be recognised following hysterectomy.[26] The staging of NECs of the cervix follows the staging of the squamous or adenocarcinoma of the cervix.[27] The poor prognosis is related to the increase in the LVSI and increased rate of extra pelvic recurrences. It is estimated that nearly 30% of stage 1B small cell cancers less than 3 cm demonstrated LVSI at the time of diagnosis.[28] The most common extra pelvic site recurrences include bone, supraclavicular nodes and lungs. Distant metastasis needs evaluation with PET/CT imaging.[29]

Prognostic factors

The factors associated with poor clinical outcome include advance stage, size of the tumour, small cell histology and smoking.[30] Early stage disease, lack of lymph node metastasis and large cell histology are associated with favourable prognosis.[31] Smoking decreases the oxygen saturation, which reduces the effect of radiation and nicotine stimulates the growth factor for small cell cancers.[32] One study reported that improved survival rates are related to a size less than 4 cm with no lymph node metastasis.[33] However, lymph node status was not an independent prognostic factor in multivariate analyses in the recent larger published series.[34] The most important determinant of prognostic factor is the surgical FIGO staging. The overall 5-year survival rates are 31–51% for early stage (I–II) and 0–6.5% for late stage (III–IV) disease for small cell carcinomas.[35] The median overall survival rates of patients with large cell carcinomas were reported as 19 months for stage I, 17 months for stage II, 3 months for stage III, and 1.5 months for stage IV.[36] One recent study investigating micro-RNA (miRNA) expression identified that downregulation of has-miR-100 was an independent prognostic factor for overall survival of small cell carcinomas.[37] However, more studies are needed to confirm the utility of miR-100 as an independent prognostic factor for overall survival. For early stage disease treatment, it is reported that multimodal treatment can achieve eighty per cent 3-year disease free survival.[38]

Management

The principles of management of small cell and large cell NEC follow the treatment strategies of cervical cancer and small cell lung carcinomas. The large cell tumours are treated the same way as small cell NEC. There is anecdotal evidence that large cell NEC histologic type generally have favourable outcomes with respect to event free survival rates and overall survival rates.[39] There are no prospective controlled trials that can guide the management given the rarity of these tumours. The evidence is generated from retrospective analysis of case series from studies reporting from large patient cohort.

Initial workup

A thorough gynaecological assessment plays a pivotal role in ensuring the success of management plans. FIGO proposes assessment for clinical staging which includes rectovaginal examination, chest X-Ray, intravenous pyelogram, cystoscopy, and proctoscopy. Nevertheless, many clinicians in more developed countries tend to forgo these basic clinical and imaging examinations in favour of more advanced radiological imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (PET). Due to the aggressiveness of NEC to metastasise, CT or PET scans of the abdomen, pelvis and lungs is recommended for initial staging. However, imaging of the brain should be reserved if the patient is symptomatic or there is a suspicion that the spread has gone beyond liver and lungs.[40]

Early stage disease (FIGO I-IIA)

Multimodal therapy: Combination of chemotherapy, surgery or radiation

Surgery

According to the Gynaecologic Cancer Intergroup (GCIG) and Society of Gynaecologic Oncology (SGO) Guidelines, patients with early-stage disease, low-volume (less than 4 cm) with clinically node-negative should undergo radical hysterectomy with lymphadenectomy followed by either chemotherapy with cisplatin and etoposide or concurrent chemo-radiation. This multimodal treatment has demonstrated 80% three year disease free survival rates in some studies.[38] As small and large cell NECs are more prevalent in younger women as compared to the HPV related squamous epithelial carcinoma, the consequences of surgery and adjuvant therapy must be thoroughly discussed with the patient. Fertility issue must be addressed and options made available. In countries where resources for advanced reproductive technique or 'egg freezing' following oocyte retrieval are scarce; the surgical option is then limited. Ovarian preservation in radical surgery followed by chemo radiation should still have a role though evidence has shown an 80% chance of ovarian failure within three years.[39]

Radical trachelectomy is another option one should think about when fertility is an issue. However, the aftermath is controversial as risk of recurrence in this type of rare but aggressive carcinoma is considerably high comparing to commoner squamous type. It is only suitable for patients with absent lymph node metastases, no or minimal lymphovascular invasion and most importantly her own preference despite the risks explained.[40]

Chemotherapy

There is vast experience of use of chemotherapy as part of multimodal treatment approach for NET cervix. The use of adjuvant chemotherapy following complete surgical resection is reported to have a significant survival advantage either with or without lymph node metastasis.[25] In studies by Boruta *et al*. and Zivanovic *et al*., good survival rates were reported in women who received vincristine, adriamycin, and cyclophosphamide alternating with cisplatin and etoposide (VAC/PE) regimen. It was also concluded that additional radiotherapy has no survival advantage.[25,33] The prognosis of patients on neoadjuvant chemotherapy (NAT) has shown mixed results. A recent study has not shown promising results with neoadjuvant chemotherapy although definitive conclusions cannot be drawn in view of limited numbers in all studies.[34]

Primary chemoradiation

There are no prospective data comparing the outcome of primary chemoradiation with primary surgery in early stage resectable small cell carcinoma of cervix. In the study by Stecklein *et al.*, primary chemoradiation demonstrated better event free survival (EFS) and better overall survival (OS) in node negative disease.[34] The author postulated that given the natural history of the disease, early hematogenous spread and early introduction of systemic therapy halt the progress of the disease. However contradicting these findings, a multicentre retrospective study investigating the optimal local treatment modalities in stage I-II small cell NET using a population-based National Registry (Surveillance Epidemiology and End Results, SEER), concluded that primary surgery is the most effective local treatment for FIGO stage I-II small cell NET. Adjuvant RT or radical RT does not improve survival compared to radical surgery, especially in patients with FIGO stage I and lymph node negative disease.[35] This concurs with the recommendations of SGO and GCIG that primary chemoradiation is for advanced or non-resectable disease.[1]

Late stage disease (FIGO stage IIB-1V) or recurrent disease

Late stage disease is treated with combination chemotherapy (cisplatin + etoposide) in addition to

concurrent radiation.[1] There are no prospective studies on the combination chemotherapy; this regimen is recommended by the SGO for treatment-naïve patients with NECC with advanced stage disease. The distant site of metastasis includes lung and bone as the more common sites and are treated with vincristine, adriamycin, and cyclophosphamide (VAC) or Cisplatin + Etoposide (PE) regimens similar to those used in the treatment of small cell neuroendocrine carcinomas of the lung.[35] The Gynaecologic Oncology Group's three drug regime consisting of topotecan, paclitaxel and bevacizunab used for recurrent cervical cancer has been suggested for recurrent and progressive small and large cell cancer.[41]

Summary of the management algorithm as shown in Figure 4

As proposed by the SGO and GCIG the following summary points apply to the management of early and late stage small cell and large cell carcinomas NEC of the cervix. In early stage disease with tumour size less than 4 cm, the treatment is cancer specific surgery which is the radical hysterectomy with lymphadenectomy and adjuvant chemotherapy with etoposide/platinum based therapies. If the tumour size is greater than 4 cm, it is treated with neo adjuvant chemotherapy, followed by surgery if the disease is resectable. In advanced stage disease or non-resectable tumours, combination chemotherapy (EP) with RT for local control should be considered. Currently such a multimodal treatment approach proves to provide the best outcome.

Well-differentiated neuroendocrine tumours (NETs): Typical Carcinoids (TC) and Atypical Carcinoids (AC)

Well-differentiated neuroendocrine tumours (NETs) include typical and atypical carcinoid tumours. These tumours represent approximately 0.5 – 5 % of cervical cancers. The most common symptom is vaginal bleeding.[1] These rare gynaecologic tumours present with histology characteristics of absence of nuclear atypia, mitotic figures and necrosis (Figure 5). The immunohistochemistry shows positivity for chromogranin, synaptophysin, and neuron specific enolase facilitating a histologic diagnosis. As they are well differentiated tumours, their disease course is thought to be indolent.[42] However, the rarity of the presentation precludes conclusions on the clinical outcomes.

Carcinoid syndrome is very rare and even in the lack of clinically evident carcinoid syndrome, it is estimated that many patients present with elevated urinary 5-hydroxyindoleacetic acid (5-HIAA). However, the diagnosis of a cervical carcinoid is frequently postoperative and laboratorial investigation is typically not helpful since it is not performed in the absence of symptoms.[6] Extrapolating from the evidence of gastrointestinal carcinoid tumours, the management involves complete surgical excision with the goal of attaining negative margins. If the diagnosis is established preoperatively, octreotide (100–500 mcg SQ/IV every 6-12 h) should be administered immediately prior to and during the resection of the tumour to prevent the rare complication of carcinoid crisis.[43] There is no supportive evidence for adjuvant therapy in the form of hormonal, chemotherapy, or radiation therapy for gynaecologic carcinoid tumours.[1] Atypical carcinoids of the cervix are also very rare and, according to a review of Yoshida *et al.* very few cases have been reported in the literature.[44]

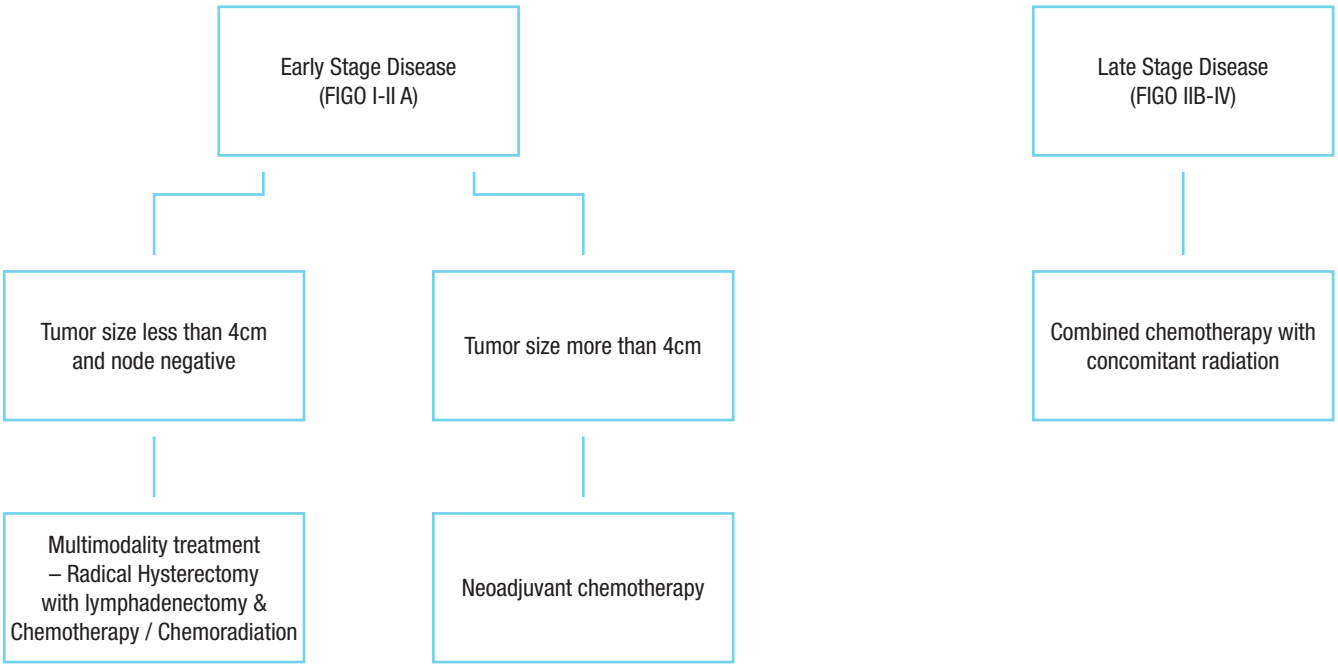

Figure 4: Cervical neuroendocrine carcinoma: Management algorithm

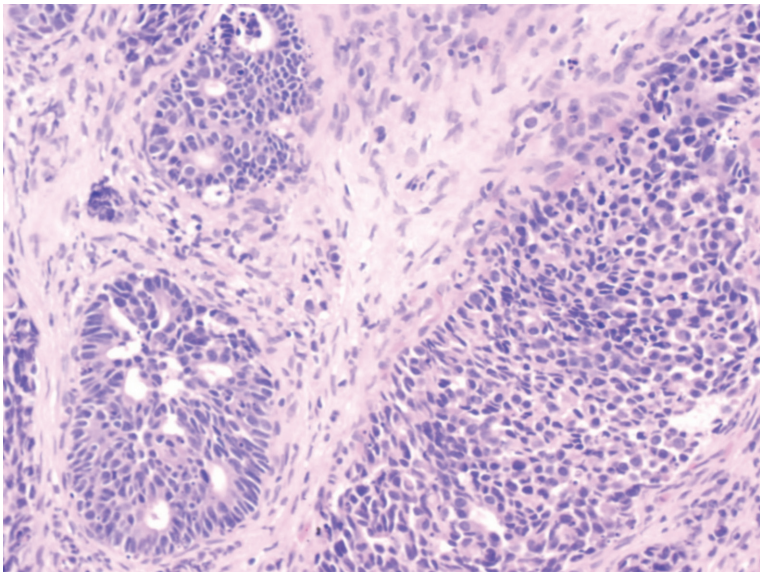

Figure 5: Atypical carcinoid/ Neuroendocrine Tumor Grade 2: Cells with glandular and trabecular growth patterns with moderate cytologic atypia and increased mitoses (400X magnification).

Conclusions

Cervical neuroendocrine carcinomas are rare and aggressive tumours with overall poor prognosis. The optimal tumour diagnostic markers include synaptophysin, chromogranin, and CD56. The small cell carcinomas are more aggressive compared to large cell with frequent metastasis and recurrences. Currently, data is available supporting multimodal therapy in early stage disease that is associated with sustainable remission and survival. However, there is a need for prospective studies that will help define optimal local management of neuroendocrine cancers of the cervix.

Future research

Future research involves developing multiple molecular therapeutic targets. The potential therapeutic targets include CD56, a neural cell adhesion molecule that is expressed by neuroendocrine cancers and Src kinase, a tyrosine kinase, which has differential expression in both small cell and non-small cell lung cancers.[1] Drugs that suppress microtubule dynamics and thereby inhibit cancer cell proliferation are currently used in the clinic as effective anticancer agents for a wide variety of tumours. Maytansine (DM), a benzoansamacrolide is a potent microtubule targeted drug which is known to induce mitotic arrest at subnanomolar concentrations. It is being evaluated for its clinical efficacy as a potential anticancer agent. The role of newer chemotherapeutic agents such as temozolomide has been evaluated and identified as a promising agent in palliative treatment for neuroendocrine tumours.[45]

Conflicts of interest

The authors declare no conflicts of interest in the preparation of the manuscript.

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