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# Primary Concurrent Chemoradiation Therapy For FIGO Stage IB1 Small Cell Neuroendocrine Carcinoma of The Uterine Cervix: Report of A Case And Review of The Literature

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***Abstract:*** *Small cell carcinoma of the uterine cervix is a very rare and exceedingly aggressive malignancy which is classified as a neuroendocrine tumor according to the current World Health Organization histological classification of tumors of the uterine cervix (2003). Actually, patients with cervical small cell carcinoma have poor prognosis in both early and advanced cancer stage. Moreover, due to the rarity of the disease there is no consensus regarding optimal treatment. Herein, we report a case of 62 year old woman with early stage of small cell carcinoma of the uterine cervix treated with primary concurrent chemoradiation therapy followed by radical surgery and discuss the clinical and pathological features, treatment and prognosis of this tumor.*
***Keywords:*** *Small cell carcinoma, Uterine cervix, Treatment approach, Prognosis*

## I. Introduction

Small cell carcinoma of the uterine cervix (SCCUC) first described by Albores-Saavedra et al. in 1972, is classified as a neuroendocrine tumor according to the current World Health Organization histological classification of tumors of the uterine cervix (2003). Although, SCCUC is an exceedingly rare malignancy which represents only 1% to 3% of all uterine cervical cancers, it remains the most common subtype of cervical neuroendocrine tumors [1,2]. This tumor is similar to its more common pulmonary counterpart, in terms of histology and biologic behavior. Thus SCCUC is extremely aggressive, and patients with such malignancy have a poor prognosis due to its propensity for lymph node and distant metastases [3]. Owing to their rarity, optimal treatments of SCCUC are controversial. Moreover, it remains unclear whether radical surgery and adjuvant chemotherapy or primary concurrent chemoradiation is preferred in early-stage disease [4].

## II. Case Report

A 62 year-old, G4 P4 Moroccan woman, with medical history of hypothyroidism under levothyroxine treatment, presented to gynecology department with complaint of spontaneous postmenopausal uterine bleeding over two months period. There were no associated urinary or rectal symptoms. Gynecological examination revealed a small lesion confined to the posterior lip of the cervix. Moreover, no vaginal or parametrial invasion were found. The cervical lesion was biopsied. Pelvic magnetic resonance imaging (MRI) was then performed and confirmed the findings of a lesion confined to uterine cervix measuring 20mm of diameter without parametrial invasion or pelvic lymph nodes involvement (Fig. 1).

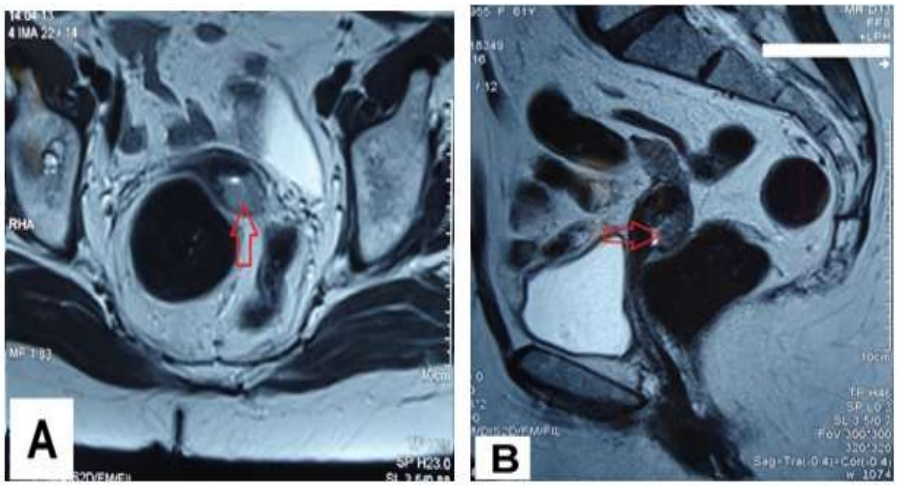


**Figure 1:** Pelvic MRI. (A) Axial view and (B) sagittal view showing a tumor mass of the cervix (Red arrows).

Histopathologic examination of biopsy specimens showed an endocervical mucosa largely infiltrated by a carcinomatous tumor proliferation arranged in sheets, trouts and cords. Tumor cells were small in size, with a high nucleocytoplasmic ratio. They were endowed with atypical nuclei that were irregular, enlarged and hyperchromatic, with scant basophil cytoplasm. Numerous apoptotic nuclei and mitotic figures were observed. Furthermore, there was no sign of squamous differentiation.

On immunochemistry, tumor cells expressed CK AE1/AE3 and EMA, while they were negative for P63 and CK 5/6. Moreover, 40% of tumor cells expressed chromogranin A and synaptophysin with granular and punctiform staining in the cytoplasm and Golgi apparatus. There was focal membranous staining for CD56 as well as a positive staining for TTF1 which was expressed by 100% of tumor cells. On the other hand, the Ki67 proliferation index was estimated at 100%. Based on such histological and immunochemical findings the diagnosis of small cell neuroendocrine carcinoma of the uterine cervix was established. Staging workup was therefore performed including MRI of the brain, computerized tomography (CT) of chest and abdomen and whole-body bone scintigraphy, all of which were negative.

The tumor was classified as FIGO stage IB1 and the case was discussed at multidisciplinary consultation meeting (RCP). The RCP decision was to treat the patient by primary concurrent chemoradiation therapy followed by radical surgery. Thus, the patient received three-dimensional conformal radiation therapy with 18 MV photons to a total dose of 46Gy in 23 fractions to the Planning target volume (PTV) corresponding to the Clinical target volume (CTV) including the cervix, the uterus body, the upper half of the vagina and the draining regional pelvic lymphatics with a marge of 0,7cm (Fig. 2).

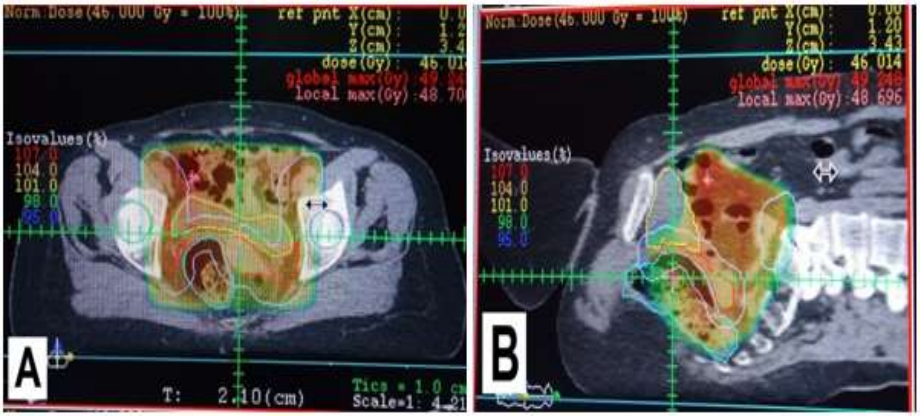


**Figure 2:** CT-scan dosimetry imaging. (A) Axial view and (B) sagittal view showing dose distribution of external beam radiation to the Planning target volume (PTV).

This radiation therapy was given concomitantly with weekly cisplatin /etoposide, with a total of four chemotherapy cycles. Due to the occurrence of neutropenia, the last chemotherapy cycle was omitted. One month after the end of radiation the patient underwent radical hysterectomy with pelvic lymphadenectomy via laparotomy. Histopathological examination of the surgical specimen showed a residual tumor of the cervix measuring 7mm. there was no lymph nodes invasion. The patient received then two sessions of vaginal High-dose-rate (HDR) brachytherapy of 5Gy each (Fig. 3). Because of neutropenia persistence, adjuvant chemotherapy could not be started and the patient was put on a close follow up schedule. After six months of follow up after the end of therapy the patient is still disease free.

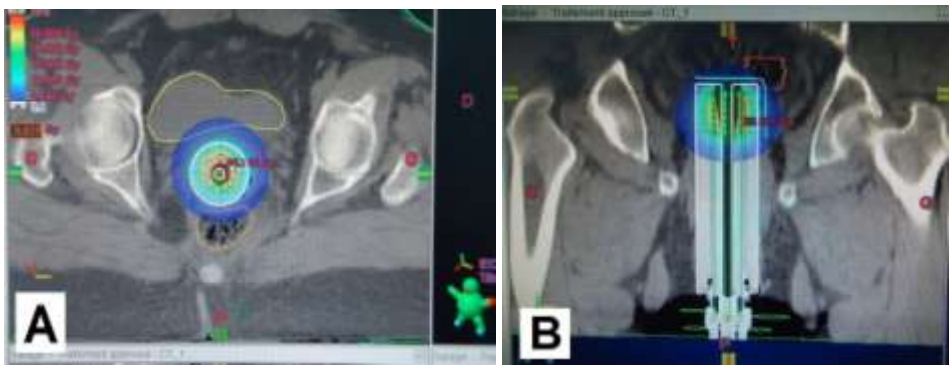


**Figure 3:** CT-scan dosimetry imaging (A) Axial view and (B) frontal view showing dose distribution of vaginal brachytherapy.

## III. Discussion

Cervical cancer is the third most common female cancer and the fourth leading cause of cancer death in women worldwide. The two most common histological subtypes of cervical cancer are Squamous cell carcinoma and adenocarcinoma. On the other hand, small cell carcinoma is a neuroendocrine tumor most frequently found in the lung. However, extrapulmonary small cell carcinoma (EPSCC) has been reported in almost every organ. The gynecologic tract is one of site where EPSCC occur more frequently, representing up to 2% of all gynecologic malignancies [2]. Small cell carcinoma of the cervix is the most common subtype of cervical neuroendocrine tumors, although it is a very rare disease, representing less than 3% of all uterine cervical cancers [1,2].

Pathologic diagnostic criteria regarding neuroendocrine tumors of the uterine cervix have known changes over time. In 1994, World Health Organization (WHO) classified these tumors into two categories, carcinoid and small cell carcinoma, whereas Albores-Saavedra et al. have classified them in1997 based on lung cancer classification. In the current WHO classification adopted since 2003, 4 categories were listed for neuroendocrine tumors of the uterine cervix consisting in carcinoid, atypical carcinoid, small cell carcinoma, and large cell neuroendocrine carcinoma on the pattern of lung neuroendocrine carcinoma [1].

The usual presenting symptom of cervical neuroendocrine tumors including cervical small cell carcinoma is vaginal bleeding, and a clinically detectable cervical mass is present in most cases [2].

Histologically, small cell carcinoma can be diagnosed by Hematoxylin and eosin staining, and on light microscopy. In addition, small cell neuroendocrine carcinoma of the uterine cervix is indistinguishable from small cell carcinoma in other sites. Characteristic features include small cells with hyperchromatic nuclei and scant cytoplasm. Nucleoli are inconspicuous or absent. Frequent mitoses as well as necrosis are commonly identified [1,5]. However, neuroendocrine immunohistochemical markers are frequently used to support the diagnosis. Actually, chromogranin A, synaptophysin and neuron-specific enolase are the most frequently used markers for immunohistochemical detection of neuroendocrine differentiation. Furthermore, as the small cell neuroendocrine carcinoma of the cervix is more likely to develop in the endocervical canal, endocervical curetting in-addition to biopsying the cervix will be required for obtaining an adequate specimen for histopathological examination [2]. Because of their rarity, the prognostic factors and optimal treatments of small cell neuroendocrine carcinoma of the cervix are controversial [4]. Regarding prognostic factors, smoking and clinicopathological characteristics, such as large tumor size, lymph node metastasis, advanced stage, depth of cervical stromal invasion (DSI), number of positive lymph nodes, and pure small cell histology have been linked to worse clinical outcome [2,3,4].On the other hand, prospective studies aiming to elucidate the impact of treatment modality on survival outcome are very difficult to undertake due to low frequency of this malignancy. Hence the necessity of relying mainly on the analysis of retrospective studies [6].

Although, some studies suggested that for cervical neuroendocrine tumors less than 4 cm, a radical hysterectomy with lymphadenectomy should be performed with the consideration of adjuvant etoposide/platinum based therapies, in a recent retrospective study conducted by Chen et al [6], authors noted that for most patients of stages I–II small cell neuroendocrine carcinoma of the cervix, primary radiation with aggressive chemotherapy resulted in a better survival outcome than primary surgery [6,7,8]. Moreover, a higher rate of loco-regional failure in the surgery group in stages I–II has been reported, and primary surgery was associated with worse survival in stages IB2–II [6].Compared to cervical cancer of common histological types, small cell neuroendocrine carcinoma of the cervix is highly aggressive subtype and has a higher recurrence rate at distant sites within a short time interval after treatment even in early-stage patients, indicating the need for systemic chemotherapy [2,3,6,7,9]. Although, adjuvant platinum and etoposide-based combination therapy was the most advocated chemotherapy regimen that offered a more favorable survival than other chemotherapeutic regimens as was reported in most studies, other studies were unable to prove any statistically significant benefit to using adjuvant chemotherapy [3].

Finally, the emphasis should also be on the toxicity of aggressive treatment for small cell neuroendocrine carcinoma of the cervix, warranting supportive management, in order to maintain the treatment schedule and prevent neutropenia-related infection [6]. In our case, the use of both of concurrent and adjuvant chemotherapy was limited due the occurrence of severe neutropenia.

## IV. Conclusion

Small cell neuroendocrine carcinoma is a very rare malignancy. Its diagnosis is based on histopathological examination and immunohistochemical staining. There is no consensus regarding optimal treatment but it seems that primary radiation with aggressive chemotherapy resulted in a better survival outcome than primary surgery in patients with early stage tumors. However, small cell carcinoma of the cervix remains highly aggressive histological subtype with poor prognosis due to its propensity for early lymph node and distant metastasis.

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