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Case report

Advanced small cell carcinoma of the cervix – Successful treatment with concurrent etoposide and cisplatin chemotherapy and extended field radiation: A case report and discussion☆

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ABSTRACT

The purpose of this article is to present a case of successful treatment of a patient with stage IVB small cell carcinoma of the cervix (SCCC) who was treated with concurrent chemoradiotherapy (CCRT) consisting of etoposide/cisplatin (EP) chemotherapy, external beam radiation therapy (EBRT), and brachytherapy. The patient has since remained without evidence of disease for nearly six years. This report reviews and summarizes the existing case literature on SCCC.

1. Introduction

Small cell carcinoma of the cervix (SCCC) is a rare neuroendocrine malignancy comprising less than 3–5% of cervical carcinomas (Lee et al., 2015). SCCC is a high-grade neuroendocrine tumor that shares numerous characteristics of small cell lung carcinoma (SCLC) and has often been considered an “extrapulmonary” small cell carcinoma (Korcum et al., 2008; Berniker et al., 2015). Classic neuroendocrine morphological characteristics of SCCC and SCLC include small “blue” cells with hyperchromatic nuclei and scant cytoplasm on hematoxylin and eosin (H&E) staining, as well as frequent mitotic figures with inconspicuous or absent nucleoli. Along with shared morphological characteristics and architectural patterns, SCCC and SCLC share many immunohistochemistry markers, such as synaptophysin, chromogranin A, and CD56 (Berniker et al., 2015; Gardner et al., 2011). The diagnosis of primary SCCC is made by cervical biopsy noting histopathologic features characteristic of small cell carcinoma, along with exclusion of primary SCLC (Berniker et al., 2015). While SCCC bears similar histopathologic features and clinical behavior to SCLC and has historically been considered an extrapulmonary variant of the same malignancy, recent advances in molecular and genetic research have indicated that small cell carcinomas in different anatomic sites carry distinct genetic markers and are actually unique diseases (Zheng et al., 2015).

SCCC is a very aggressive malignancy with frequent lymph node involvement at the time of diagnosis (Lee et al., 2015). Most patients treated for SCCC experience treatment failure secondary to early local recurrence as well as distant metastases, which occur most commonly in the lung, liver, brain and bone (Lee et al., 2015; Chen et al., 2015). The combined survival rate reported for all stages of SCCC ranges from 11 to 54%, with the overall prognosis being poor for advanced disease (Lee et al., 2015; Chen et al., 2015). The present report describes treatment of a patient with Stage IVB SCCC who has remained without evidence of disease for nearly six years following treatment and provides a discussion on treatment recommendations for locally advanced SCCC.

2. Case report

A 31-year-old G2P0020 female presented to the emergency department with increasing vaginal bleeding accompanied by lower abdominal and pelvic pain as well as left lower extremity edema of three months duration. Physical exam demonstrated a 16-week gestational size uterus fixed in the pelvis with non-palpable adnexa, evidence of tumor involving the bilateral pelvic sidewalls, and a palpable, enlarged

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left inguinal lymph node. Computed tomography (CT) scan without contrast of the abdomen and pelvis revealed a large heterogeneous mass arising from the cervix measuring 5.4 × 4.3 × 6.8 cm and metastases to the para-aortic, iliac, and inguinal lymph nodes, with a left common iliac nodal mass encasing the left external iliac artery and vein. The tumor was noted to be invading the superior portion of the bladder and the medial portion of the left psoas muscle. Biopsies of the cervix and endometrium were performed and found to be consistent with small cell neuroendocrine carcinoma. The patient underwent positron emission tomography (PET)-CT scan for further disease staging, which was consistent with CT findings with no distant disease identified.

The patient received concurrent chemoradiotherapy (CCRT) with adjuvant etoposide/cisplatin (EP) chemotherapy for a total of 6 cycles along with external beam radiation therapy (EBRT) and brachytherapy. Chemotherapy was initiated concurrently with radiation and continued adjuvantly following radiation for a total of 6 cycles. Chemotherapy consisted of intravenous cisplatin with 50 mg/m^2 given on the first day of every 3-week cycle and etoposide with 100 mg/m^2 given on the first three days of every three-week cycle. RT consisted of extended field RT (EFRT) delivered to the pelvis and regional nodal beds (Fig. 1), including the para-aortic, iliac, and inguinal nodes. EFRT was performed as described by Small et al. (2011), with the addition of inguinal radiation, using 10 MV photons in a four-field technique with a dose of 45 Gy prescribed to the 98.0% isodose line. The dose was delivered in 25 fractions with a dose of 1.8 Gy per fraction. This was followed by brachytherapy (Fig. 2) and an EBRT boost to the parametria and gross nodal disease. Radiation therapy (RT) was completed three months after presentation, and chemotherapy was completed five months after presentation.

Following completion of CCRT, post-treatment imaging revealed complete response to primary therapy. The patient had an MRI of the brain with and without contrast one month after completion of therapy, which showed no evidence of metastatic disease. No prophylactic cranial irradiation (PCI) was delivered. At the time of this report, the patient remains without evidence of disease.

3. Literature review

The largest and most recent study to date analyzing locally advanced SCCC is a retrospective review by Wang et al. that examined 179 patients who underwent primary treatment of FIGO stages I–IV SCCC between 1987 and 2009 at member hospitals of the Taiwanese Gynecologic Oncology Group (TGOG) (Wang et al., 2012). Of the patients with stages IIB–IVB disease (n = 56), any primary treatment with EP for at least five cycles was associated with significantly better 5-year failure-free survival (FFS) (42.9% vs. 11.8%, p = 0.041) and cancer-specific survival (CSS) (45.6% vs, 17.1%, p = 0.035) relative to other treatments (Wang et al., 2012). Additionally, Wang et al. demonstrated that CCRT utilizing at least five cycles of EP was associated with a markedly improved FFS (62.5% versus 13.1%, p = 0.025) and 5-year CSS (75.0% versus 16.9%, p = 0.016) compared to other treatments (Wang et al., 2012). This TGOG study additionally underscored the superiority of CCRT over chemotherapy alone.

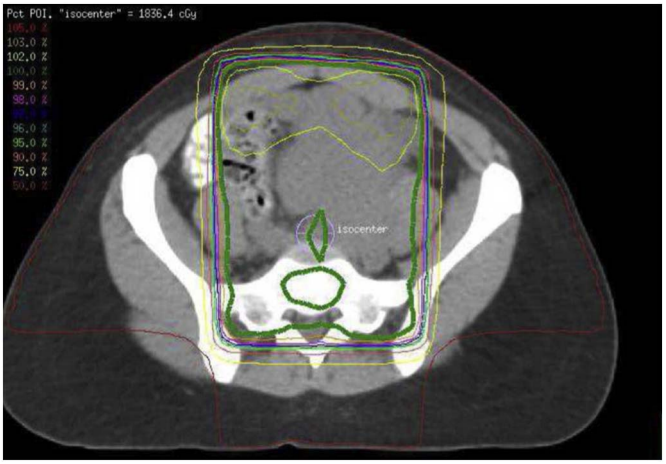

Fig. 1. Pelvic CT scan showing isodose curves of a four-field standard beam arrangement. Treatment plan generated following urgent CT simulation.

While SCCC has historically been regarded an extrapulmonary variant of SCLC, recent advances have indicated that small cell carcinomas in different anatomic sites carry distinct genetic markers and are unique diseases (Zheng et al., 2015). Consequently, although the chemotherapy agents utilized for SCCC have been chosen based on studies conducted on SCLC in the absence of phase II or phase III data (Frumovitz, n.d.), local treatment with RT for this malignancy should emulate local treatment for non-neuroendocrine cervical carcinomas as opposed to the RT regimen utilized for SCLC. A recently conducted National Cancer Database analysis studying patients with locally advanced SCCC found that brachytherapy is an integral aspect of definitive CRT for SCCC and should not be omitted (Robin et al., 2016). Of the 100 patients with locally advanced SCCC analyzed, the addition of brachytherapy was associated with a median survival benefit of 27 months compared to EBRT alone (48.6 vs. 21.6 months, HR: 0.475, 95% CI: 0.255–0.883, p = 0.019).

The largest dataset to date aimed at studying PCI for extra-pulmonary small cell carcinoma was compiled by Naidoo et al. and studied 280 patients, of whom 186 patients had extensive-stage disease, 65 patients had limited stage disease, and 29 patients had an unknown stage (Naidoo et al., 2013). Of the 280 patients analyzed, 18 patients (6.4%) developed brain metastases. Only 2.5% of the patient cohort presented with brain metastases at initial diagnosis, which is a significantly lower incidence than is seen for SCLC. Overall, the data published by Naidoo et al. does not support the use of PCI due to low incidence of brain metastases in SCCC.

4. Conclusion

Currently, there are no established treatment guidelines that exist for locally advanced SCCC, as it is a rare and aggressive tumor. Research on this malignancy has been limited to a few retrospective studies with small sample sizes due to the rarity of the disease. In spite of the insufficient number of cases of SCCC studied, there exists substantial support for the use of CCRT with adjuvant EP chemotherapy in the treatment of locally advanced SCCC.

SCCC is a rare and aggressive malignancy that is histopathologically and clinically similar to SCLC, but is a distinct disease entity. Based on the treatment guidelines for SCLC, with support from existing data describing outcomes of patients with locally advanced SCCC, the authors believe that the treatment regimen of choice for SCCC is CCRT. Adjuvant chemotherapy should be EP for at least 5 or more cycles. Radiation for locally advanced SCCC should mimic the treatment for locally advanced non-neuroendocrine cervical cancers and consist of EBRT accompanied by intracavitary brachytherapy and boost treatments to areas felt to be at risk and not adequately treated by brachytherapy. PCI is generally not indicated but may be discussed with the patient.

The patient presented in this case report was diagnosed with stage IVB SCCC. She received CCRT consisting of adjuvant chemotherapy with 6 cycles of EP and RT utilizing EFRT with boosts to the pelvis, para-aortic nodes, and parametria in addition to intracavitary brachytherapy. The patient has been followed for 6 years and has remained without evidence of disease. Due to the low incidence of SCCC and the paucity of studies examining the optimal therapeutic regimen for locally advanced SCCC, further research must be conducted to attain a greater understanding of the best approach in managing patients with

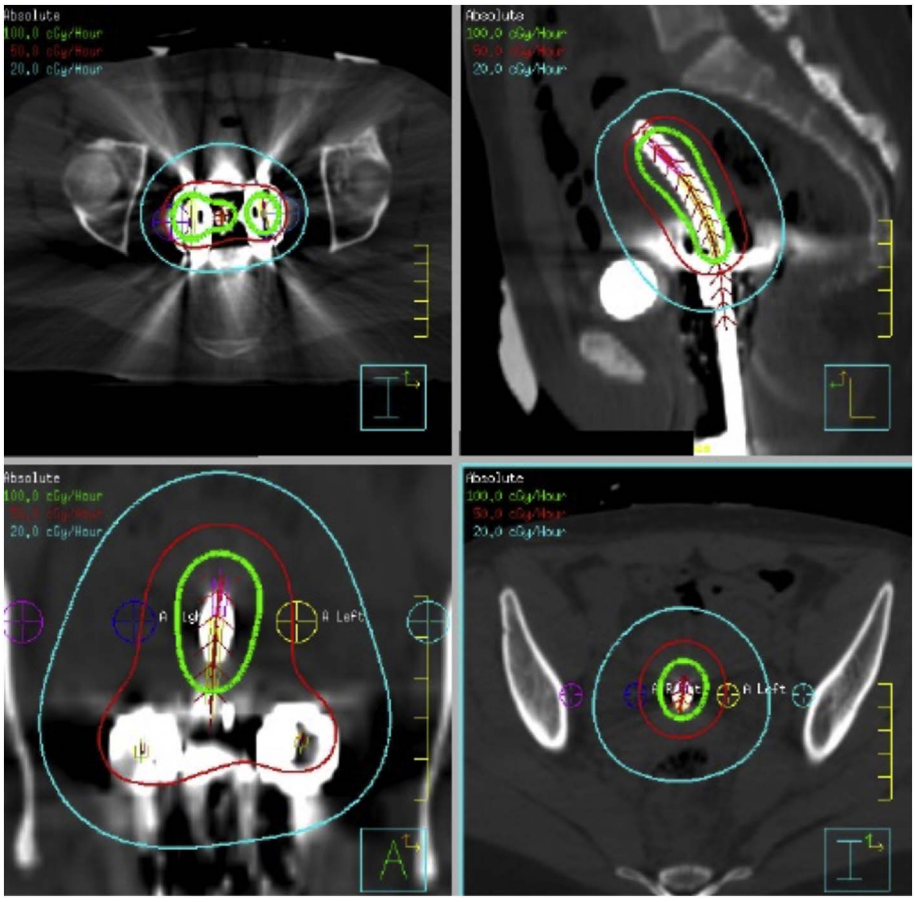

Fig. 2. Isodose curves for LDR brachytherapy implant using isotopes CS-137 and Ir-192 delivering 34.6 Gy to Point A at 45.9 cGy/h over 75.4 h.

this condition.

Conflicts of interest notification

The authors have no conflict of interest to disclose.

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