EXCEPTIONAL LONG-TERM SURVIVAL OF AN ELDERLY PATIENT WITH METASTATIC SMALL CELL NEUROENDOCRINE CARCINOMA OF THE CERVIX – A CASE REPORT

Ho YY[1], Hiew NWY[1], and Ho GF[1].
[1]Clinical Oncology Unit, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Correspondence:
Ho Yun Yi,
Clinical Oncology Unit, Faculty of Medicine,
Universiti Malaya, Lembah Pantai,
59100 Kuala Lumpur, Malaysia
Email: In26my@gmail.com

Abstract

Small cell neuroendocrine cervical carcinoma (SCCC) is known for its aggressive nature and poor prognosis. There are no standard treatments so small cell lung cancer treatments are often referenced due to their similar morphology. Typical treatment options include a combination of external beam radiotherapy and brachytherapy for localised disease and palliative chemotherapy for advanced disease. The 5-year survival rate for patients presenting with advanced disease is dismal, around 0–14%. Here, we report a case of a 75-year-old woman who was diagnosed with small cell neuroendocrine cervical carcinoma (SCCC) in 2015. She presented with locally advanced SCCC with vaginal involvement, as well as solitary lung and peripancreatic metastases. She was treated with a combination of chemotherapy, chemoradiation and stereotactic radiotherapy, followed by maintenance etoposide, and achieved a very long-term survival. The patient continues to survive today.

Keywords: Cervical Small Cell Carcinoma, Oligometastases, Stereotactic Body Radiotherapy, Etoposide

Introduction

Small cell neuroendocrine cervical carcinoma (SCCC) is a rare disease accounting for less than 3% of all cervical cancers. The mean age at diagnosis is about 45 years (1), and it is associated with a poor prognosis. Studies have shown that the 5-year survival rate is 31.6–36.4% for early-stage SCCC and 0–14% for advanced-stage SCCC respectively (2). Small cell carcinomas are fast-growing and highly aggressive compared to other types of cancers. Common sites for distant metastasis are lungs, bone and liver (3). As a result, the PFS (progression-free survival) and OS (overall survival) are significantly shorter in SCCC patients compared to those with squamous cell carcinoma of the cervix (4).

Case report

A 75-year-old Chinese woman, ECOG PS grade 2, presented with daily spotting in 2015. She has two children and good family support, with a history of total replacement for her left knee 20 years ago and was unable to stand for long periods of time due to knee pain. Upon examination, a fungating mass was found at the cervix with involvement of the upper third of the vagina and nodules at the posterior wall.

She was diagnosed with small cell cervical carcinoma with vaginal involvement. An MRI scan showed a posterior mass measuring 22 mm x 28 mm x 10 mm (AP x T x CC) infiltrating the cervical stroma circumferentially up to a uterocervical junction, extending into the upper third of the vagina and a right pulmonary nodule. PET and CT scans showed a solitary lung metastasis, peripancreatic metastasis, and the presence of pulmonary embolism and left deep vein thrombosis (Figure 1, 2 and 3).

She was anticoagulated and started on palliative chemotherapy with cisplatin (60 mg/m²) and irinotecan (120 mg/m²) two-weekly for three cycles. External beam radiotherapy using 3D conformal technique was delivered using 10MV photons to the pelvis and treated to a dose of 50Gy in 25 fractions over five weeks in February 2016. Concurrent chemotherapy with cisplatin 40 mg/m^2 was given weekly during radiotherapy, followed by three sessions of intrauterine brachytherapy delivering 7 Gy to point A and completed in February 2016. The patient tolerated treatment well and clinically the cervical mass had resolved. She was then treated with stereotactic body radiotherapy at a dose of 55 Gy in five fractions over one week to the right lung metastasis in December 2016.

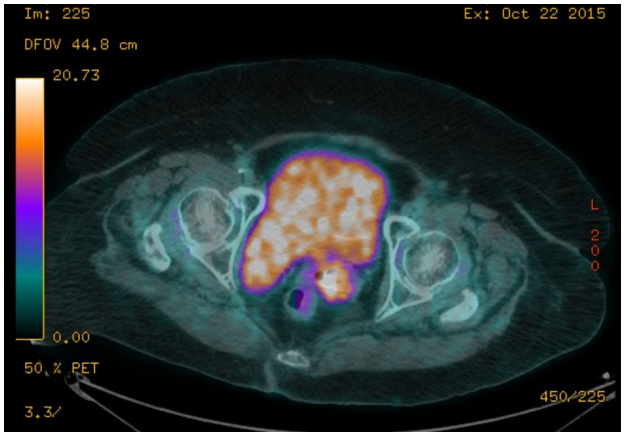

Figure 1: PET scan of the pelvis, Oct 2015

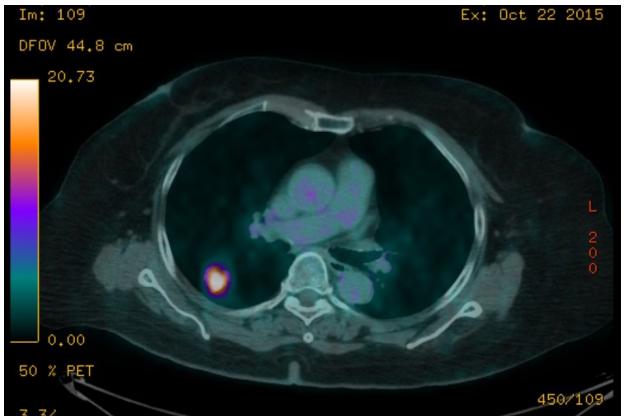

Figure 2: PET scan of the lung before SBRT, Oct 2015

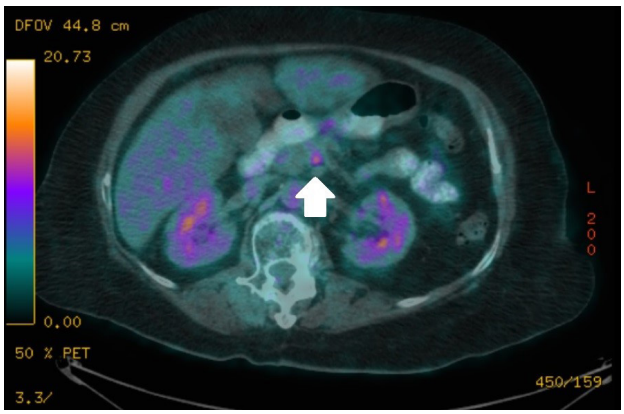

Figure 3: PET CT scan of the pancreatic lesion (white arrow), Oct 2015

A PET scan 3 months following chemoradiation showed a good response in the pelvis and lung. However, a bone scan was done and uptake was seen at T10-T12. Three-monthly zoledronic acid 4 mg was commenced (Figure 4). The patient started on maintenance oral etoposide 100 mg twice a day for four days, repeated every 28 days in May 2017. She continued this regime until October 2019.

A Follow-up PET-CT scan in July 2019 showed that the bone metastasis remained unchanged, while the metabolic activity of the right lung mass had resolved. There was no other metabolically active disease detected elsewhere (Figure 5 and 6).

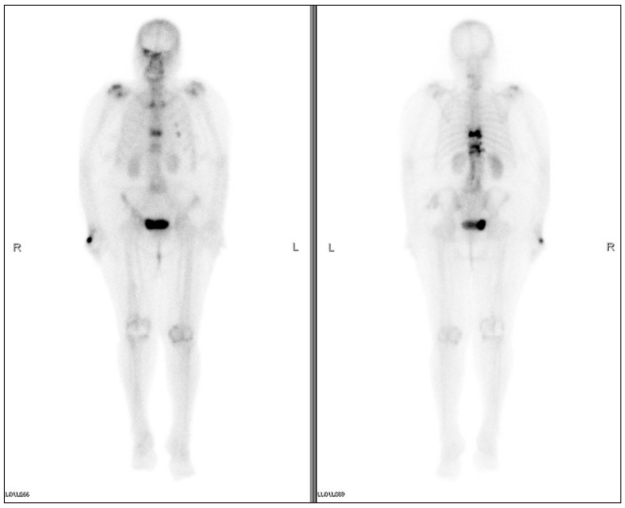

Figure 4: Bone scan showing metastases at T10 and T12, May 2017

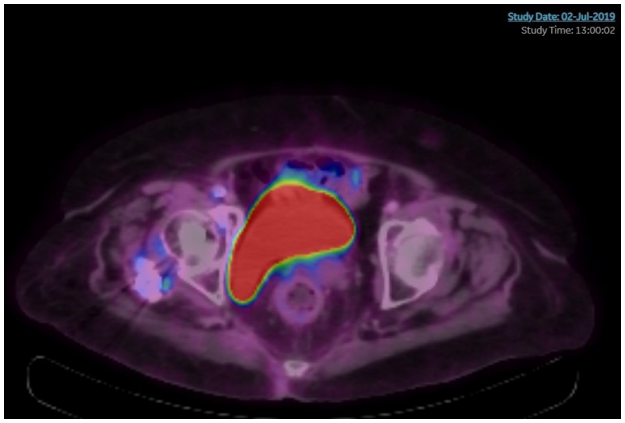

Figure 5: PET scan of the pelvis, July 2019

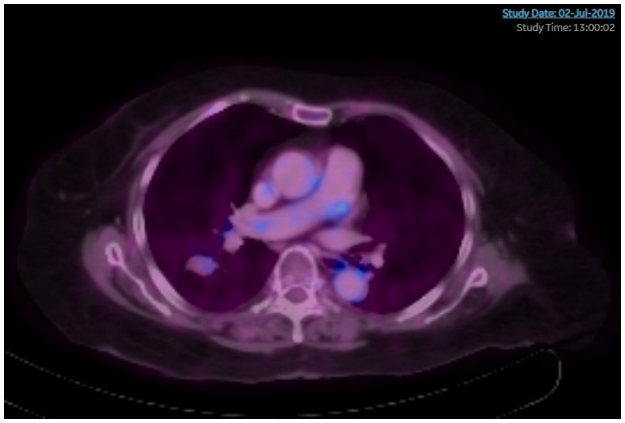

Figure 6: PET scan of the lung post SBRT

The patient was reviewed in October 2019 and decided to stop etoposide as she was starting to be troubled by symptoms of grade 2 drowsiness, reduced appetite and hair loss. She also had a fall in December causing her pain in the left shoulder. There was no swelling or inflammation, and she was managed with physiotherapy.

In August 2020, the patient presented with grade 2 lower gastrointestinal haemorrhage, acute deep vein thrombosis of the left leg and pulmonary embolism. She was managed accordingly and made a good recovery. Zoledronic acid was later discontinued as she was not keen on further treatment and scans, opting for supportive care. The patient was last reviewed in clinic in August 2022 and had survived for over seven years since the initial diagnosis of the advanced SCCC.

Discussion

SCCC is a rare but aggressive subtype of cervical cancer, accounting for only about 2% of all cervical malignancies. Histologically, cervical NEC is characterised by small to medium-sized tumour cells with high nuclear-to-cytoplasmic ratios, scant cytoplasm, and finely granular chromatin pattern. Cervical NEC is typically positive for neuroendocrine markers, such as chromogranin A, synaptophysin, and CD56, while SCC is negative for these markers. In a group study on prognostic factors of SCCC of the cervix, the median cancer-specific survival (CSS) was 24.8 months, yet patients with stage IVB SCCC had a very poor prognosis with a 5-year CSS of 0% (5).

Due to the rarity of the malignancy and its poor prognosis, there is currently no standard therapy for SCCC. As it has similar morphological characteristics to small cell lung carcinoma (SCLC), SCLC treatments are often referenced in the treatment of SCCC (6). Chemotherapy consisting of carboplatin or cisplatin is often used together with etoposide for metastatic SCLC, with immunotherapy used as maintenance to improve the survival outcome (7). Radiotherapy to the thorax and brain is used to palliate symptoms of stage IV SCLC and to improve local disease control. For SCCC, similar methods are often incorporated, using surgery or chemoradiation for localised disease, and systemic therapy with either cisplatin or carboplatin, with etoposide, topotecan or paclitaxel for advanced disease (8, 9).

Zhang et al. (2) conducted a meta-analysis on 20 studies and concluded that patients with stage IIB-IVA SCCC should receive three cycles of neoadjuvant chemotherapy (NACT) followed by cisplatin-based concurrent chemoradiotherapy, and three additional cycles of adjuvant chemotherapy, whilst patients at stage IVB should initially receive chemotherapy, then palliative radiotherapy to the pelvic area. Prophylactic cranial irradiation (PCI) can be considered for patients with highly selective lung metastasis.

Stereotactic body radiotherapy (SBRT) is a specific, high-dose form of radiation therapy to ablate the local tumour (10). A study of 61 patients with oligometastatic lung tumours was published by Ricardi et al. (11). The OS rates at two and three years were 66.5% and 52.5% respectively and PFS rates at two and three years were 32.4% and 22.3%. Many studies concluded that SBRT is a safe and effective treatment for early peripheral lung tumours, although there is still considerable controversy regarding SBRT for central lung tumours, as well as oligometastases and spinal metastases. The reported studies are mainly observational, single-armed or pooled analyses, without a suitable set of controls (12). However, currently available evidence suggests that in carefully selected cases, SBRT is a useful tool to improve local disease control.

The present case was treated with maintenance therapy of etoposide and zoledronic after receiving radiotherapy and neoadjuvant chemotherapy. Etoposide is a cytotoxic drug that primarily targets the topoisomerase II-DNA cleavage complex (13). It stabilises the cleavage complex formed by topoisomerase II in its catalytic cycle and once the cleavage complex accumulates, permanent DNA strand breaks are caused. This can trigger repair pathways and initiate death pathways of the cell (14). Maintenance etoposide has been shown to be effective and well tolerated in SCLC patients. Hanna et al. (15) reported the use of maintenance daily oral etoposide for three months after four cycles of induction etoposide, ifosfamide and cisplatin for extensive SCLC, and showed a significant improvement in median PFS for the maintenance group compared to the observation group (8.2 versus 6.5 months, $P = 0.0018$).

There was also a trend in the improvement of median survival (12.2 versus 11.2 months), 1-year (51.4% versus 40.3%), 2-year (16.7% versus 6.9%) and 3-year (9.1% versus 1.9%) survival favouring the maintenance group over the observation group. The toxicity of etoposide in patients was mild and overall, the results show an improvement in PFS. Hence, maintenance oral etoposide has been shown to improve PFS in non-progressing patients with extensive SCLC and is associated with improved OS (16, 17). From this study, we deduced that etoposide might be beneficial as a maintenance treatment for SCCC.

Recent studies have shown immunotherapy also to have promising efficacy. Rudin et al. (reported in a KEYNOTE-604 study, which showed the 24-month OS estimate for patients receiving pembrolizumab with etoposide and platinum-based chemotherapy of 22.5%, double of the placebo group at 11.2% (18-22). Durvalumab in combination with tremelimumab shows promising activity and a tolerable safety profile in pretreated stage IV SCLC. In the CASPIAN study, durvalumab + tremelimumab with platinum-etoposide was tested against durvalumab with platinum-etoposide in extensive-stage SCLC. The results showed numerically improved OS in the tremelimumab branch (though statistical significance was not reached) and a sustained OS benefit after more than three years of median follow-up (23-25). Studies on the effectiveness of immunotherapy on SCCC are limited in number and further studies will need to be done for conclusive results.

Conclusion

In this case, the patient was diagnosed with small cell cervical cancer with lung and peripancreatic metastasis. Treatment of maintenance etoposide after combination therapy may be the reason for her long-term survival despite the malignancy of SCCC and her old age. We can conclude that the eradication of oligometastases followed by maintenance of low-dose etoposide is a low-cost, feasible and possibly effective therapy for SCCC with oligometastases.

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Competing interests

The authors declare that they have no competing interests.

Ethical clearance

Informed consent form was signed by the patient for inclusion in this report on 26th August 2022.

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