

Metastatic endometrial carcinoma in the lung: unusual timing and site

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Introduction

Endometrial cancer is the seventh most common gynecological malignancy. The standard of care is surgery, followed by further treatment based on the surgical and histological findings.¹ Usually, recurrences (80%) from endometrial cancer are seen within three years of hysterectomy and late recurrences are rare. The incidence of isolated lung recurrences is approximately 2.3-7%.^{2,3} This is a case report of endometrial cancer with locoregional and distant recurrence.

Case study

A 56-year-old woman was diagnosed with carcinoma of the endometrium in 2002. She underwent a hysterectomy and bilateral salpingo-oophorectomy, without lymph node dissection. The histopathology was endometrioid adenocarcinoma FIGO 1988 stage Ic, grade 2. She had external beam radiation therapy to the whole pelvis, with a dose of 40 Gy at peripheral centre. The patient refused the planned vaginal brachytherapy. In 2005, she presented at our institute with vaginal bleeding. Clinically, she had a proliferative growth in the right lateral vaginal wall, with indurations of the vault. At the time, a magnetic resonance imaging evaluation showed vaginal vault disease only, with no enlarged nodes. She was salvaged with conformal external beam radiotherapy to the true pelvis with a dose of 40 Gy, followed by three sittings of vaginal brachytherapy. Clinically, she achieved complete response and was kept on regular follow-up.

She presented again in October 2012, with complaints of coughing. She was evaluated with a positron emission tomography (PET) computed tomography (CT) scan, which showed abnormally increased fluorodeoxyglucose uptake in a heterogeneously enhancing soft tissue mass lesion involving the upper lobe of the right lung, it was closely abutting the mediastinal pleura, superior vena cava and trachea, and encasing the right upper lobe bronchus, causing abrupt cut-off, with a standardised uptake value maximum of 12 (Figure 1). There were no other PET-positive lesions elsewhere. The possibility of a second malignancy was considered and a CT-guided biopsy was obtained from the lung lesion. The histopathology reported a well-differentiated adenocarcinoma. The considered differential diagnoses were primary lung malignancy and metastasis. Since the patient had been treated for endometrioid carcinoma, with the morphological appearance was that of a back-to-back arrangement of glands under microscopy suggestive of an endometrioid pattern, a diagnosis of metastasis from endometrial malignancy was favoured. To confirm this, immunohistochemistry was performed. In view of the delay in obtaining a conclusive diagnosis, the patient was started on concurrent chemoradiation, with a provisional diagnosis of unresectable primary adenocarcinoma of the lung. The final immunohistochemistry showed moderate to intense nuclear and cytoplasmic positivity for oestrogen and progesterone, and focal positivity of cytokeratin (CK) 7. CK20 and thyroid transcription factor (TTF)-1 were negative. The cells also showed focal cytoplasmic positivity for the oestrogen receptors. The morphological features and oestrogen, progesterone

and CK7 positivity, as well as negative lung marker, TTF-1, secured a diagnosis of metastatic endometrioid carcinoma.

The patient received weekly carboplatin, with a dose of 150 mg (area under the curve 2), given concurrently with a radiation dose of 46 Gy in 23 fractions, to the whole tumour. Once endometrial metastasis was confirmed through immunohistochemistry, the response was assessed using CT screening. By then, she had completed 18 fractions of radiation, and the screening showed a 67% reduction in tumour

size (Figure 2). In view of the good response, a boost dose of 14 Gy in seven fractions was also offered. She completed treatment in November 2012. A chest radiograph that was taken after treatment was negative for any tumour, showing a complete response (Figure 3). The patient was advised to undergo systemic chemotherapy, which she deferred. She was started on oral progesterone and is on regular follow-up, at three-monthly intervals, with ongoing chest imaging. She is disease free to date.

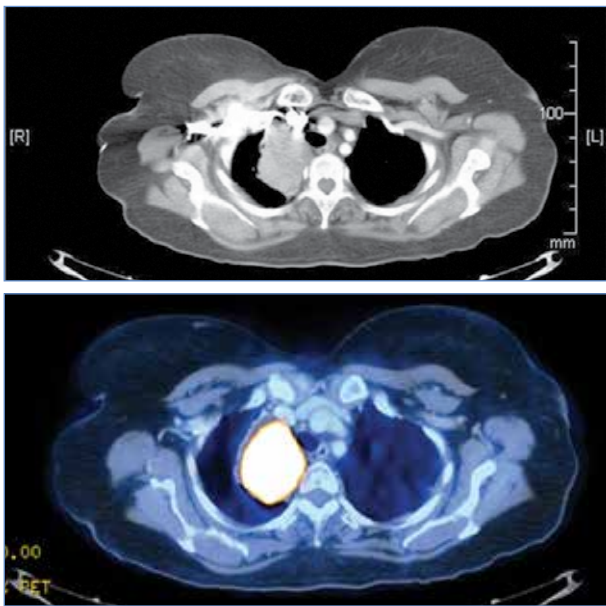


Figure 1: CT (top) and PET (bottom) scan images showing the lesion in the lung

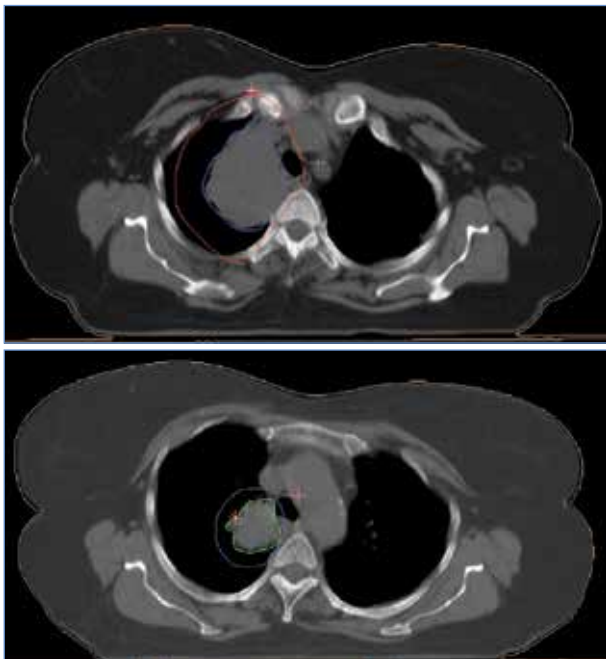


Figure 2: The initial radiation treatment volume (top), and the reduced volume (bottom)



Figure 3: Chest radiographs before treatment (top) and after treatment, showing the response (bottom)

Discussion

Most women with endometrial cancer are diagnosed in the early stages, when the disease is confined to the uterus. The involvement of the outer third of the myometrium has been considered to be the surrogate marker for lymph node involvement and distant metastasis, with a fivefold increase in the risk of the lymph nodes being affected.

Vaginal brachytherapy is an important modality in the care of intermediate- and high-risk endometrial cancer, with fewer treatment sittings and a better toxicity profile compared to that of external beam radiotherapy. The Post Operative Radiation Therapy in Endometrial Cancer (PORTEC)-2 trial results recommended vaginal brachytherapy as a safe substitute for stage I and IIa endometrial carcinoma with high- to intermediate-risk features.⁴ PORTEC-2 showed that with vaginal brachytherapy, the five-year vaginal recurrence rate was 1.8%, while with the addition of external radiation, it was 1.6%. Five-year disease-free survival of 83% vs. 78%, and overall survival of 85% vs. 80% for vaginal brachytherapy versus external beam radiation, was also observed.⁵ Vaginal brachytherapy offers better quality of life, with none of the incapacitating bowel symptoms reported with external beam radiation.

This patient had more than 50% myometrial invasion and grade 2 histology, and hence might have benefited from vaginal brachytherapy initially, together with external beam radiation. However, the fact that she was salvaged with external beam radiation and vaginal brachytherapy, even when she had a recurrence, and the seven-year disease-free interval, suggest that radiation can be used if, and when, there is local recurrence.

Approximately 10-15% of patients with early-stage endometrial cancer experience a recurrence.⁶ Roughly 80% of recurrences from endometrial cancer occur within the first three years after definitive treatment.⁷ In their analysis of patterns of failure, Gadduci et al reported that the median time to recurrence was 18.5 months, with a range of 3-129 months.⁸ The longest reported interval for recurrence was 26.5 years (in the vaginal vault) reported in 1987 by Lederman et al.⁷ Three-year survival after vaginal vault recurrence has been documented as 73%, as opposed to 8% and 14% for pelvic and distant metastases,⁵ and is salvageable with radiation therapy.

Endometrial carcinoma metastasising as a solitary lung lesion is quite rare and accounts for approximately 2.3-7%.^{2,9,10} Dowdy et al examined the treatment and outcomes of pulmonary recurrence in patients with endometrial carcinoma³ after primary surgery at the

Mayo Clinic, and reported a 3% isolated lung failure, while overall failure was 9% and median time to recurrence was 35 months. The longest interval for a pulmonary recurrence was reported by Hiroyuki Ito to be 17 years after initial treatment, with the next longest interval being 14 years.^{2,11} Our patient had a vaginal vault recurrence and then a lung recurrence 10 years after initial treatment.

Late recurrences have been explained by the cancer stem cell model,¹² which proposes that the growth and progression of many cancers is driven by a small subpopulation of cancer stem cells. Cancer stem cells undergo epigenetic changes, analogous to the differentiation of normal cells, forming phenotypically diverse non-tumourigenic cells that compose the bulk of cancer cells in a tumour. It is not known whether cancers cells differ from non-tumourigenic cells based on epigenetic, rather than genetic, factors. Studies have shown that endometrial adult stem or progenitor cells are responsible for endometrial regeneration.¹³ A rare population of human endometrial epithelial and stromal colony-forming cells and side-population cells have been identified. Further studies have shown that these endometrial stem cells have the capacity to form malignant cells, or to convert to mesenchymal tissue.

The prognostic factors (proposed by Dowdy et al, Anraku et al and Otsuko et al), which can predict good survival in primary endometrial malignancy metastasising to lung are a disease-free interval > 12 months, grade 1-2 histology, oestrogen-receptor positivity, < 50% myometrial invasion, unilateral lung lesions, lesion < 2 cm in size, and < 5 nodular lesions in one lung.^{14,15} In most cases, the treatment is surgery, followed by systemic chemotherapy. The reported nonsurgical treatments were radio-frequency ablation, regional chemotherapy, systemic chemotherapy, cryotherapy, stereotactic radiosurgery, and stereotactic body radiotherapy. Intrabronchial artery infusion chemotherapy with systemic chemotherapy and radiotherapy were investigated by Yonezawa et al, with > 2-year survival.¹⁰ In addition, hormonal treatment has also been used.

Dowdy et al³ suggested that the most significant predictive factors of outcome after treatment were grade 1-2 tumour, greatest diameter < 2 cm of the lesion, use of treatment other than chemotherapy and the presence of oestrogen receptors. Their results showed no survival difference in patients treated with hormonal therapy or surgical resection. A 33% overall response was documented in the Gynecology Oncology Group (GOG) 119 phase II trial, on daily tamoxifen acting as an oestrogen surrogate, alternating with weekly progestin (medroxyprogesterone acetate) in patients with advanced or recurrent endometrial

cancer.¹⁶ The response was 44% for oestrogen-positive tumours, while it was 25% for oestrogen-negative tumours. Progestogens and tamoxifen were used, with good results. Concurrent chemoradiation has been attempted in solitary metastatic lymph nodes after definitive surgical resection of the primary and lymph nodes in oesophageal cancer, with a 40% chance of long-term survival.¹⁷ Our patient showed a good response with the concurrent chemoradiation protocol.

Conclusion

If diagnosed after a long, disease-free interval, a solitary pulmonary metastasis from endometrial carcinoma can be considered to have a fairly good prognosis. Adequate evaluation of the solitary lung lesion against the background of an earlier malignancy of the endometrium is mandatory in the clinical setting of our country, where primary lung malignancy is common. The possibility of a curative-intent, single-modality approach like surgery, or combined modality options such as chemoradiation and follow-up maintenance with hormonal treatment, predicts a better outcome in these patients. Vigilant follow-up and prompt evaluation of suspicious findings help to secure improved survival.

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