Review Article

Pulmonary metastasectomy in uterine malignancy: outcomes and prognostic factors

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Abstract: Metastatic uterine cancer is a form of systemic disease. As for other solid tumours, it is advocated by some authors that in selected patients, lung metastasectomy may play a role in long-term disease control. The practice of lung metastasectomy is however open to criticism as there is lack of convincing evidence, and over-encouraging outcomes may be attributed to intrinsic selection bias. The case of metastatic uterine tumours is reviewed in the light of the available literature, in order to identify common patterns and prognostic factors that may influence and determine an individualised and informed patient decision.

Keywords: Lung; metastasectomy; uterine cancer

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Introduction

Metastatic uterine cancer is by definition a form of systemic disease and there is general agreement that it should be treated as such. While extensive spread to distant organs precludes any attempt of radicality, some authors advocate that in selected patients metastasectomy may indeed play a role in long-term disease control (1,2). As is the case with many other solid tumours, the practice of metastasectomy is open to criticism as there is lack of convincing evidence, and over-encouraging outcomes may be attributed to intrinsic selection bias (3). The accepted criteria for pulmonary metastasectomy include lesions that are completely resectable with acceptable operative risk, in the absence of extrapulmonary spread, when the primary tumour is completely controlled and when alternative or more effective treatment options are unavailable (1,2).

As to these conditions are infrequently all present in uterine cancer, the number of published reports (all retrospective and small) is scarce, and the likelihood of a randomised trial is effectively speculative. Comparative analysis of these studies is made even more difficult by a number of additional limitations. These include the variability of different tumour types with very different prognoses and a wide variety of treatments to control the primary tumour including any combination of surgery, chemotherapy and radiotherapy. Similarly, once pulmonary metastasis was apparent, a variety of complementary treatment options may be offered and with different timing, sometimes inconsistently within the same series, and with a different approach towards the extent of the lung resection and the use of repeated metastasectomy.

However, they all have merit in highlighting prognostic factors that may direct and inform an individualised patient decision.

Overview of epidemiology

In gynecologic cancers the rate of lung metastases is higher for choriocarcinoma and sarcoma than in patients with

epithelioid cancer such as cervical, endometrial or ovarian, although these three are rather more frequent (4). All major studies report an average age of 55–59 years at the time of lung resection, with a wide range spanning from the very young age (<20) to the more elderly (>80) (5). About 80% of cases present with multiple or bilateral metastases, while synchronous metastases are reported in about 20% of cases (6).

Endometrial cancer is the most common tumour of the female genital tract in Western countries (4,7). Extra uterine spread is reported in about 25% of cases, most commonly through pelvic and paraaortic lymph nodes or pelvic organs such as peritoneum and adnexa. Lung dissemination is the most common site of extrapelvic disease, especially for locally advanced cases, although it may occur in early stage disease (4). It is however relatively rare with reports ranging between 2.3–4.6% of cases depending on the series (8).

On the other hand, cervical cancer is the most common gynecological cancer in developing countries, with a reported 1.8% of lung metastases in a study on 2,075 women in Sri Lanka (4). Isolated lung metastases are reportedly seen in 1.1–6% of cases (9). These figures drop to barely 0.37% in stage I–II cervical cancer, which is a far more common presentation than more advanced stages (10).

Uterine leiomyosarcoma accounts for only 1–3% of uterine cancers, however seems to contribute to about 25% off all uterine-cancer related deaths. Lung metastasis is much more common in as much as 30% of cases (11).

In other areas of gynecological oncology, ovarian cancer seems uniquely to exhibit a specific affinity to pleural spread (reflecting its mesothelial origin), presenting with effusion and pleural lesions rather than isolated pulmonary nodules (4). Likewise, choriocarcinoma (rarer) is usually chemo-sensitive, therefore lung resection is relatively unusual and reserved solely to chemoresistant oligometastatic disease (4).

History and outcomes of lung resection

The first case of a pulmonary resection for uterine adenocarcinoma was reported by Torek in 1930 (12).

A limited number of case reports or small series followed in the years (4,8,13), but the first larger surgical series to appear was a study from Memorial Sloan Kettering Cancer Centre in 1992 (14). Forty-five patients with pulmonary metastases from uterine sarcomas were resected (29% bilaterally). All had potentially resectable lesions but only 74% eventually had a complete resection. Five- and 10-year survival was respectively 65% and 50% from diagnosis and 43% and 35% from metastasectomy, with the only significant predictor of survival identified in unilateral versus bilateral location.

Since then, a number of surgical series as well as mixed series including both surgical and non-surgical patients have been published with sometimes controversial results.

In some mixed series including surgical and non-surgical patients, for example, oestrogen receptor status and the use of hormonal therapy seemed to be the only therapeutic option able to prolong survival, whereas neither surgery nor chemotherapy seemed to, with reported survival of 28, 18 and 14 months respectively (15,16). Likewise, in another Japanese study, patients who developed pulmonary recurrence 2 years after the initial therapy had a significantly longer survival than those who developed it within 2 years (31 versus 10 months, P=0.01), but this was regardless of whether they underwent lung resection or not (17). On the contrary, another series identified patients with 1–3 nodules, smaller than 3 cm and with negative local (abdominal) nodal metastases to be optimal candidates for lung resection (18).

Purely surgical series are limited in number

In 2001, a median survival of 26 months after lung resection for uterine body cancer was reported by Anderson, rising up to 46 months if the histology was adenocarcinoma. In the same series, a median survival of 36 months was seen if the tumour was instead originating from the cervix (13).

In 2004, 7,748 patients with stage IB or II cervical cancer who underwent curative initial treatment in 22 hospitals, were reviewed by Yamamoto and colleagues. Twenty-nine (0.37%) of these underwent subsequent resection for non-synchronous lung metastases. The results were quite polarised between patients who had less or more than 3 metastases (5-year survival of 42% *vs.* 0% respectively) and patients who had squamous versus non-squamous histology (5-year survival of 47% and 0% respectively) (10).

In the largest series published in 2004, 133 patients were reviewed from the Registry of the Metastatic Lung Tumour Study Group of Japan. In the whole cohort, 38 patients underwent bilateral metastasectomy (single-stage or two-stage), while other 12 patients underwent more than one and up to four repeated metastasectomies. Of note, this study included 8 patients (6%) with evidence of extrapulmonary metastatic disease. Overall 5- and 10-year survival was 54.6% and 44.9% respectively. Breaking down by histology, choriocarcinoma held the best 5-year survival (86%), followed by endometrial adenocarcinoma (76%), endometrial squamous cell carcinoma (47%), both

adenocarcinoma and squamous cell carcinoma of the cervix (40%) and leiomyosarcoma (38%). Uterine body tumours seemed therefore to fare better than cervical cancers, largely dependent though on specific histology. Statistically significant negative prognostic factors were cervical location of primary tumour, and a disease-free interval (DFI) from primary tumour resection of less than 12 months (59.8% *vs.* 36.8%). The difference was even more striking after excluding a minor proportion (n=6) with synchronous metastases (59.8% *vs.* 17.1%). However, 5-year survival of patients with shorter DFI but only one metastasis was 48%, and in fact equally significant factors negatively affecting survival were number of metastases >4 and tumour size >3 cm.

About a third of the patients underwent mediastinal lymphadenectomy, 34% showing pathologically positive lymph nodes. Although they seemed to have a worse survival than those with negative nodes, no difference was found with those not undergoing lymphadenectomy (5).

In another large series published by the *Mayo Clinic* in 2006, 70 patients were reviewed with a median DFI of 24 months after primary gynaecological procedure; 7% had an incomplete lung resection. Overall 5- and 10-year survival was 46.8% and 34.3% respectively. However, median DFI after metastasectomy was only 8 months, with a 3-year disease-free survival of only 14.3%. Seventy-eight percent of patients eventually developed a recurrence, in about half of the cases involving again the lung. In almost all of these cases, a policy of repeated metastasectomy was adopted by this group. Although cervix represented only 10% of the total population, this was found again to be a negative predictive factor together with a DFI of less than 24 months. A total of 35 patients (50%) died, while 35 still were still alive after a median follow up of 36 months (19).

In a smaller Spanish series, 27 cases were analysed with a very long median disease free interval between diagnosis and metastasectomy of 58 months. Median survival after metastasectomy was 94 months with a 5-year survival of 84% (again largely better for endometrial than for cervical or sarcoma origin, 100% and 60% respectively) (7). Beyond the sensational results, these figures are however far from being effective supporting evidence in favour of metastasectomy, as they rather seem to point out quite eloquently in this case how the impact of selection bias can stretch the actual numbers.

In a more recent comparative study by Adachi *et al.*, data for 37 patients with isolated lung metastases were retrospectively reviewed. A group of 23 patients who received lung resection and chemotherapy was identified and compared to a group of 14 patients who received non-surgical treatment only due to inoperable mass or chemoresistant nodules. This series only included epithelial tumours, including 5 of ovarian origin. Five-year survival, calculated from time of diagnosis, was 81.7% in the surgical group versus 49.5% in the non-surgical, although the difference was not statistically significant. Eight-year survival was again 81.7% versus 24% respectively. Similarly to previous studies, operated cervical cancer metastases seemed to do slightly worse (5-year survival 61%) compared to endometrial (100%). These survival figures are largely higher than what reported in other studies, which is probably in keeping with the restrictive exclusion criteria such as number of nodules >3 or synchronous metastases, already known to impact on survival.

Recurrence-free interval greater than 2 years was 100% in the surgical group versus 41.7% in the non-surgical. In the former, 5 of 6 lung re-recurrences who underwent further surgery were reported to be still alive at last follow up, although no specific intervals are provided (9).

In another recent series, 29 patients were reviewed. Despite the fact that histology was sarcoma in 41% of cases, that 41% had more than three nodules and 28% had metastases-related symptoms, 5-year for the whole cohort was still 48% with a median overall survival of 26 months. At multivariate and univariate analyses, presence of symptoms and number of metastases greater than 3 negatively affected survival, while DFI <12 months also did but not significantly (8).

The results of all these studies are briefly summarised in *Table 1*.

The case of uterine leiomyosarcomas

There is debate as to whether leiomyosarcomas of uterine origin and non-uterine origin may in fact be considered as similar entities and grouped together rather than per vicinal anatomy, with opposite evidence provided by different studies (20-22).

Uterine leiomyosarcomas are notoriously resistant to chemotherapy and prognosis is limited when lung metastases occur. This is reflected in a series from 2013, where in 192 patients with metastatic disease the presence of lung metastases was found to be a significantly negative prognostic factor. Those patients selected for and who survived extensive resection of the primary and lung metastasectomy had a more favourable outcome than the 5- and 10-year disease-specific survival of 30% and 15% respectively for the whole group. Notably all survivors

Table 1 Major series reporting outcomes and prognostic factors of surgical management

First author	Year	Patients (n)	5-year survival (%)	Median survival (months)	Negative prognostic factors	Positive prognostic factors	Comment
Levenback	1992	45	43	–	Bilateral lesions	–	Sarcoma histology only
Anderson	2001	25	–	26 [36–46]	Cervical origin; non-adenocarcinoma histology	–	–
Yamamoto	2004	29	0–47	–	>3 lesions	Non-squamous histology	Cervical cancer cases only
Anraku	2004	133	38–86	–	DFI <12 months; size >3 cm; >4 lesions	Endometrial origin; epithelial histology	Multicenter study
Clavero	2006	70	46.8	–	Cervical origin; DFI <24 months	–	Including 2 from ovarian cancer, 1 from vaginal cancer
Gonzales-Casaurran	2011	27	60–100	94	Cervical origin	–	Median DFI 58 months
Adachi	2015	23	82 [60–100]	–	Cervical origin	–	Comparison with chemotherapy only patients (n=14); excluded >3 nodules excluded synchronous metastases
Paik	2015	29	48	26	>3 lesions	–	–

DFI, disease-free interval.

at 10 years underwent complete surgical resection with disease limited to a single organ, most commonly the lung. Multiple lesions or dissemination to different organs were less likely to be resected, reflecting more aggressive biological behaviour of these sarcomas (11).

The case of benign metastasizing leiomyoma (BML)

BML is a rare disease and is defined as the growth of tissue from benign uterine leiomyoma in distant organs, most commonly the lungs. Previous history of benign uterine myoma is almost always present and nodules usually result histologically identical to the primary uterine tumour (23). Metastases to organs other than lung have been described, as well as miliary, giant, cystic and cavitary forms (24-27). Less than 100 cases have been reported in literature.

Lesions are usually slow-growing, although symptoms such as cough and chest pain are not rarely reported (28,29). At least one case of death from respiratory failure due to massive hilar metastases and a case of potentially fatal haemoptysis have been described (30,31). Cases of malignant transformation have also been described (32,33). Surgical removal should therefore be considered depending on patient fitness and on the chances of complete resectability. Unresectable disease may be treated with hormone therapy with usually excellent long-term control, although cases not responding to medical treatment have not rarely been described (34).

Cases of BML diagnosed in patients with previous history of malignant cancers (renal, bone sarcoma, ovarian) have been reported (35-38), and as prognosis for treated BML is very good compared to metastatic cancer, surgical biopsy should be considered when previous history of uterine myoma is also present, justifying in this case even a very aggressive removal of all lesions (39).

Conclusions

The treatment of metastatic uterine cancer with lung metastasectomy remains controversial. The evidence for surgery is limited to highly selected cases with the best prognosis (40). Favourable prognostic factors include a longer DFI and a limited number of lung lesions that

are completely resectable. However, the proof that these patients would have done as well without surgery is lacking and in this rare disease a randomised controlled trial seems unlikely. The question remains if "doing the patient no harm" is a sufficient indication for an operation. Metastasectomy may be considered only with the patient fully understanding the doubts that this practice inevitably implies (41).

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Footnote

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