Surgical management of lung metastases

Management of pulmonary metastases has evolved considerably over the last few decades but is still controversial. The surgical management of lung metastases is outlined, discussing the preoperative management, indications for surgery, the surgical approach and outcomes according to the primary histology.

Recognition of pulmonary metastases from an extrathoracic primary tumour is important from a clinical and psychological point of view. The therapeutic goal immediately changes from living without evidence of disease to living with systemic disease. Many primary tumours metastasize to specific target organs. The first reported pulmonary metastasectomy consisted of the removal of a single renal cell deposit in 1930, and the patient lived for two more decades (Barney and Churchill, 1939). The development of systemic adjuvant chemotherapy, with its promise of increased survival, sparked a renewed interest in this surgical approach in the attempt to achieve cure.

However, the role of surgical resection of metastatic disease is not universally accepted. To date, no randomized trial has been constructed to establish a survival advantage or otherwise of pulmonary metastasectomy. The multitude of variables that would have to be included in the eligibility criteria (e.g. number of metastases, cell type, disease-free interval, cardiorespiratory reserve) makes it unlikely that such a randomized trial will be ever performed. Treasure and colleagues (2012) are currently leading a UK-wide project to assess the effectiveness of pulmonary metastasectomy in colorectal cancer. To the best of the authors' knowledge this is the only attempt to perform a randomized controlled trial in this field.

It is generally accepted that patients who benefit the most from surgical resection have completely resectable disease, a long disease-free interval and control of the primary tumour. Although many articles, mostly case series of varying sizes, claim a survival advantage, these patients may live longer with their disease even without surgical resection. Most articles do not report the total number of patients referred with pulmonary metastasis and only consider a highly selected group, making selection bias extremely likely, so it is not possible to infer any advantage. For example, patients with dozens of metastases or rapid recurrence after a previous pulmonary metastasectomy or primary resection are not usually considered for surgery, likewise a very elderly patient with a slow-growing metastasis that would require pneumonectomy for resection might be better treated in other ways.

In spite of these caveats, surgical resection of oligometastatic disease has become a widely accepted treatment in a highly selected subgroup of patients (Pastorino et al, 1997). However, opinions vary widely regarding the utility of surgical resection in treating multiple metastases, lung and lymph node metastases, or repeat metastases after a previous pulmonary metastasectomy. There is also discordance about the need for lung palpation and the need for mediastinal staging. This article explores each of these topics and provides the best evidence to date. It also examines current indications for pulmonary metastasectomy, outcomes of surgery and prognostic indicators by cell type where data are available.

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Is imaging enough to detect all metastasis or do we still need lung palpation?

Assessment of pulmonary lesions typically begins with a chest computed tomography scan. McCormack et al (1993) found that, despite the use of high resolution thin-section computed tomography scans, 20–25% of nodules were still not imaged, suggesting that intraoperative manual palpation should be performed. With the development of computed tomography technology, nodules as small as 1 mm can be detected, narrowing the disparity between computed tomography scanning and manual palpation. Positron emission tomography scans are frequently performed on patients with epithelial-based primary tumours and melanoma. Mayerhoefer and colleagues (2012) showed that the larger is the lesion, the more sensitive the positron emission tomography results, ranging from 7.9% sensitivity for nodules between 4 and

5 mm to 100% sensitivity for nodules of 12 mm or more. The authors believe that modern imaging reviewed by an experienced chest radiologist is enough to detect even very small lesions, so lung palpation is unlikely to provide any extra benefit. In case of particularly small nodules, perioperative or intraoperative localization is advantageous (Bertolaccini et al, 2015).

Is invasive mediastinal staging necessary?

Mediastinal and hilar lymph nodes should also be evaluated on preoperative imaging. Lymph node involvement is an important negative prognostic factor in patients undergoing metastasectomy regardless of histology (Hamaji et al, 2012). For this reason, patients with mediastinal adenopathy may benefit from surgical staging by mediastinoscopy or endobronchial ultrasound before surgical metastasectomy in order for the patient to give fully informed consent. Although the presence of hilar or mediastinal lymph node involvement is a negative prognostic indicator, the presence of lymph node metastasis is not an absolute contraindication to metastasectomy (Murthy et al, 2005).

Current indications for pulmonary metastasectomy

The criteria for pulmonary metastasectomy were originally described 6 decades ago by Ehrenhaft et al (1958):

1. Candidates should be of appropriate risk for surgical intervention
2. The primary malignancy should be controllable
3. There should not be evidence of metastatic disease in any other part of the body
4. Imaging should show only metastases to one lung.

With anaesthetic, surgical, radiological and clinical care advances some of these criteria have been expanded. Nowadays the criteria include:

1. **The primary malignancy should be controlled or controllable**
   It is imperative that the site of primary malignancy is thoroughly evaluated. If the primary site is still present when metastases are discovered, this should be resected before metastasectomy.
2. **There is no extrathoracic metastasis that is not controlled or controllable**
   In almost all cases extrathoracic metastases are a contraindication for pulmonary metastasectomy performed with radical intent. The exception is patients with limited resectable hepatic metastases from colon cancer and pulmonary metastases.
3. **All of the tumour must be resectable, with adequate remaining pulmonary reserve**
   For patients with multiple metastases, there is no consensus as to how many lesions is too many. If the lesions can be completely excised allowing adequate remaining function, then resection can be pursued even if the lesions are numerous, bilateral or if an anatomical resection is required.
4. **There are no alternative medical treatment options with lower morbidity**
   No medical option has a proven survival advantage over pulmonary metastasectomy for most tumour histologies. Exceptions are patients with non-seminatous germ tumours and potentially those with breast cancer. Paradoxically, doing nothing might also be a treatment option since there is no proof that surgery may increase survival.

Open surgical approach for pulmonary metastasectomy

Two main principles direct the surgical approach for resection of pulmonary metastases: complete resection of malignancy and maximal sparing of normal lung tissue. Complete resection is not only the goal but also an important predictor of survival in nearly all reported series. For peripheral nodules a wedge resection is required, while for deeper nodules segmentectomy may be the resection of choice. Mortality rates of pulmonary metastasectomy do not differ from those of resection for lung cancer and range between 0.6% and 2% (Pastorino et al, 1997).

The choice of incision for unilateral disease is somewhat controversial. Posterolateral thoracotomy with muscle-sparing technique has been described as the most common approach to pulmonary metastasectomy. Median sternotomy has the advantage of simultaneous examination of both lungs, with identification of contralateral occult disease. Its disadvantage is the poor exposure of the posterior costovertebral angle and the left lower lobe. Bilateral anterior thoracotomy (clamshell incision) provides excellent exposure of both lung fields but requires transection of both mammary arteries and is often complicated by prolonged postoperative pain. Known bilateral lesions are simultaneously resected with median sternotomy or a clamshell incision, or sequentially managed with axillary thoracotomy.

Regardless of the surgical incision many techniques have been proposed as alternatives to the stapled wedge resection or segmentectomy to save as much surrounding lung as possible and reduce trauma to patients with low cardiopulmonary reserve. These include:

Cautery resection

Deep-seated lesions or nodules located on the broad surface of the lung may be excised by coring them out of the parenchyma using cautery (Cooper et al, 1986). The precision cautery dissection technique requires the lung to be inflated, so this cannot easily be performed by video-assisted thoracic surgery.

Laser resection

Laser resection has three major advantages: it permits excision of deep-seated lesions, there is minimal deformity or damage to the adjacent lung tissue and if a lesion is located near a major bronchus or vessel, the lesion can be

safely removed with no injury to these structures. A major disadvantage is that this technique is tedious and time consuming (Kodama et al, 1991).

Ligasure system and harmonic scalpel

Both techniques produce minimal smoke and reduce lateral spreading of heat which allows surgery near vulnerable structures, so they can both be used safely via a video-assisted thoracic surgery approach (Eichfield et al, 2000).

Video-assisted thoracic surgery approach for pulmonary metastasectomy

Minimally invasive surgical techniques (video-assisted thoracic surgery) were introduced into thoracic surgical practice in the mid-1990s and applied to pulmonary metastasectomy.

With the widespread acceptance of this surgical approach for the treatment of primary lung conditions, many surgeons have challenged the need for open approaches to pulmonary metastasectomy. Video-assisted thoracic surgery minimizes the immunological impact of surgery with reduced levels of proinflammatory cytokines and measurably increased numbers of endogenous antitumour natural killer cells compared with thoracotomy (Migliore et al, 2015). Ensuring speedy recovery and minimizing systemic insult is a priority in patients with metastatic disease, as surgery will frequently be coupled with systemic therapy and delays may result from prolonged hospitalization and deconditioning. The lung is the most common site of relapse after pulmonary metastasectomy for both epithelial cancers and sarcoma. Several studies (Temple and Brennan, 2002; Monteiro et al, 2004) demonstrated that repeat pulmonary metastasectomy can re-establish control providing survival benefit. Therefore, given the likelihood of recurrence, the decreased formation of adhesions and potentially easier repeat operation after video-assisted thoracic surgery metastasectomy, a minimally invasive approach may be preferred.

The ability to successfully perform repeat metastasectomy questions the benefit of bimanual palpation to identify lesions below the detection threshold of computed tomography as these lesions can be treated on subsequent operation once detected on follow-up imaging. There are concerns that a thoracoscopic approach leads to missed lesions at metastasectomy and only with the open approach can every nodule be found and removed. Data from Brigham and Women's Hospital (Jaklitsch et al, 2001) suggest that leaving behind nodules that fall below the size threshold may not be as clinically significant as once assumed. Taken together, data suggest several benefits to thoracoscopic pulmonary metastasectomy.

Lymph node dissection during pulmonary metastasectomy

Systematic mediastinal lymphadenectomy or sampling is routinely performed for primary neoplasm of the lung, including adenocarcinoma, squamous cell carcinoma and neuroendocrine tumours. Despite a paucity of randomized clinical trial data, it is now generally accepted that overall survival for many tumour types is improved with resection of limited metastases in carefully selected patients (Pastorino et al, 1997). However, controversy exists surrounding the need for assessment of mediastinal lymph nodes during pulmonary metastasectomy. Given the current understanding of tumour biology, it is assumed that metastases to thoracic lymph nodes would convey a worse prognosis. No randomized trials exist but retrospective studies suggest a worse prognosis for patients with lymph node metastases across many different tumour types (*Table 1*).

Table 1. Five-year survival with or without lymph node metastases at the time of pulmonary metastasectomy

Reference	Histology	Negative nodes: 5-year survival	Positive nodes: 5-year survival	*P* value
Seebacher et al (2015)	Different primary carcinomas	30.2%	25%	0.1
Renaud et al (2014)	Renal cell	71%	37%	0.003
Bölükbas et al (2014)	Colorectal	59%	23%	0.03
Hamaji et al (2012)	Colorectal	49.3%	20%	0.047
Ercan et al (2004)	Carcinomas	68%	38% (3y)	0.001
Pfannschmidt et al (2003)	Colorectal	38.7%	0%	0.03
Kamiyoshihara et al (1998)	Carcinomas	24.7%	0%	NS
Pfannschmidt et al (2002)	Renal cell	42%	24%	0.016
Inoue et al (2000)	Colorectal	49.5%	14.3%	0.003
Saito et al (2002)	Colorectal	48.5% (4y)	6.2% (4y)	0.001
Okumura et al (1996)	Colorectal	50%	6.7%	0.0004
Piltz et al (2002)	Renal cell	48%	0%	0.001

Considering the wide spectrum of survival rates based on lymph node involvement more thorough preoperative assessment of patients before metastasectomy was proposed (García-Yuste et al, 2010), excluding patients with thoracic lymph node involvement. Menon et al (2007) performed mediastinoscopy for mediastinal lymph node assessment. Although any potential effect of thoracic mediastinal lymph node dissection is unclear, pathological assessment of mediastinal and hilar nodes is necessary to assess disease burden given the impact on prognosis. The primary benefit of pulmonary metastasectomy is to allow proper stratification for potential treatment strategies. For example, patients with completely resected disease and no lymph node metastases can receive long-term follow up while patients with positive lymph nodes may be candidates for systemic therapy.

Ablative approach for pulmonary metastases

Surgery is the standard approach to managing clinically evident metastases in medically fit patients with a minimal burden of systemic disease (Pastorino et al, 1997). However, a significant number of patients are not ideal candidates for surgical metastasectomy, whether they have surgically unresectable tumours, medical comorbidities, short disease-free interval or extensive extrathoracic disease. Non-invasive or minimally invasive approaches such as stereotactic body radiation therapy, thermal ablation via radiofrequency and microwave ablation can be used to manage patients who are not candidates for standard surgery.

Stereotactic body radiation therapy

Stereotactic body radiation therapy is a form of high precision radiotherapy delivery characterized by the use of an extremely high biological dose of radiation (equivalent to 100 Gy or more) usually delivered in three treatment fractions within a 2-week period. A reproducible immobilization system is used to avoid patient movement during treatment sessions.

With stereotactic body radiation therapy tissue surrounding the tumour receives a minimal radiation dose, so reported lung toxicity is usually a minor problem (Baumann et al, 2008). Ablative radiation has demonstrated efficacy for pulmonary metastases of many different histologies, including sarcoma (Dhakal et al, 2012), renal cell carcinoma (Alexander and Haight, 1947), melanoma, and colorectal (Hoyer et al, 2006) and gynaecological malignancies. Although these histologies have historically been considered 'radioresistant', no tumours have been shown to be resistant to ablative radiotherapy. Some series suggest that certain histologies are associated with worse tumour control and survival (Takeda et al, 2011) while others have not found histology to be a determinant of tumour control (McCammon et al, 2009). Overall, across many studies (Yamamoto et al, 2014; Davis et al, 2015), metastasis control is 70–90% 2 years after treatment, which is comparable to pulmonary metastasectomy.

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Radiofrequency ablation

Radiofrequency ablation uses alternating electrical current of 400–500 kHz delivered to the target tissue via probe. Using temperatures above 60°C it leads to coagulative necrosis with a treatment time of 12–15 minutes. Similar to ablative radiation, the tumour location must be considered in planning the procedure as the proximity to blood vessels (that can serve as a heat sink) or the location of the tumour itself may require tailored radiofrequency ablation settings (Iyengar et al, 2014). Most commonly electrodes are placed through a single needle either with computed tomography guidance (with conscious sedation) or, for more central lesions, through a small thoracotomy under general anaesthesia.

In terms of outcome, follow-up computed tomography and selective positron emission tomography imaging of primary lung tumours managed via radiofrequency ablation revealed an incomplete ablation rate approaching 40% (Ambrogi et al, 2011). Prospective studies with a median follow up of 24 months (range 18–35 months) have found an average survival at 2 years, 3 years and 5 years respectively of 57%, 56% (Petre et al, 2013; Koelblinger et al, 2014) and 51% (de Baère et al, 2015). The studies showed similar rates of pneumothorax – from 25.5–39% of the treated population. There are no randomized studies comparing radiofrequency ablation, surgical resection and/or ablative radiotherapy.

Microwave ablation

Similar to radiofrequency ablation, microwave ablation causes tumour destruction via hyperthermia. Microwave ablation uses higher frequencies of 915 MHz to 2.45 GHz, inducing rapid heating of tumours in about 2–5 minutes (faster than radiofrequency ablation; Smith and Jennings, 2015). Outcomes of microwave ablation are less robust than those of radiofrequency ablation as it is newer, although given the mechanism of action similar outcomes may be expected (Vogl et al, 2011).

The role of lung metastasectomy in patients with multi-site metastatic cancer

Occurrence of tumours at multiple sites is a hallmark of malignant cancers and contributes to the high mortality. The formation of multi-site cancers has conventionally been regarded as a result of haematogenous spread of a primary tumour to secondary sites. Although oligometastases are a recent vogue in lung cancer, the concept was originally described by Hellman and Weichselbaum in 1995. They theorised that metastases

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occurred as a 'metastatic progression' from localized disease to widespread systemic disease.

Colorectal cancer is one of the most common cancers. About half of patients will develop hepatic metastases and 20% will develop pulmonary metastases during the course of their disease (Liu et al, 2003). With isolated hepatic or pulmonary metastases, metastasectomy is an established treatment for resectable metastasis with a 58% 5-year survival rate in patient with hepatic metastases (Shah et al, 2007) and up to 56% 5-year survival rate in patients with pulmonary metastases (Hornbeck et al, 2011; Zabaleta et al, 2011). Encouraged by these results many centres offer pulmonary and hepatic metastasectomy to selected patients with synchronous metastases. However, such an aggressive approach is controversial (Kneuertz et al, 2015) and the role of surgery in the management of patients who have both liver and lung metastases is not well defined.

Marudanayagam et al (2009) demonstrated good long-term survival after combined liver and lung resections of metastases from colorectal cancer with overall 5-year survival of 53%. Overall survival was significantly better in patients where the pulmonary metastases developed more than 6 months after liver resection (metachronous group) than in those who developed lung metastasis within 6 months of liver resection (synchronous group). Other factors affect the outcome after resection such as age, number of metastases, disease-free interval, carcinoembryonic antigen level before metastasectomy, mediastinal lymph node involvement and bilateral or multiple lung metastases (Miller et al, 2007). An aggressive surgical approach and multidisciplinary decision making for the management of sequential liver and lung resection for metastases from colorectal cancer is associated with satisfactory long-term survival in selected patients.

Cell types and outcomes

Retrospective series on lung metastasectomy report an overall 5-year survival rate of 30–40% (Pastorino et al, 1997). Data from the International Registry of Lung Metastases showed that after complete resection in patients with a disease-free interval of 0–11 months after control of the primary tumour 5-year survival was 33% and for those with a disease-free interval greater than 36 months 5-year survival was 45% (Pastorino et al, 1997). The literature on cell type-specific experience with pulmonary metastasectomy is growing:

Colorectal cancer

No standard chemotherapy significantly improves survival in patients with colorectal metastases to the lung. The overall 5- and 10-year survival rates are 35–45% and 20–30% respectively (Girard et al, 1996; Okumura et al, 1996). Number of pulmonary metastases, carcinoembryonic antigen level and regional lymph node involvement are the main prognostic factors.

Renal cell cancer

Lung metastasectomy for renal cell cancer provides a 5-year overall survival between 20% and 50% (Murthy et al, 2005). According to Murthy et al (2005), the strongest risk factor for time-related mortality is incomplete resection. Other risk factors included larger nodule size, increasing number of involved lymph nodes. For completely resected patients, shorter disease-free interval is a risk factor.

Germ cell cancers

Management of pulmonary metastases has dramatically changed with the advent of effective chemotherapy which is now the first line of treatment. Surgical resection is limited to adjuvant therapy for patients who have a complete serological response to chemotherapy. Pulmonary resection is used both diagnostically and therapeutically to determine whether active microscopic disease is still present after normalization of serum markers and removal of residual tumour. The 5-year survival for these patients is 68–82% (Liu et al, 1999).

Sarcoma

Sarcomas are a heterogeneous group with over 50 different histological subtypes. The most common histological patterns that metastasize to the lung are malignant fibrous histiocytoma, synovial sarcoma and leiomyosarcoma. Isolated pulmonary metastases occur in 23–54% of patients with sarcoma (Putnam et al, 1993).

Breast cancer

Dramatic improvements in chemotherapy, hormone therapy and molecular targeting therapy have made pulmonary resection less common. Retrospective data sets have shown that metastasectomy for breast cancer can provide equal or better long-term results than chemotherapy and hormone therapy with 31–50% 5-year survival (Friedel et al, 2002). It is better to use excisional biopsy to manage solitary pulmonary nodules in patients with a history of breast cancer as the tissue diagnosis may be compatible with the lung primary. Medical treatment should be the first line for multiple metastases.

Gynaecological cancers

Good results have been reported for lung metastasectomy for uterine cancers, with 5-year survival of 47% for squamous cell subtype, 33–40% for cervical adenocarcinoma, 76% for endometrial carcinoma and 86% for choriocarcinoma (Anraku et al, 2004).

Melanoma

Although melanoma that metastasizes to a distant site is generally associated with a median survival of only 6–8 months, certain metastatic sites including the lung may carry a better prognosis than others, with 1-year, 3-year and 5-year survival rates of 77%, 37% and 27% for surgical patients compared with 32%, 7% and 3% for non-surgical patients (Tafra et al, 1995).

Head and neck cancers

Postoperative survival after resection of lung metastases varies by cell type – 5-year survival is 34% for squamous cell carcinoma, 64% for glandular tumours and 84% for adenoid cystic carcinomas (Liu et al, 1999).

Conclusions

The role of surgical resection of metastatic disease in the lung is still not universally accepted, with no randomized trial constructed to establish a survival advantage or otherwise.

With the development of more effective systemic therapy for metastatic disease, it is likely that more patients will be considered candidates for management of pulmonary metastases. In order to achieve the best outcomes a complete understanding of the biology, preoperative assessment and options for treatment is essential. **BJHM**

Conflict of interest: none.

KEY POINTS

- Preoperative evaluation for lung metastasectomy patients has two purposes: to determine a patient's fitness for surgery and to determine whether the metastases are resectable.
- Both video-assisted thoracic surgical techniques and open thoracotomy are accepted as surgical approaches for lung metastasectomy.
- Regardless of the surgical incision many techniques have been proposed as alternatives to the stapled wedge resection or segmentectomy to save as much surrounding lung as possible and reduce trauma to patients with low cardiopulmonary reserve.
- Controversy exists surrounding the need for mediastinal lymph node assessment during pulmonary metastasectomy. No randomized trials have been published. Retrospective studies suggest a worse prognosis for patients with lymph node metastases across many different tumour types.

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