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Local recurrence after laser-assisted pulmonary metastasectomy

Lokalrezedivrate nach laserunterstützter pulmonaler Metastasektomie

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Abstract

Objective

Indications for surgery and resection techniques for pulmonary metastasectomy (PM) are controversial. However, a recent consensus favoured pulmonary parenchyma-sparing resection as it preserves functionally healthy lung tissue, although this can increase the risk of local recurrence at the surgical margin. Laser-assisted PM (LPM) is a relatively recent innovation that is particularly useful when applied for multiple metastatic pulmonary nodules. This study investigated the rate of local recurrence after LPM and evaluated the influence of various clinical and pathological factors.

Methods

Retrospectively, a total of 280 metastatic nodules with different histopathological entities in 101 patients were studied after LPM between 2010 and 2018. All nodules were resected using a diode-pumped neodymium-yttrium aluminium garnet (Nd:YAG) 1,318-nm laser maintaining a safety margin of 5 mm. The patients were observed postoperatively on average for 44 ± 17 months. Cox regression model was used to investigate the risk of local recurrence per nodule.

Results

Local recurrence at the surgical margin following LPM was found in 7 of the 101 patients (6.93%) and 9 nodules out of 280 nodules (3.21%). Local recurrence at the surgical margin occurred postoperatively after 20 ± 8.5 months. Two nodule features were associated with a significantly increased risk of local recurrence at the surgical margin: incomplete resection (p = <0.01) and the size of the nodule (p = <0.01). The histology of the primary disease showed no impact on local recurrence. The 3- and 5-year survival rates were 84% and 49%, respectively. Local recurrence had no significant influence on survival (p = 0.9).

Conclusion

Following LPM, the rate of local recurrence was low. This was influenced by the size of the metastatic nodules and the completeness of the resection. A safety margin of 5 mm seemed to be sufficient.

Zusammenfassung

Ziel und Hintergrund

Die pulmonale Metastasektomie (PM) ist eine häufig durchgeführte Operation. Allerdings ist der Evidenz ihrer Wirksamkeit auf Register-Daten und chirurgische retrospektive Serien basiert. Trotz der fehlenden randomisierten Studien deuten mehrere Fallberichte und kleine Serien darauf hin, dass eine Resektion das Überleben verlängert und dass bei einigen Patienten mit isolierter Lungenbeteiligung ein langfristiges rezidivfreies Überleben (oder sogar eine Heilung) möglich ist. PM kann mit verschiedenen chirurgischen Techniken durchgeführt werden. Beim Nd:YAG-Laser ist eine vollständige Resektion in einer signifikanten höheren Anzahl von Metastasen möglich. Bezüglich eines akzeptablen Sicherheitsabstandes zur Vermeidung von Lokalrezidiven, gibt es jedoch bisher keine Daten.

Methoden

Retrospektiv wurde von 2010 bis 2018 insgesamt 280 metastasierte Herde unterschiedlicher Primarien in 101 Patienten nach laserunterstützter Lungenmetastasektomie untersucht. Alle Herde wurden mit einem diodengepumpten Nd:YAG 1.318 nm Laser mit einem Sicherheitsabstand von 5 mm reseziert. Die eingeschlossenen Patienten wurden durchschnittlich 44 ±17 Monate nach der Operation beobachtet. Das CoxRegressionsmodell wurde verwendet, um das Risiko eines Lokalrezidivs pro Herd und pro Patient zu untersuchen.

Ergebnisse

Bei 9 aus 280 Herde (3,21%) und bei 7 von 101 Patienten (6,93%) wurde ein lokales Rezidiv nach laserunterstützter Lungenmetastasektomie festgestellt. Ein lokales Rezidiv trat durchschnittlich 20 ±8,5 Monate nach der Operation auf. Zwei Merkmale, waren mit einem signifikant erhöhten Risiko eines Lokalrezidivs am Operationsrand verbunden: eine unvollständige Resektion (p=<0,01) und die Größe des Herdes (p=<0,01). Die Histologie der Primarius zeigte keinen Einfluss auf das Lokalrezidiv. Das Drei- und

Fünfjahresüberleben betrug 84% bzw. 49%. Das Antreten eines Lokalrezidivs hatte keinen signifikanten Einfluss auf das Überleben (p=0,9).

Schlussfolgerungen

Nach einer laserunterstützten Lungenmetastasektomie ist die Lokalrezidivrate niedrig. Dies wird durch die Größe des Herdes und die Vollständigkeit der Resektion beeinflusst. Ein Sicherheitsabstand von 5 mm scheint ausreichend zu sein.

Introduction

Background

Pulmonary metastasis is defined as a secondary malignant tumour of the lung or pleura originating from a different organ of the body [1]. The lung is one of the most common organs to have metastases from different primary malignancies. Autopsy reports demonstrate that up to 54% of patients diagnosed with cancer had pulmonary metastases [1]. Accordingly, pulmonary metastasectomy (PM) is the second most performed operation in thoracic surgery [2]. Compared to the abundant literature on primary lung cancer surgery, especially non-small cell lung cancer (NSCLC), evidence regarding a safe resection margin for PM is either lacking or unclear [3], [4]. Pulmonary metastases are usually resected as an atypical resection using stapling devices as a standard technique [2]. Laser-assisted pulmonary metastasectomy (LPM) is a relatively recent innovation that is especially useful when applied for multiple metastatic pulmonary nodules.

Historical note

The first description of a PM is believed to have been made in 1927 by Davis [5]. In 1939, Barney and Churchill performed a lobectomy for renal cancer metastasis [6]. Blalock described pneumonectomy as a treatment option for metastatic colon cancer in 1944 [7]. Alexander and Haight, having performed the first large series of metastasectomies in 1947, proposed the first set of criteria for surgery [8]. Since then, PM became a popular and widely accepted treatment modality for pulmonary metastases. The International Registry of Lung Metastases (IRLM) was established in 1990, and video-assisted thoracic surgery (VATS) thrived in the 2000s as a diagnostic and operative technique for different pulmonary diseases, including PM. In parallel, multiple studies were carried out using neodymium-yttrium aluminium garnet (Nd:YAG) 1,318-nm laser for pulmonary resections based on experience with 1,064-nm Nd:YAG lasers for endobronchial interventions [9]–[12]. Rolle et al. (2002) published

promising PM outcomes using a 1,318-nm Nd:YAG laser on a group of 100 patients [13].

Pathophysiology of metastases

The question of why certain tumours metastasise to certain organs has been studied for over a hundred years. In 1889, the English surgeon, Paget, concluded that certain tumour cells, which he called the ‘seed’, had a special affinity for the environment of certain organs, which he called the ‘soil’ [1]. Later, Ewing challenged this ‘seed and soil’ theory by proposing that metastases occur purely due to mechanical factors based on the anatomical structure of the host organ [1]. Advances in biomolecular, cellular and bioimaging techniques have elucidated that the metastatic process is complex and multistep. This process is known as the metastatic cascade [14]. Tumour cells have to directly or indirectly enter the circulatory system via the lymphatic system, so they need to survive in the bloodstream by avoiding the host’s defences until they can arrest in the destination organ, where they extravasate into the tissue. Here at the new site, they have to initiate and maintain growth.

Labelling cancer cells showed that within the first 24 hours after entering circulation, <0.1% of tumour cells were viable and <0.01% of these cells survived to produce metastases [15]. Such observations posed the question what does this metastatic cascade really represent. Is it just fortunate survival and growth of very few tumour cells or whether the primary tumour is becoming more malignant and stochastically spreading metastatic cells without modifying its genetic profile. Recent breakthroughs in gene expression profiling have shed light on the characteristic gene signatures of metastatic tumours [16]. Moreover, the presence of metastases in a variety of adenocarcinomas is predictable in laboratory experiments [17]; however, such studies in humans are yet to be performed. Nevertheless, identifying and understanding the steps of the metastatic cascade will provide insight into potential treatment options.

Diagnosis of pulmonary metastases

Metastatic nodules in the lungs are usually rounded and well circumscribed. They are found as an incidental finding or, as in the majority of cases, detected by routine chest computed tomography (CT) as part of a follow-up for a primary malignancy (Fig. 1) [1], [18]–[20]. Hilar or mediastinal lymphadenopathy may indicate lymph node metastases. These nodules occasionally present elements consistent with the site of the primary disease, such as calcification in metastatic osteosarcoma [1]. CT scans have replaced plain radiographs as the standard screening modality. High-resolution CT (HRCT) can detect lung nodules as small as 1 mm [21]. HRCT and conventional CT have a 100% sensitivity for 10 mm and larger nodules [22], but this sensitivity drops as the nodule size decreases [23]. The sensitivity of positron emission tomography (PET) scans varies significantly depending on the primary malignancy. For example, squamous cell carcinoma has a sensitivity of 93% whereas sarcoma has a sensitivity of only 44% [20], [24].

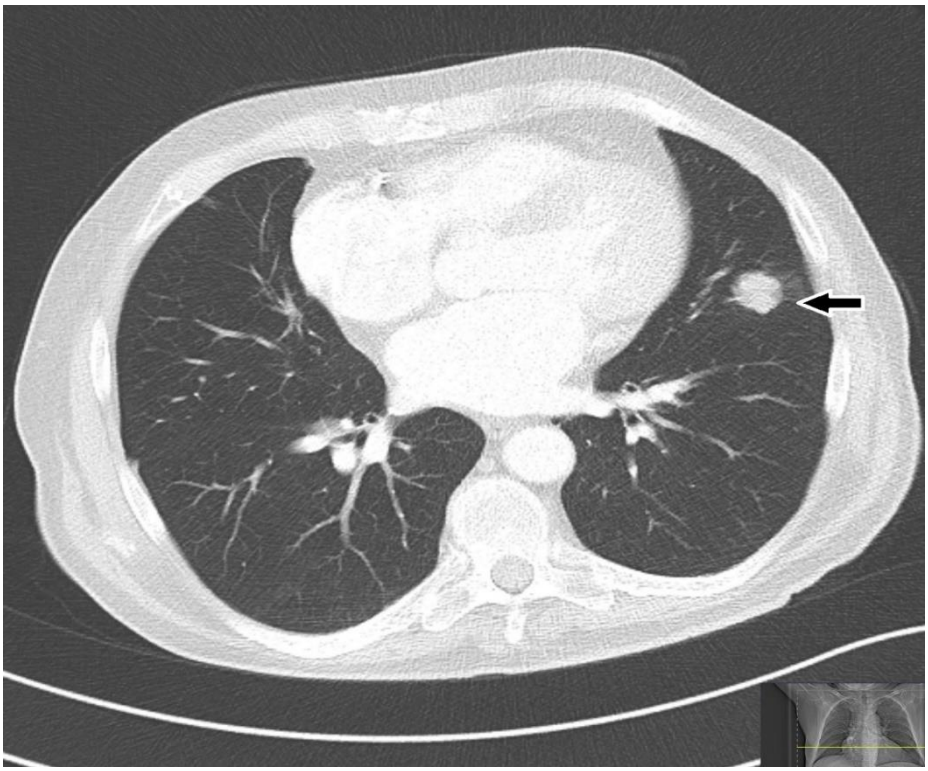

FIGURE 1. Chest computed tomography scan demonstrating a well-rounded, smooth-surfaced pulmonary metastasis in the left upper lobe (arrow).

Patients with pulmonary metastases usually have no symptoms that confirm its incidental finding, with the minority presenting with cough or haemoptysis if the metastases have invaded a central airway. Shortness of breath might be the case if an airway is blocked, causing atelectasis or, in cases of advanced disease, producing pleural effusion. Chest wall or pleura invasion can make pain the presenting symptom [18], [19].

General management of pulmonary metastases

Per definition and in terms of TNM staging, having distant metastases from a primary malignancy reflects an advanced stage of the disease that requires systemic therapy. Systemic therapy is used as the mainstay of therapy for patients with widespread metastatic disease. Sensitivity to chemotherapy is a major determinant of the treatment modality. This ranges from primary chemotherapy, where surgery is only for residual nodules, to mainly surgery for chemotherapy-resistant tumours [1][25]–[27]. In different histologies, chemotherapy is used adjunct to surgery [1], [27]–[29]. Chemotherapy can be also given as isolated perfusion of the lung, which allows selective delivery of high doses of chemotherapy with fewer systemic adverse effects. This is still experimental and quite invasive as it requires an extracorporeal circuit [30]. The impact of the new emerging und rapidly developing immunotherapy is highly anticipated. Compared to the systemic therapy, other treatment modalities target only the metastatic nodules. Local control of pulmonary metastases is mainly achieved by the following:

- Radiofrequency ablation (RFA)

The principle of RFA is to cause tumour necrosis by creating frictional heat in the tissue using an alternating current. Metastatic nodules should be peripheral, small and not abut mediastinal structures, which can act as heat buffers [1], [31], [32]. The complications of RFA are mostly mild and self-limiting but can include pain, pneumothorax, fever, hemoptysis, pleural effusion and

abscess formation [31]. Studies have reported significant differences in response and survival for nodules >3 cm vs those <3 cm [31], [32]. Complete ablation after RFA is seen in <40% of nodules [33]. Two-year survival after RFA for metastatic nodules of varying histology was about 68% [31]. These results are considered inferior to those after surgical resection. Therefore, RFA should be used for medically unfit patients or for those who refuse surgery [1][27].

- Stereotactic body radiation therapy (SBRT)

SBRT is precisely targeted radiation, where a high dose of radiation is delivered to the target point (the tumour), aimed at tumour control while minimizing harmful effects on neighbouring healthy tissue. SBRT candidates should meet the same criteria as for RFA [1]. Complications, seen in around 5% of patients, are mostly pneumonitis (grade 2 or higher) and rib fractures [1], [34]. The limitations of SBRT are seen in tumours with larger diameters or when dealing with multiple nodules as attempting to minimize tissue toxicity is challenging. Data regarding SBRT for pulmonary metastases is scarce. A multi-institutional phase I/II trial showed a median survival of 19 months [34]. Similar to RFA, SBRT can be a good alternative for medically unfit patients or those who refuse surgery, but it is not a good primary modality for treatment [1], [27].

- Surgical resection: pulmonary metastasectomy (PM)

In 1947, Alexander and Haight set criteria for recruiting patients for PM surgery [8], and while their selection criteria have been modified over the years, its broad principles have been preserved [35], [36]. The current criteria for PM, as clearly presented by Kondo et al., is shown in (Table 1) [36].

Casiraghi et al. argued that improved surgical techniques and more effective systemic therapies, which expand the role of surgery, have made PM the standard therapy for properly selected patients [37]. With the appropriate selection of patients, 5-year survival rates, as reported to the IRLM, were 20%–40% in 1997 [38]. A more recent series reported a 5-year survival rate of 50%, demonstrating the potential of reaching a 64% 5-year survival rate [37], [39], [40].

Table 1. Current general criteria for pulmonary metastasectomy

• The patient's risk for surgery must be low
• The site of the primary malignancy is controlled
• No extrapulmonary metastases, or, if present, they can be controlled by surgery or any different treatment modality
• Pulmonary metastases are thought to be completely resectable

In the real-life practice of PM, different approaches (i.e. VATS, thoracotomy and sternotomy) and different surgical techniques are widely accepted and applied. Surgeons differentiate between risk and benefit measurements. Some tend to minimize surgical trauma and postoperative pain using minimally invasive techniques (i.e. VATS). Others favour open techniques, which allow bimanual palpation of the whole lung, to maximise the likelihood of detecting and resecting all nodules, especially those not seen by CT. As previously mentioned, the inability to completely resect all metastatic nodules is globally considered a contraindication to PM. Survival data indicate that complete resection of metastases is linked to better outcomes. According to the IRLM series, for example, the 5-year survival with complete vs incomplete resection was 36% vs 13% [38]. The resection of lung parenchyma in general, or metastatic nodules in this case, can be performed anatomically or non-anatomically (atypical) using different resection or energy devices. Anatomical resection is based on the anatomical fissures and segmental tree of the lung, including segmentectomies, lobectomies and pneumonectomies. Non-anatomical resection or atypical resection includes resecting lung parenchyma or lung nodules as a wedge or the enucleation of lung nodules irrespective of fissures and the segmental tree of the lung. Regardless of the approach used, aiming to preserve lung parenchyma, which directly means preserving pulmonary function, while performing PM is critically important [2], [27].

Achieving a complete resection, even at the microscopic level (R0 resection [41]), is the main tenet of PM. Consequently, this determines the extent of the resection [27]. Large or centrally located nodules usually require lobectomy, pneumonectomy is less indicated and should be avoided.

Segmentectomy, which can also be performed with VATS, plays an important role for nodules where wedge resection is technically impossible and lobectomy is not necessary [42]. According to Berry et al., segmentectomy accounts for 3%–23% of PM procedures, and they also reported lower mortality and morbidity rates than for lobectomy [43]. As most metastatic lung nodules are located in the periphery of the lung, they are usually resected non-anatomically [44]. This is easy and mostly performed using stapling devices, which is widely considered the standard technique [2]. Alternatively, nodule enucleation by electrocautery or laser can be used for PM. Compared to laser, the risk of bleeding, fistula and air leakage is increased after monopolar-cutter resection [45].

Nd:YAG LPM

Because the core selection criteria for PM have remained unchanged over the years, surgical techniques and advances have shown remarkable development and major breakthroughs. A global tendency towards non-anatomical resections was recently translated into a consensus that considers parenchyma-sparing resections the recommended gold standard [27]. New modalities, such as electrocautery, LigaSure and 1,318-nm Nd:YAG laser were introduced to serve this concept. In 1967, Minton et al. pioneered the use of the Nd:YAG laser in thoracic surgery in their experiment using a 1,064-nm Nd:YAG laser in a rabbit lung model [46]. Since then, further experiments have investigated different laser wavelengths. Rolle and his colleagues demonstrated in several publications the superiority of the 1,318-nm Nd:YAG laser compared to the 1,064-nm Nd:YAG laser for lung resection [10], [12], [47], [48]. In 2002, Rolle et al. published the outcomes of the first 100 PM patients' 1,318-nm Nd:YAG laser resections [13]. In their animal model, Kirschbaum et al. demonstrated lower risks of bleeding, fistula and air leakage after Nd:YAG laser resection compared to monopolar electrocautery [45].

Relatively few studies have reported results after LPM. A potential advantage of the Nd:YAG laser is its ability to resect a significantly higher number of pulmonary metastases with minor parenchymal loss [2]. The ability to resect more nodules even in a bilateral setting by LPM without a negative influence on survival has been presented by more than one study [49]–[51]. Moreover, the need to perform anatomical resections is significantly reduced [51]. In a review of published LPM studies, Macherey et al. summed a 0% mortality rate after LPM reported in 8 studies, where the morbidity rate ranged between 8.7% and 24.2%, while it was 1.2% in the largest collective of 328 patients [52]. Furthermore, LPM in a VATS-based approach was reported to be safe and doable [53], [54]. Although the unneglectable disadvantage of 1,318-nm Nd:YAG laser is its high cost, the cost could be recovered after approximately 300 surgical cases not using parenchymal staplers [55].

Local recurrence at the resection margin following PM

The shift from anatomical resections towards parenchyma-sparing resections is accompanied by a higher frequency of local recurrence at the surgical margin, which represents a significant downside (Fig. 2) [42], [56], [57]. Over the years, this has not been sufficiently addressed, and perhaps only recently, more detailed analysis has been on pulmonary metastases from colorectal origin [42], [56], [58]. This focus on colorectal origin has mainly arisen for two reasons: it is the most common pathological entity of pulmonary metastases and it has a higher local recurrence rate at the surgical margin than metastases from other malignancies [42], [56]. Local recurrence at the surgical margin reflects molecular-biological properties along the PM mechanical resection line. Tumour biology, nodule size, the number of undetected micrometastases (i.e. aerogenous spread with floating cancer cell clusters [ASFC]) and, most importantly, the completeness of the resection are all proven factors of significance [56], [57], [59]. However, this important histo-biological information is only available postoperatively after pathological examination [42].

In general, local recurrence at the surgical margin after PM is estimated to occur after 4%–31% of PMs [56], [59], [60]. In comparison, it has been suggested that local recurrence at the surgical margin after segmentectomy is lower than after wedge resection, although no comparative studies have been published [42], [61].

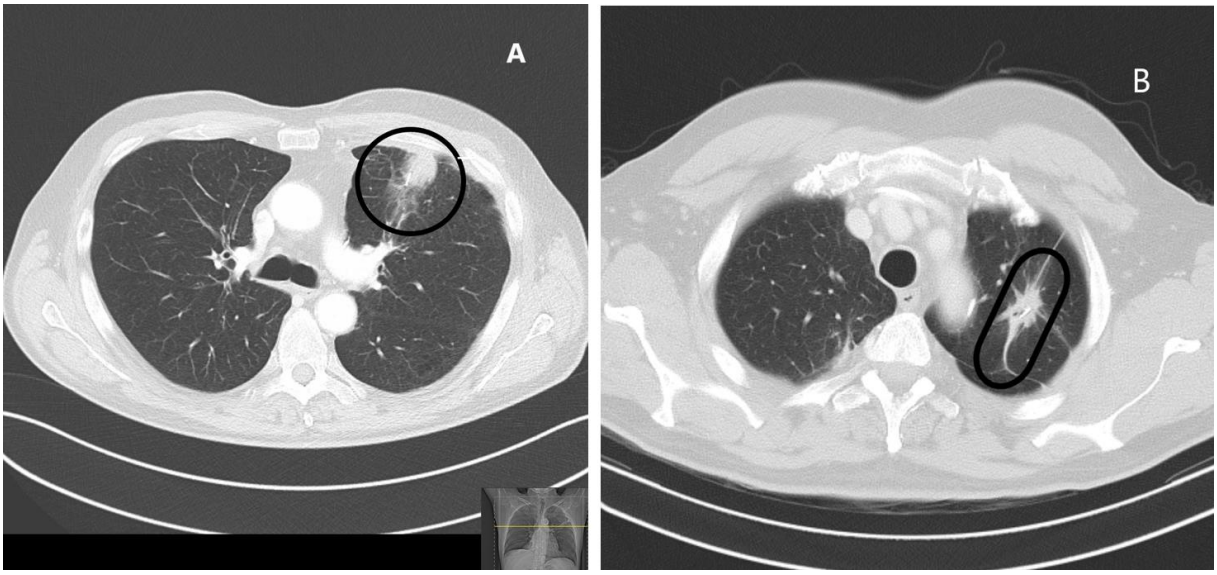

FIGURE 2. A) and B): Chest computed tomography scan demonstrating the radiological appearance of a local recurrence at the resection site after laser-assisted pulmonary metastasectomy. In both sections (circled), a new mass has emerged at the former resection site. A surgical metallic clip can be seen within the mass.

Objective and purpose

PM is the second most common surgical procedure in thoracic surgery, occupying 15%–50% of the thoracic surgery workload in Europe [2]. Yet, PM remains one of the most debatable topics in thoracic surgery. In 2008, after surveying its members, the European Society of Thoracic Surgeons (ESTS) reported a wide range of opinions and practices concerning timing, indications, surgical technique, appropriate extent and limitations of PM [62]. Nevertheless, in 2019, the american society of thoracic surgeons (STS) went on to publish expert recommendations regarding indications and surgical techniques: non-anatomical resection was recommended as the standard technique for PM [27].

This ongoing shift towards non-anatomical parenchyma-sparing resections raised the concern of an increased local recurrence rate at the surgical margin. This challenging problem has not been sufficiently addressed, and the mechanism of local recurrence and its determinant factors are only partially understood. The use of an Nd:YAG laser for PM causes vaporization and coagulation of lung tissue, which thereby increases the safety margin around resected nodules. Thus, the application of an Nd:YAG laser for PM could be the answer; that is, parenchyma-sparing PM with reduced risk of local recurrence at the surgical margin. Evidence for this is scarce in the literature, although Franzke et al.'s study reported a local recurrence rate of 0.8% after LPM, even though this was not the primary question of their research [63]. While not significantly lower than non-laser PM, Franzke et al observed a trend.

The current work aimed to

- evaluate local recurrence at the surgical margin after LPM,
- investigate the efficacy of the 5-mm safety margin applied in LPM, and
- identify the major risk factors for local recurrence after LPM.

Patients and methods

Patients

This retrospective study aimed to investigate local recurrence after LPM. Patients who underwent any operation with the code ‘laser-assisted pulmonary metastasectomy’ were identified using intraoperative coding and documentation. Between January 2010 and December 2018, 220 patients with different primary malignant diseases underwent ‘laser-assisted pulmonary metastasectomy’ at the department of thoracic and vascular surgery at the Löwenstein Lung Medical Centre, Löwenstein, Germany.

A retrospective analysis of these patients based on their medical and radiological records was performed. In all of these cases, the primary malignancy had been successfully controlled. Some patients had other non-pulmonary metastatic nodules that had been already controlled or were controllable. The indication for PM was individually set for each patient, and the same was applied for repeated PM for disease recurrence (new nodules), so these patients were also included. This study was approved by the ethical committee of the state medical association of Baden-Württemberg.

Study design, inclusion and exclusion criteria

The main outcome of this study was the local recurrence rate at the surgical margin. Secondary outcomes were to identify risk factors that influence local recurrence at the surgical margin and survival and local recurrence-free survival. Here, we studied and followed up patients and analysed the risk for local recurrence at the surgical margin per nodule resected. Follow-up was performed by CT of the chest at 3-, 6- and 12-month intervals. The follow-up was performed by either the surgical team in the outpatient clinic or the patient’s oncologist or pulmonologist. Postoperative follow-up imaging was reviewed for evidence of local recurrence at the surgical margin. Follow-up CTs were reviewed by a board-certified radiologist or the surgical team.

All patients who underwent LPM with pathologically confirmed metastatic nodules were included. Exclusion criteria were a pathologically malignant surgical margin (R1 or R2 [41]), re-operated nodules after local recurrence, explosive disease recurrence hindering follow-up of the resected nodules, no follow-up CT/data or a follow-up at <24 months (Fig. 3). In cases where intraoperative diversions from the plan had occurred, for example, conversion to segmentectomy or the use of monopolar cautery was necessary, nodules resected not using Nd:YAG laser were excluded from the study but not the whole patient.

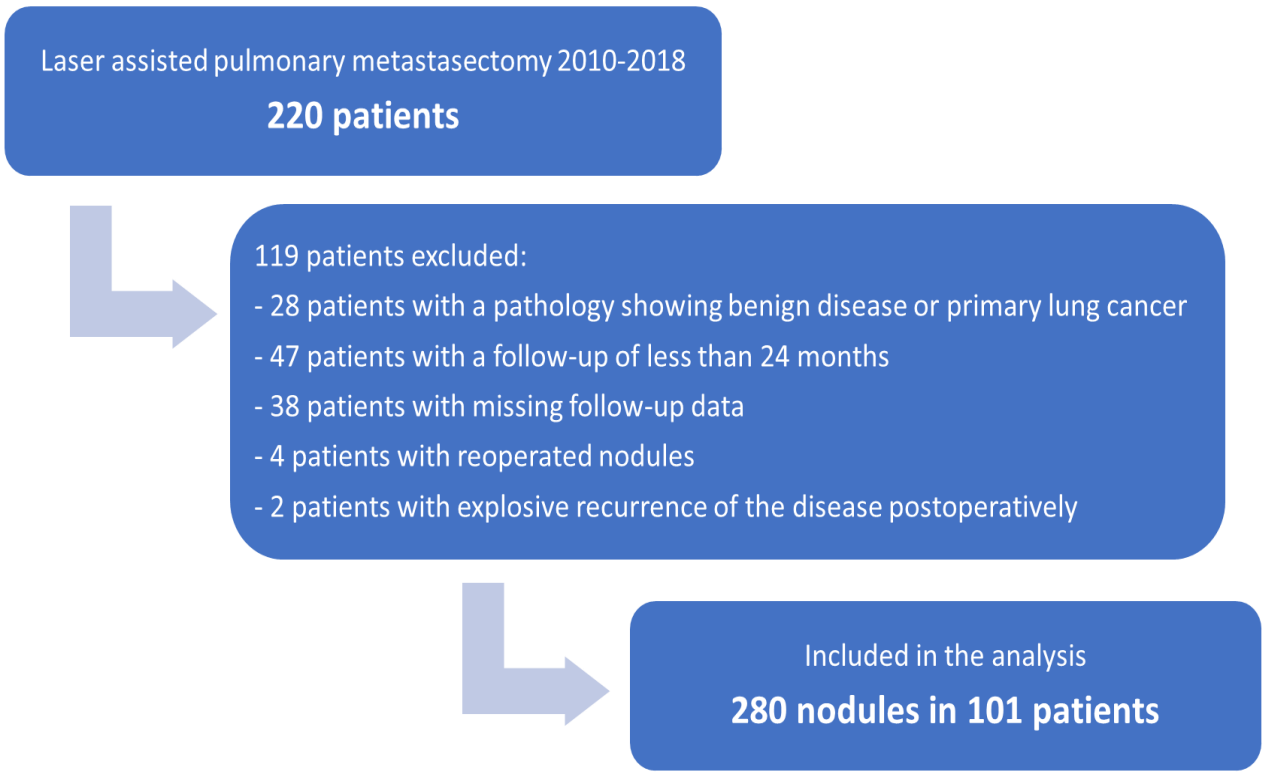

FIGURE 3. Inclusion flowchart showing the exclusion criteria.

Data collection and variables definitions

Data collection for patients followed up at the Löwenstein Lung Medical Centre was performed by reviewing their local medical records. Data collection for patients who were followed up by their oncologist or pulmonologist required access to the most recent patient records. The oncologists and pulmonologists were contacted and asked to send copies of these records.

The following parameters were obtained and analysed: age, gender, primary disease and its stage, disease-free interval (DFI), use of systemictherapy, number of nodules and their size and location, pleural involvement, lymph node metastasis, surgical approach (i.e. VATS vs anterolateral thoracotomy), complications, mortality, follow-up period, completeness of resection (R status) and local recurrence at the surgical margin.

DFI was defined as the interval between the resection of the primary malignancy and the first detection of pulmonary metastases. DFI was considered to be zero in cases where pulmonary metastases developed synchronously with the primary malignancy. Nodule size was defined as the size measured on the gross pathological examination. Completeness of the resection (R status) was the one given by the pathologist. When tumour cells reached the coagulation zone, the Rx was given. Local recurrence at the surgical margin was defined as postoperative tumour development at the resection line (coagulation zone) detected by CT by the radiologist or surgical team (Fig. 2) or pathologically confirmed post resection.

Surgical technique

A diode-pumped Nd:YAG laser (Limax; KLS Martin Group, Germany) was used for all PMs. LPMs over nine years were performed by different surgeons under the supervision of one head of department. Nevertheless, the local surgical standard that insists on resecting a 5-mm safety margin from each nodule was strictly followed. The operative approach (i.e. VATS vs anterolateral

thoracotomy) was set by the surgical team after thorough preoperative planning by chest CT scans and considering the patient’s status and fitness. In cases of bilateral disease, staged resections were performed 4–6 weeks apart. All LPMs were performed under general anaesthesia with single-lung ventilation in the lateral decubitus position. The clinical completeness of the resection was fulfilled for each nodule.

Statistical analysis

Cox proportional hazard model was used to investigate the factors associated with increased risk of local recurrence at the surgical site after LPM in univariate and multivariate analyses. All reported *p* values are from two-sided tests, and the significance level was set to <0.05. The statistical significance of each factor's effect on local recurrence was assessed using a logrank test. All analyses and plots were performed using the ‘survival’ and ‘survminer’ packages of R®, Version 4.0.3.

Results

Patient characteristics

From the 101 patients included in this study, 280 nodules were studied and analysed. On average, each patient had 2.77 nodules, while 41 patients had a single-nodule disease. Of the 101 patients, 65 (64.3%) were male, with a mean age of 58.8 years, and 36 (35.6%) were female, with a mean age of 66.5 years. In general, the mean age at operation was 65.7 years (range: 27–82 ±10.8). Baseline data per patient and per nodule are described in Tables 2 and 3. A total of 129 operations were performed, and the VATS approach was used for 5 operations (5 patients). The included patients were postoperatively observed on average for 44 ± 17 months.

Table 2. Baseline data per patient. DFI: disease-free interval.

	Number (percent)	**Local recurrence / patient (percent)**
Sex		
Male	65 (64.36%)	5 (5/65 = 7.6%)
Female	36 (35.64%)	2 (2/36 = 5.5%)
Spread of the disease	n=92	
Bilateral disease	54 (58.6%)	5 (5/54 = 9.2%)
Ipsilateral disease	38 (41.3%)	2 (2/38 = 5.2%)
Single nodule	41 (40.6%)	2 (2/41 = 4.8%)
Multiple nodules	60 (59.4%)	5 (5/60 = 8.3%)
DFI	n= 92	
DFI < 36 m	61 (66.3%)	4 (4/61 = 6.5%)
DFI ≥ 36 m	31 (33.7%)	2 (2/31 = 6.4%)
Perioperative chemotherapy	n= 90	
Chemotherapy	67 (74.4%)	6 (6/67 = 8.9%)
No chemotherapy	23 (25.5%)	1 (1/23 = 4.3%)
OP approach		
Anterolateral-thoracotomy	96 (95.04%)	7 (7/96 = 7.29%)
VATS	5 (4.95%)	0
Lymphnode metastases		
Present	7 (6.93%)	0
Abscent	94 (93.06%)	7 (7/94 = 7.44%)
Total	**101**	**7 (7/101 = 6.93%)**

Table 3. Baseline data per nodule. UL: upper lobe, ML: middle lobe, and LL: lower lobe.

	Number n=280 (percent)	**Local recurrence / nodule (percent)**
Sex		
Male	183 (65.36%)	7 (7/183 = 3.83%)
Female	97 (34.64%)	2 (2/97 = 2.06%)
R status		
R0	217 (77.50%)	5 (5/217 = 2.30%)
Rx	63 (22.50%)	4 (4/63 = 6.34%)
Size		
<12 mm	188 (67.14%)	3 (3/188 = 1.59%)
≥12 mm	92 (32.85%)	6 (6/92 = 6.52%)
Spread of the disease	n=268	
Bilateral disease	203 (75.74%)	7 (7/203 = 3.44%)
Ipsilateral disease	65 (24.25%)	2 (2/65 = 3.07%)
Location		
UL	108 (38.57%)	4 (4/108 = 3.70%)
ML	31 (11.07%)	1 (1/31 = 3.22%)
LL	141 (50.35%)	4 (4/141 = 2.83%)
Total	**280**	**9 (9/280 =3.21%)**

The majority of the primary malignancies were colorectal carcinoma (48.5%), followed by renal cell carcinoma (21.7%). Metastases from primary lung cancer contributed to 8.9% of the patients, while other types of cancer contributed to the rest (20.8%). A detailed distribution of the patients based on primary malignancy is presented in Table 4. Perioperative chemotherapy was administered in 67 (74.4%) patients; this varied according to the primary disease and its stage. Clinical completeness of the resection was achieved in all patients and for each nodule. Rx, was found in 63 (22.5%) nodules. Lymphadenectomy was performed in 92 patients (91.0%), and among these, 7 patients (7.6%) showed evidence of lymph node metastases. Postoperative complications were seen after 10.8% of LPM.

Table 4. Patient distribution in respect of primary disease.

Primary disease	Number of patients (n=101)	Percentage
Colorectal adenocarcinoma	49	48.51%
Renal cell carcinoma	22	21.78%
Endometrial Cancer	2	1.98%
Esophageal adenocarcinoma	1	0.99%
Soft tissue sarcoma	6	5.94%
Maxillary sinus carcinoma	1	0.99%
Melanoma	2	1.98%
Neuroendocrine Tumor of the GI	1	0.99%
Urothelial carcinoma	2	1.98%
Pancreatic Cancer	1	0.99%
Pappillary Thyroid Cancer	2	1.98%
Pleomorphic adenoma (Submandibular gland)	1	0.99%
Prostate cancer	2	1.98%
Pulmonary adenocarcinoma	6	5.94%
Pulmonary squamous carcinoma	3	2.97%
Thymoma	1	0.99%

Table 5. Local recurrence at the surgical margin in respect of primary disease per nodule.

Primary disease	Number of nodules	Local recurrence n=9 (% per disease), {% of nodules with reccurence}
Colorectal adenocarcinoma	139	7 (5.03%) {77.77%}
Endometrial cancer	6	0
Esophageal adenocarcinoma	6	0
Leiomosarcoma	3	0
Liposarcoma (Retroperitoneum)	1	0
Maxillary sinus carcinoma	2	0
Melanoma	2	0
Neuroendocrine Tumor of the GI	2	0
Urothelial carcinoma	4	1 (25.00%) {11.11%}
Pancreatic cancer	1	0
Papillary Thyroid cancer	7	0
Pleomorphic adenoma (Submandibular gland)	7	0
Pleomorphic liposarcoma	2	0
Pleomorphic sarcoma	3	1 (33.33%) {11.11%}
Prostate cancer	4	0
Pulmonary adenocarcinoma	8	0
Pulmonary squamous carcinoma	4	0
Renal cell carcinoma	70	0
Thymoma	9	0
Total	**280**	**9**

Local recurrence and associated factors

After a minimum postoperative follow-up of 24 months, local recurrence at the surgical margin was detected in 9 nodules (3.2%) in 7 patients (6.9%). Local recurrence occurred on average after 19.6 ± 8.6 months postoperatively. Of these 9 nodules with local recurrence, 7 (77%) were pulmonary metastases from colorectal origin. Local recurrence was found in 5% of colorectal metastatic nodules. All nine nodules were reoperated, and local recurrence at the surgical margin was resected. The distribution of nodules with local recurrence among primary malignancies is shown in Table 5. The DFI varied grossly for nodules with local recurrence, ranging from 0 (synchronous pulmonary metastases) to 60 months, and the DFI was on average 18.3 ± 22 months. Further specifications of local recurrence are listed in Tables 1 and 2.

Local recurrence was significantly influenced by the size of the nodule (hazard ratio [HR]: 1.08, 95% CI: 1.0%–1.1%, p = <0.001 logrank test). The size was significantly higher in nodules with local recurrence (p = 0.02, Welch's two-sample t-test). Nodules with local recurrence had an average size of 17.3 ± 8.3 mm (mean 17), while nodules that did not develop local recurrence had an average size of 9.5 ± 6.5 mm (mean 8). Moreover, the HR of the local recurrence showed a significant cut-off point of 12 mm (HR: 4.08, 95% CI: 1.2%–16.3%, p = 0.03 logrank test). This is demonstrated in Fig. 4. The location of the nodule according to the anatomical lobes of the lung did not affect local recurrence (p = 0.97).

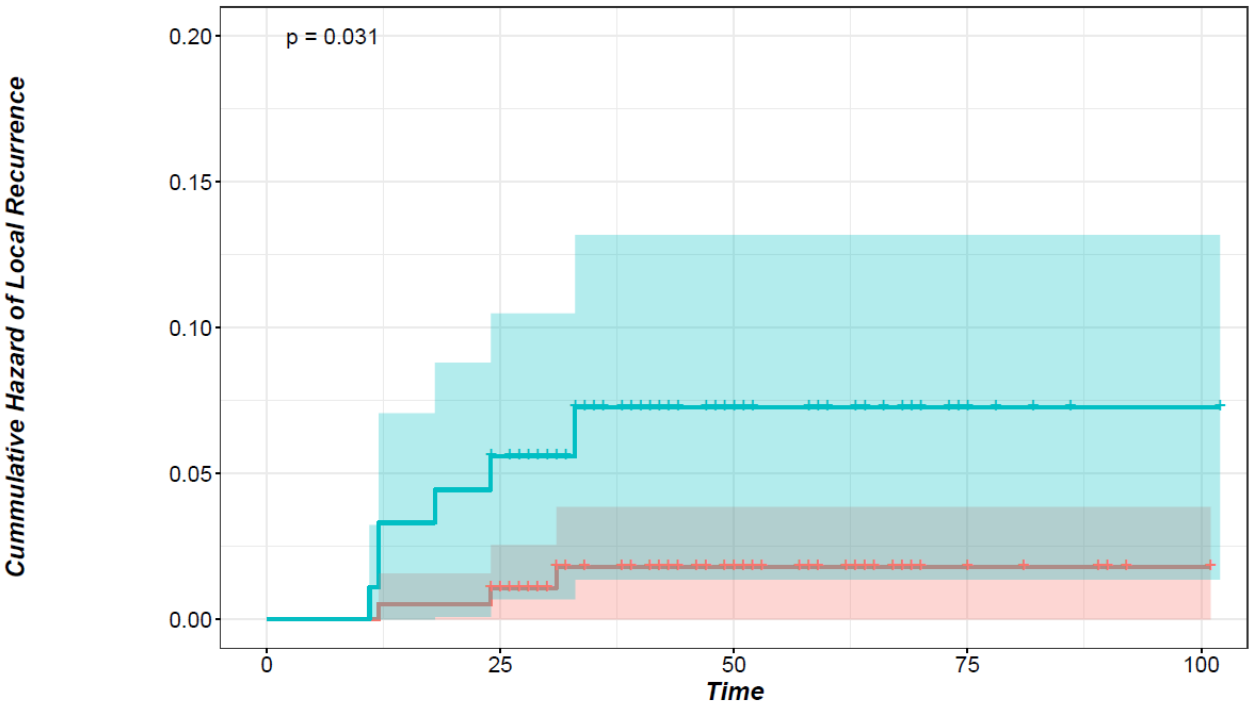

Figure 4. Cumulative hazard of local recurrence for the size of the nodule with 12 mm as the cut-off point. Time in months. Green curve: nodules ≥12 mm, red curve: nodules <12 mm. *P* = 0.03 (logrank test).

Completeness of the resection based on the R status postoperatively given by the pathologist had a significant impact on local recurrence (HR: 12.2, 95% CI: 2.5%–58.7%, $p < 0.001$ logrank test). The local recurrence for nodules with Rx status was 6.3%, while the local recurrence of nodules with R0 status was only 2.3%. The cumulative hazard for local recurrence according to R status is shown in Fig. 5.

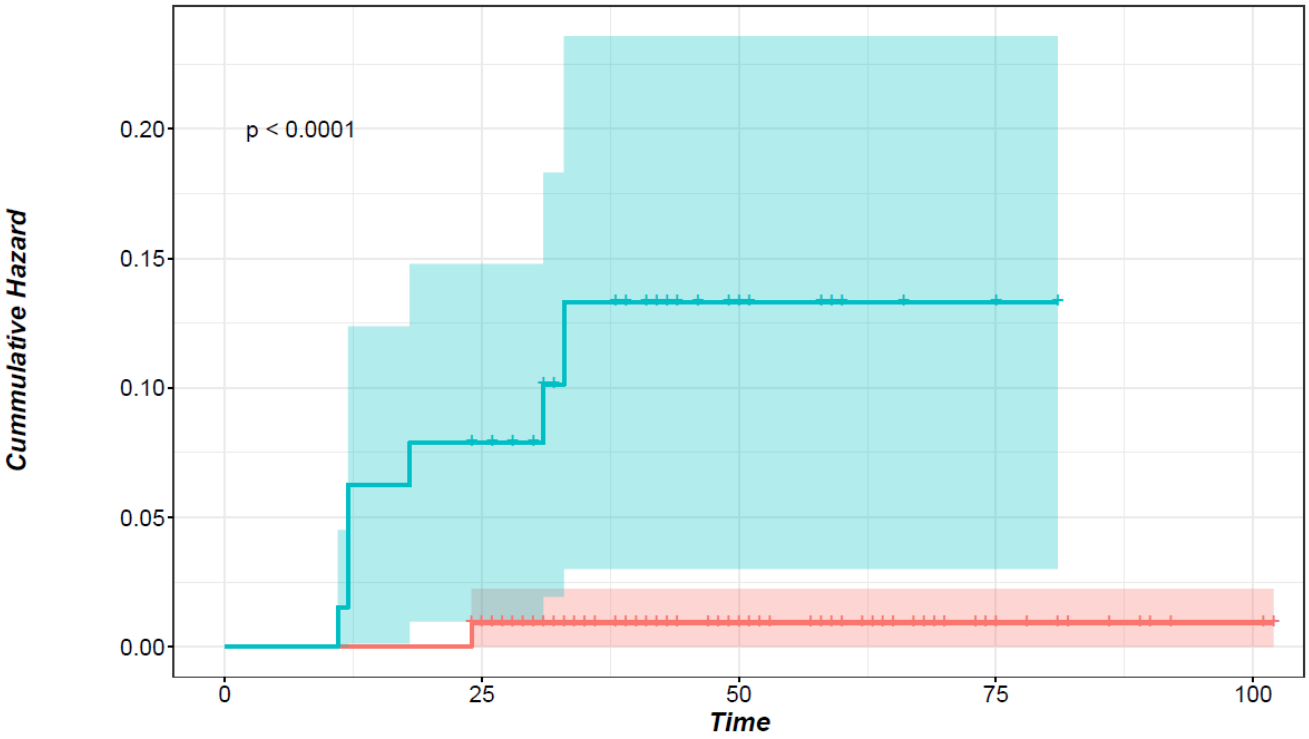

Figure 5. Cumulative hazard for local recurrence for R status. Time in months. Green curve: Rx nodules, red curve: R0 nodules. *P* < 0.001 (logrank test).

Focusing on local recurrence per patient and per nodule, none of the other measured factors, such as DFI, gender, perioperative chemotherapy, lymph node metastases, operative approach and single-nodule disease, had no significant influence on local recurrence for both univariate and multivariate analyses. A trend was observed in patients with bilateral disease, but this was statistically insignificant (see Table 6). The effect of primary disease histology on local recurrence could not be detected in these 101 patients as the results of both the univariate and multivariate analyses were insignificant.

Table 6. Univariate analysis for different measured factors and local recurrence at the surgical margin per patient and per nodule.

Variable	Hazard Ratio	95% CI	p Value	Type of analysis
Sex	0.64	0.1% - 3.3%	0.5970	Per patient
Age	1.02	0.9% - 1.1%	0.4760	Per patient
R status (R0 vs Rx)	12.19	2.5% - 58.7%	0.0018	Per nodule
Spread of the disease				Per patient
Single vs multiple nodules	1.18	0.2% - 6.1%	0.8380	
Bilateral disease	1.26	0.2% - 6.4%	0.7830	
Size of nodule	1.08	1.0% - 1.1%	0.0009	Per nodule
<12 mm vs ≥12 mm	4.08	1.0% - 16.3%	0.0469	
OP approach (VATS vs thoracotomy)	<0.001	0.0 - ∞	0.6000	Per patient
Lyphnodemetastases	<0.001	0.0 - ∞	0.5000	Per patient
Perioperative chemotherapy	0.45	0.0% - 3.7%	0.4610	Per patient
DFI	0.99	0.9% - 1.0%	0.6020	Per patient
<36 months vs ≥36 months	1.00	0.1% - 5.4%	0.9960	

Survival analysis

Survival-related data could be collected from 96 (95%) of the 101 patients: 21 (21.8%) of them died and 75 (78.1%) were censored. Survival-related data in patients with local recurrence could be collected from five of seven patients: two of them died and three were censored. The 3- and 5-year overall survival (OS) were 84% and 49%, respectively, for all patients. Median survival for patients who had local recurrence was 45 months, whereas the other patients had a median survival of 49 months.

There was no significant difference in OS between patients with local recurrence and patients without (see Fig. 6); however, a significant correlation between age and survival was found (HR: 1.07, 95% CI: 1.01%–1.14%, $p = 0.01$ logrank test). No significant association was found between survival and gender,

perioperative chemotherapy, bilateral disease, lymph node metastases or DFI. However, a trend for better survival when the DFI was ≥36 months was detected (HR: 0.84, 95% CI: 0.35%–2.02%, *p* = 0.7 logrank test).

P=0.98.

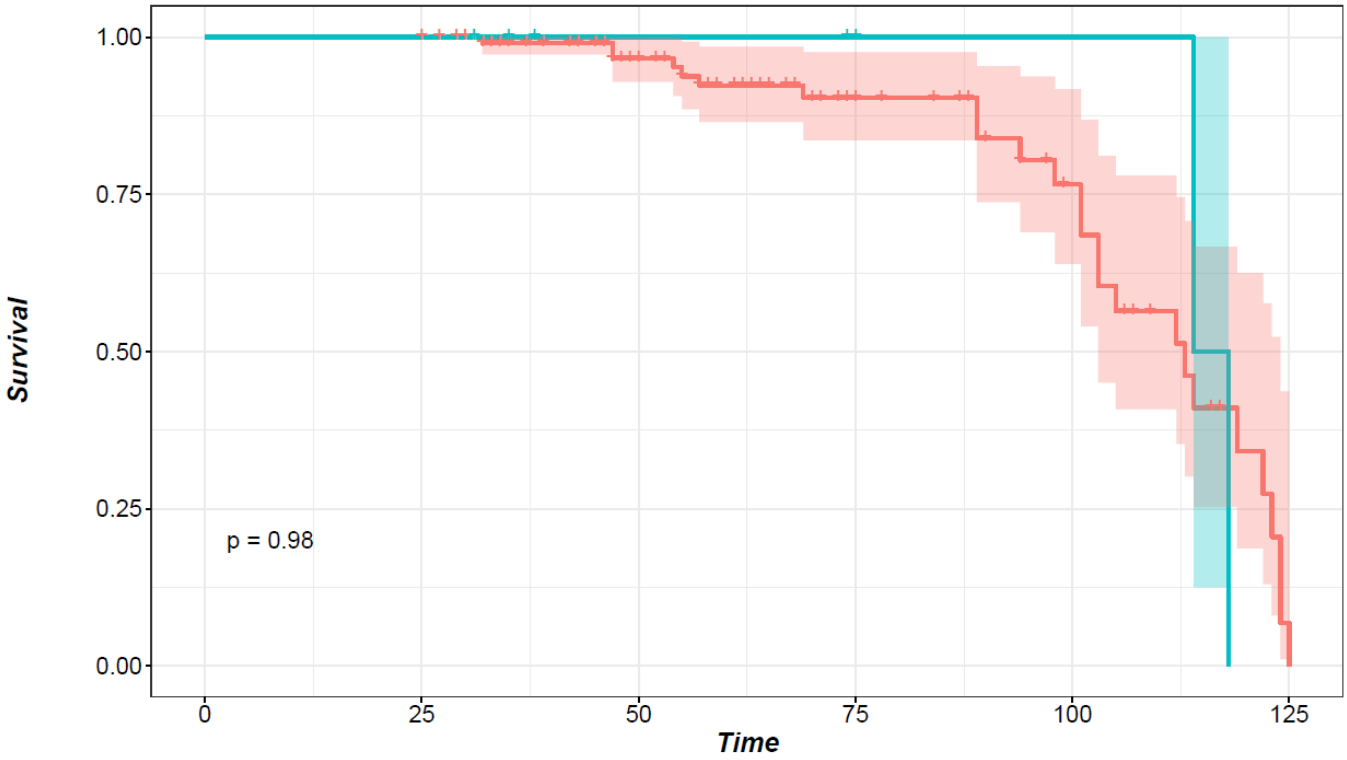

Figure 6. Kaplan–Meier curve showing no significant survival difference for local recurrence at the surgical margin. Time in months. Green curve: patients with local recurrence, red curve: rest of the patients.

Discussion

Before the 1990s, although PM had been performed for decades, data in support of PM were lacking. Over the last 30 to 40 years, more than 1000 publications have addressed PM without a single randomized controlled trial (RCT) [27]. The PM literature contains a large set of publications with pervasive selection bias, no comparative analysis, variable follow-up length and inconsistent descriptions of adjacent local or systemic therapies [27]. Thus, surgical and non-surgical voices, as early as 1980, questioned the effectiveness of PM by arguing that this improved survival could be due to selection bias. In 1980, Aberg et al. demonstrated that the reasoning that assumed that survival would be zero without surgery was fallacious [64].

Therefore, the IRLM was founded in 1991 to establish the long-term results of PM. In 1997, an analysis of 5,206 cases of PM from 18 institutes across Europe, the USA and Canada with different pathological entities was published [38]. In this analysis, actuarial 5-, 10- and 15-year survival was 36%, 26% and 22%, respectively. This is the largest and the most influential publication in the PM literature. A few other registry articles defined and defended the practice of PM, and more importantly, indicated the significance of the selection criteria [27]. The benefit of PM was further demonstrated and supported by a multivariate analysis of 440 patients and a recent 10-year single-institute analysis of 708 PMs [37], [40]. The lack of RCTs was and still is a major flaw in the PM literature, and the main critique to the practice of PM is based on this issue [65], [66]. As a result of a later appeal to initiate a well-established RCT, a British trial, PulMiCC (pulmonary metastasectomy in colorectal cancer), funded by Cancer Research UK was launched in 2011. This trial was highly anticipated by oncologists and surgeons, but it was unfortunately stopped due to low recruitment. Nevertheless, the trial was published in 2019 as it randomized 65 patients with pulmonary metastases from colorectal origin to surgery (PM) or active monitoring [29]. The authors reported a 5-year survival of 38% (23%–62%) after PM and 29% (16%–52%) in well-matched controls.

Although this trial was underpowered to prove the benefit of PM and conclude its superiority, it serves as a verification of similar five-year survival rates frequently reported in the PM literature, thereby indirectly showing the superiority of PM.

Historically, the aim of PM has been to cure. This means the definitive treatment of primary disease and all secondary metastases, and it is measured by long-term survival without disease recurrence, which is referred to as disease-free survival (DFS). This is challenging as there is no clear time frame that represents ‘long-term’ and is simultaneously applicable to both indolent and rapid growing tumours. Although OS could be exchanged with DFS, this is an imperfect exchange [27]. Based on this, PM has been shown to provide long-term DFS and OS or a ‘cure’ across different pathologies in accordance with historically established selection criteria. In some patients, PM is the only therapeutic option [67], but in daily practice, PM in the majority of patients is never considered in isolation. PM is mostly considered in the context of a possible systemic therapy, which can be either alternative or adjunct [27].

In general, most of the cancer patients seek medical help late and present with an advanced stage of the primary disease with distant metastases, in this case, pulmonary metastases. Having one to five metastatic lesions, which are all manageable, is defined as oligometastatic disease [68]. Despite having distant pulmonary metastases, making it a stage IV disease, if this well selected group of patients with oligometastases underwent PM, they would have a 5-year survival reaching 64% [40], [69]. This special entity for oligometastases, based on gene expression analysis, justifies the widespread use of PM as a therapeutic option for this selected group [70]. However, setting a treatment plan for these patients is not straightforward and can be quite challenging. Nowadays, carefully individualized decision making within a multidisciplinary team is widely favoured [27].

A global-wide tendency towards more lung parenchyma-sparing PMs was recently confirmed by an expert consensus statement [27]. A lung parenchyma-

sparing technique is critically important considering the possible need for further future resections for bilateral disease or in cases of disease recurrence. The occurrence of new pulmonary metastatic nodules after PM or even disease recurrence at a previous resection site is not uncommon. In certain populations, such as colorectal cancer or soft tissue sarcoma, this can be as high as 75% of the patients appealing a second resection in functionally fit patients [71]. In their study based on IRLM patients, Pastorino et al. reported 5- and 10-year survival rates after a second PM of 44% and 29%, respectively, compared with 34% and 25%, respectively, in patients with only one PM [38].

Although non-anatomical resections are considered parenchyma-sparing compared to anatomical resections, they are still associated with an unnecessary sacrifice of lung parenchyma. Wedge resection using staplers results in the loss of ‘healthy’ lung tissue due to the wedge form, especially in more deeply located nodules. Moreover, assuring a sufficient resection margin in VATS-based wedge resection might lead to a bigger sacrifice of lung tissue. Curved staplers were recently introduced to address this, but their use is not widely adopted. Therefore, the use of a 1,318-nm Nd:YAG laser for PM has emerged to serve this concept. For a given metastatic lung nodule of 25 mm, LPM resulted in a 7-times reduction in lost lung volume compared to standard wedge resection with a stapler [72]. Here, the Nd:YAG laser presents itself capable of resecting a significantly higher number of pulmonary metastases and reducing the need for lobectomy without negative influence on survival [2], [47]–[49], [63].

The purpose of this study was to estimate the rate of local recurrence at the surgical margin after LPM and evaluate the influence of various clinical and pathological factors. The inability to completely resect all metastatic nodules is widely considered a contraindication to PM [27]. Nearly all the PM literature demonstrates that complete resection of metastases is linked to better outcomes [27], [38], [56]. Regardless of the different factors proven to increase the risk of local recurrence at the surgical margin, local recurrence is at its core a form of incomplete resection at a microscopic level. Thus, local recurrence is

a significant adverse event that has a negative influence on survival [42], [73], [74]. The application of 1,318-nm Nd: YAG laser for PM is assumed to decrease the risk of local recurrence at the resection site due to the formation of a 5-mm coagulation zone at the resection line (see Fig. 7). In this coagulation zone, elevated temperatures destroy recessive tumour cells formed by ASFC. This study, aimed at testing this hypothesis, is the first to describe the rate of local recurrence at the surgical margin following LPM.

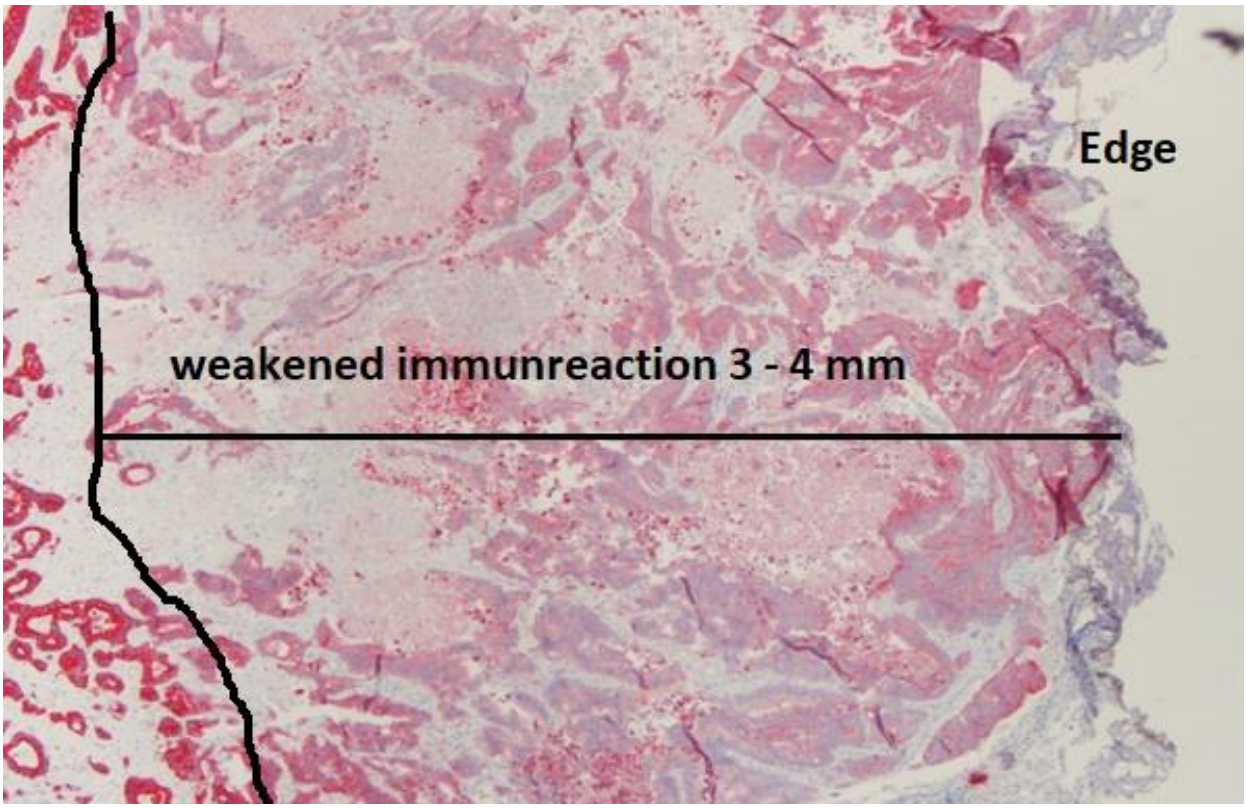

Figure 7. Weakened immunoreaction due to elevated temperatures in the coagulation zone at the resection line (on the right-hand side) of the specimen as seen by the pathologist.

This study included 280 metastatic pulmonary nodules with different histologies from 101 patients who underwent a total of 129 LPMs. After a minimum postoperative follow-up of 24 months, 9 nodules (3.2%) from 7 patients (6.9%) showed local recurrence at the surgical margin after an average of 19.6 ± 8.6 months from the operation date. Of the 9 nodules, 7 (77%) (5 of 7 patients, or 71.4%) with local recurrence were pulmonary metastases from

colorectal origin. Local recurrence was found in 5% of colorectal metastatic nodules. Nevertheless, the effect of primary disease histology on local recurrence could not be seen in these 101 patients dominated by colorectal disease because the results of both the univariate and multivariate analysis were insignificant. In a histopathological analysis of pulmonary metastatic nodules, Welter et al. reported that ASFC (Fig. 8) was almost absent in metastases from sarcoma, melanoma and renal cell carcinoma, whereas metastases from colorectal carcinoma had the highest rate of ASFC [60]. They further reported that lymphangitic spread was seen in the metastases of renal cell carcinoma, but it was highest in melanoma metastases, and sarcoma metastases infiltrated the pleura the most [60]. Whether these differences in growth patterns between primary diseases would influence local recurrence after LPM should be investigated in a larger group of patients.

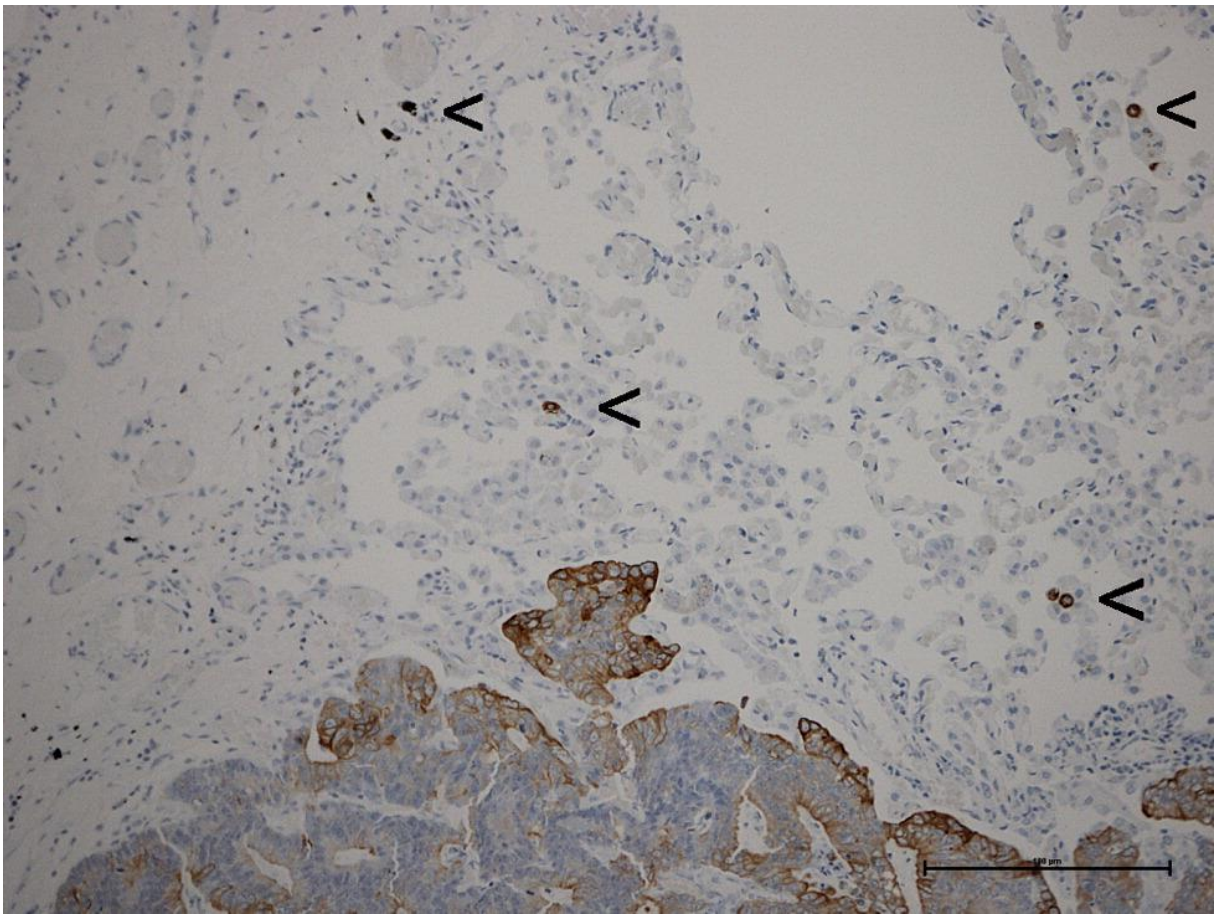

FIGURE 8. Satellite tumour cells, shown by CK20 staining (black arrows), floating around a pulmonary metastasis of colorectal origin [57].

In each patient, a safety margin of approximately 5 mm was maintained for each resection to ensure the clinical completeness of the resection for each nodule. Completeness of resection with a negative surgical margin (R0) is considered the key factor for avoiding local recurrence [61], [75]. After LPM, it is difficult and sometimes impossible to histopathologically confirm a complete resection due to the vaporization of the resection line and the pronounced coagulation zone. Therefore, this entity should be taken into consideration intraoperatively, and the completeness of the resection clinically evaluated [52], [61], [63]. In this case, if tumour cells reach the coagulation zone at the edge of the specimen, the pathologist would call it Rx 'undetermined', even though another 5–10 mm of vaporization and coagulation zone is yet to follow. Rx was determined by the pathologist for 63 (22.5%) nodules (Table 3). Four nodules showed local recurrence, which was significantly increased, reaching 6.34% for all Rx nodules compared to only 2.3% local recurrence for R0 nodules ($p < 0.001$) (Fig. 5). This suggests that despite the coagulation zone on both sides of the resection line, some of the Rx resections were incomplete (R1), thus necessitating the intraoperative role of clinical evaluation of the margins.

Even when complete resection was histopathologically confirmed (i.e. R0), local recurrence occurred. This phenomenon, although only partially understood, is well known and observed in non-laser PM. Satellite micrometastases due to ASFC, which is pathognomonic for pulmonary malignancies, have been presented to explain this issue [56], [57], [60]. Kawaguchi et al. recently showed that mucus extension in resected mucinous tumour hosts despite R0 resection had an increased risk for local recurrence after PM [76]. These factors persist as risk factors for local recurrence in R0 resections after LPM.

The local recurrence rate at the surgical margin after non-laser PM is relatively high, with published reports ranging between 9% and 30% [56], [58], [61], [77]. The numbers speak for themselves; the difference in local recurrence rate between LPM and non-laser PM is major. A 3.2% local recurrence rate after LPM manifests the protective effect of the coagulation zone produced, and

presents a safer resection if ASFC is suspected. Also, of note, almost all local recurrence studies after non-laser PM addressed colorectal pulmonary metastases. In the current study, the population with colorectal cancer had a 5.0% local recurrence rate (Table 5), which is still far less than non-laser PM. Shiono et al. tried to explain this issue: when both stapler jaws close in wedge resections, the surgical margin could be compromised even when a safety margin is obtained [56]. Moreover, the surgical margin could be even more compromised in a VATS-based wedge resection [63]. As mentioned earlier, data on LPM are limited, and only one study has reported on local recurrence after LPM. In their retrospective comparison of surgical outcomes after LPM and non-laser PM, Franzke et al. commented on local recurrence as a secondary outcome [63]. They reported an interestingly low local recurrence rate of 0.8% after LPM vs 3.1% after non-laser PM. However, around 60% of their patients in both groups were followed up for <24 months, enhancing the possibility of latterly undetected local recurrence. Moreover, the detection of local recurrence after LPM in the early postoperative phase is quite hard, even for an expert. Minimal local tissue damage after laser application often forms haematomas, which have the same radiological appearance of early local recurrences. In other words, local recurrence in the early postoperative phase could be missed when considered as a haematoma. Or, local recurrence has not occurred yet. This makes their 0.8% and 3.1% local recurrence rates questionable.

In the current study, local recurrence was significantly (p = 0.02) correlated with nodule size. Nodules with local recurrence had an average size of 17.3 ± 8.3 mm (mean 17), while nodules that did not develop local recurrence had an average size of 9.5 ± 6.5 mm (mean 8). This is in accordance with published studies that investigated local recurrence after non-laser PM; as tumour size increases, the risk for local recurrence at the surgical margin increases [60], [78]. A significant cut-off point was found at 12 mm (p = 0.03), where tumours larger than 12 mm had an increased risk of local recurrence (Fig. 4). Nelson et al. reported a 12% risk for 1– 2 cm tumours and an increased risk (31%) in tumours larger than 2 cm [78]. Welter and colleagues successfully

demonstrated in two different publications supported by histopathological analyses that an increase in tumour size reflects an aggressive local growth of the tumour and an increase in the number of satellite cells and their distance from the tumour [57], [60]. Consequently, an increased safety margin for larger tumours was recommended. Affirmatively, Nelson et al. demonstrated an increased risk for local recurrence with larger tumours that diminished with the application of a sufficient margin [78].

The depth of a tumour within the lung tissue (defined as the longest perpendicular distance between the visceral pleura and the deepest margin of the tumour) showed a correlation with local recurrence in wedge resections [61]. After a tumour-depth cut-off point of 23 mm, the risk for local recurrence was significantly increased [61]. This is reasonable and approved by daily practice; control over the safety margin in deeper tumours is vulnerable in wedge resections. This could be overcome by the use of the Nd:YAG laser, which would not only save valuable lung tissue and reduce the need for lobectomy but also reduce the risk of local recurrence.

OS rates 3- and 5-years post LPM were 84% and 49%, respectively. Younger patients had significantly better survival ($p = 0.01$). The median survival for patients with and without local recurrence was 45 and 49 months, respectively. No significant difference in OS was found in respect to local recurrence at the surgical margin, which could be explained by the fact that all patients who had local recurrences were reoperated (i.e. the recurrence was resected). Schmid et al. confirmed this assumption in their study on LPM in sarcoma, which is well known for disease recurrence, as repeated resections showed longer OS [79]. Jaklitsch et al. reported a >33% 5-year survival rate in up to 5 operative sessions after sequential PM in patients with metastatic pulmonary nodules from various primary tumours [80]. Two-year survival dropped to 19% as local tumour control was lost (i.e. incomplete resection), and they concluded that repeated PM is justifiable provided complete resection is possible [80].

Perioperative chemotherapy, DFI, OP approach and lymph node metastases did not influence local recurrence. However, the spread of the disease in terms of bilateral disease showed a weak trend (HR: 0.7, $p = 0.8$). A similar trend was seen for single-nodule disease reducing the risk of local recurrence (HR: 1.5, $p = 0.6$). When the DFI was more than 36 months, a weak correlation with better survival was observed (HR: 0.8, $p = 0.7$). The low number of patients with local recurrence and colorectal dominance over the study's population contributed to shading the presumed effect of the primary disease on local recurrence.

VATS LPM was performed in only five patients (Fig. 9). Most of the VATS LPM took place in the latter years of the study, reflecting the time taken by the surgeons to learn and master LPM via a minimally invasive approach. None of these patients developed local recurrence. Although these patients had fewer and more peripherally located and smaller nodules, this presents VATS LPM as a doable and reliable option and raises the credibility of VATS PM in well selected patients. However, evidence in support of VATS LPM is currently lacking, although positive experiences with this technique are emerging [54], [81].

Althagafi et al. reported that in 36% of PM (both VATS and the open approach), new nodules, not seen on CT, were detected [82]. Eckardt et al. showed that this was more the case for VATS than the open approach [83]. On the one hand, a study found that up to 48% of these intraoperatively detected lung nodules were benign lesions [21]. On the other hand, Cerfolio et al. reported that 20% of the patients had new malignant nodules not detected on CT [84]. In the 2008 ESTS's members survey, only 28% of the surgeons preferred VATS approach for PM [62].

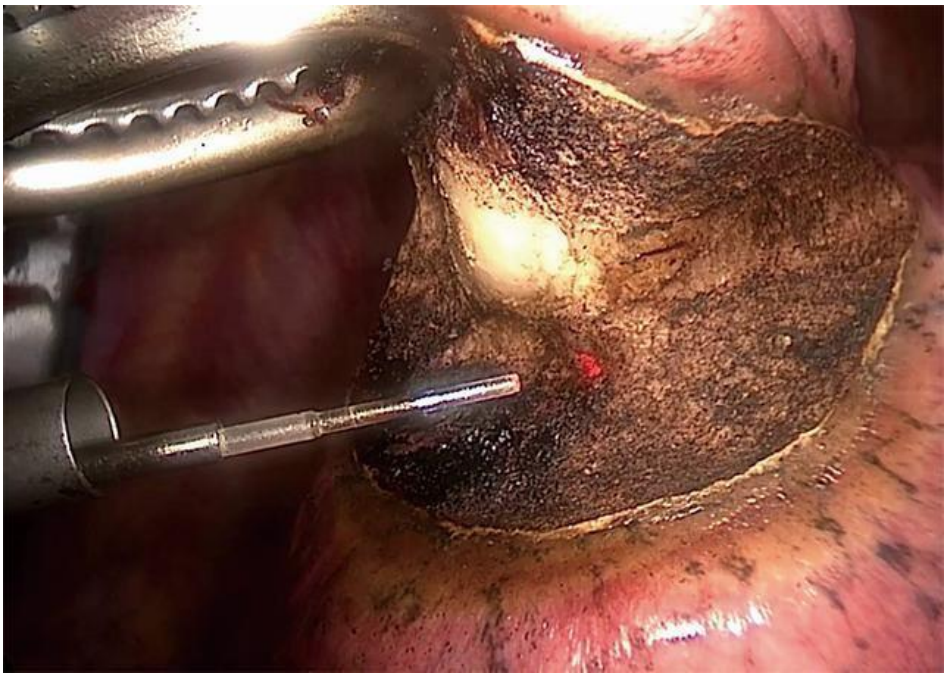

Figure 9. Resection of a metastatic nodule using an Nd:YAG laser in a video-assisted thoracic surgery approach. The pilot light marks the area targeted by the laser beams [54].

In contrast, Krüger et al. defended the sensitivity of HRCT in a study of 125 open PMs; only 2 malignant nodules were not detected by CT [85]. Furthermore, patients who underwent thoracotomy for PM had significantly more complications than those who underwent a similar VATS resection[86]. According to an expert consensus statement issued by the ESTS, the VATS approach is preferred because of its shortened recovery and lessened effect on short-term quality of life [27]. This improved detection and resection (due to bimanual palpation) in a conventional approach did not improve survival in retrospective studies [2], [27], [86]–[89].

Limitations

This study contained some limitations, so caution is required when interpreting the results. Nevertheless, these limitations should not disrupt the main finding that the local recurrence rate at the surgical margin after LPM is low.

- This study was retrospective and included a relatively small number of patients after the application of the exclusion criteria.
- The 129 LPMs in this study were performed by different surgeons, and the specimens were reviewed by different pathologists, which raised the margin of human error.
- Postoperative haematomas and fibrous scar tissue at the resection site have the same radiological appearance as local recurrence in the early postoperative phase. Thus, undetected local recurrence at the surgical margin cannot be excluded.
- The high number of censored patients (i.e. alive at the end of the study) and the low number of patients who had local recurrence weakened the statistical analysis regarding survival and masked the factors associated with increased risk for local recurrence at the surgical margin.
- The risk of residual cofounders could not be excluded; unmeasured biological and pathological factors that may have influenced local recurrence could have existed.
- The primary malignancies were heterogeneous and not equally presented in this population with colorectal dominance. This limits the generalizability of the results and conclusions.

Conclusion

The use of the 1,318-nm Nd:YAG laser for PM is safe and provides adequate tumour resection for a significantly high number of nodules and thereby preserves valuable lung tissue. The local recurrence rate at the surgical margin after LPM is low when a 5-mm safety margin is obtained. Larger nodules might require larger safety margins. In selected cases, LPM can be also performed per VATS.

List of abbreviations

PM	pulmonary metastasectomy
LPM	laser-assisted pulmonary metastasectomy
ESTS	the European Society of Thoracic Surgeons
NSCLC	non-small cell lung cancer
VATS	video-assisted thoracic surgery
Nd:YAG	neodymium-yttrium aluminium garnet
nm	nanometre
RFA	radiofrequency ablation
SBRT	stereotactic body radiation therapy
mm	millimetre
CT	computed tomography
DFI	disease-free interval
HRCT	high-resolution CT
PET	positron emission tomography
IRLM	International Registry of Lung Metastases
RCT	randomized controlled trial
DFS	disease-free survival
OS	overall survival
PulMiCC	pulmonary metastasectomy in colorectal cancer
HR	hazard ratio
95% CI	95% confidence interval
ASFC	aerogenous spread with floating cancer cell clusters

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