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Pulmonary Metastasectomy: An Analysis of Technical and Oncological Outcomes in 301 Patients with a Focus on Laser Resection

Pulmonale Metastasektomie: Analyse technischer und onkologischer Ergebnisse bei 301 Patienten mit Fokus auf die Laserresektion

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Key words
- pulmonary metastases
- surgical technique
- laser surgery
- long-term results

Schlüsselwörter
- Lungenmetastasen
- chirurgische Technik
- Laserchirurgie
- Langzeitergebnis

Abstract

Background: Resection of lung metastasis is an important component in the therapy of patients with metastatic solid tumors. The aim of this analysis was to compare the technical and oncological outcomes of laser-assisted pulmonary metastasectomy with those of standard resection techniques such as electrocautery and stapling.

Patients/Material and Methods: We retrospectively analyzed all patients who had undergone curative intended pulmonary metastasectomy in our department between January 2005 and June 2010. Follow-up was accomplished by visits in the outpatient department of our medical center or by questionnaires of the primary physicians.

Results: Three hundred and one patients were identified. In 62 patients (20.6%), the Nd-YAG laser was used for resection. Despite a significantly higher number of resected lesions in the laser-assisted resection group in comparison to the group with wedge and anatomic resections (median: 7.0 vs. 2.0; $p < 0.01$), there was no significant difference in surgical and overall morbidity except for a higher rate of pneumonia (11.3 vs. 2.9%; $p < 0.01$). Follow-up was completed for 85.4% of the patients. After a median follow-up of 27.2 months (range: 2.3 to 60.6 months), 42.5% of the patients suffered from recurrence and 29.2% had died. Mean disease-free interval was 12.9 months (range: 0 to 60.6 months). Although a higher number of metastases were resected in the laser group, we did not see a significant correlation between surgical technique and long-term survival ($p < 0.8$). Regression analysis confirmed the number of metastases to be a significant factor influencing survival ($p < 0.02$), but subgroup analysis of laser-assisted resections no longer showed significance in respect to the number of metastases.

Conclusion: The number of metastases has an influence on prognosis but seems to be of second-

Zusammenfassung

Hintergrund: Die Resektion von Lungenmetastasen ist ein wichtiger Baustein in der Therapie metastasierter solider Tumoren. Ziel der vorliegenden Untersuchung ist es, die Bedeutung der laserassistierten Metastasektomie zu evaluieren und mit anderen Resektionstechniken zu vergleichen.

Patienten/Material und Methoden: Retrospektiv wurden die Daten aller zwischen Januar 2005 und Juni 2010 mit kurativer Intention in unserer Abteilung primär pulmonal metastasektomierten Patienten analysiert. Der Krankheitsverlauf wurde anhand von Ambulanzberichten oder Versand von Fragebögen an die nachsorgenden Ärzte ermittelt.

Ergebnisse: 301 Patienten gingen in die Auswertung ein. Ein Nd-YAG-Laser wurde bei 62 Patienten eingesetzt (20,6%). Trotz einer signifikant höheren Anzahl resezierter Läsionen bei Verwendung des Lasers als bei anderen Resektionsmethoden (Median: 7,0 vs. 2,0; $p < 0,01$) fand sich, abgesehen von einer höheren Pneumonierate (11,3 vs. 2,9%; $p < 0,01$), kein signifikanter Unterschied in der Häufigkeit postoperativer Komplikationen. Der Krankheitsverlauf wurde für 85,4% der Patienten ermittelt. Nach einem medianen Follow-up von 27,2 Monaten (Streubreite: 2,3–60,6 Monate) hatten 42,5% Patienten ein Rezidiv und 29,2% waren verstorben. Das mittlere krankheitsfreie Intervall betrug 12,9 Monate (Streubreite: 0–60,6 Monate). Trotz der höheren Zahl resezierter Metastasen bei der mit Laser metastasektomierten Gruppe zeigte sich keine Korrelation zwischen Resektionstechnik und Langzeitüberleben ($p < 0,8$). In der Regressionsanalyse erwies sich die Anzahl der Metastasen als signifikant ($p < 0,02$) für das Überleben, in der Subgruppenanalyse der laserassistiert operierten Patienten war die Metastasenanzahl jedoch nicht mehr relevant.

Schlussfolgerung: Die Anzahl an Metastasen hat einen Einfluss auf die Prognose. Sie scheint jedoch, insbesondere wenn unter Zuhilfenahme

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ary importance, particularly if complete technical resectability with the aid of a laser is given.

des Lasers eine Resektion aller Läsionen technisch möglich ist, von zweitrangiger Bedeutung zu sein.

Introduction

The resection of pulmonary metastases of the most diverse primary tumors is a common procedure in the therapy of patients with oligometastatic solid tumors [1]. Even if, in the absence of prospective randomized controlled studies, a survival benefit from pulmonary metastasectomy is, to date, unproven, numerous retrospective studies following complete pulmonary metastasectomy demonstrate five-year survival rates of 30–50%, which are far superior to those of other methods of treatment [2]. We have already reported elsewhere in this journal on the generally recognized indications of pulmonary metastasectomy [3]. The technique of metastasectomy is highly variable in this context and tends to depend upon the surgical college, surgical training and upon personal convictions rather than upon the evidence [4]. The influence of the number of metastases is furthermore a matter of debate [5]. Laser metastasectomy significantly reduces parenchymal loss, but the impact on long-term survival is unclear [6]. We have been unable to find in the literature a comparison of perioperative complication rates between laser-based and conventional resection techniques. Our aim was therefore to investigate the influence of dissection techniques on complications and long-term results.

Patients/Materials and Methods

We conducted a retrospective analysis of all patients admitted to our department for curative pulmonary metastasis resection between January 2005 and June 2010, regardless of the entity of the primary tumor. Patients who were admitted for purely diagnostic metastasis resection secondary to diffuse pulmonary or multilocular extrathoracic tumor disease were excluded. We also disregarded any patients who had initially presented for revision surgery for pulmonary metastases during the registration period. Patients who had, however, presented anew for metastasis resection during the investigation period after primary surgery were not excluded from the analysis. The resection technique was not laid down and was chosen individually by the operating surgeon in question, based on his or her own experience and depending on the findings. For laser-assisted metastasectomy, an Nd-YAG laser with a wavelength of 1318 nm (MY 40, as from 2009 Limax 120; manufactured by KLS Martin, Tuttlingen, Germany) was used. Following the complete resection of all palpable findings, the resulting parenchymal defects were oversewn with PDS4–0 (Ethicon, Norderstedt, Germany). Non-laser-assisted, atypical resections were carried out either using stapling devices or, in the case of individual peripheral metastases, by clamping, electrocautery resection and oversewing with PDS4–0. The perioperative process was determined with the aid of electronic patient records, with the criteria of the professional code of conduct of the Baden-Württemberg Regional Medical Board for quality assurance of the surgical treatment of pulmonary carcinoma (**Table 1**) being taken as the basis for the definition of pneumonia and pleural empyema [7].

With regard to resected lesions, the number of metastases and the classification of resection status, only the histopathological findings and not the intraoperative assessment by the operating surgeon were regarded as relevant. The post-discharge course of the disease was assessed with the aid of outpatient reports or the sending of questionnaires to the physicians providing aftercare.

Data analysis was carried out with the Statistical Package for the Social Sciences 18.0 for Windows (SPSS, Inc., Chicago, Illinois, USA). To evaluate independence between the variables, the Pearson's correlation coefficient was calculated. Group comparisons were carried out by means of the Mann-Whitney U test. The probabilities of survival times were described and compared by means of the Kaplan-Meier estimator.

Results

We investigated 326 patients who had undergone pulmonary metastasectomy for curative purposes in our department over the stated registration period from January 2005 to June 2010. Twenty-five patients had already presented initially for revision surgery and were not included in this analysis, which meant that 301 patients were evaluated. These comprised 133 female and 168 male patients (ratio 1 : 1.3) with an age of 11 to 86 years at the time of the pulmonary surgery (median: 64 years). Pulmonary metastases of colorectal carcinomas were by far the commonest indication, followed by renal cell carcinoma and pulmonary metastases associated with malignant melanoma. **Table 2** provides an overview of the distribution of the various primary tumor entities in our population.

We used the Nd-YAG laser for resection in a total of 62 patients (20.6%), with the laser being preferred in particular in patients with multiple metastases (median 7.0 vs. 2.0; $p < 0.01$) (**Fig. 1**).

Table 1 Criteria used to define pneumonia and empyema (in accordance with quality assurance for the surgical treatment of pulmonary carcinoma, Baden-Württemberg Regional Medical Board).

Pneumonia	Infiltrate(s) in the chest X-ray or CT scan	Temperature > 38.5 °C	Leukocytes < 4 000 or > 11 000	Purulent bronchial secretion
Empyema	Pathogen detection	pH < 7.2	Glucose < 40 mg/dl	LDH > 1 000 IU/dl

Table 2 Distribution of the various primary tumor entities associated with the pulmonary metastasis resections performed by us as part of this study.

Primary tumor	Number n = 301 (100%)
Colorectal carcinomas	101 (34%)
Renal cell carcinomas	36 (12%)
Malignant carcinomas	22 (7%)
Carcinomas of the breast	19 (6%)
Soft-tissue sarcomas	19 (6%)
ENT tumors	17 (6%)
Pulmonary carcinomas	17 (6%)
Ovarian/endometrial/cervical carcinomas	13 (4%)
Osteosarcomas	12 (4%)
Germ cell tumors	11 (4%)
Thyroid carcinomas	6 (2%)
Other entities	28 (9%)

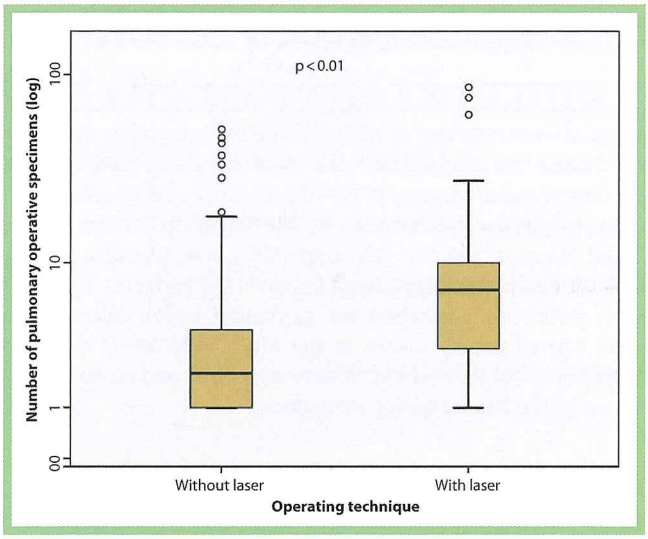

Fig. 1 In the case of laser-assisted pulmonary metastasis resection, there were significantly more resected lesions than for other techniques (median 7.0 vs. 2.0).

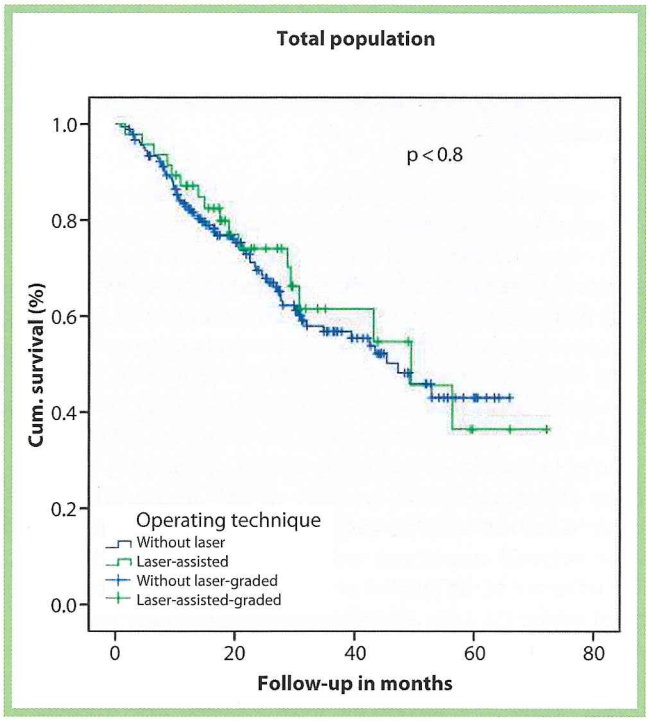

Fig. 2 The operating technique does not influence calculated cumulative survival after pulmonary metastasis resection.

As regards to the complications recorded, there was no significant difference associated with resection technique, apart from a higher pneumonia rate (11.3 vs. 2.9%; $p < 0.01$). ▶ **Table 3** provides an overview of the frequencies and significance level of the differences in the two treatment groups.

We determined a significant difference in the histopathologically documented tumor-free resection margins in favor of the laser technique, which was due in particular to classification as R1 or Rx (▶ **Table 4**). Despite this, evidence for an influence on survival by the surgical technique was not demonstrated (▶ **Fig. 2**).

The further course of disease in terms of recurrence status was assessed for 85.4% of patients. Information on survival status was obtained for 77.3% of patients. After a median follow-up of 27.2 months (range: 2.3–60.6 months), 42.5% of patients developed recurrence and 29.2% had died. The mean disease-free interval was 12.9 months (range: 0–60.6 months). Although there was a significant difference between laser-based and conventional resection techniques with regard to confirmation of tumor-free resection margins (R0) ($p < 0.01$), no correlation arose between resection technique and survival ($p < 0.8$).

Table 3 Frequencies of complications after pulmonary metastasectomy as a function of the resection technique adopted.

Resection technique	Pleural drainage > 7 d	Revision surgery	Repeat drainage	Pneumonia	Empyema	Death	Other	Total
Without laser n = 239 79.4%	3 1.3%	4 1.7%	7 2.9%	7 2.9%	3 1.3%	0 0.0%	27 11.3%	51 21.4%
Laser-assisted n = 62 20.6%	0 0.0%	2 3.2%	1 1.6%	7 11.3%	1 1.6%	0 0.0%	4 6.5%	15 24.2%
p value (Mann-Whitney U test)	0.37	0.44	0.56	< 0.01	0.83		0.26	0.64

Table 4 Histopathological classification of resection status in association with resection technique. The significant difference in favor of the laser technique is no longer demonstrable in the subgroup analysis of 103 patients with more than two pulmonary metastases.

R status	Total	Laser-assisted vs. without laser	p value	> 2 Metastases laser-assisted vs. without laser	p value for > 2 metastases
R0	228 (75.7%)	39/62 vs. 189/234	< 0.01	21/43 vs. 34/59	0.38
R1	24 (8.0%)	10/62 vs. 14/234	< 0.01	9/43 vs. 9/59	0.46
R2	4 (1.3%)	0/62 vs. 4/234	0.30	0/43 vs. 1/59	0.39
Rx	40 (13.3%)	13/62 vs. 27/234	0.05	13/43 vs. 15/59	0.59
Absent	5 (1.7)	0		1	
Total	301 (100.0%)	62 (20.6%) vs. 239 (79.4%)		103 (34.2%)	

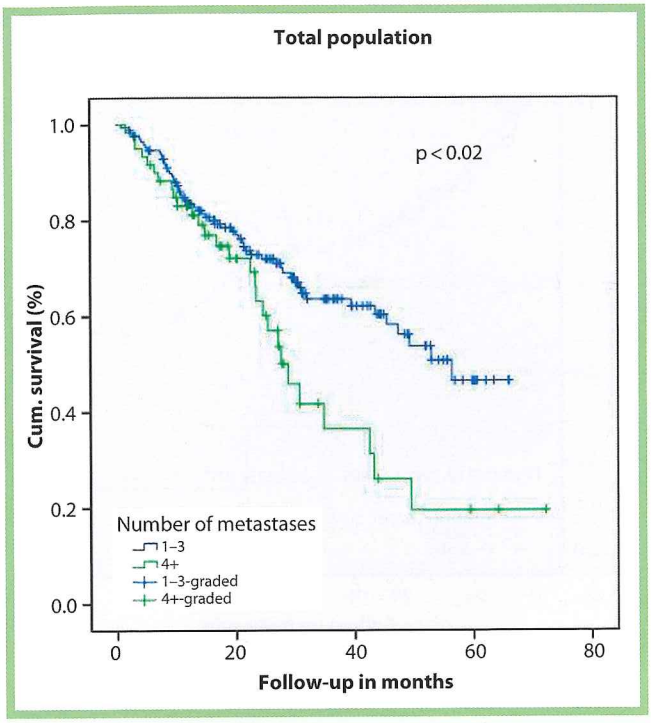

Fig. 3 For the entire patient population, the number of metastases has an influence on calculated survival with a significant cutoff at up to 3 or more pulmonary metastases.

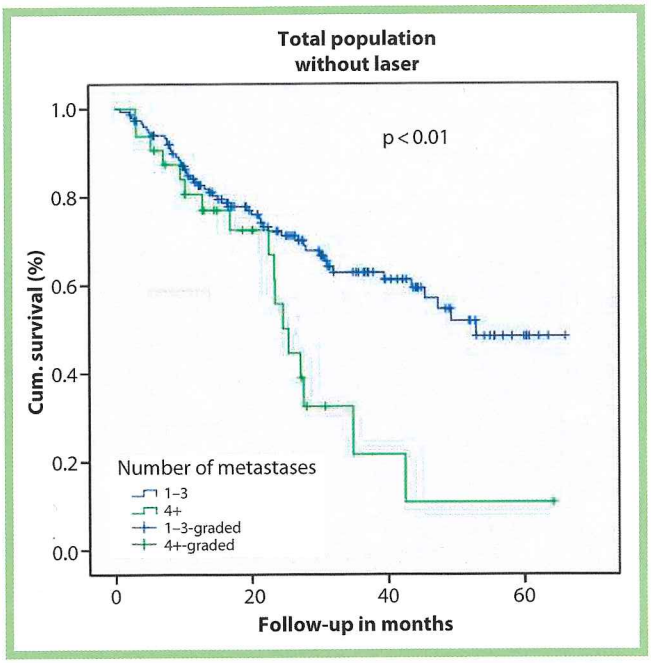

Fig. 4 In the subgroup of the patients operated on without using laser, the influence of the number of metastases on calculated survival becomes even clearer.

In the regression analysis, the number of metastases for the total population proved to be a significant factor ($p < 0.02$) for calculated survival (**Fig. 3**). We determined a significant cutoff after differentiating between patients with ≤ 3 or > 3 pulmonary metastases. Unlike with patients operated on using a conventional technique, subgroup analysis of patients operated on with the assistance of a laser nevertheless showed that patients with > 3 metastases did not present a significantly more unfavorable survival compared with patients with ≤ 3 pulmonary metastases (**Fig. 4** and **5**). Because anatomical resections had also been conducted in our population (**Table 5** provides an overview of the extent of resections), we examined the influence of the tumor spread on this observation via a subgroup analysis of the exclusively extra-anatomical resections. With approximately equal frequency of the exclusively extra-anatomical resections in the two treatment groups, the outcome from the total population was confirmed with proof of a significantly less favorable survival ($p = 0.034$) after differentiating between patients with ≤ 3 or > 3 pulmonary metastases for patients operated on without a laser, which was no longer detectable in the laser-assisted group ($p = 0.62$) (**Fig. 6** and **7**). In the subgroup analysis for the largest group of patients with colorectal carcinoma metastases (101 patients) carried out as an example, the difference in calculated survival function that was suspected graphically as a function of the number of metastases (≤ 3 or > 3) was no longer statistically significant, so that any further differentiation according to operating technique no longer yielded a measurable prognostic advantage in favor of one of the treatment groups, with > 3 metastases owing to low case numbers. In 8 of the 101 patients with colorectal carcinoma metastases, there were mediastinal lymph node metastases in the specimen. This meant that it was not possible to derive an influence on survival time by means of the Kaplan-Meier estimator.

Table 5 Overview of the extent of resections.

Resection procedure		Frequency	Percent
Without laser	atypical pulmonary resection	183	76.6
	segmental/bisegmental resection	17	7.1
	lobectomy/bilobectomy	10	4.2
	extended lobectomy	2	0.8
	pneumonectomy	4	1.7
	extended pneumonectomy	1	0.4
	combination with extra-anatomical procedure	22	9.2
	total	239	100.0
With laser	atypical pulmonary resection	48	77.4
	combination with segmental/bisegmental resection	14	22.6
	total	62	100.0

Discussion

Although prospective randomized studies are lacking, pulmonary metastasectomy forms an important component in the interdisciplinary treatment concept for oligometastatic patients. This applies in particular to most solid epithelial tumors for which current systemic therapeutic options generally do not provide a curative approach. The question thus arises as to whether, through the use of modern dissection techniques, patients who would otherwise be regarded as inoperable could undergo a potentially curative operation. The apparent inoperability is often justified by an allegedly high degree of parenchymal loss associated with central metastases or by a large number of smaller nodules located in various lobes of the lung. For several years the optimized Nd-YAG laser has been used for the dissection of lung tissue, allowing the bloodless precise resection of even central nodules and also the resection of multiple individual nodules

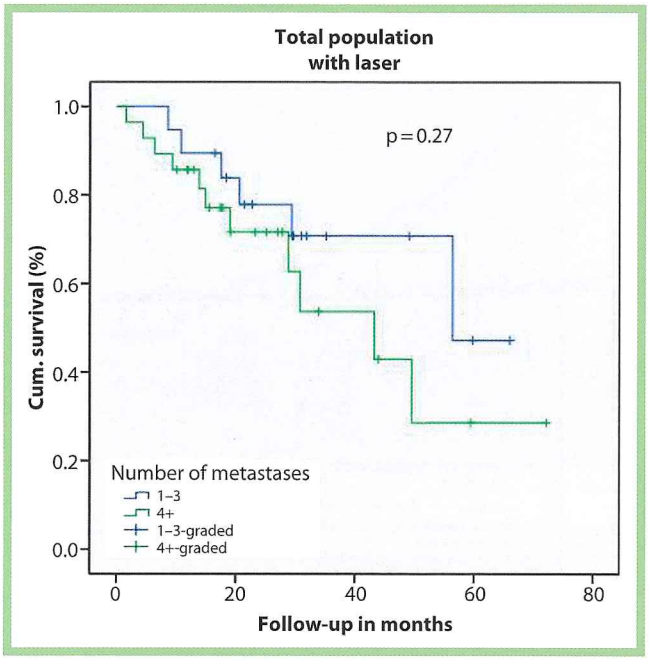

Fig. 5 In the subgroup analysis of laser-assisted metastasis-resected patients, the influence of the number of metastases on calculated survival is no longer detectable.

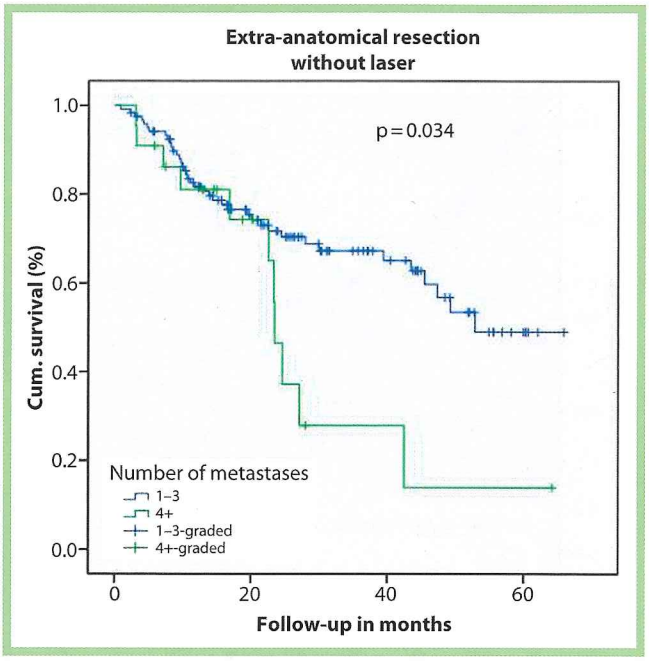

Fig. 6 In the subgroup of extra-anatomical resections without laser, the influence of the number of metastases on calculated survival is significant.

while preserving palpation capacity on the part of the operating surgeon. Use of the laser seems advantageous in particular for multiple and centrally located metastases in the interests of parenchyma-sparing resection and for the precise dissection of metastases located directly near sensitive structures (bronchus, vessels). In our investigation we therefore turned our attention to the question of whether laser metastasectomy is associated with an increase in the rate of perioperative complications and what the long-term results are following the resection of multiple metastases. In analyzing the criteria recorded by us, such as revision surgery and repeat drainage as well as extended drainage retention time as a sign of parenchymal leakage, postoperative empyema or other complications (chiefly secretion retention and heart rhythm disorders), we have not been able to identify any difference in the complication rate despite a significantly higher number of operative specimens after laser dissection (median: 7 vs. 2). Happily, no perioperative death was recorded in our series. Only the pneumonia rate was significantly increased after laser resection. Concomitant edema secondary to photothermal laser resection is known [8]. We would therefore like to qualify this by stating that the criteria adopted by us for defining pneumonia were broadly framed and that differentiation is not possible between genuine bacterial pneumonia and thermally/mechanically-induced pneumonitis as a result of heat development due to the laser at the dissection level and manipulation at multiple locations in connection with multiple metastases.

Complete resection of all metastases is the aim of the operation and is regarded as a confirmed prognostic factor [9]. We have been able to establish that, after laser dissection, R0 resection was not certified significantly more frequently. Conversely, however, we were unable to identify an influence of the dissection technique on survival. Our explanation for this lies in the more precise histopathological examination of the pulmonary parenchyma after laser dissection. Three zones can typically be defined in the technique employed by us using a focusing handpiece and non-contact with the tissue (**Fig. 8**). These three zones present an outer coagulation zone so that, owing to cauterization artefacts with a necrotic zone at the resection margin, it is more frequently difficult here to establish what R status exists, and the pathologist must therefore declare the classification Rx more frequently. Laser resection leaves behind an edge of carbonized tissue approx. 5 mm wide at the resection margin, which matches a safety margin [10].

Several studies prove that the number of metastases is an independent prognostic factor [11]. In our population, too, a significant worsening of the prognosis is confirmed as a function of the number of metastases, with this having become clear chiefly in patients with more than three metastases. The subgroup analyses nevertheless presented a sharp difference in the further course between patients who underwent conventional and those after laser-assisted metastasectomy. The prognostic influence of the number of metastases in the latter group thus seems to be rather of secondary importance. This tallies with an earlier study by Rolle, which showed in 328 patients that, in the case of complete laser metastasis resection, the prognostic value of the number of metastases is given a rating of up to 9 [5]. One factor in the resection of multiple individual nodules by laser could be preservation of the palpation capacity of the lung by the operating surgeon. In his study of the safety margin after pulmonary metastasectomy, Welter found a large number of satellite tumor cells and therefore recommended a safety margin of 3 mm for small metastases [12]. A further explanation could therefore be the edge of carbonized tissue at the resection margin after laser resection, which matches in some way a safety margin. The proportion of laser resections in our population, which at 20.6% was on the low side, could be justified by the equipment setup for laser resection, which is sometimes felt to be somewhat elaborate.

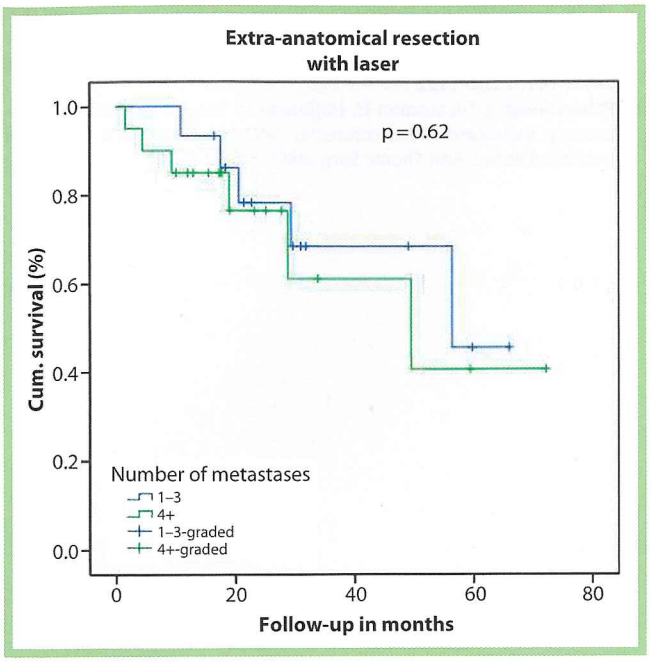

Fig. 7 In the subgroup analysis of extra-anatomical resections by means of laser, the influence of the number of metastases on calculated survival is no longer detectable.

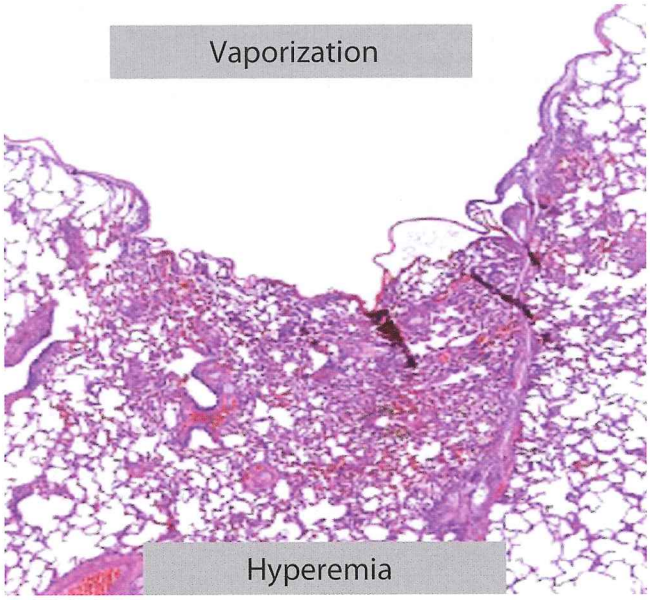

Fig. 8 Histological evaluation of pulmonary parenchyma after laser dissection (photograph: Pathology Dept., University Medical Center Freiburg, staining: HE, 10 × original magnification).

With an approximately equal frequency of extra-anatomical resections in the two treatment groups, additional anatomical resection was also required in 22.6% of cases among patients who underwent laser-assisted surgery. These cases were, however, exclusively segmental or bisegmental resections, which may give the impression that lobe-sparing or perhaps even pneumonectomy-avoiding operations could, where appropriate, also have been performed in the other treatment group with the use of a laser.

A critical feature of our study is that we did not undertake separate analysis for epithelial tumors, melanoma metastases, sarcomas and germ cell tumors. However, we deliberately did not do this because, as can be seen on taking the largest subgroup of patients with colorectal carcinoma metastases as an example, we would in some cases have compared very small patient numbers with one another and thus the possibility of drawing conclusions would also have been limited. The influence of mediastinal lymph node status for patients with colorectal carcinoma metastases, which became evident in larger series', was also not detectable in our subgroup analysis [13].

Conclusions

In our analysis, the Neodym-YAG laser was used in particular in patients with multiple pulmonary metastases for resection purposes. Despite a significantly higher number of specimens among the laser-assisted metastasectomies, complication rates were not elevated, except for the increased rate of pneumonia. Following the criteria we adopted for the definition of pneumonia, no differentiation was made between bacterial pneumonia and non-infection pneumonitis secondary to thermal operative trauma. Although laser resections were classified significantly more frequently as non-R0 operative specimens, which was first and foremost attributable to the classification of Rx due to cauterization of the resection margins, the resection technique had no bearing on survival. An explanation for this could be that laser resection leaves an edge of carbonized tissue approx. 5 mm wide at the resection margin, which matches a safety margin. The number of metastases has an influence on prognosis, but seems to be of secondary importance, particularly where the resection of all lesions is technically possible with the aid of a laser.

Conflict of interest: None

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