REVIEW ARTICLE

# Surgical Intervention for Pulmonary Metastases

Joachim Pfannschmidt, Gerlinde Egerer, Marc Bischof, Michael Thomas, Hendrik Dienemann


## SUMMARY

Introduction: Autopsy studies of persons who died of cancer have shown the lungs to be the sole site of metastasis in about 20% of cases. The resection of pulmonary metastases is indicated for palliative purposes if they contain a large volume of necrotic tumor, infiltrate the thoracic wall to produce pain, or cause hemoptysis or retention pneumonia. Metastasectomy with curative intent may be indicated for carefully selected patients.

Methods: This review is based on a selective search of the PubMed database for articles that were published from 2006 to 2011 and contained the keywords "pulmonary metastasectomy," "lung resection of metastasis," and "lung metastasectomy."

Results: No prospective comparative trials have been performed to date that might provide evidence for prolongation of survival by pulmonary metastasectomy; nor have there been any randiomized, controlled trials yielding evidence that would assist in the decision whether to treat pulmonary metastases with surgery, radiotherapy, or chemotherapy (or some combination of these). The indication for surgery is a function of the histology of the primary tumor, the number and location of metastases, the lung capacity that is expected to remain after surgery, and the opportunity for an R0 resection. Favorable prognostic factors include a long disease-free interval between the treatment of the primary tumor and the discovery of pulmonary metastases, the absence of thoracic lymph node metastases, and a small number of pulmonary metastases. The reported 5-year survival rates after pulmonary metastasectomy, depending on the primary tumor, are 35.5% to 47% for renal-cell carcinoma, 39.1% to 67.8% for colorectal cancer, 29% to 52% for soft-tissue sarcoma, 38% to 49.7% for osteosarcoma, and 79% to 94% for non-seminomatous germ-cell tumors. For the latter two types of tumor, chemotherapy is the most beneficial form of treatment for long-term survival.

Conclusion: When there is no good clinical alternative, the resection of pulmonary metastases can give some patients long-lasting freedom from malignant disease. Patients should be carefully selected on the basis of clinical staging with defined prognostic indicators.



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Department of Thoracic Surgery at the Thoraxklinik, Heidelberg University Hospital: Prof. Dr. med. Pfannschmidt, Prof. Dr. med. Dienemann

Department of Internal Medicine V: Hematology, Oncology and Rheumatology, Heidelberg University Hospital: PD Dr. med. Egerer

Department of Radiation Oncology and Radiation Therapy, Heidelberg University Hospital: Prof. Dr. med. Bischof

Department of Thoracic Oncology at the Thoraxklinik, Heidelberg University Hospital: Prof. Dr. med. Thomas


Pulmonary metastases are often found in advanced metastatization from carcinoma of the colon and rectum, kidney, breast, prostate, and oropharynx. In addition, chorionic carcinoma, osteosarcoma, soft tissue sarcoma, testicular tumors, Ewing sarcoma, and thyroid carcinoma all metastasize preferentially to the lungs.

If metastases are restricted to the lungs, the use of surgery within the overall oncological treatment is justified.

However, since a prediction of survival cannot be done without an operation, and the utility of surgery has not yet been tested in a prospective randomized study, the decision for or against metastasectomy must be made on a case-by-case basis (e1).

The aim of this review article is to give an up-to-date overview of surgical intervention for pulmonary metastases, based on a selective literature search of PubMed using the search terms "pulmonary metastasectomy", "lung resection of metastasis," and "lung metastasectomy." Radiotherapy will also be discussed as an alternative local treatment method.

## Principles for selection of patients for metastasectomy

As early as 1965, Thomford et al. put forward principles for patient selection that largely still apply today (1). The criteria for selecting patients to undergo surgical resection of lung metastases are:

- Technical resectability
- Tolerable general and functional surgical risk
- Control of the primary tumor process, and
- Exclusion of any further, extrathoracic metastasis.

In patients with widespread diffuse pulmonary metastases, or if the lesions are technically or functionally inoperable, local interventions such as surgery and radiotherapy are at best palliative.

In 1991 the International Registry of Lung Metastasis was constituted with the aim of developing a rationale of surgical intervention for lung metastases (2). To this end, 5206 patients who had undergone pulmonary metastasectomy with curative intent and with various primary tumor histologies were analyzed. Patients with complete resection (R0) of a solitary disease focus and a disease-free interval of more than 3 years after surgery to treat the primary tumor showed the most favorable prognosis. Although this study contained no control group of nonoperated patients, the significantly more favorable 5-year survival after R0

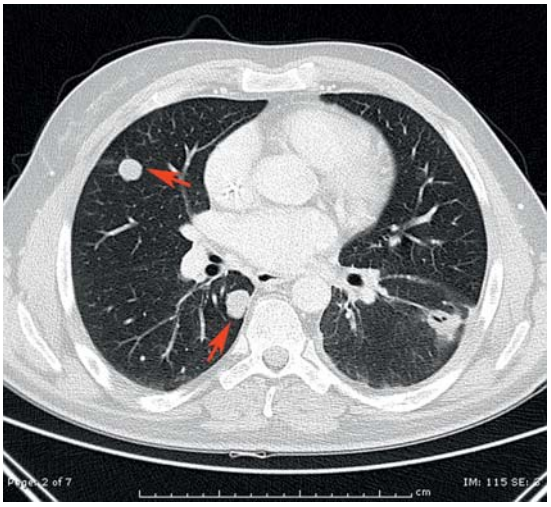

**Figure 1:** Lung metastases from a nonseminomatous testicular carcinoma after chemotherapy. Computed tomography shows two solid foci on the right (segments 5 and 6) and a single metastasis with central necrosis in the left lower lobe (segment 6)

resection (36%) compared to incomplete resection (13%) indicates the chances of success of metastasectomy (2). Operative mortality was 1%.

Today, the decision for surgical metastasectomy with curative intent should be taken by an interdisciplinary tumor board on a case-by-case basis. If no reasonable treatment options exist, the decision for surgical resection may in some cases be made even in the presence of unfavorable prognostic factors such as synchronous metastases.

## Resection of recurrent metastases

In patients who show a solitary recurrent metastasis in the lung, it should be investigated whether repeat resection is indicated. A longer time interval between the first metastasectomy and the appearance of recurring metastases appears to be prognostically more favorable (e2). Jaklitsch and co-authors (e3) have shown for various primary tumors that patients who undergo one recurrence metastasectomy achieved a median survival time of more than 60 months; with two recurrence metastasectomies median survival was 34.7 months, and with three or more it was 45.6 months. Patients in whom further surgery appeared impossible had a median survival of 8 months.

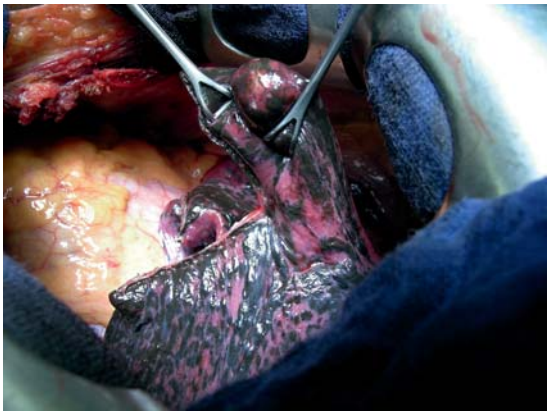

**Figure 2:** Intraoperative finding; wedge resection of a lung metastasis, segment 8, left side

## Diagnostic procedures

Staging examinations depend on the underlying tumor: usually, abdominal ultrasonography and computed tomography (CT) of the abdomen, bone scintigraphy, and cranial magnetic resonance imaging (MRI) are carried out.

Local tumor recurrence must always be ruled out by specialist examinations. Investigation techniques usually include CT or MRI of the primary tumor region and, for colorectal tumors, colonoscopy.

CT is essential in the planning of lung metastasectomy (e4). FDG-PET (fluorodeoxyglucose-labeled positron emission tomography) enables extrathoracic tumor manifestations to be ruled out while at the same time characterizing pulmonary focuses of disease on a metabolic basis. This last can be important especially in the case of a solitary pulmonary disease focus or thoracic lymph node involvement (e5, e6). MRI, on the other hand, has not improved the diagnosis of lung metastases compared with conventional CT. It is specifically indicated for showing tumor invasion of the great vessels, chambers of the heart, chest wall, and spinal column, and can be helpful in ruling out synchronous liver metastases.

Lesions may remain after chemotherapy in the form of "sterilized metastases." Histologically, in the best case these formations contain fibrosis and necrosis but no viable tumor cells (*Figure 1*).

Flexible tracheobronchoscopy is a standard component of the preoperative diagnostic workup. Its purpose is to allow evaluation of the mucosa and secure confirmation of the histology of centrally located metastases. In addition, it can be helpful, when used in combination with endobronchial ultrasound, in determining the status of the peribronchial and mediastinal lymph nodes (e7).

To secure the histology of peripheral foci up to 3 cm in size, video-assisted thoracic surgery (VATS) has become established for use as a diagnostic procedure with a low complication rate. How far lung metastasectomy by VATS can be used as a curative procedure to achieve local radical resection comparable with that achieved by thoracotomy has yet to be studied.

In one recent prospective randomized study, malignant pulmonary foci that had not been detected by preoperative CT were detected in 20% of patients by intraoperative palpation (3). Hence, so far thoracoscopic procedures have not been generally recommended for curative intent, since the lung tissues are not accessible to palpation as they are in the open procedure (e8).

## Surgical procedure

The standard procedure is a circumscribed atypical (lung tissue sparing) resection; more rarely, anatomic resection such as pulmonary segmentectomy or lobectomy is required (*Figure 2*).

**TABLE 1**

**Five-year survival and prognostic factors after lung metastasectomy—important studies**

| Primary tumor | Period (years) | Total no. of patients (no. with R0) | 5-year survival (R0) % | Prognostic factors |
|---|---|---|---|---|
| **Colorectal carcinoma** | | | | |
| Watanabe 2009 (e39) | 1992–2004 | 122 | 67.8 | Serum CEA, lymph node involvement |
| Riquet 2010 (e40) | 1985–2007 | 127 | 35.1 before 2000<br>63.5 after 2000 | Radicality, treatment period |
| Welter 2007 (e41) | 1993–2003 | (169) | (39.1) | Number, lymph node involvement, disease-free interval |
| **Renal cell carcinoma** | | | | |
| Meimarakis 2011 (e42) | 1986–2006 | 202 (175) | 39 (45) | Radicality, size, thoracic and primary lymph node involvement, disease-free interval, pleural infiltration |
| Kanzaki 2011 (e43) | 1973–2008 | 48 | 47 | Radicality, disease-free interval |
| Kawashima 2011 (e44) | 1998–2008 | 25 | 35.5 | Radicality |

R0, resection status 0; CEA, carcinoembryonic antigen

Central metastases involving structures near the hilum may necessitate pulmonectomy. If the functional reserve does not permit anatomic resection, atypical resection in central lung segments or of multiple metastases using a neodymium:YAG laser must be attempted (4).

Postoperative complications are reported in 10% to 15% of patients after lung metastasectomy. The main ones are recurrent postoperative secretion retention leading to atelectasis and pneumonia, cardiac arrhythmias, and bronchopleural fistulas. Morbidity is determined mainly by the patient's general condition, the surgical approach, and the extent of the resection (e9, e10).

For a number of tumor entities, involvement of intrathoracic lymph node stations as a sign of tumor dissemination is associated with a significantly poorer prognosis (5, 6). The question of the necessity and extent of thoracic lymph node dissection in addition to metastasectomy has not yet been adequately answered. According to a survey of European thoracic surgeons, in most hospitals lymph nodes are merely sampled (e11).

## Radiotherapy

Stereotactic radiotherapy is an effective and at the same time noninvasive, tissue-preserving treatment alternative for solitary lung metastases in functionally inoperable patients. With detailed radiation planning and accurate irradiation, biologically effective doses totaling more than 100 Gy can be delivered in one to five dose fractions (e12). A steep dose gradient at the margin of the lesion ensures that surrounding healthy tissue is preserved as much as possible.

Even in the case of metastatic melanoma and renal cell carcinoma, which are regarded as radioresistant, stereotactic radiotherapy allows local control rates of 88% after 18 months (e13). Because of the small radiation volumes, treatment-related side effects are rare (e12).

## Special aspects of particular primary tumors

### Colorectal carcinoma

Lung metastatectomy is a treatment option in 1% to 2% of patients with colorectal carcinoma (e14). The following are regarded as unfavorable prognostic factors after lung metastatectomy (*Table 1*):

- Histologically confirmed thoracic lymph node involvement
- Short disease-free interval
- Raised serum CEA (carcinoembryonic antigen) tumor marker
- Multiple lung metastases (7).

While patients with stage IV disease have a median survival of up to 24 months with modern antibody treatment (e14), a 5-year survival rate of up to 68% can be achieved after metastasectomy (7).

If synchronous liver metastases are present, a 5-year survival rate of 42% is reported after sequential lung and liver metastasectomy. Metachronous metastases are regarded as prognostically more favorable than synchronous metastases, as is the appearance of liver metastases before lung metastases (e15, e16).

The role of adjuvant and neoadjuvant chemotherapy combined with liver metastasectomy is currently under discussion (8). To what extent similar approaches can be developed for metastasectomy in the lung remains to be seen.

### Renal cell carcinoma

Renal cell carcinoma (*Table 1*) metastasizes preferentially to the lung, either hematogenically or lymphogenically.

Although systemic therapy with tyrosine kinase inhibitors and mTOR inhibitors is associated with an

**TABLE 2**

**Five-year survival and prognostic factors after lung metastasectomy—important studies**

| Primary tumor | Period (years) | Total no. of patients (no. with R0) | 5-year survival (R0) % | Prognostic factors |
|---|---|---|---|---|
| **Breast carcinoma** | | | | |
| Planchard 2004 (e45) | 1972–1998 | 125 (96) | 45 | Disease-free interval, size |
| Welter 2008 (12) | 1998–2007 | 47 | 36 | Receptor status |
| Chen 2009 (11) | 1991–2007 | 41 | 51 | Disease-free interval, number |
| **Head and neck tumors** | | | | |
| Shiono 2009 (e46) | 1980–2006 | 114 | 26,5 | Sex, oral cancer, lymph node involvement, radicality |
| Winter 2008 (e47) | 1984–2006 | 67 (40) | 20.9 (27.7) | Radicality, perioperative complications, neoadjuvant treatment for the metastases |
| Chen F, et al. 2008 (e20) | 1991–2007 | (20) | (59.4) | Sex, disease-free interval, histology |

R0, resection status 0

improvement in progression-free survival, lung metastasectomy continues to be accepted within the framework of treatment with curative intent (9, e17).

Factors that are favorable for surgery are metachronous, solitary foci or a few peripheral lesions. A 10-year survival rate after lung metastasectomy of 42% has been reported (10). Synchronous occurrence of thoracic lymph node metastases, however, which is relatively frequent (30% to 45% of cases), is associated with a much less favorable prognosis. Mean survival of patients with mediastinal and pulmonary lymph node involvement has been reported as 26 to 29 months, compared to 64 to 92 months without lymph node metastases (5, 6). For this reason, patients with mediastinal lymph node metastases should not be assigned to surgery with curative intent.

### Breast cancer

Advanced breast cancer (*Table 2*) often infiltrates the lungs and pleurae by direct invasion or lymphogenic or hematogenic dissemination. Patients with isolated lung metastases are rare; usually, local or diffuse lymphangitis with single or multiple lung metastases is found.

For patients with metachronous metastases and a limited number of foci, predominantly in one pulmonary lobe, 5-year survival rates of 40% to 50% are reported after pulmonary metastasectomy has been carried out and all the options for systemic therapy have been used up (11, 12).

Debate exists as to the necessity of surgical resection of metastases. In a retrospective study in which patients who underwent pulmonary metastasectomy showed better long-term survival (36%) than those treated conservatively (11%), Staren et al. (e18) emphasized the importance of surgery. Tanaka et al. (13), on the other hand, point out that mean survival times of 2 to 3 years are reported in patients receiving systemic therapy alone.

Notwithstanding, solitary foci in the lungs—which are discovered in the course of tumor follow-up care—often pose a problem for the differential diagnosis. If there are no extrathoracic tumors, these foci should be surgically removed, the more so since in most of these cases a primary lung carcinoma turns out to be a secondary tumor, more rarely metastatic breast cancer or a benign lesion (e19).

### Head and neck carcinomas

Distant metastases are most often found in the lung. Five-year survival rates of 20.9% to 59.4% after lung metastasectomy have been reported (14, e20); a longer disease-free interval appears to be particularly favorable. Because of their high coincidence with lung carcinoma, solitary pulmonary lesions in a patient who is locally tumor-free in the head and neck (ear, nose, and throat) should undergo diagnostic workup (*Table 2*). Often, however, even after histological analysis, the differential diagnosis between lung cancer and metastases remains unclear.

### Malignant melanoma

Over 70% of all patients with metastatic melanoma (*Table 3*) develop lung metastases, but only about 10% of them have lung metastases alone (e21). It frequently happens that a malignant melanoma is only diagnosed through histological analysis of newly discovered lung foci (e22).

Surgery is the procedure of choice for solitary foci, and the prognosis, with 5-year survival rates of 21.0% to 35.1% (e21, e23) is significantly better than with multiple metastases. Other significant factors for a favorable prognosis are a disease-free interval of more than 12 months before the occurrence of a lung metastasis, and the absence of thoracic lymph node metastases (e24). Because of the extensive metastasization in other organ systems, FDG-PET is particularly relevant in the preoperative staging (e25).

**TABLE 3**

**Five-year survival and prognostic factors after lung metastasectomy—important studies**

| Primary tumor | Period (years) | Total no. of patients (no. with R0) | 5-year survival (R0) % | Prognostic factors |
|---|---|---|---|---|
| **Malignant melanoma** | | | | |
| Schuhan 2011 (e23) | 1995–2007 | 30 | 35.1 | |
| Andrews 2006 (e48) | 1988–2005 | (86) | (33) | Number |
| Petersen 2007 (e21) | 1970–2004 | 318 (249) | (21) | Histology, disease-free interval, number, extrathoracic metastases |
| **Germ cell tumors** | | | | |
| Kesler 2011 (15) | 1980–2006 | 431 | 79 | Age, histology of metastases, histology of testicular cancer |
| Besse 2009 (e27) | 1980–2003 | 53 | 94 | |
| Pfannschmidt 2006 (e49) | 1996–2001 | 52 (40) | 75.8 (82.8) | Radicality, tumor markers in serum: AFP, hCG ↑ |

R0, resection status 0; AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin

### Nonseminomatous germ cell tumors

In nonseminomatous testicular cancer (*Table 3*), all lesions remaining after chemotherapy (cisplatin-based combinations) should be removed so far as possible.

Although a response to chemotherapy is often accompanied by a sharp fall in tumor markers (α-fetoprotein, β-HCG), normalization of the tumor marker values does not imply that residual tumors in the lungs and mediastinum need not be removed. These can still show viable tumor cells in the histological workup, in addition to necrosis and scar tissue. The following are regarded as indications for the resection of lung foci (e26):

- All residual tumors after chemotherapy and normalization of tumor marker values
- Lack of response to chemotherapy
- Partial response to chemotherapy
- Recurrence after chemotherapy.

In addition to a large number of metastases and advanced patient age, the demonstration of viable tumor cells in the residual tissue and an absence of tumor marker normalization have proved to be clinically unfavorable prognostic factors in patients with exclusively pulmonary metastases; 5-year survival rates of 79% to 94% have been reported in studies (15, 16, e27). Postoperatively, therefore, histologically complete remission in response to chemotherapy in patients with solitary and monolateral metastases and negative retroperitoneal lymph node status is regarded as the most favorable set of characteristics (15, 16).

### Soft tissue sarcoma

Between 20% and 50% of all patients with soft tissue sarcoma (*Table 4*) develop lung metastases in the course of their disease, most of these being discovered as metachronous metastases in the course of follow-up care for the primary tumor (17).

Lung metastases from soft tissue sarcomas should be surgically removed so long as complete surgical resection appears technically possible, because they are usually only moderately chemosensitive (17, e28, e29).

In a retrospective nonrandomized study the natural course of patients with lung metastases showed a median survival of 11 months compared to 33 months for those who were treated surgically; however, it may be assumed that these results are biased by stringent selection of patients for surgical treatment (e28).

Favorable prognostic factors are a long disease-free interval before the appearance of lung metastasis and a low histological grade; 5-year survival rates after surgical metastasectomy are reported at between 29% and 52% (18, e29, e30).

### Osteosarcoma

Despite the progress in chemotherapy, radiotherapy, and surgical treatment of metastatic osteosarcoma (*Table 4*), the 5-year survival rates—among these patients who are mostly young—are between 20% and 40% (19–21).

Treatment of metastatic osteosarcoma today is tied to clinical studies (COSS/Cooperative Osteosarcoma Study, EURAMOS-1/European-American Osteosarcoma Study, and EUROB. O.S.S./EUROpean Bone Over 40 Sarcoma Study), is multidisciplinary, and takes into account the systemic and local manifestations (e31, e32). For synchronous lung metastases of the highly malignant osteosarcoma, this means aiming at complete resection of the lung metastases after chemotherapy and radical surgery of the primary tumor (e33). Postoperatively, therapy must be stratified according to tumor response.

Patients with primary metastatic osteosarcoma must be assumed to have a poorer prognosis than those with metachronous metastasization (e34).

Surgical resection is also considered to be particularly important for recurrent lung metastases, irrespective of whether chemotherapy is carried out (22).

**TABLE 4**

**Five-year survival and prognostic factors after lung metastasectomy—important studies**

| Primary tumor | Period (years) | Total no. of patients (no. with R0) | 5-year survival (R0) % | Prognostic factors |
|---|---|---|---|---|
| **Soft tissue sarcoma** | | | | |
| Predina 2011 (18) | 1995–2007 | 48 | 52 | |
| Pfannschmidt 2006 (e30) | 1996–2002 | 50 | 37.6 | Radicality |
| Canter 2007 (e29) | 1990–2005 | 138 | 29 | Radicality, disease-free interval |
| **Bone sarcoma** | | | | |
| Letourneau 2011 (e50) | 1985–2000 | 84 | | Location (central/peripheral) |
| Briccoli 2005 (19) | 1980–2001 | 94 | 38 | Disease-free interval, number |
| Diemel 2009 (e51) | 1993–2006 | 93 | 49.7 | |

R0, resection status 0

### Other tumors

For lung metastases of other primary tumors, the list of general indications applies: that is, local resection should be carried out if this is technically and functionally feasible, so long as the primary tumor has been removed or is under control and no more effective local or systemic treatment is available.

## Summary

The diagnosis of lung metastases is often associated with a very poor prognosis with a short survival time. In these situations, palliative chemotherapy is usually initiated. First, however, an interdisciplinary tumor board should discuss the possibility of metastasectomy. If reasons are found for carrying out palliative resection, local radical resection is fundamentally the aim as well as symptom control (e35).

Functional operability must be confirmed before surgery in accordance with the European Respiratory Society/European Society of Thoracic Surgeons guidelines (e36).

Survival after lung metastasectomy depends on the nature of the primary tumor, and in the case of chemotherapy-sensitive tumors is related to surgery only to a limited extent. The objection that surgical resection of metastases is a local procedure applied to a disseminated disease, the success of which has not been validated in prospective randomized studies, is justified (e37). The first prospective randomized studies of the effect of surgical resection of lung metastases have been started with the PulMiCC-Trial (Pulmonary Metastasectomy in Colorectal Cancer) in colorectal carcinoma and the SMAT study (a prospective randomized multicenter phase 2 study of surgical resection of lung metastases of clear-cell renal cell carcinoma ± sunatinib therapy for 1 year) in renal cell carcinoma (23, 24). Data on lung metastasectomy can be found only in the current S1 guideline for osteosarcoma (e32) and the S3 guideline for colorectal cancer (e38). Even in these, the evidence base still rests on published results of retrospective case series.

**Conflict of interest statement**

Dr Egerer has received consultancy fees from MSD and lecture fees from MSD and Pfizer. She has also received third-party study funding from MSD.

Professor Thomas has received consultancy fees and reimbursement of registration fees for conferences/training events and travel costs from Lilly, Pfizer, Novartis, and Roche.

Professor Dienemann has received consultancy fees from Lilly and lecture fees from AstraZeneca.

Professor Pfannschmidt and Professor Bischof declare that no conflict of interest exists.

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**KEY MESSAGES**

- Today, surgical resection of lung metastases is a standard component of cancer therapy. A favorable effect on long-term survival after curative surgery is probable.
- Before surgery with curative intent is undertaken, extrathoracic metastases must always be ruled out, and curative treatment of the primary tumor must be assured or already complete.
- The perioperative complication rate is reported at between 10% and 15%, and is essentially dependent on the patient's general condition and the extent of the resection. Operative mortality is less than 2%.
- Surgical resection of recurrent lung metastases is subject to the same technical, functional, and oncological provisions as the first resection.
- Patients should be selected by a tumor board that takes into account known prognostic factors. The decision for surgery must be taken on the basis that complete resection is expected.


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**Corresponding author**
Prof. Dr. med. Joachim Pfannschmidt
Chirurgische Abteilung der Thoraxklinik am Universitätsklinikum Heidelberg
Amalienstraße 5
69126 Heidelberg, Germany
joachim.pfannschmidt@thoraxklinik-heidelberg.de


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