Thieme

Lung Metastasectomy for Pulmonary Metastatic Breast Carcinoma

Lungenmetastasenchirurgie beim pulmonal metastasierten Mammakarzinom

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Key words
breast carcinoma, breast cancer, lung metastases, metastasectomy, R_0 resection

Schlüsselwörter
Mammakarzinom, Brustkrebs, Lungenmetastasen, Metastasektomie, R_0-Resektion

received 28.2.2017
revised 21.3.2017
accepted 2.4.2017

Bibliography
DOI https://doi.org/10.1055/s-0043-108252
Geburtsh Frauenheilk 2017; 77: 645–650 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0016-5751

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Deutsche Version unter:
https://doi.org/10.1055/s-0043-108252

ABSTRACT

Breast carcinoma with pulmonary metastasis can be treated locally or systemically. Following primary tumour resection patients with isolated, completely resectable pulmonary nodules and definite functional operability can be offered lung metastasis resection. Following metastasectomy a median survival of 32 to 96.6 months can be achieved with corresponding five-year survival rates between 30.8 and 54.4%. The procedure is associated with a mortality rate of 0 to 3%. The most important independent prognostic factor for long-term survival is complete resection of all lung lesions. The configuration and pattern of metastasis as well as disease-free interval, hormone and HER2/neu receptor status also appear to influence prognosis, but are of lesser importance. Intrapulmonary recurrence of metastases may, after careful selection on a case-by-case basis, also be treated operatively. In some cases this is associated with a favourable long-term prognosis. Pulmonary metastasectomy should be the treatment of choice for selected patients with metastatic breast carcinoma.

ZUSAMMENFASSUNG

Das pulmonal metastasierte Mammakarzinom kann systemisch oder lokal therapiert werden. Nach erfolgter Primärtumorresektion können Patientinnen mit isolierten, vollständig resektablen Lungenrundherden und sichergestellter funktioneller Operabilität einer Lungenmetastasektomie zugeführt werden. Nach Metastasenresektion wird ein medianes Überleben von 32 bis 96,6 Monaten erreicht, korrespondierende 5-Jahres-Überlebensraten liegen zwischen 30,8 und 54,4%. Der Eingriff ist mit einer Mortalität von 0–3% verbunden. Der wichtigste unabhängige Prognosefaktor für das Langzeitüberleben ist die vollständige Resektion aller Lungenmetastasen. Die Metastasenkonfiguration und das Metastasierungsmuster scheinen ebenso wie das krankheitsfreie Intervall, der Hormon- und HER2/neu-Rezeptorstatus für die Prognose zwar relevant, jedoch von nachrangiger Bedeutung zu sein. Intrapulmonale Metastasenrezidive können nach sorgfältiger Indikationsstellung ebenfalls reseziert werden. Dies kann in Einzelfällen ein günstiges Langzeitüberleben ermöglichen. Die Lungenmetastasenchirurgie sollte die Therapie der Wahl für selektionierte Patientinnen mit pulmonal metastasiertem Mammakarzinom sein.

▶ **Table 1** Operative data.

Study	Patients	Single metastasis	VATS (% of total)	Anatomical resection	R_0 resection	Postoperative morbidity	Postoperative mortality
Friedel et al. [2]	467	66%	3.6%	38.8%	84%	–	–
Ludwig et al. [3]	21	61.9%	0%	17%	100%	23.8%	0%
Planchard et al. [4]	125	59.2%	0%	26.4%	76.8%	12.8%	–
Tanaka et al. [5]	39	38.5%	0%	–	84.6%	–	–
Rena et al. [6]	27	88.9%	–	–	–	–	–
Chen et al. [7]	41	51.2%	34%	22%	100%	–	0%
Welter et al. [8]	47	61.7%	–	31.9%	57.4%	5.8%	0%
Yoshimoto et al. [9]	90	86.7%	–	88.9%	–	–	–
Kycler et al. [10]	33	42.4%	0%	–	–	18.2%	3%
Meimarakis et al. [11]	81	63%	–	27.2%	81.5%	7.6%	0%

VATS: video assisted thoracoscopy; R_0 resection: complete metastasis resection; –: not specified.

Introduction

Breast carcinoma is the most common malignancy in women [1]. Apart from genetic predisposition in the presence of BRCA-1 or BRCA-2 mutations, risk factors described in the literature include early menarche, late menopause, hormone replacement therapy during and after menopause and lifestyle-associated factors such as obesity, alcohol and tobacco consumption [1]. In 2013 more than 17 800 women died from a breast cancer in Germany [1]. Various local, systemic or combination treatments are available for advanced stage tumours dependent on the pattern of metastasis. This systematic review article summarises the current literature on lung metastasectomy for isolated pulmonary metastasis following primary tumour treatment for breast cancer. The evidence for thoracic surgical procedures and an analysis of prognostic factors are presented.

Overview

Methods

A structured literature search was performed using the search terms “breast cancer”, “breast carcinoma”, “lung metastasis”, “lung metastases”, “pulmonary metastasis”, “pulmonary metastases”, “lung resection”, “pulmonary resection”, “lung surgery”, “pulmonary surgery”, “lung metastasectomy” and “pulmonary metastasectomy”. Publications from 1 January 2000 and after, in English or German were taken into account. The literature search performed on 15 February 2017 had 2426 hits in MEDLINE and found one review article in the Cochrane library. After step-wise appraisal 11 studies where identified each with at least 20 patients having had lung metastasectomy following primary tumour treatment with curative intent [2–12].

Ten of the reviewed studies were case series, together reporting on over 971 patients with treated breast carcinoma and pulmonary metastasectomy [2–11]. Operations were performed between 1960 and 2007. In addition a meta-analysis from 2015 analysing 1937 patients was included in our review [12]. According to the Oxford University classification the ten case series were rated with an evidence level (EbM-level) of 4 and the meta-analysis of 3 [13].

Metastasectomy

Pulmonary metastasectomy can be performed as an open surgical procedure or as a video-assisted thoracic surgery (VATS) procedure. In the studies analysed VATS was used far less often than open thoracic surgery (▶ **Table 1**). Open surgery is mostly performed via thoracotomy. The larger incision allows manual palpation of the entire unilateral lung parenchyma, which may detect tumour suspicious lesions not found on imaging [14]. The VATS procedure is most suited to patients with a single peripherally located lung lesion.

Metastasis resection can be performed according to the anatomical boundaries of the lung as a segment-, lobe- or pneumonectomy. Depending on the size of metastasis non-anatomical resection is also possible (e.g. laser enucleation or wedge resection). Whereas anatomical resection provides more safety in terms of oncological radicality, it also results in more loss of potentially vital lung tissue. The proportion of anatomical resections in the various case series lay between 17 and 88.9% (▶ **Table 1**).

Metastasectomy can be part of both palliative and curative treatment strategies. For palliation metastasectomy is useful for symptom control (dyspnoea and haemoptysis) when functional operability is assured. Indication criteria for lung metastasis surgery with curative intent include:

1. the breast tumour is completely removed
2. synchronous, extrathoracic metastases have been excluded
3. functional operability is assured
4. complete resection of all lung lesions appears feasible

The studies included documented complete resection (R_0 resection) of metastases in 57.4 to 100% of patients (▶ **Table 1**). In the context of metastasis resection mediastinal lymphadenec-

▶ **Table 2** Survival after metastasis surgery.

Study	Time period of resection	Patients	Median DFI	Median survival	3-year SR	5-year SR	10-year SR
Friedel et al. [2]	1960–1994	467	–	35 months	–	35%	20%
Ludwig et al. [3]	1989–1998	21	99.2 months	96.9 months	–	53%	–
Planchard et al. [4]	1972–1998	125	–	50.4 months	58%	45%	30%
Tanaka et al. [5]	1992–2001	39	66.8 months	32 months	–	30.8%	–
Rena et al. [6]	1990–2003	27	50 months	–	–	38%	18%
Chen et al. [7]	1991–2007	41	55 months	–	–	51%	51%
Welter et al. [8]	1998–2007	47	–	32 months	–	36%	–
Yoshimoto et al. [9]	1960–2000	90	67.2 months	75.6 months	–	54%	40%
Kycler et al. [10]	1994–2002	33	51.9 months	73.2 months	81.8%	54.4%	–
Meimarakis et al. [11]	1982–2007	81	–	82.4 months	–	–	–
Fan et al. [12]	1960–2007	1937	–	–	–	46%	–

DFI: disease-free interval, defined as time from primary tumour resection to detection of metastasis; SR: survival rate; –: not specified.

tomy is also often considered. Only a small proportion of patients in the case series underwent lymphadenectomy, however, of these, 7.8 to 44% were found to have mediastinal lymph node metastasis [2–4, 8, 9, 11]. The original studies did not evaluate the prognostic significance of lymphadenectomy among metastasectomy patients. The influence on long-term survival therefore remains uncertain and should be addressed in future studies.

Postoperative complications are described in 5.8 to 23.8% of patients, with mild complications such as atelectasis, pneumothorax and haemothorax, pneumonia and arrhythmias being most common. Lung metastasis surgery has an associated postoperative mortality of 0–3% and can be regarded as a safe treatment option (▶ **Table 1**).

Survival after metastasis surgery

Median follow-up for the case series was between 20.6 and 102 months [4, 7–11]. Pulmonary metastasectomy resulted in a median post-metastasectomy survival of 32 to 96.6 months (▶ **Table 2**) [2–5, 8–11]. Five-year survival rates were between 30.8 and 54.4%, while 10-year survival rates were between 18 and 51% [2–10]. One meta-analysis from the year 2015 analysed the survival prognosis of patients with breast carcinoma after lung metastasis surgery quantitatively [12]. The authors pooled data from 1937 patients from 16 case series. The calculated five-year survival rate was 46% (95% confidence interval: 43 to 49%), however on sensitivity analysis significant heterogeneity was found [12]. In summary, qualitative analysis allows the conclusion that selected patients will benefit from metastasectomy and may have favourable prognosis.

Despite complete resection of metastases intrapulmonary recurrences are possible. These recurrences may also be treated surgically if they again fulfil the general indication criteria for metastasectomy and the patient wishes to have a repeat metastasectomy. In the study by Friedel et al. the subgroup of patients with repeat metastasectomy achieved a 40% five-year survival rate which was better than that of the study collective overall (35%) [2]. Following repeated metastasectomy median post-metastasectomy survival was approximately 47 months in the study by Meimarakis et al. [11]. The favourable long-term survival following repeat metastasectomy may seem surprising since an aggressive primary tumour/high tumour cell load can be assumed. Indeed, strict criteria should be applied when indicating both initial and repeat metastasectomy. Patients fulfilling these strict criteria do not have disseminated metastasis, usually have favourable general condition and may benefit from repeat metastasectomy if all metastases are removed.

Prognostic factors for survival after metastasis surgery

Univariate prognosis model

▶ **Table 3** shows qualitative results for prognostic factors based on univariate analysis models for the individual case series. These study results suggest that neither patient age nor the extent of resection (anatomical or non-anatomical resection) or surgical approach (thoracotomy versus VATS) affect patient prognosis significantly. The disease-free interval, defined as the time period between definitive treatment of the primary tumour and metastasis diagnosis, is regarded as an important general oncological predictor of tumour cell load. For this prognostic factor results were heterogeneous between the studies analysed: six studies found a statistically significant influence on post-metastasectomy survival for this parameter while four author groups found no evidence for a significant influence on prognosis. Despite shortened disease-free intervals of below 36 months patients achieved a median survival of 28.8 to 34.4 months and five-year survival rates of 21 to 33.3% following lung metastasis surgery [4, 6, 7, 9]. Complete resectability of all lung lesions is considered to be the most important indication criterion for lung metastasis of surgery. Patients with R_0 resection had a statistically significant survival advantage in three out of four case series [2, 10, 11]. In the study by Welter and colleagues patients with R_0- and R_1 resections (median survival: approx. 30 months) were pooled and compared with macroscopi-

▶ **Table 3** Prognostic factors for survival after metastasectomy (univariate analyses).

Prognostic factors (based on univariate analyses)	Friedel et al. [2]	Ludwig et al. [3]	Planchard et al. [4]	Tanaka et al. [5]	Rena et al. [6]	Chen et al. [7]	Welter et al. [8]	Kycler et al. [9]	Yoshimoto et al. [10]	Meimarakis et al. [11]
Age	–	–	–	–	–	n. s.	n. s.	–	n.s	n. s.
Disease-free interval (threshold value)	s. (36 mo.)	n. s. (24 mo.)	s. (36 mo.)	n. s. (60 mo.)	s. (36 mo.)	s. (36 mo.)	n. s. (36 mo.)	s. (36 mo.)	s. (36 mo.)	n. s. (24 mo.)
Number of metastases	n. s.	n. s.	n. s.	n. s.	–	s.	s.	n. s.	n. s.	s.
Metastasis size	–	–	s.	–	–	–	–	n. s.	n. s.	s.
Distribution of metastases (uni- vs. bilateral)	n. s.	–	n. s.	n. s.	–	s.	–	s.	–	n. s.
Estrogen receptor status of LM	–	n. s.*	n. s.*	–	–	–	s.	n. s.*	–	s.*
Progesterone receptor status of LM	–	n. s.*	n. s.*	–	–	–	–	n. s.*	–	s.*
HER2/neu receptor status of LM	–	–	–	–	–	–	s.	–	–	n. s.
Resection status	s.	–	–	–	–	–	n. s.	s.	–	s.
Extent of resection	n. s.	–	–	–	–	–	–	n. s.	n. s.	–
Surgical approach	–	–	–	–	–	n. s.	–	–	–	–
Repeat metastasis surgery	n. s.	–	–	–	–	–	–	s.	–	n. s.

LM: lung metastasis; n. s.: not statistically significant in the respective study; s.: statistically significant prognostic factor in respective study; –: not tested for significance or not specified in the study; * estrogen and progesterone receptors pooled together as hormone receptor.

cally incomplete resections (median survival: approx. 16 months), showing a clinically relevant though statistically non-significant difference [8].

The case series showed divergent results for number, size and distribution (uni- versus bilateral) of metastases. It is noteworthy that patients with bilateral lung metastases and staged resection achieved a median survival of up to 47 months [11].

The HER2/neu, estrogen and progesterone receptor status is of fundamental importance in the immunohistochemistry workup of breast carcinoma. Lung metastases may express these receptors, however receptor status between primary tumour and metastasis may differ [8, 11, 15]. The univariate analysis showed varying results with respect to prognostic relevance and a definite influence has not yet been demonstrated.

Multivariate prognosis model

▶ **Table 4** summarises the qualitative study results for prognostic factors on the basis of multivariate analysis models that take the interaction of prognostic factors into account. All three study cohorts showed a significant survival advantage for patients with a disease-free interval greater than 36 months, however even shorter disease-free intervals were associated with favourable long-term survival [4, 7, 10]. Fan et al. calculated a hazard ratio of 1.7 for patients with a disease-free interval less than three years in their meta-analysis [12]. Two studies demonstrated a significant survival advantage for R_0 resection [10, 11], smaller metastasis size [4, 11] and number of metastases [7, 11]. The meta-analysis also showed significant prognostic relevance for these three factors [12]. Chen et al. and Kycler et al. evaluated the influence of distribution of involvement on survival prognosis. No evidence for a statistically significant difference between patients with unilateral or bilateral lung metastases was found in either of the studies [7, 10].

In the study by Welter et al. hormone receptor-positive metastases were associated with a significant survival advantage. Results of the study by Kycler et al. in contrast showed no statistically significant difference [8, 10]. Meimarakis et al. considered progesterone and estrogen hormone receptors together, finding a statistically significant difference in favour of hormone receptor-positive lung metastasis [11]. This result is in agreement with Fan et al. who calculated a hazard ratio of 2.3 for hormone receptor-negative metastases [12]. In summary, immunohistochemical examination of metastasis receptors before targeted additional or monotherapy seems prudent, since receptor status may differ from that of the breast tumour [8, 11, 15].

Lung metastasis surgery recommendations

According to the currently valid S3-guideline for the treatment of breast carcinoma, lung metastasectomy may be indicated in the absence of disseminated metastases, when unilateral lung metastasis is present and the disease-free interval is more than one year (good clinical practice guideline) [16]. The “Working Group for Gynaecological Oncology” (AGO) in its recommendation “special situations and locations in metastatic breast cancer” concludes that in the presence of unilateral metastasis, resection of lung lesions has no associated benefit and should therefore only be considered in individual cases [17]. In the presence of bilateral lung metastasis metastasectomy should generally not be considered [17].

▶ **Table 4** Prognostic factors for survival after metastasectomy (multivariate analyses).

Prognostic factors (based on multivariate/pooled analyses)	Planchard et al. [4]	Chen et al. [7]	Welter et al. [8]	Kycler et al. [10]	Meimarakis et al. [11]	Fan et al. [12]
Disease-free interval (< 36 months vs. > 36 months)	s.	s.	–	s.	–	s. HR: 1.7 (1.37–2.1)
Number of metastases	–	s.	–	–	s.	s. HR: 1.31 (1.13–1.5)
Size of metastases	s.	–	–	–	s.	–
Distribution (uni- vs. bilateral)	–	n.s	–	n. s.	–	–
Resection status	–	–	–	s.	s.	s. HR: 2.06 (1.63–2.62)
Estrogen receptor status	–	–	s.	n. s.	s.*	s.* HR: 2.30 (1.43–3.7)
Progesterone receptor status	–	–	–	–	s.*	s.* HR: 2.30 (1.43–3.7)

n. s.: statistically non-significant; s.: statistically significant prognostic factor; –: statistical significance not tested or reported; HR: hazard ratio (95 % confidence interval); * estrogen and progesterone receptors pooled to hormone receptor

Six studies reported explicitly on patients with disease-free intervals less than 12 months [4–9]. With the exception of one case series, all other studies included patients with bilateral metastasis [2–5, 7–11]. On the basis of survival data presented here, breast cancer patients with pulmonary metastasis would seem to benefit from metastasectomy both when disease-free interval is less than 12 months and in the case of bilateral lung metastases.

Conclusion

Metastasectomy is a safe procedure to be considered in both curative and palliative treatment situations. Every patient with successfully treated primary tumour and isolated synchronous or metachronous lung metastases should be presented to an interdisciplinary tumour conference. Pulmonary metastasectomy should be considered when functional operability and resectability of all lung lesions seems to be feasible. The most important prognostic factor for post-metastasectomy survival is undisputedly the complete resection (R_0 resection) of all metastases. The number of lung lesions may be a limiting factor, however on the basis of current evidence, is of minor importance for surgery indication. A disease-free interval of < 12 months and bilateral lung metastases are not absolute contraindications to metastasectomy. These patients in particular require careful interdisciplinary treatment decision-making. Hormone and HER2/neu receptor status of lung metastases and the primary breast tumour may differ. Receptor status of the breast tumour is not the primary consideration for lung metastasectomy indication, rather the receptor status of the lung metastases themselves appears to influence post-metastasectomy survival. Repeat metastasectomy of isolated intrapulmonary recurrences may be considered when medically indicated and requested by the patient; in individual cases this may be associated with favourable prognosis. Lung metastasis surgery is the treatment of choice for selected patients with metastatic breast carcinoma.

Conflict of Interest

The authors declare that they have no conflict of interest.

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