

Results of lung metastasectomy from breast cancer: prognostic criteria on the basis of 467 cases of the international registry of lung metastases[☆]

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Abstract

Objective: Metastatic breast cancer is still defined as an incurable disease. Although the prognosis after resection of isolated metastases to the lung is much better than after chemotherapy most oncologists and gynecologists disapprove of lung metastasectomy. **Methods:** In order to summarize the experience of pulmonary metastatic surgery and to achieve more relevant data by an increased number of cases, we evaluate the data of the International Registry of Lung Metastases of 467 patients having lung metastases from breast cancer with regard to long-term survival and prognostic factors. **Results:** In 84% a complete metastatic resection was possible. The survival rates are 38% after 5 years, 22% after 10 years, and 20% after 15 years. Prognostic factors are a disease-free interval of ≥ 36 months with 5-year survival of 45%, a 10-year survival of 26% and a 15-year survival of 21% ($P = 0.0001$), solitary lung metastasis is associated with a survival rate of 44% after 5 years and of 23% after 10 and 15 years, but this is not statistically significant compared to multiple metastases. When establishing prognostic groups as suggested by Pastorino and the International Registry of Lung Metastases based on the risk factors disease-free interval, number of metastases and complete resection the group with the best prognosis showed 5-year survival of 50%, 10- and 15-year survival of 26% with a median survival of 59 months. **Conclusion:** Considering the low morbidity and mortality rate, we think that lung metastasectomy today is the best treatment option in selected cases of lung metastases from breast cancer. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Breast cancer; Lung metastases; Lung metastasectomy; Prognostic factors

1. Introduction

With an incidence of 20–25% in Europe, breast cancer still is the most frequent malignant disease in women. In about 30%, the tumor disease recurs within 5 years, 36% of these patients have local recurrences and 56% metastases [1]. In the metastatic stage, about 15–25% of women have an isolated metastatic development in the lung and the pleural space [2,3]. Therapy of metastatic breast cancer is still controversial ranging from best supportive care to

high-dose chemotherapeutic regimes [4]. The present therapeutic concept offers three different procedures alone and in combination, i.e. chemotherapy, radiotherapy and hormone therapy. Since it is assumed that metastatic breast cancer is a systemic, incurable disease, local surgical measures are generally rejected. However, on the basis of admittedly small numbers of cases, it has been suggested that the resection of pulmonary metastases from solid tumors in nearly all cases provided better long-term results than systemic therapy alone. In order to summarize the experience of pulmonary metastatic surgery and to achieve more relevant data by an increased number of cases, the International Registry of Lung Metastases was established in 1991. In cooperation with specialized centers from Europe, the United States, and Canada, the data of altogether 5206 resections of pulmonary metastases from

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different primary tumors were collected [5]. In the following, we evaluate the data of the registry of those patients having lung metastases from breast cancer with regard to long-term survival and prognostic factors.

2. Patients and methods

The Istituto Nazionale Tumori di Milan developed a stringent database for the registration of lung metastasectomies. The database includes a record form for each patient and is divided into four sections: identification of the patient; therapy of primary neoplasm; description of each lung metastasectomy performed (date of surgery, size and number of resected metastases, kind of surgery, histology, and adjuvant forms of therapy) and a complete follow-up (recurrence in the lung or/and in other organs, therapy and survival data). Combined metastatic surgery in several organs was also registered. Planned bilateral thoracotomies were considered as one intervention, even if they were performed separately.

Patients who underwent surgery for lung metastases with a potentially curative intention were included in the Registry, this means that there were no signs of carcinosis or local inoperability. If a complete resection turned out to be impossible intraoperatively, this was documented and the patient was nevertheless included in the database. Interventions with a primary palliative approach were not included. Simultaneous resections of the primary tumor and metastases in other organs were included as well.

The number of patients included with regard to the different centers is listed in Appendix A.

Data analysis was performed by an independent agency, the Institute of Drug Development (ID2) in Brussels. Evaluation was performed using the StatView Analysis System under the license of the SAS Institute (Cary, NC).

The following variables were tested: number of resected as well as pathologically proved metastases, disease-free interval (DFI), uni- or bilateral metastases, surgical approach, method of resection, time of adjuvant chemotherapy, redo surgery and prognostic groups as suggested by the International Registry [5].

Using the Kaplan–Meier method, survival was calculated from the time of the first metastatic resection to the last follow-up or the time of death. Significances were calculated using the log–rank test.

Altogether, 481 patients with lung metastasectomies from breast cancer were included in the database. The documented metastatic resections were performed between 1960 and 1994. Four patients were excluded from the analysis for missing follow-up data, three patients for negative definite histology. In addition, seven male patients were excluded from the analysis. The following evaluation was thus performed on the basis of 467 female patients.

The patients data were detailed in Table 1 relating to the

treatment of the primary tumor as well as to the metastasectomy. A radical resection of the primary tumor was documented in 376 (81%) of cases, no data were available in 62 (13%) patients and 23 (5%) patients were without surgical therapy.

3. Results

In 84 % a complete metastatic resection (R0) was performed. Incomplete resections were performed in 77 (16%) patients because of a microscopic (R1) ($n = 14/3\%$) or macroscopic (R2) ($n = 63/13\%$) residual tumor.

Table 1
Patients' features

	Complete	Incomplete	Total
<i>N</i>	390	77	467
<i>Primary tumor</i>			
Tumor resection	318	58	376
Absent	15	8	23
Not specified	51	11	62
<i>Adjuvant treatment</i>			
Chemotherapy	49	16	65
Radiotherapy	90	14	104
Chemo- and radiotherapy	58	10	68
<i>Local recurrence</i>			
1	32	9	41
>1	3		3
<i>Metastasectomy</i>			
Age (yr) mean (range)	53	53	53 (21–87)
<i>Disease free interval</i>			
≥36 months	236	47	283
<36 months	154	27	181
Not specified			3
<i>Approach</i>			
Thoracotomy	296	56	352
Monolateral	283	56	339
Bilateral	13		13
Sternotomy	79	16	95
Thoracoscopy	16	1	17
Not specified	1	2	3
<i>Resection</i>			
Wedge	234	52	286
Segment	51	5	56
Lobectomy	98	16	114
Pneumonectomy	5	1	6
Not specified	3	2	5
<i>Number</i>			
1	272	36	308
2–3	87	12	99
>3	33	16	49
Not specified			11
<i>Diseased nodes (N_{1-2})</i>	19	15	34
<i>Chemotherapy</i>			
Preoperative	30	7	37
Postoperative	58	29	87
Pre- and postoperative	25	5	30
<i>Redo surgery</i>			
2	19	1	20

Mean age of the patients at the time of the first metastatic resection was 53 years (21–87 years). The median interval between primary and metastatic surgery was 43 months. Sixty percent had a free interval of more than 35 months. Surgical approach was thoracotomy in 75% and sternotomy in 20%. Thoracoscopic resections were performed in 4%, in 1% the approach was not specified. Unilateral thoracotomy was applied in 72%, bilateral in 3%. The usual surgical procedure was wedge or segmental resection in 73%. In 24% a lobectomy and in only 1% a pneumonectomy were performed, also in 2% the procedure was not specified. A solitary metastasis was found in 66% i.e. in 58% of complete resections and in 8% of incomplete resections. Major causes of incomplete resections were tumor occupation of lymph nodes or chest wall or diaphragm infiltration with short or tumerous resection margins. In 21% of patients, two to three pathologically proved metastases were resected and in 10% more than three metastases. Involved mediastinal lymph nodes were found in 7%; 4% in complete resections and 3% in incomplete resections. Thirty-three percent received an additional chemotherapy, 8% prior to metastatic resection, 19% thereafter, and 6% before and after resection. In 20 (4%) patients recurrent metastases were treated surgically.

On 1 March 1995, 186 (48%) of 390 patients with completely resected metastases were still alive, one patient more than 15 years, 12 (3%) more than 10 years and 58 (15%) more than 5 years. Of 77 patients having incomplete resections, 26 (35%) were survivors, 4 (5%) of them more than 5 years. Six patients (1%) died within 30 days after metastatic surgery.

The total group of 467 patients has a cumulative 5-year survival rate of 35%, a 10-year survival rate of 20%, and a 15-year survival rate of 18%. Median survival is 35 months.

Fig. 1 presents survival data with regard to complete and incomplete resection of metastases. The survival rates associated with complete resection are 38% after 5 years, 22% after 10 years, and 20% after 15 years. Median survival is 37 months. Incomplete resections are associated with a 5-year survival of 18% with median survival being 25 months. The difference in the log-rank test is significant with $P = 0.0009$.

The analysis of cumulative survival times in complete resections with regard to the prognostic factor disease-free interval shows a 5-year survival of 45%, a 10-year survival of 26% and a 15-year survival of 21%, with a median survival of 50 months for a DFI of ≥ 36 months. A DFI of < 36 months is associated with survival rates of 28, 16, and 16% after 5, 10 and 15 years, respectively, with a median survival

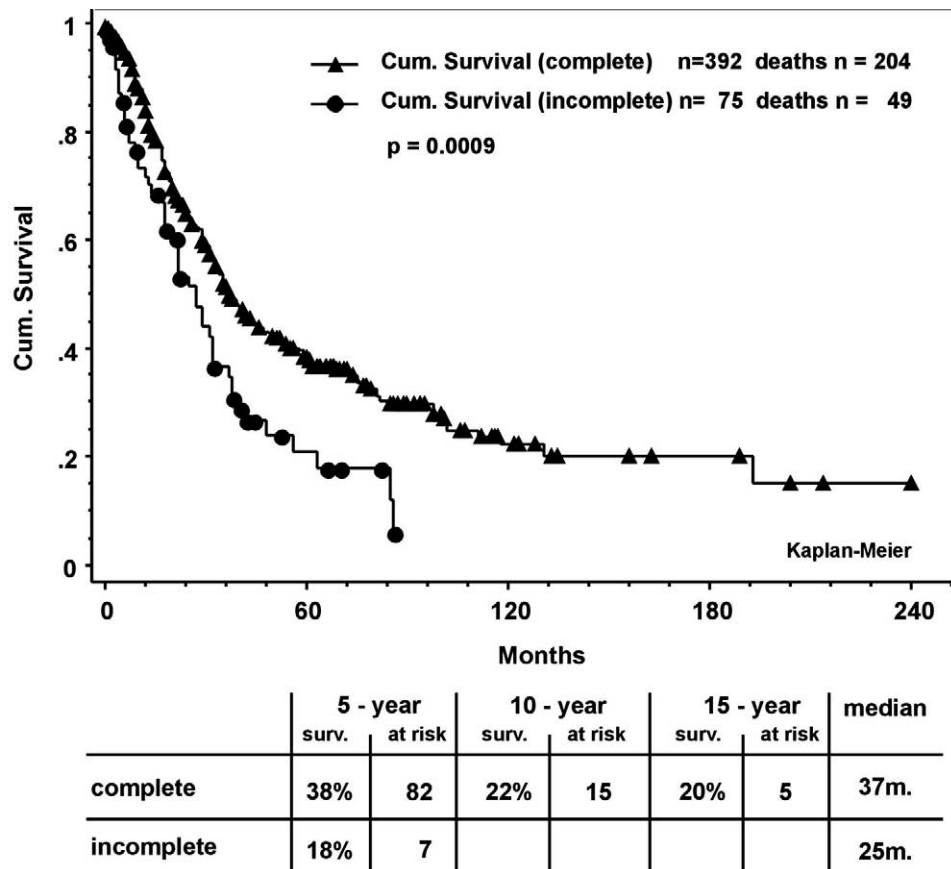


Fig. 1. Complete vs. incomplete resections.

of 23 months. The difference is significant with $P = 0.0001$ (Fig. 2). Equally, in incomplete resections, patients with a DFI ≥ 36 months have a more favorable prognosis with a median survival of 29 months compared to 21 months.

When evaluating the prognostic factor number of pathologically proved metastases in completely resected patients, it turns out that a solitary lung metastasis is associated with a survival rate of 44% after 5 years and of 23% after 10 and 15 years with a median survival of 41 months. In case of two to three metastases, survival rates after 5, 10, and 15 years are 25, 18, and 14%, respectively, with a median survival of 33 months. Four and more metastases are associated with 5-, 10-, and 15-year survival rates of 25% with a median survival of 37 months. These differences are not significant in the log-rank test (Fig. 3).

As to the surgical procedure there is no significant difference between the kind of resection applied, i.e. wedge and segmental resection, lobectomy, and pneumonectomy in completely resected patients. The most favorable results are provided by wedge resections with a 5-year survival of 40% and a median survival of 42 months. In only five pneumonectomies, median survival is 10 months and 5-year survival is not achieved, while segmental resection and lobectomy show cumulative 5-year survival rates of 34 and 36%, respectively. Neither does the kind of surgical

approach show any major differences in survival. Unilateral thoracotomy is associated with a survival rate of 41% after 5 years, 23% after 10 years, and 21% after 15 years with a median survival of 39 months. Sternotomy is associated with a 5-year survival of 30% and a 10-year survival of 25% with a median survival of 36 months. Other approaches such as bilateral synchronous or metachronous thoracotomy and video-assisted thoracoscopy provide varying results given very small numbers of cases [6,7,16].

Among complete resections, bilateral metastases have worse results compared to unilateral ones with a 5-year survival of 21 vs. 40%. However, the difference is not statistically significant. The median survival was 39 months in unilateral metastases and 34 months in bilateral ones (Fig. 4).

There is no difference when comparing primary and repeated interventions. Primary procedures have a 5-year survival of 37%, repeated interventions of 40%. Median survival is 36 months in primary and 51 months in repeated procedures (Fig. 5). Additional chemotherapy before, after or before and after metastasectomy does not provide any major advantages either. Five-year survival in completely resected patients without further therapy is 39%, with chemotherapy prior to metastasectomy 20%, with chemotherapy after metastatic resection 44% and with chemotherapy before and after metastatic resection 0%.

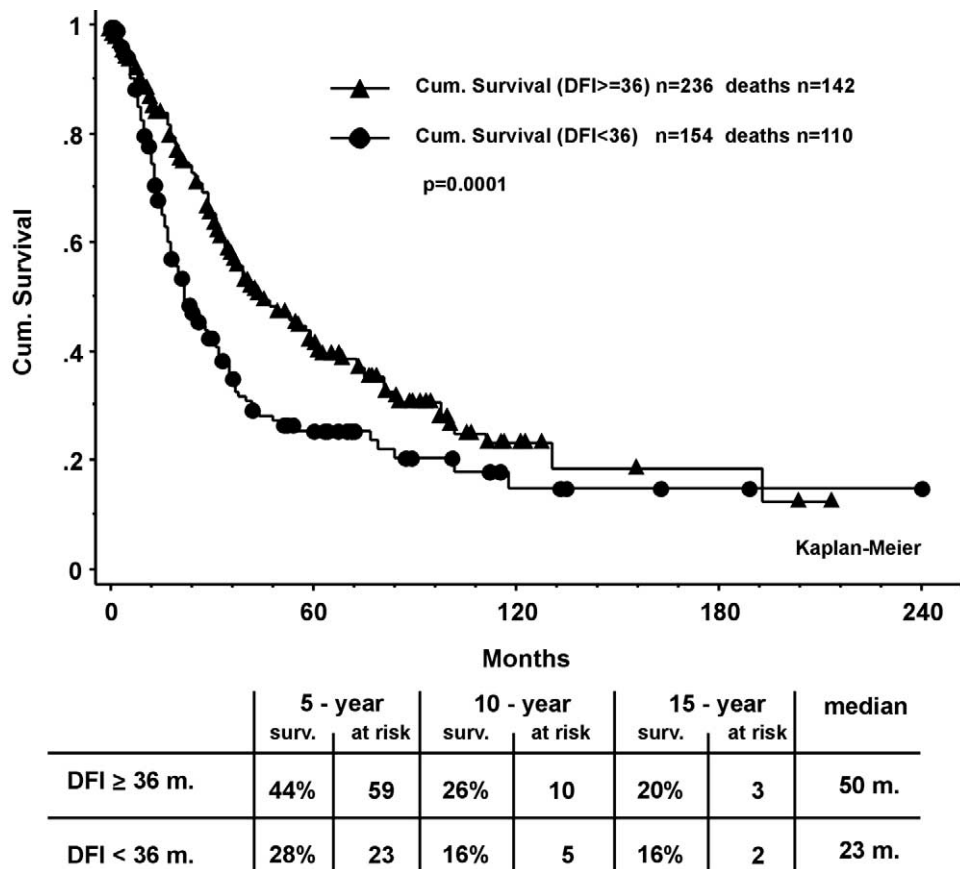
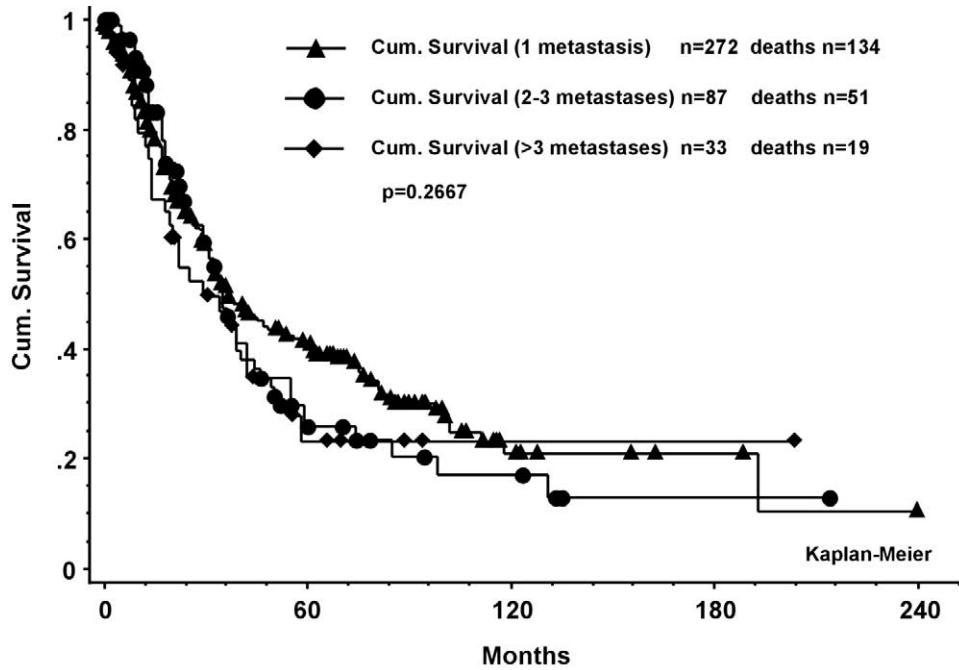


Fig. 2. Complete resections according to DFI.



	5 - year		10 - year		15 - year		median
	surv.	at risk	surv.	at risk	surv.	at risk	
1 metastasis	44%	67	23%	9	23%	3	42 m.
2-3 metastases	25%	11	18%	5	14%	1	33 m.
> 3 metastases	25%	4	25%	1	25%	0	34 m.

Fig. 3. Complete resections according to number of metastases.

When establishing prognostic groups as suggested by Pastorino and the International Registry of Lung Metastases based on the risk factors disease-free interval, number of metastases and complete resection, which showed no significant differences in the analysis of all metastatic resections, there are the following survival data:

Group I: Complete resection, DFI \geq 36 months, solitary metastasis 5-year survival 50%, 10 and 15-year survival 26% with a median survival of 59 months.

Group II: Complete resection, DFI < 36 months or multiple metastases 5-year survival 35%, 10-year survival of 21% and 15-year survival of 18% with a median survival of 36 months.

Group III: complete resection, DFI < 36 months and multiple metastases survival after 5 and 10 years 13% with a median survival of 25 months.

Group IV: Incomplete resection. Five-year survival of 18% with a median survival of 25 months.

The differences between the groups I and II compared to groups III and IV are statistically significant (\log -rank $P < 0.001$, $\chi^2 = 30.014$) (Fig. 6).

Of 390 patients with complete resections, 130 (33%) are alive without recurrences. Mean survival is 42 months. Sixteen patients (4%) underwent surgery for a relapse and are also alive for 42 months from the time of their first metastasectomy. Thirty-six (9%) live with a recurrence for a mean time of 37 months. One hundred and sixty-eight (43%) patients died from a recurrence after a mean survival time of 28 months.

Mean follow-up period of all patients is 34 months (max 240, min 0), that of patients with complete resections 36 months (max 240, min 0).

4. Discussion

Medical and gynecological oncologists still regard metastatic breast carcinoma as an incurable disease. Based on the assumption that it is a systemic disease, local surgical measures are rejected or only considered as palliative procedures in symptomatic metastases. This is mainly true for bone metastases implying a risk of fracture and symptomatic cerebral metastases. However, systemic therapies applied in the last years have achieved little

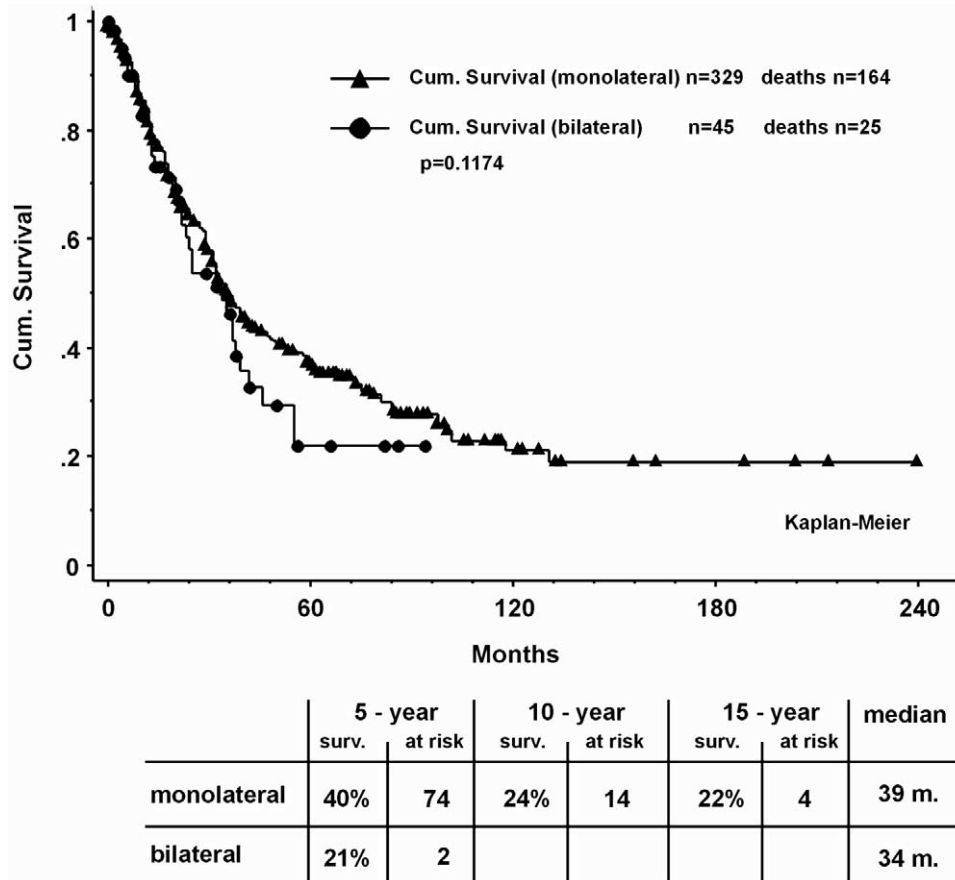
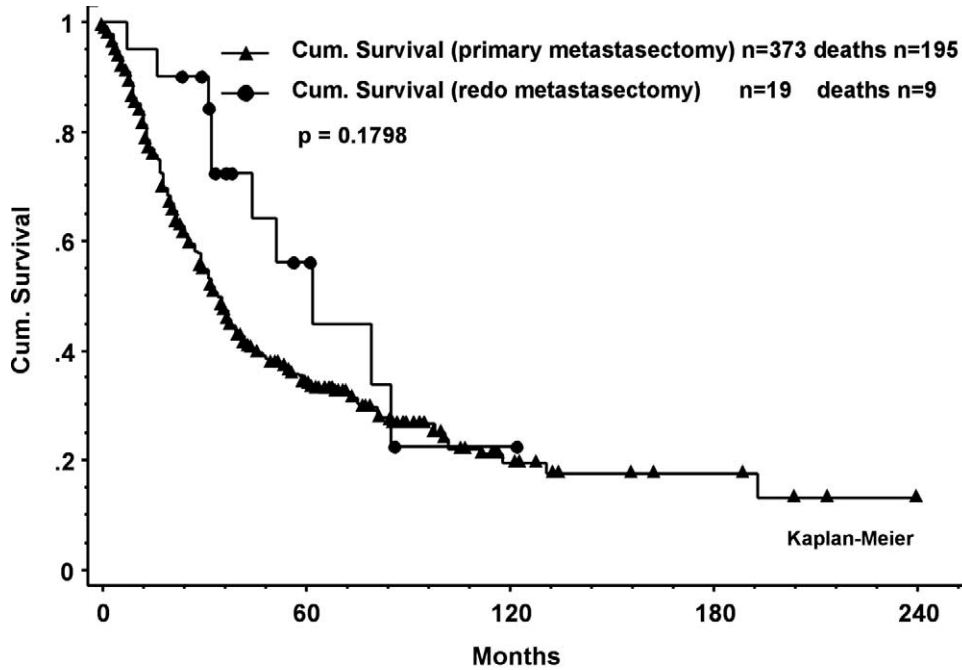


Fig. 4. Complete resections according to mono- or bilateral metastases.

progress in terms of prolongation of life. Median survival after chemotherapy is 10–20 months. In the last years, high-dose chemotherapy with stem-cell transplantation has been increasingly applied in trials. In this connection, the possibility of a curative therapy is mentioned for the first time [6]. Median survival after high-dose chemotherapy is only 20–30 months partly due to the very high therapy-associated mortality of up to 5% [4,7]. There are only very few reports on the outcome of isolated lung metastases after chemotherapy or hormone therapy. Schlappack reports on the course of 41 patients with a median survival of 13 months and a 5-year survival of 10% after chemotherapy and/or hormone therapy. Three of the patients additionally underwent resection of pulmonary metastases. In patients with a DFI > 18 months, prognosis was statistically not significantly better with a 5-year survival of 25%. There was no difference in survival between solitary and multiple lung metastases [8]. In a randomized chemotherapeutic study, Heidemann et al. among others report on 20 patients with isolated lung metastases whose 5-years survival was 21% with a median survival of 25 months. Prognostic factors were DFI > 18 months and a positive receptor status [9]. The new molecular target therapy like inhibition of Her2-neu receptor or

VEGF-receptor-2 antibody or *p53* gene replacement are still under observation in preclinical or phase I/II studies.

Surgery of lung metastases of almost all solid tumors is reported to provide good long-term results [10]. In its first publication, the International Registry of Lung Metastases reports on a 5-year survival of 36% in 4572 patients having complete resection of lung metastases. Since after 15 years 22% of the patients are still alive, metastatic surgery represents a curative approach in almost one quarter of patients [5]. In contrast to these results, surgical therapy of lung metastases is of minor importance in the oncological field. Only in case of germ cell tumors and increasingly in osteosarcomas, metastatic surgery plays a role in the multimodal overall concept [11,12]. Equally in renal cell carcinomas, the results of lung metastatic surgery are increasingly recognized because of the obvious failure of systemic therapeutic approaches [13]. Metastatic surgery for breast cancer, however, still is highly controversial. Although in the last years metastasectomy has provided markedly better results than systemic therapy even in lung metastases from breast cancer, this kind of therapy is strongly rejected by most oncologists. In 1992, Staren reports on 27 patients after resection of lung metastases. Five-year survival in this group is 35% with a median survival of 55 months. The



	5 - year		10 - year		15 - year		median
	surv.	at risk	surv.	at risk	surv.	at risk	
primary	37%	77	22%	14	20%	5	35 m.
redo	53%	5	27%	1			61 m.

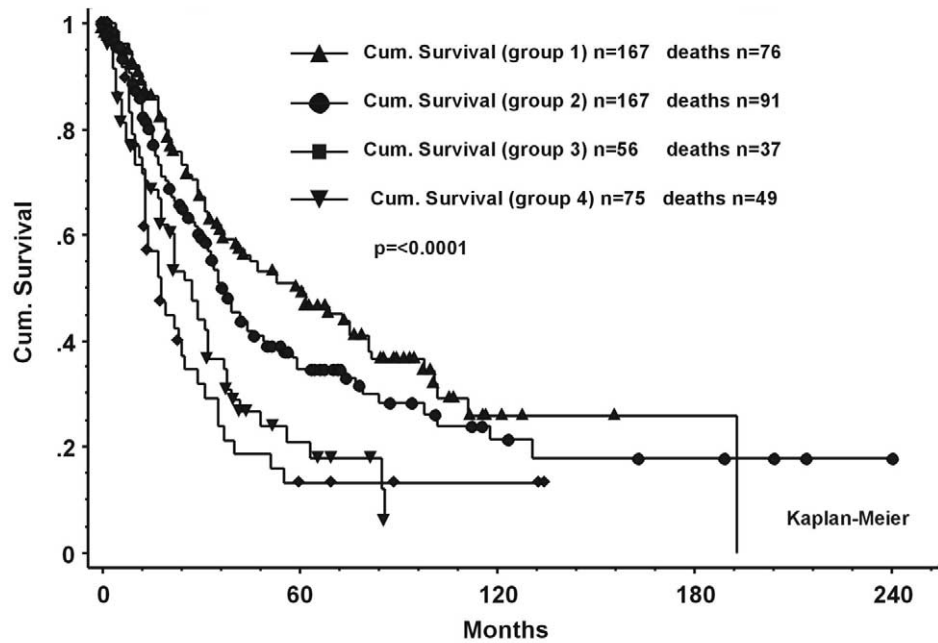
Fig. 5. Complete resections according to number of metastasectomies.

number of metastases in this report was not a prognostic factor and the DFI was not documented [14]. Lanza examined 44 patients after resection of lung metastases from breast cancer. In 37 cases, a complete resection could be achieved. The median survival in this group was 47 months with a 5-year survival of 49%. A significant prognostic factor was a DFI > 12 months with a 5-year survival of 57% [15]. In a study with 68 completely resected patients Friedel reported a 5-year survival of 31% with a median survival of 36 months. There were no statistically significant prognostic factors, but a tendency of a prolonged survival for patients with solitary metastases and a DFI \geq 24 months. In the group with both prognostically favorable factors, there was a 5-year survival of 40% [16]. McDonald et al. investigated 60 patients with the surprising result that incomplete resections provided better results in terms of long-term survival than complete resections. All other authors report on the complete resection as a significant prognostic factor. The 5-year survival of the whole group also exceeded the results of chemotherapy with 37.8% [17].

The opponents of lung metastatic surgery have criticized that the results presented so far are based on too small numbers of cases. For this reason, the International Registry of Lung Metastases was established presenting exactly

documented long-term courses of patients after lung metastatic resection in large numbers also with regard to individual tumor entities. To our knowledge, the course of disease of such a large number as 465 patients with lung metastases from breast cancer has not been published so far. The cumulative 5-year survival of 35% in the total group has so far not been achieved by any other therapeutic approach [2,6,8,9]. Significant prognostic criteria include the resectability of the metastases and the disease-free interval. However, the group of metastases, which cannot be resected completely, has to be defined or documented more exactly in future prospective studies. In previous retrospective analyses, this group includes patients with pleural disease, tumor debulking i.e. R2 resections as well as patients with R1 resections or lymph node involvement. It can be assumed that this group differs in its prognosis depending on the amount of residual metastases.

In the group of completely resected patients, the disease-free interval is the only univariate significant prognostic parameter, which is a DFI of \geq 36 months in this study. In other studies, it varies between 12 and 48 months [5,15,16]. The number of pathologically proved metastases shows a tendency towards longer survival for patients with solitary metastasis, but it is not statistically significant.



	5 - year		10 - year		15 - year		median
	surv.	at risk	surv.	at risk	surv.	at risk	
Group 1 (no risk factor)	50%	47	26%	5	26%	1	59 m.
Group 2 (1 risk factor)	35%	31	21%	8	18%	4	36 m.
Group 3 (2 risk factors)	13%	4	13%	2			18 m.
Group 4 (incomplete res.)	18%	7					25 m.

Fig. 6. Complete resections according to risk groups.

This is also confirmed by Bodzin [18]. The prognostic groups suggested by our registry also show their relevance in this investigation [5]. Risk group I comprising patients with solitary metastases and a DFI ≥ 36 months shows a 5-year survival of 50% according to the Kaplan–Meier method. Fifteen-year survival in this group is 25%, thus we regard lung metastatic surgery for breast cancer as a curative approach. In group II with one risk factor, 5-year survival is still 35% while declining to 13 and 18% in groups III and IV, respectively. The differences are statistically significant with $P = 0.0001$. The choice between unilateral or bilateral approach does not provide any relevant difference in survival. Neither was there any major differences concerning the kind of surgery. Pneumonectomy being performed in only five cases and 60% having died within only 2 years. This underlines the demand that pneumonectomy is only justified in exceptional cases. Additional chemotherapy does not appear to provide a major advantage. The most favorable results were achieved in patients without chemotherapy. As well chemotherapy before, or before and after metastasectomy provides worse

results including patients in the prognostically favorable risk group I. There are other important prognostic factors like TNM-status of the primary tumor, hormone receptor status of primary tumor and metastasis as well as the new molecular markers like proliferating markers, angiogenic factors and onco- or suppressor-genes which have to be considered in future trials undoubtedly.

Recurrent metastases from breast cancer are rarely treated surgically. In 19 cases, recurrent metastases were resected. A 5-year survival of 53% shows that these patients benefit from redo surgery and we think that this option should be chosen more frequently.

In conclusion, this study with the largest documented number of resected lung metastases from breast cancer shows that metastasectomy at present provides better long-term results than chemotherapy and hormone therapy. Whether high-dose chemotherapy with stem cell support is able to achieve comparable survival data has to be clarified by future studies. This applies also to the new therapeutic options like immunotherapy with HER2 monoclonal antibodies or the new hormone agents. At least in risk group I as

defined by the International Registry of Lung Metastases, metastatic surgery at present has to be regarded as the therapeutic option with the longest survival rates thus to be offered to the patients as the most effective therapeutic procedure. In our opinion, with 15-year survival rates of 26%, the statement that a curative approach is not possible in lung metastases from breast cancer is not tenable. Further prospective studies on multimodal therapeutic concepts including metastatic surgery are urgently needed.

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Appendix A. Participating institutions and responsible researcher

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	Professor Heikki Toomes, Dr Godehard Friedel Thoraxchirurgie, Klinik Schillerhoehe, Stuttgart-Gerlingen	104
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Poland	Dr A. Pietraszek, Maria Sklodowska, Warsaw	13
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	Dr Giuliano Maggi Chirurgia Toracica, Università di Torino	14
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	Dr Carmack Holmes Thoracic Surgery, University of California (UCLA), Los Angeles	1
	Dr Harvey Pass National Cancer Institute, Bethesda	4
Canada	Dr Michael Johnston Thoracic Surgery, Mount Sinai Hospital, Toronto	5

Appendix B. Conference discussion

Dr H.-B. Ris (Lausanne, Switzerland): You made the comment that you had a 80% five-year survival rate in patients with R2 disease. Does that mean that you left visible disease behind? And could you please comment whether or not there was a statistical significance between incomplete resection and complete resection but multiple metastases?

Dr Friedel: Patients with so called R2 resections are problematic to evaluate. These are patients with pleural carcinosis and left gross disease. So this is a very mixed group. Another group consists of patients with nodal tumor invasion. I showed in my presentation the significant differences of some prognostic factors. There are significant differences between a disease-free interval of more or less than 36 months, but after 10 or 15 years the groups showed equal survival curves. That is why it is problematic to stress the significance.

Dr Ris: I just want to stress out whether or not in your results it is justified, do you think it is justified if you have an 80% five-year survival rate in R2 disease, pleural metastases, comparing with about a 28% five-year survival rate and complete resection with multiple metastases or a short disease-free survival? In other words, should these category II or III patients be considered for metastasectomy for breast cancer with your result in mind?

Dr Friedel: I don't really understand your question. You must have misunderstood my interpretation of the results, we don't have an 80% five year survival rate in R2-disease, the five year survival in incomplete resection was 18%.

Dr Ris: You said that you had an 18% five-year survival rate in R2 disease, and you had a 25% five-year survival rate after complete metastasectomy but more than one metastasis.

So if these results are not significantly different at five years, is it justified to recommend metastasectomy for more than one metastasis in breast cancer?

Dr Friedel: You can perform metastasectomies for more than one metastasis. This is a collection of about 400 patients and it is the largest series in the world with breast cancer, but the number of patients are not enough to differentiate prognosis between groups with one, two or more metastases.

Dr A. Chapelier (Le Plessis-Robinson, France): I have a comment and a question. Regarding the 44% five-year survival after resection of a single metastasis and considering that most patients won't have another lung metastasectomy for breast cancer, we could consider that this group of patients with a single metastasis would benefit from a lobectomy rather than a wedge resection. Did you observe a difference of survival between wedge resection and lobectomy in these patients? We participated to the collective work you have reported today ; we have now more than 50 patients who underwent a lobectomy for a single metastasis with a five-year survival of 55%.

Dr Friedel: We have not differentiated the wedge resection versus lobectomy for the single metastasis group. Benign lesions and primary tumors of the lung must be excluded. We made an evaluation of the whole group of metastasectomy and there was no difference in outcome between lobectomy and wedge resection. For the metastasectomy, the wedge resection is the standard operation, if it could be performed.