

**Case Report****Outcome after resection of breast cancer liver metastases**

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**Abstract**

**Background:** Goal of our study was to evaluate the outcome of patients who underwent hepatic resection as part of a multimodality-treatment. **Methods:** 38 female patients with a median age of 55.2 years underwent hepatic resection with curative intent from 1998-2006. The liver was the only site of metastatic disease. **Results:** 15 patients underwent major (>3 segments), 11 patients minor hepatic resections, and 12 were only explored. Median hospital stay was 14.6 days, with a postoperative morbidity of 7%, and a 30-day mortality of 7%. One-, 3-, and 5-year survival among resected patients was 88%, 53% and 44%, respectively. The corresponding disease free survival was 48%, 8%, and 8%. There was no association between treatment- or patient-specific variables and survival. **Conclusions:** Resection seems to benefit a cohort of patients with breast cancer metastases involving only the liver. Further delineation of prognostic markers is required.

**Introduction**

Although significant progress has been made in the multimodality treatment of patients with breast cancer, including the use of more effective systemic chemotherapy, antihormonal therapy and directed biologic agents, approximately 50% of all women with breast cancer develop liver metastases [1-3]. In the majority of patients, this is associated with tumor deposits at other sites, indicating advanced disease with poor outcome and a short overall survival of 1-4 months [4]. However, a small proportion of patients (1-3%), present with isolated liver metastases [5, 6]. Traditionally, the presence of breast cancer liver metastases has been a particularly poor prognostic factor, with reported median survivals which range from 15 months when responding to chemotherapy to as low as 3 months when not responding. This group may benefit from a more

aggressive surgical approach. Single institutional series have demonstrated 5-year survival rates after hepatectomy for liver metastases from breast cancer to be about 20-37%, with a median survival time of 20-32 months [3, 7-10]. Liver resection is a safe procedure in most centers, with an operative mortality of ca. 5% and a morbidity of 20%. Nevertheless, the contemporary role of hepatic resection for metastasis from breast cancer is still not clearly defined.

The aim of our study was to evaluate our experience with hepatic resections in the treatment of breast cancer metastases.

**Patients and Methods**

Between April 1998 and April 2007, 990 consecutive patients were treated for liver metastases at the Department of General- and Transplantation Surgery at the University Hospital Essen, Germany. Thirty eight (n=38) of these patients had breast cancer metastases involving only the liver. Clinical and pathologic parameters evaluated included: age at diagnosis, tumor size, lymph node status, tumor staging, estrogen and progesterone receptor status, tumor margins, time lapse from diagnosis of the primary tumor to the discovery of metastases, response to preoperative chemotherapy, number, grade and location of the metastases, type and length of the surgical procedures, intraoperative blood loss, and postoperative complications.

Prior to liver resection, all patients underwent our protocol work-up that included clinical examination, abdominal ultrasound, and computed tomography or MRI of the abdomen, chest and pelvis.

Resection was undertaken in cases that fulfilled the following criteria: a) curative intent, b) technical feasibility, and c) absence of extrahepatic disease. All deaths within 30

days of surgery were considered perioperative mortality. Length of follow up ranged from 7 to 105 months, with a median of 60 months.

Disease free- and overall survival rates were calculated with Kaplan-Meier and log-rank tests. Uni- and multivariate Cox regression analyses were used to identify potential predictors of mortality. P values <.05 were considered statistically significant. Statistical analyses were performed using SPSS 11.5 and SAS 8.

## Results

### Patient and Tumor Characteristics

Median patient age at the time of referral was 55.2 years (range 35-77 years). Sixteen (n=16) had undergone lumpectomies, while the remaining 22 mastectomies. Lymph node dissections were performed in all cases. Histological sections demonstrated invasive-ductal carcinoma in 36 instances, and invasive-lobular carcinoma in 2 cases. 29 patients had positive axillary nodes. According to the TNM nomenclature, 5 cases were classified as stage I, 28 as stage II, 4 as stage III, and 1 as stage IV. Twelve (n=12) tumors were positive for both estrogen and progesterone receptors (ER+/PR+), 11 for either ER or PR, and 15 were negative for both ER and PR. All patients received either radio-/chemotherapy (25) or chemotherapy alone (13) after resection of the primary breast tumor (table 1). Only 1 patient had synchronous liver metastases at the time of diagnosis of the primary breast lesion. The disease free interval from the time of diagnosis of the primary tumor to the development of liver metastases ranged from 0-228 months (median 59 months). Thirteen (n=13) of the 38 patients presented with single liver metastases, 10 had more than 1 lesion confined to one lobe of the liver, and 15 had bilateral metastases (table 2).

### Surgical Results

Twelve (n=12) patients underwent only explorative laparotomies with no liver resection because of extrahepatic (n=8) or unresectable (n=4) tumors. The remaining 26 patients underwent: right hepatectomy (n=6), left hepatectomy (n=1), left trisectorectomy (n=4), left lateral resection (n=4), and sectorectomy (n=11, 4 more than 3 segments). Twenty four (n=24) patients had R0-resections, while 2 had R1-resections. The median length of surgery was 220min (range 120-640). Median packed red blood cell

transfused and length of hospital stay were 2 Units (range 0-5) and 14 days (range 7-45) respectively (table 2).

### Morbidity and Mortality

There was an overall morbidity rate of 30%, with 6 (23%) minor and 2 (8%) major complications. Postoperative complications included pleural effusions (n=4), wound infections (n=1), lower extremity deep venous thrombosis (n=1), postoperative bleeding (n=1), subphrenic abscess (n=1). Two patients (8%) required reoperation to treat their complications. Two (n=2) patients (8%) died within 30 days postoperatively (table 2)

### Patient Outcome

One-, 3- and 5-year survival rates for patients with R0/1 resections were 88%, 53% and 44% respectively (Figure 1). The corresponding disease free survival rates were 48%, 8% and 8% respectively. Patients who only underwent exploration had 1- and 3-year survival rates of 79% and 36% respectively, with no patients surviving more than 3.5 years. Disease free survival regarding the liver though was 92%, 73% and 73%.

There was no significant association between any of the parameters evaluated and survival or recurrence by either univariate or multivariate analyses (table 2).

## Discussion

Women with visceral metastases of breast cancer are usually considered to have a poor prognosis. A small subgroup of patients though presents with liver metastases as the only manifestation of recurrence. The discussion as to whether this subgroup might benefit from an aggressive approach including live resection is still ongoing and remains controversial. With improved surgical techniques, better perioperative assessments, and advances in anesthesia and medical care, liver resection has become a safe procedure and mortality rates have dramatically decreased from 20% in the 70s to the current rate of less 5% [11-13]. The decrease of mortality and morbidity rates has led to a broadening of the indication for hepatic resection. Despite reported favorable result, systemic chemotherapy and/or hormone therapy are still considered the treatment option of choice in these patients. Although these therapies achieved response rates between 40-70%, the median survival time has been reported to be no more than 5 to 12 months [14, 15]. Reasons

for reluctance to refer these patients to surgical evaluation are manifold. First, most patients with breast cancer liver metastases also have extrahepatic metastases [16], a finding that has traditionally been considered a contraindication to hepatic resection. Secondly, breast cancer has been considered a systemic disease since its onset. Therefore, this concept seems to contraindicate any surgical therapy and treatments with a minimal toxicity profile have been preferred over aggressive treatments such as resection [7].

Others point out that patients with isolated liver metastases from breast cancer may benefit from liver resection [1-3, 7-10, 15, 17, 18]. Selzner et al. and Elias et al. reported 5 year overall survival rates of 22% and 34% respectively in patients who underwent resection [1, 3]. Adam et al. recently published the largest series so far, with 84 resected patients and a 5 year overall survival of 34% [7]. In our own study, the 5 year overall survival was 44% after resection.

The encouraging overall survival rates may nevertheless not be deceiving the high recurrence rates. Among our patients, 65% developed tumor recurrence within the first 2 years, a rate similar to that of other studies [1, 3]. Our data provide a strong impetus to identify prognostic factors and subsequently a potential group of patients, who are most likely to benefit from surgery. Several prognostic factors such as age at diagnosis, lymph node status, estrogen and progesterone receptor status of the primary and the liver metastases, metastases size, metastases number, grading, tumor margin status as well as time to develop liver metastases and the response to preoperative chemotherapy. In our series, none of the investigated parameters were predictive of overall and disease free survival. This is in contrast to the findings by Selzner et al, who reported decreased survival in patients who developed liver metastases within a short time span [3], and to Martinez et al. and Elias et al. who identified hormone receptor negativity as a negative predictor of survival [1, 19]. In addition, Adam et al. showed that response to preoperative chemotherapy, resection margins, and repeat hepatectomy for intrahepatic recurrence were of prognostic significance [7].

The series currently available are unlikely to provide a definite answer. Most span over prolonged time periods, and are influenced by major breakthroughs such as the introduction of avastin and herceptin [20]. While some consider resection as an ineffective debulking process [21,

22], others believe it is an intervention that increases the likelihood of success with chemotherapeutic agents by reducing the tumor load [19].

So does liver resection result in an increase in survival? Clearly yes as we have shown in our series. But for now we are far from being able to define this group of patients by the preoperative variables available to date that will benefit the most. The low morbidity and mortality may justify an aggressive surgical approach. A diminished recurrence rate however may only be achieved as long as liver resections are accompanied by innovative and effective adjuvant or neoadjuvant therapies. At the present time, the decision to proceed with surgery can solely be based on technical criteria.

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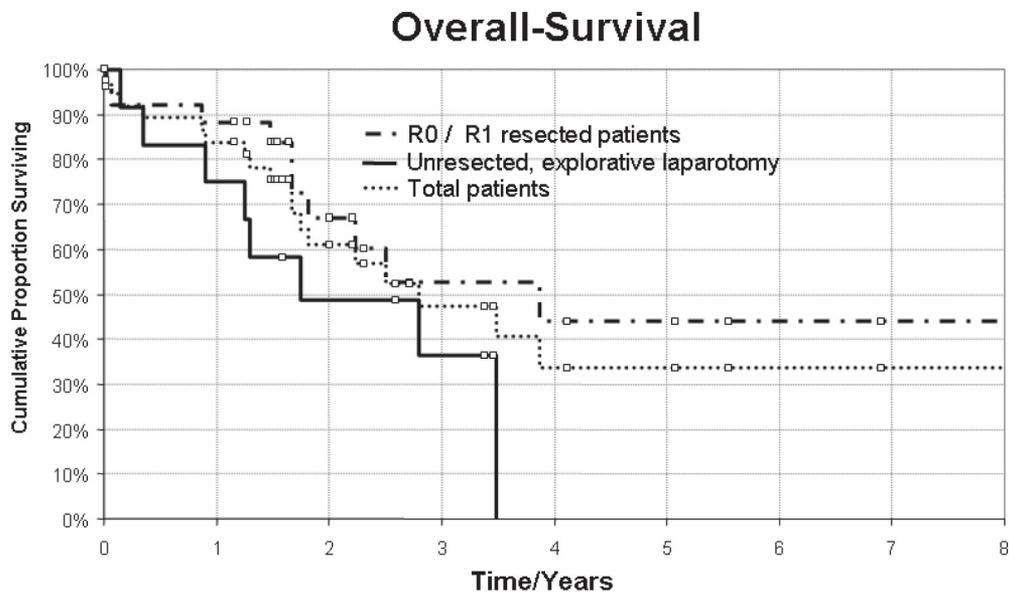
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**Table 1.** Characteristics and treatment of primary tumors and their respective p-value tested by multivariate analysis

		N (%)	p
Age (years)	Range	35-77	0.975
	Median	55.2	
Histology	Invasive-ductal	36 (94)	Not tested
	Invasive lobular	2 (6)	
Stage	I	5 (13)	0.714 - 0.774
	II	28 (74)	
	III	4 (10)	
	IV	1 (3)	
Surgery	Breast-conservation	16 (42)	0.712
	Mastectomy	22 (58)	
Receptor status	ER-/PR-	15 (39)	0.962
	ER+/PR+	12 (31)	
	ER+/-, PR+/-	11 (28)	
Systemic Therapy	Chemo-/Radiotherapy	25 (66)	Not tested
	Chemotherapy	13 (33)	

**Table 2.** Characteristics and treatment of liver metastases and their respective p-value tested by multivariate analysis

		N (%)	p
Time to Metastases (months)	Range	0-228	0.611
	Median (mos)	58	
Number of Metastases/Distribution	1/unilateral	13 (34)	0.550
	>1/unilateral	10 (26)	
	>1/bilateral	15 (39)	
Response to preoperative chemotherapy	No response	4 (12)	0.32
	progression	32 (88)	
Type of Surgery	Major	15 (58)	0.423
	Minor	11 (32)	
Grading	G1	1 (3)	0.971
	G2 /G2-3	27 (71)	
	G3	10 (26)	
Receptor status	ER-/PR-	16 (42)	0.469
	ER+/PR+	11 (29)	
	ER+/-, PR+/-	8 (21)	
Outcome			
Morbidity	Minor	6 (23)	
	Major	2 (7)	
Recurrence	liver	6 (23)	
	other	13 (50)	
Time to Recurrence	Median (mos)	17	
30-Day-Mortality		2 (7)	



**Figure 1.** Cumulative proportion surviving between unresectable and resectable cases. Differences in survival were not statistically significant.