

Hepatic metastasectomy as a cytoreductive strategy for the treatment of liver metastases in breast cancer: Review of literature

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Summary

The resection of liver metastases in breast cancer patients is a controversial therapeutical approach. No data of prospective randomized trials are available, thus evidence for the potential role of hepatic metastasectomy rests on retrospective studies with a small number of patients. Technical advances however have rendered hepatic metastasectomy safe and the long-term results of some studies possibly support the role of a surgical approach in selected patients.

Key words: Breast cancer; Liver metastases; Hepatic metastasectomy.

Breast cancer affects one in ten women in Germany. Due to widespread mammography and advances in adjuvant therapy, the mortality rates of breast cancer have dropped in recent years, while the incidence of metastatic breast cancer has remained unchanged. Furthermore, the survival for patients with distant metastases has not improved substantially. Thus, it is unlikely to cure breast cancer with conventional forms of treatment, if the disease has spread beyond the regional lymph nodes. More than 50% of patients with metastasizing breast cancer show at some point in time involvement of the liver. The incidence of isolated metastases limited to the liver are less frequent and are observed at autopsy in about 2-12% of all patients with distant metastases. However accurate data is unavailable, so that it is likely that an even greater proportion of patients have metastases isolated to the liver [1, 2].

The rationale for hepatic metastasectomy is as follows: – there are metastases from breast cancer isolated to the liver, – metastatic deposits in the liver may give rise to further dissemination to other organs according to the hypothesis of the “cascade” phenomenon, – cure of metastatic breast cancer is unusual using chemotherapy alone, – liver metastases are particularly resistant to most hormonal and chemotherapeutic agents, – high-dose chemotherapy as one alternative is associated with considerable attendant morbidity and mortality, – hepatic resection can be performed with mortality rates well below 5% and is associated with good long-term results in selected patients, – new models on the development of breast cancer metastases suggest that achievement of a complete response is most critical for long-term control of the disease [1-5].

The major goal of treatment of metastatic breast cancer is improvement in the quality of life. Today, patients are treated in a multidisciplinary approach. The main strategy of the treatment is a coordinated and optimized use of systemic and local therapies in order to obtain a rapid improvement of the symptoms. Stabilization of disease is a realistic goal of the therapy that can be called successful.

In metastatic breast cancer, cytoreductive surgical strategies do not play a substantial role and are usually used in combination with radiation therapy or chemotherapy. Thus, chemotherapy and hormonal therapy are currently the mainstays of treatment strategies for metastatic breast cancer [20]. However recurrence after each response to chemotherapy seems to be inevitable so that chemotherapy in metastatic breast cancer delays progression and possibly prolongs survival, but rarely cures the disease. Nonetheless, surgical strategies like metastasectomy can be a helpful tool and should be taken into consideration in the following situations: – acute situation, – isolated hepatic metastases, – progression of metastases during local therapy, – increasing symptoms.

Breast cancer has proved to be a heterogeneous disease. This heterogeneity has consequences in terms of response to chemotherapy and pattern of the spread of metastases. If surgical treatment is taken into account, a

careful re-staging appears necessary in order to precisely assess the individual stage of the disease before starting hepatic metastasectomy. In addition, an interdisciplinary and individual approach is crucial in order to obtain optimal results from the treatment. Individual constellations like age and performance status, clinical signs and characteristic features of the tumor must be evaluated prior to the therapy in order to achieve the best therapeutic results [6].

The median survival of breast cancer patients with visceral metastases is reported as 11-24 months. Up to 5% of all women with metastatic breast cancer show long-time survival and prognosis depends on the localization of the metastases (median survival: bone metastases: 14-34 months; lung metastases: 17-20 months; liver metastases: 6-12 months) [7-10].

Hepatic metastasectomy in breast cancer patients with visceral metastases should be considered due to the low success achieved with systemic therapies (endocrine therapy and/or chemotherapy). Nevertheless, some conditions should be fulfilled prior to using this therapeutic option: - isolated metastases to the liver, - possibility of complete resection (R0-resection), - good general constitution or adequate life expectancy of the patient [11].

In individual cases hepatic metastasectomy in combination with chemotherapy can be a treatment option that depends on factors like the number of metastases, disease-free interval and speed of metastatic growth. Although all these factors are not well validated because no prospective randomized studies have been carried out, in analogy to other tumors (colorectal cancer) a hepatic metastasectomy should only be performed if metastases are limited to one lobe of the liver and if the number of metastases is low (< 3-5). Table 1 shows an overview of the literature concerning metastatic breast cancer and hepatic metastasectomy. However, a direct comparison between systemic treatment and hepatic metastasectomy has never been published. In addition, in all existing studies only a small number of patients has been evaluated. The morbidity rate after hepatic metastasectomy is reported as 31% and the mortality rate as 3%. The median survival time after resection of hepatic metastases is described to be between 24 and 59 months. Surgical treatment was usually followed by chemotherapy, thus it cannot precisely be concluded from these studies how far the hepatic metastasectomy was decisive for patient survival [6, 11].

Table 1. — Overview of the literature concerning hepatic metastasectomy.

Authors	N	Morbidity (%)	Mortality (%)	% Chemotherapy	Survival rate		
					Median (months)	5-yr (%)	5-yr (%)
Elias [7]	12/12	8	0	100	37 vs 17	—	—
Schneebaum [16]	6/6	—	0	100	42	—	—
Elias [15]	21/21	9.5	0	90	38	78	24
Pocard [9]	21/21	5	0	100	59 vs 28	100	60 vs 11
Harrison [19]	7/96	—	0	—	—	—	14
Raab [10]	34/34	31	3	6	27	—	18
Elias [18]	35/147	—	2	98	—	—	20/36
Selzner [13]	17/17	—	6	60	24	—	22
Yoshimoto [14]	25/25	—	0	96	34.3	71	27
Maksan [8]	36/36	—	0	33	—	—	51

Table 2. — R0-resection of liver metastases as a prognostic factor.

Authors	N	Type of resection (n)	Median (months)	Survival rate		p
				3-yr (%)	5-yr (%)	
Raab [10]	34/34	total	27	18	—	< 0.001
		R0 (30)	41	22	—	
		R1, 2 (5)	5	0	—	
Selzner [13]	17/17	total	24	22	22	—
		R0 (30)	27	25	25	
		R1, 2 (5)	5	0	0	
Lang [12]	34/127	total	20	29	—	—
		R0 (30)	38	35	—	
		R1, 2 (5)	3	0	—	

R0: complete resection. R1, 2: incomplete resection with microscopic or macroscopic tumor residual.

followed by chemotherapy, thus it cannot precisely be concluded from these studies how far the hepatic metastasectomy was decisive for patient survival [6, 11].

In spite of the small number of evaluated patients, it can be concluded from existing studies that several prognostic factors are important for the use of hepatic metastasectomy. In most studies, complete resection (R0) of the hepatic metastases is regarded as the most relevant prognostic factor. In the literature (Table 2) there are three publications [10, 12, 13] examining the value of complete resection of hepatic metastases in breast cancer patients. However, from all these studies only the study of Raab *et al.* [10] was able to show a significant improvement in the survival rate after R0-resection. Another important prognostic factor discussed in the literature is the number of metastases appearing in the different lobes of the

liver. Under this aspect, the study of Yoshimoto *et al.* [14] compares breast cancer patients with one or multiple metastases of the liver. A median progression-free survival of 37,6 months was shown for patients with only one liver metastasis versus 26.9 months for patients with multiple hepatic metastases, while in terms of 5-year survival no significant differences were seen (25% vs 27%). Regarding other prognostic factors like lymph node status and disease-free interval the data are not conclusive. Both Elias *et al.* [15] and Yoshimoto *et al.* [14] have examined the value of hepatic lymph node status in breast cancer patients with hepatic metastasectomy and they did not reveal any significant differences in survival rates in terms of hepatic lymph node positive or negative patients (median survival: N+: 15 and 31.9 months; N -: 28.5 and 29.3 months). However there was a tendency towards better survival for hepatic lymph node negative patients (5-year-survival: 67% vs 0%). Regarding the disease-free interval only Selzner *et al.* [13] could show in a small number of patients (n = 17) that patients with a disease-free interval of more than one year had a significantly better survival (27 months vs 12 months) compared to women with a disease-free interval of less than one year. In contrast to this result Yoshimoto *et al.* [14] did not find any differences in survival with regard to the disease-free interval.

In the literature there are no reliable data concerning the sequence of the therapy regimens. There are also no sufficient data for the use of regional chemotherapies [16] via the hepatic artery, thus these procedures play no substantial role in the treatment of hepatic metastases. Most interventional procedures (Port-systems, Seldinger Catheter) are evaluated in studies after systemic chemotherapy or after surgery. The rationale of this kind of treatment is to put a high concentration of the appropriate drug directly into the tumor via a catheter that is situated in the hepatic artery. In spite of achieving response in up to 50% of the breast cancer patients with hepatic metastases – with a significant survival advantage for these patients – this procedure however should only be applied in individual cases. In the literature there are some reports concerning the use of cryotherapy, laser-induced interstitial therapy (LITT) and radiofrequency ablation in breast cancer patients with hepatic metastases. However, these results are preliminary and these procedures should only be considered in individual cases [17].

In summary, the resection of liver metastases in breast cancer patients is a controversial therapeutical approach. No data of prospective randomized trials are available, thus evidence for the potential role of hepatic metastasectomy rests on retrospective studies with a small number of patients. Technical advances however have rendered hepatic metastasectomy safe and the long-term results of some studies possibly support the role of a surgical approach in selected patients.

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