The role of surgery in metastatic breast cancer

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Abstract

Some of the patients who present with breast cancer already have distant metastatic disease. According to recent literature, these patients may benefit from resection of the breast tumour. One explanation for the effect of this resection is that reducing the tumour load influences metastatic growth. Results of future randomised controlled trials should indicate whether surgery of the breast tumour truly improves survival.

Selected patients could even benefit from metastasectomy of liver and lung metastases; survival seems to improve and these procedures seldom lead to major complications. When metastasectomy is not possible, minimally invasive techniques can be used in selected patients for the treatment of breast cancer liver metastases, radiofrequency ablation (RFA) being discussed most in the literature.

Patients with locally advanced breast cancer are treated multidisciplinarily and with curative intent. Part of the treatment is surgery to reduce tumour load. Regarding treatment of the axilla, in a clinically negative axilla sentinel node biopsy is advised before neoadjuvant treatment; an axillary lymph node dissection is not warranted.

In local recurrence, surgery is the primary treatment. Axillary staging can be done in patients with a previous negative sentinel node biopsy. Regional recurrence after breast-conserving surgery or mastectomy is treated with surgery followed by radiotherapy.

I. Surgery in primary metastatic breast cancer

Of all patients with breast cancer, 5% have primary distant metastases at initial presentation. Because metastatic breast cancer is considered an incurable disease, the aim of the treatment for these patients is to provide palliation with systemic therapy. Breast surgery is performed only if the tumour is symptomatic. Until recently it was believed that, once distant metastases have occurred, (aggressive) local therapy provides no survival advantage and should not be the treatment of choice. However, several retrospective studies indicate that patients who have primary distant metastatic breast cancer may benefit from resection of the breast tumour [1–8].

Surgery as treatment for the primary tumour

In an analysis of 8,000 patients with primary distant metastatic breast cancer between 1995 and 2008 in the Netherlands, an improvement of 6 months in the median survival of these patients was observed, resulting in a median survival of 2 years [9]. The improved survival was most pronounced in patients younger than 50 years. Patients receiving systemic treatment, locoregional radiotherapy or breast surgery had a significantly lower risk of death compared to patients not receiving these treatments.

This section discusses the possible benefits of surgery; also, in order to provide some guidelines for the use of surgery, the protocol of the SUBMIT study (Systemic therapy with or without Up front surgery of the primary tumour in Breast cancer patients with distant Metastases at Initial presenTation) is utilised. The SUBMIT study investigated the effect of up front surgery of the primary tumour in patients with distant metastatic breast cancer at initial presentation. The study protocol can be used as a guideline since there is no consensus for the use of surgery of the primary tumour (with distant metastases at initial presentation) nowadays.

Review of literature

Until now, 8 retrospective studies regarding surgery in patients with primary metastatic breast cancer have found that surgical removal of the breast lesion is associated with a significantly higher overall survival rate [1–8]. In 3 studies only a trend towards better survival was found [10–12]. Surgical resection of the primary tumour was performed in 33–61% of all

Table 1
Results of literature on surgery in patients with primary distant metastatic breast cancer

Author (Year)	No. of patients	Surgery (%)	HR	95% CI	Median survival (months)			
					Surgery			No surgery
					All	Lumpec	Mastec	
Khan (2002) [1]	16023	57	0.61	0.58–0.65	–	27	32	19
Babiera (2006) [2]	224	37	0.50	0.21–1.19	–			–
Rapiti (2006) [3]	300	42	0.60	0.4–1.0	[a]			–
Fields (2007) [5]	409	46	0.53	0.42–0.67	32			15
Gnerlich (2007) [4]	9734	47	0.63	0.60–0.66	36			21
Blanchard (2008) [6]	395	61	0.71	0.56–0.91	27			17
Cady (2008) [10]	622	38	–	–	–			–
Leung (2009) [11]	157	33	–	–	25			13
Ruiterkamp (2009) [7]	728	40	0.62	0.51–0.76	31			14
Bafford (2009) [12]	147	41	0.47	–	42			28
Neuman (2010) [8]	186	37	0.71	0.47–1.06	40			33

HR: Hazard ratio; 95% CI: 95% confidence interval.
[a] 5-year specific survival: 27% for surgery with negative margins, 16% for surgery with positive margins, 12% for surgery with unknown margins and 12% for no surgery.

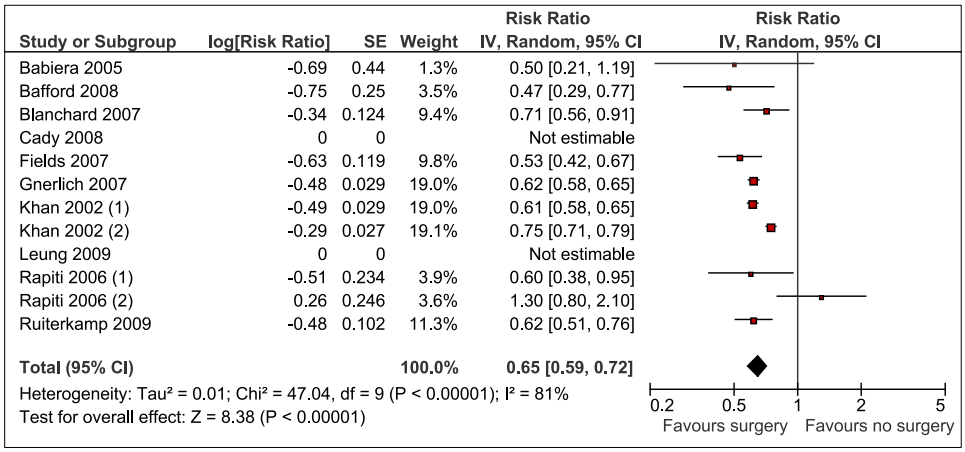

Fig. 1. Pooled analysis of Hazard Ratios for overall mortality for surgery versus no surgery for patients with stage IV breast cancer. (1): patients with free surgical margins; (2): patients with positive surgical margins.

patients (Table 1). The hazard ratios (HR) for overall mortality varied from 0.47 to 0.71 and pooled HR was 0.65 (95% confidence interval [CI] 0.59–0.72) in favour of patients undergoing surgery (Fig. 1) [13]. Other significant co-variates for better survival were age, characteristics of the primary tumour (hormone receptor status and Her2Neu status), margin status, number (more than one) and type of metastatic site and treatment with systemic therapy. Furthermore, patients who were selected for surgery of the primary tumour were significantly younger [2–7,10,11,14,15], had smaller tumours [3–8], were less likely to have metastases at more than one site [1–3,6–8,12], and were less likely to have visceral metastases [1–3,5–7,12], compared to patients who were not treated with surgery of the breast tumour. Three studies investigated the effect of margin status; they concluded that patients who were treated with a complete resection of the tumour tended to have a better survival than patients with positive tumour margins [1,3,16]. Only one study found no survival advantage for patients treated with a complete resection of the primary tumour compared to patients with positive margins [8]. In two studies the effect of an axillary lymph node dissection was analysed; both studies found a trend towards better overall survival for patients who were treated with an axillary dissection, but the difference was not significant [3,7].

A randomised controlled trial (RCT) should be performed to provide evidence for the use of surgery in patients with primary metastatic breast cancer, because the results of the retrospective literature may be biased, especially by selection for surgery. Based on the study design from the Dutch SUBMIT study, recommendations for surgical treatment follow.

Recommendations

In considering patients with primary metastatic breast cancer for surgery of the breast tumour, account should be taken of studies that indicate that younger patients and those who have only one metastatic site, benefit most from surgery. Patients can be treated with a lumpectomy or mastectomy, as long as the intention is a complete resection, with negative resection margins. Importantly, surgery should be followed by systemic therapy, according to local practice.

In case of a incomplete resection a re-excision or mastectomy or locoregional radiotherapy is advised. This should be considered in close communication with the patient; an incomplete resection can be accepted if the patient does not wish to have more/other local treatment. An axillary lymph node dissection is recommended in case of clinical evidence for lymph node involvement, proven by cytology or histology. Surgery of metastases is also an option, although no literature is available on timing in case of primary distant metastatic breast cancer. The SUBMIT study protocol recommends to treat metastases surgically >6 months after surgery of the breast tumour. For more information about metastasectomy in (secondary) metastatic breast cancer, see section IV.

Theoretical explanations of the effect of surgery

If the total tumour burden plays a role in survival, then the removal of the breast lesion is part of a multimodality strategy in preventing further growth and dissemination of the disease [17]. This hypothesis was confirmed by several studies in which a strong correlation was found between the level of circulating tumour cells (CTCs) and the prognosis of metastatic breast cancer; the number of circulating tumour cells before treatment is an independent predictor of overall survival in patients with metastatic breast cancer [18–20]. Also, patients who after treatment converted from elevated CTC levels to non-elevated levels showed a clinical response [21]. Thereby, an association is found between the median CTC level, determined in the course of the treatment, and the time to progression in metastatic breast cancer [22]. This may indicate that the clinical response is correlated with a decrease in CTCs and thus with a reduction of tumour burden.

Improvement in survival can also be caused by the fact that surgical resection restores the immune system, even in patients with metastatic disease [23]. Tumour-induced immunosuppression is a mechanism allowing tumours to escape immune destruction. It is reasonable that immunosuppression intensifies with increasing tumour burden. Surgery reduces the quantity of immunosuppressive factors, allowing the immune response to recover.

Contrary to the proposed biological mechanisms in favour of surgical removal of the primary tumour, there have been observations indicating that surgical resection of the breast lesion in metastatic disease may accelerate relapse by two mechanisms: (1) due to removal of inhibitors of angiogenesis there will be an angiogenic surge; (2) surgical wounding will lead to the release of growth and immunosuppressive factors [4,24].

Different study designs (RCT)

Worldwide, efforts are made to investigate the effect of surgery in patients with primary distant metastatic breast cancer. Ideally, randomised controlled trials (RCTs) should be conducted. At present, only three studies regarding this subject are recruiting participants [25]. The first is an observational study; *Analysis of Surgery in Patients Presenting With Stage IV Breast Cancer,* conducted by the Memorial Sloan-Kettering Cancer Center in the USA, started in July 2009. The second is a study carried out by the Medical University of Vienna, Austria, called POSYTIVE (*Primary Operation in SYnchronous meTastasized InVasivE Breast Cancer*), started in May 2010. The third study, *Early Surgery or Standard Palliative Therapy in Treating Patients With Stage IV Breast Cancer*, is performed by the National Cancer Institute (NCI). Two other studies, both RCTs, started in 2005 and 2007, in India and Turkey respectively [25]. The first, *Assessing Impact of Loco-regional Treatment on Survival in Metastatic Breast Cancer at Presentation*, performed by the Tata Memorial Hospital, is ongoing, but not recruiting participants. The second, *Local Surgery for Metastatic Breast Cancer,* is conducted by Istanbul University. This RCT is currently recruiting participants. Unfortunately, no (preliminary) results of these two studies are available. The SUBMIT study, performed by the Jeroen Bosch Hospital in The Netherlands, will start recruiting patients in the autumn of 2011. To our knowledge, these are the only studies concerning the

Box 1. Surgery in primary metastatic breast cancer

- Younger patients and patients with only one metastatic site benefit most from surgery.
- Surgery can be a lumpectomy or mastectomy, as long as the intention is a complete resection.
- Ask patients to participate in RCTs, in order to investigate the effect of surgery of the breast tumour in patients with primary distant metastatic disease.

surgical treatment of the breast tumour in patients with primary distant metastatic breast cancer. In order to investigate the effect of surgery, these studies are essential. We strongly suggest asking patients to participate, if a study is available.

Summary

This section is summarised in Box 1.

II. Surgery in secondary metastatic breast cancer

Secondary metastatic breast cancer is defined as recurrence of disease by distant metastases. In case of breast cancer, sites of metastases are bone (85%), liver (40–50%), pleuritis carcinomatosa (20%) lung (15–25%) and brain (6–16%). Median survival of these patients nowadays is 58 months after recurrence, with a 5-year overall survival of 44% [26]. Recent study results on metastasectomy of liver- and lung metastases have raised questions concerning the effect of this type of extensive treatment. Furthermore, in view of the serious implications of metastases in the vertebrae and femur, treatment of these types of metastases is highlighted also.

Metastasectomy of breast cancer liver metastases

A small part (5%) of all patients with breast cancer develop liver metastases without extrahepatic disease. If treated with chemotherapy, median survival of breast cancer patients with only liver metastases or with limited disease elsewhere is 19 to 26 months [27].

Review of literature

Eight reports on metastasectomy in hepatic metastases from breast cancer have been published in the last decade (Table 2) [28–36]. All of these reported single-institution studies, with 17 to 85 patients, treated between 1986 and 2004. All patients received metastasectomy of hepatic metastases. Median survival ranged from 27 to 63 months, with a 5-year overall survival between 21% and 61%. No control groups were available, except in 2 studies comparing complete resection with incomplete resection [31,34]. In case of R0 (complete macroscopic and microscopic) resection, 5-year survival was 43%, compared to 42% in R1 (microscopic residual disease) resection and 10% in R2 (macroscopic residual disease) resection, described in the study of Adam and colleagues [34]. In the study of Elias and colleagues the completeness of the resection did not appear to be of significant prognostic value [31]. Reported proportions of complete resection ranged from 65% to 86% [28,31,34].

Postoperative mortality was very low, with none of the studies reporting surgery-related deaths (Table 3). Overall or postoperative morbidity occurred – in case it was reported – in 0–22% of all patients. Recurrence of disease in liver and/or at other sites occurred in 52–76% of all patients. In 13–56% of all cases the first location of recurrence was in the remaining liver. Only 2 studies reported the number of patients who received a rehepatectomy for recurrent metastases; Sakamoto and colleagues reoperated 5% (1) of the patients who had hepatic recurrence, but Adam and colleagues described at least 1 rehepatectomy in almost half of the patients with recurrent disease in the liver [33,34]. Patients who had at least 1 repeated hepatic resection had a higher 5-year overall survival (81%) than patients with unresectable liver recurrences and patients without any hepatic recurrence following the first hepatic resection (5-year overall survival of 29%) according to the results of Adam and colleagues [34].

Prognostic factors influencing overall survival were disease-free interval (DFI), hormone positive tumour, extrahepatic disease, failure to respond to chemotherapy and R2 resection.

Retrospective analyses, small numbers of patients, relative long study intervals, use of different outcome parameters, and the absence of control groups to compare results, make it difficult to draw conclusions. All studies included only patients selected for surgery, thereby causing bias. Also, information about the timing of metastasectomy is missing. Nevertheless, median survival for patients treated with hepatic metastasectomy was higher compared to patients who did not have surgery. Further, there are no reports of serious surgery-related incidents.

Table 2
Results of studies regarding liver metastasectomy

Author (year)	Pt.	Period	Study	R0	Overall survival in years					Prognostic factors for OS	Median survival		
					1	2	3	4	5		R0	R1/2	All
Pocard (2000) [28]	52	1988–1997	single	86%	86%	79%	65%			DFI >48 mo	n.a.	n.a.	42 mo
Pocard (2001) [29][a]	65	1988–1999			90%		71%	46%		DFI >36 mo			n.a.
Yoshimoto (2000) [36]	25	1985–1998	single			71%			27%				34 mo
Selzner (2000) [30]	17	1987–1999	single						22%	DFI >12 mo			27 mo (16 pt)
Elias (2003) [31]	54	1986–2000	single	81%			50%		34%	HR+	n.s.	n.s.	34 mo
Vlastos (2004) [32][b]	31	1991–2002	single			86%			61%				63 mo
Sakamoto (2005) [33]	34	1985–2003	single						31%[c]	Extrahepatic disease			36 mo
Adam (2006) [34]	85	1984–2004	single	65%					41% all 10% R2 42% R1 43% R0	Failure to respond to preoperative CT, R2 resection, absence of repeat hepatectomy			46 mo
Martinez (2006) [35]	20	1995–2004	single			61%			33%	ER, her2neu			32 mo

n.a. = not available; n.s. = not significant.
[a] Article in French, only abstract used.
[b] Resection and/or RFA.
[c] 31% without extrahepatic recurrence, 21% if also extrahepatic recurrence.

Table 3
Results of studies regarding complications and recurrence for liver metastasectomy

Author (year)	Postop. mortality	Postop. morbidity	Overall morbidity	Recurrence (RRL)				Recurrence (RRL + new mets)				Rehepatectomy (% of recurrence)
				12 mo	24 mo	36 mo	Overall	12 mo	24 mo	36 mo	Overall	
Pocard (2000) [28]	0%	n.a.	12%	23%	39%	49%		27%	55%	64%		n.a.
Pocard (2001) [29]	0%	n.a.	18%			n.a.[a]						n.a.
Yoshimoto (2000) [36]	0%	0%	n.a.				67%				72%	n.a.
Selzner (2000) [30]	6%	n.a.	0%				47%				71%	n.a.
Elias (2003) [31]	0%	13%	n.a.				46%				56%	n.a.
Vlastos (2004) [32]	0%	n.a.	n.a.				13%				52%	n.a.
Sakamoto (2005) [33]	0%	n.a.	n.a.				56%				76%	5%
Adam (2006) [34]	0%	22%	n.a.				48%				69%	48%
Martinez (2006) [35]	n.a.	n.a.	n.a.				n.a.				n.a.	n.a.

RRL: recurrence in remaining liver; n.a. = not available.
[a] Analysed, but not available in abstract (article in French).

Recommendations

Metastasectomy for liver metastases in patients with colorectal cancer is accepted nowadays [37]. Based on the above results, some indications for hepatic metastasectomy in breast cancer patients may be given. Liver surgery is beneficial for selected patients: (1) young(er) patients, (2) low operation risk, (3) long interval (more than one year) between breast cancer surgery and liver metastases, (4) positive hormone receptor status of primary tumour, (5) no extrahepatic disease (except bone metastases), (6) less than four metastases, (7) demonstrated disease regression or stability with systemic therapy (chemotherapy or hormonal treatment) before resection, (8) normal liver function tests, (9) resection with intent of a complete (R0) resection of liver metastases. Based on the little information about rehepatectomy in case of recurrence of disease in the remaining liver after initial liver metastasectomy, one could argue that this might be a valuable treatment to prolong survival.

Table 4
Results of studies regarding minimally invasive techniques as treatment of breast cancer liver metastases

Author (year)	Pt.	Period	Study	No. mets	Technical success	Survival						
						Overall					Median	Mean
						1	2	3	4	5		
RFA												
Livraghi (2001) [38]	24	1996–1999	two	64	92%						n.a.	
Gillams (2005) [39]	19	n.a.	single	n.a.	n.a.			42%			n.a.	
Gunabushanam (2007) [40]	14	2002–2005	single	16	100%	64%					n.a.	
Sofocleous (2007) [41]	12	1999–2005	single	14	93%	100%		70%		30%	5.0 yrs	
Jakobs (2009) [42]	43	1999–2006	single	111	96%	92%		70%		39%	4.9 yrs	
Meloni (2009) [43]	52	1996–2008	single	87	97%	68%		43%		27%	2.5 yrs	
Laser												
Mack (2001) [44]	127	1993–2000	single	332	n.a.	97%	75%	65%		34%		4.3 yrs
Mack (2004) [45]	232	1993–2002	single	578	n.a.	96%	80%	63%		41%		4.9 yrs
Vogl (2010) [46]	161	2001–2007	single	n.a.	n.a.	89%	56%	37%		14%		2.7 yrs
Microwave												
Abe (2005) [47]	8	2000–2004	single	11	91%						n.a.	n.a.

n.a. = not available.

Minimally invasive techniques in the treatment of breast cancer liver metastases
Author: Dieuwertje L. Kreb, MD

Introduction

When surgical resection of liver metastases is not possible, due to, for instance, the location of the tumours, multifocality and/or an insufficient liver reserve, several minimally invasive techniques are available for localised intrahepatic tumour destruction, including radiofrequency ablation (RFA), laser-induced thermotherapy (LITT) and microwave thermocoagulation.

Review of literature

Six reports on the treatment of breast cancer liver metastases with radiofrequency ablation have been published so far (Table 4) [38–43]. Most of these reported on single-institution studies, with 12–52 patients, treated between 1996 and 2008. Median survival was not specified in three studies en ranged from 2.5 to 5.0 years in the remaining three. No control groups were available. None of the studies reported procedure-related deaths. Pleural effusion and subcapsular haematoma of the liver were the most common side effects, but these rarely needed treatment (Table 5).

Three studies on the treatment of breast cancer liver metastases with laser-induced thermotherapy (LITT) were all reported by one study group from Frankfurt, Germany [44–46]. In 2004 Mack and colleagues [45] described their results after treating 578 lesions in 232 patients. The 5-year overall survival rate and mean survival were 41% and 4.9 years, respectively, and there was a low complication rate. Vogl and colleagues [46] presented their results in 2010, describing 161 patients who were treated with transarterial chemoembolisation (TACE) to achieve the size and number of metastatic lesions that met the requirements for LITT. The complication rate was higher than in their previous study, and 5-year overall survival rate and mean survival were lower: 14% and 2.7 years.

Only one study describing the effect of microwave thermocoagulation on breast cancer liver metastases has been published [47]. Eleven nodules in 8 patients were treated with a technical success rate of 91%. Unfortunately, overall survival rates and median survival were not reported. After a mean observation period of 25.9 months, 62.5% of the patients were alive with new metastatic foci.

Discussion

Minimally invasive treatment of breast cancer liver metastases can be performed in selected patients. Similarly as with surgical resection, available studies on this subject are retrospective and lack control groups. No randomised controlled trials have been conducted. When metastasectomy is not possible because of the location of the tumours, multifocality

Table 5
Results of studies regarding complications in minimally invasive techniques

Author (year)	Complications
Livraghi (2001) [38]	perirenal haematoma (4%) pain due to diaphragmatic thickening (4%)
Gilliams (2005) [39]	n.a.
Gunabushanam (2007) [40]	pleural effusion (14%) peri-hepatic fluid collection (7%)
Sofocleous (2007) [41]	prolonged shoulder pain (8%) pleural effusion (8%)
Jakobs (2009) [42]	subcapsular haematoma (4.6%) haematoma of the abdominal wall (2.3%) pleural effusion (11.6) severe intrahepatic bleeding (4.6%) bile duct injury (2.3%)
Meloni (2009) [43]	perirenal haematoma (2%) biloma (2%) pleural effusion (10%)
Mack (2001) [44]	n.a.
Mack (2004) [45]	pleural effusion (0.9%) liver abscess (0.4%) injury to bile duct (0.2%) subcapsular haematoma (4.4%) non-symptomatic pleural effusion (9.1%)
Vogl (2011) [46]	chemotherapy-associated steatohepatitis (7.5%) reactive pleural effusion (35.4%) biloma (9.3%) subcapsular haematoma (6.8%) basal lung atelectasis (10.6%)
Abe (2005) [47]	high fever e.c.i. (9%)

n.a. = not available.

and/or an insufficient liver reserve, minimally invasive techniques can be considered as an alternative treatment. The technique that has been studied most is radiofrequency ablation.

Metastasectomy of breast cancer lung metastases

A solitary pulmonary nodule in patients with (a history of) breast cancer appears to be a metastasis of the breast in 33–40% of all cases. Only 3% of all breast cancer patients develop such a solitary lesion [27]. In general, median survival in case of isolated pulmonary metastases (due to breast cancer) is 13 to 25 months, but there are very few reports on this subject [48].

Review of literature

In recent years, 9 studies regarding metastasectomy in patients with pulmonary metastases were published (Table 6) [48–56]. Most studies included 15 to 47 patients, but three were larger, with 90, 125 and 467 patients [48,50,53]. All patients were treated in the period between 1960 and 2007, and most of the studies reported single-institution results, except for the study of Friedel and colleagues, which was based on results of the International Registry of Lung Metastases [48]. Generally, all studies reported 5-year overall survival rates, ranging from 31% to 54%, except for the study of Yhim and colleagues, who described a 4-year overall survival of 82% for patients with less than 4 metastases [56]. Reported 10-year overall survival ranged from 18% to 40% in five studies. Median survival, reported in half of the studies, ranged between 32 and 76 months. Friedel and colleagues reported separate median survival results for patients with R0 resection (37 months) and patients with R1/2 resection (25 months) [48]. The percentage of patients who were treated with a complete resection varied from 57% to 100%.

Postoperative mortality, described in five of all studies, was low, and occurred in 0–1% of all cases (Table 7). Only Planchard and colleagues reported the incidence of postoperative morbidity, which occurred in 13% of all patients [50]. Recurrence of lung

Table 6
Results of studies regarding lung metastasectomy

Author (year)	Pt.	Period	Study	R0	Overall survival in years[a]						Prognostic factors for OS	Median survival		
					3	4	5	10	15	20		R0	R1/2	All
Friedel (2002) [48]	467	1960–1994	registry	84%			38%	22%	20%		DFI >36 mo	37 m	25 m	35 m
Ludwig (2003) [49]	21	1989–1998	single	100%			53%				None			96.9 mo
Planchard (2004) [50]	125	1972–1998	single	77%	58%		45%	30%			DFI >36 mo, size largest met			4.2 yr[b]
Tanaka (2005) [51]	39	1992–2001	single	85%			31%				None			32 mo
Rena (2007) [52][c]	27	1990–2003	two				38%	18%			DFI >36 mo			n.a.
Yoshimoto (2008) [53]	90	1960–2000	single	89%			54%	40%		25%	DFI >36 mo, stage I breast cancer			6.3 yr
Welter (2008) [54]	47	1998–2007	single	57%			36%				ER+			32 mo
Chen (2009) [55]	41	1991–2007	single	100%			51%	51%			DFI >36 mo, <4 mets			n.a.
Yhim (2010) [56][d]	15	1997–2007	single			82%[e]					DFI >24 m, HR +			[f]

n.a. = not available; n.s. = not significant.
[a] No data available for 1- and 2-year overall survival.
[b] No difference between R0/1/2.
[c] Selection: only solitary pulmonary nodule.
[d] Surgery vs systemic treatment, <4 mets.
[e] Versus 32% no surgery.
[f] Median survival for metastasectomy not reached, median survival in case of no metastasectomy 34 m.

Table 7
Results of studies regarding complications and recurrence for lung metastasectomy

Author (year)	Postop. mortality	Postop. morbidity	Recurrence		Reoperation
			Pulmonary	Pulmonary + other sites	
Friedel (2002) [48]	n.a.		9%	n.a.	4%
Ludwig (2003) [49]	0%	Yes[a]	n.a.	n.a.	n.a.
Planchard (2003) [50]	1%	13%	28%	67%	n.a.
Tanaka (2005) [51]	n.a.		n.a.	n.a.	n.a.
Rena (2007) [52]	n.a.		n.a.	n.a.	n.a.
Yoshimoto (2008) [53]	1%	Yes[a]	13%	69%	n.a.
Welter (2008) [54]	0%		n.a.	68%	n.a.
Chen (2009) [55]	0%		n.a.	n.a.	n.a.
Yhim (2010) [56]	n.a.		n.a.	n.a.	n.a.

n.a. = not available.
[a] Not specified.

metastases was recorded in 3 studies and ranged from 13% to 28%. Recurrence of disease (lung metastases and/or other locations) was approximately 60%. Re-operation for recurrent lung metastases was described only by Friedel and colleagues and was performed in 4% of all patients who had pulmonary recurrence. The 5-year survival of these patients was 53%, suggesting a benefit from redo surgery [48].

Prognostic factors in favour of prolonged survival were disease-free interval (DFI) >36 months, hormone receptor positive breast cancer, stage I breast cancer, small size of largest metastasis and less than 4 metastatic sites. In the only study that compared metastasectomy to systemic therapy, surgery was a independent prognostic factor for progression-free survival, but not for overall survival [56].

All studies were retrospectively analysed and only one study compared patients who received metastasectomy with patients treated with systemic therapy only. Most studies were small, single-institution studies and

only one study was registry based [48]. Similarly as with the studies regarding hepatic metastasectomy, study periods were relatively long. Median survival after metastasectomy in general was quite reasonable.

Recommendations

First, metastasectomy in lung metastases is an important diagnostic tool, allowing for differential diagnosis, like primary lung cancers and benign lesions [27,37]. Second, this potentially beneficial procedure can be discussed for a selected group of patients, to prolong survival [37]. In addition to general indications, like performance status and age, as described in the subsection on liver metastases, for metastasectomy in patients with lung metastases DFI is also important. However, in lung metastases a DFI of more than 36 months (instead of 1 year as in liver metastases) is an indication for metastasectomy. Further, a complete (R0) resection should be possible and lung metastases should be of small volume. With regard to surgical procedure, there were no significant differences between types of resection [48]. In case of a solitary pulmonary nodule, video-assisted thoracoscopic surgery (VATS) is a good procedure for diagnostic management; when breast cancer metastases are diagnosed, an open procedure must be performed to palpate the entire lung to exclude previously undetected nodules [52].

Discussion

Metastasectomy in case of liver- or lung metastases of breast cancer can be performed in selected patients. Studies about this subject are retrospective and lack control groups. No randomised controlled trials have been conducted. Further, no research has been done about the right timing for metastasectomy, therefore no good advice about this subject can be given. It is generally accepted that in all cases systemic therapy should be administered. Metastasectomy can be an adjuvant treatment, but when distant metastases have occurred, the disease should be considered and approached as a systemic problem. Best results are generated if a combination of systemic therapy and surgery can be realised.

Treatment of breast cancer metastases in the vertebrae and femur

In patients with breast cancer who develop bone metastases, these metastases occur mostly in long bones and the spine. Most common indications for surgery in these cases are complete fracture, impending fracture and spinal neurologic deficit or pain [57]. In case of painful bone metastases radiotherapy is an effective treatment. Most patients experience a significant reduction of the pain and in 33–50% of all patients the pain disappears completely [58,59]. In large, osteolytic lesions with (the risk of) a pathological fracture or in metastases in the vertebrae with (the risk of) spinal cord compression, surgical stabilisation in combination with postoperative radiotherapy is advised. The latter is recommended to prevent luxation of the osteosynthesis [60]. Especially in case of spinal cord compression patients should receive treatment as soon as possible. Neurosurgical and/or orthopaedic surgery followed by radiotherapy causes improved recovery of function compared to radiotherapy alone [61]. The primary goal of surgery in these patients is to prevent or delay pathological factures or spinal cord compression, so bone lesion progression should be monitored closely. Patients with large osteolytic lesions on weight-bearing areas should receive surgical stabilisation. If pathological fracture has occurred, surgery may stabilise bones, and may facilitate healing [62]. A population-based study on the surgical treatment for skeletal breast cancer metastases showed that after surgery, pain decreased in 77% of all patients and function improved in 65% (n = 107). Approximately 10% of the patients underwent a reoperation, in which experience in treating pathological fractures seems to play a role. In case of proximal femur fractures, less complications were seen in endoprosthetic replacement compared to osteosynthetic devices [57]. In patients who received spinal surgery (n = 87), pain was reduced significantly postoperative (reduction of pain level measured by visual analog scale [VAS] from 6 to 2) and 75% of the patients who were non-ambulatory regained ambulation. 26% of all patients who received surgery had major complications, which is in line with other studies [63].

Treatment of breast cancer metastases in the brain

A very small proportion of patients with metastatic breast cancer have a solitary brain metastasis. Surgery of the solitary metastasis in combination with postoperative radiotherapy can be considered, and this intensive treatment can lead to a significant improvement in survival [64]. Stereotactic radiotherapy can be a good alternative for surgery [65,66]. The largest retrospective study on surgery of brain metastases illustrated that craniotomy followed by whole-brain radiotherapy (WBRT) can positively impact survival. Overall median survival in patients who received craniotomy (n = 70) was 16.2 months after diagnosis of the brain tumour. There was no statistical difference

Box 2. Surgery in secondary metastatic breast cancer

- Metastatic breast cancer should be considered as a systemic problem so in all cases systemic therapy should be given.
- Metastasectomy of liver and lung metastases is beneficial for selected patients, based on results of small retrospective studies.
- When metastasectomy is not possible, minimally invasive techniques can be used in the treatment of breast cancer liver metastases, RFA being discussed most in the literature.
- Surgical treatment of metastases in femur and vertebrae is warranted only to prevent or treat pathological fractures or spinal cord compression (administer postoperative radiotherapy)
- Surgery should be performed in brain metastases, in case of a solitary or two or even three accessible metastases, followed by WBRT.

in survival for patients who had single or multiple lesions. In multivariate analysis, adjuvant WBRT after craniotomy and the absence of meningeal carcinomatosis were the only significant predictive variables for longer survival. The frequency of complications after surgery was not described. It is recommended that patients with a single metastasis or two or even three accessible metastases from breast cancer be considered for local treatment, such as surgery [67].

Summary

This section is summarised in Box 2.

III. Surgery in locally advanced breast cancer

Patients with locally advanced breast cancer have no distant metastatic disease, but due to excessive local disease they are not eligible for the same surgical treatment as patients with early-stage breast cancer. That is, surgical treatment is possible only if tumour size can first be decreased by systemic therapy. The five-year survival of patients with locally advanced breast cancer ranges between 40% and 60% and 10-year survival rate is approximately 25%, depending on tumour load. Inflammatory breast cancer or mastitis carcinomatosa (TNM classification T4D) is a different type of locally advanced breast cancer, which has a worse prognosis with a 5-year survival of 20–40% [68,69].

Multimodality treatment

Locally advanced breast cancer is a disease that needs a multidisciplinary approach. Because the prognosis of patients with locoregional disease is worse compared to patients with early-stage breast cancer, a more critical approach towards mutilating treatment (surgery) is needed. Cure in these patients is possible and treatment is with curative intent. Neoadjuvant treatment (NAT) makes it possible to perform breast-conserving surgery, thereby increasing locoregional control [70,71]. Evidence regarding survival advantage after neoadjuvant treatment is lacking [72–76]. Therefore, the most common treatment of locally advanced breast cancer consists of neoadjuvant chemotherapy (NAC), followed by more or less extensive surgery and locoregional radiotherapy. In case of a hormone receptor positive tumour adjuvant hormonal treatment is advised.

Role of surgery of the breast tumour

There is no level A evidence that surgery of the breast tumour increases locoregional control or (disease-free) survival in patients with locally advanced breast cancer. On the other hand, locoregional control after radiotherapy is increased in case of a smaller tumour load [69,77–79]. Locoregional control can be achieved by neoadjuvant chemotherapy followed by either mastectomy or lumpectomy [80–84]. Most authors advise surgery before radiotherapy (and not radiotherapy alone) [81,85–88]. In case of irresectability after NAC, first radiotherapy can be given, followed by surgery of the breast tumour. A separate entity is inflammatory breast cancer (T4D). In these patients surgery does not seem to be part of the treatment; chemotherapy and radiotherapy are the modalities to be chosen in these cases [68,69,89–94].

Role of surgery of the axilla

What to do with the axilla remains unclear. An axilla without evidence of tumour does not seem to benefit from axillary lymph node dissection (ALND). In case of a clinically or radiologically proven macroscopic tumour, treatment is advised. However, surgery and radiotherapy together results in an increase of toxicity from the treatment [95,96]. Radiotherapy could be

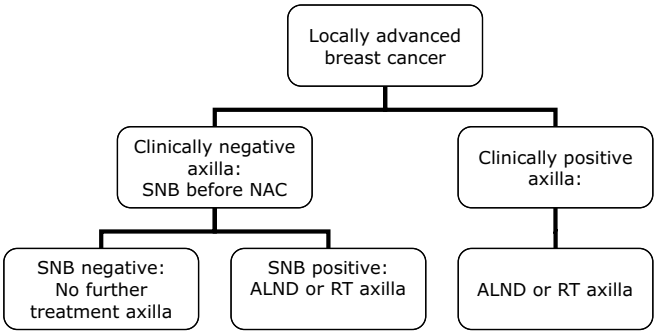

Fig. 2. Algorithm for axillary treatment in locally advanced breast cancer.

Box 3. Surgery in locally advanced breast cancer

Patients with locally advanced breast cancer are treated multidisciplinarily and with curative intent. Treatment steps are:
- Neo-adjuvant chemotherapy (or neo-adjuvant hormonal treatment)
- Surgery to reduce tumour load
- Locoregional radiotherapy
- Adjuvant hormonal treatment in case of receptor positive tumour

Regarding treatment of the axilla:
- Clinically negative axilla: SNB before NAT, surgery (ALND) is not warranted
- Clinically positive axilla: ALND

applied to the axilla, as an alternative for ALND, to achieve sufficient axillary control [82,97].

Sentinel node biopsy

Axillary lymph node dissection has traditionally been the standard of care for staging patients undergoing NAC. Since sentinel node biopsy (SNB) has been introduced in the 1990s, this less invasive procedure could also be used in the neoadjuvant setting. Two important difficulties arise with the use of SNB in this setting. First, if SNB is performed before administration of NAC, the effect of the chemotherapy to the axilla is neglected, since part of the patients who are node positive, become pathologically node negative after chemotherapy. Second, if SNB is performed after treatment with NAC, this may influence the reliability of the SN procedure. One of the few studies in patients with locally advanced breast cancer and SNB before NAC state that 15% of the patients did not have to undergo ALND or axillary radiotherapy, because of negative SLN before NAC. None of these patients presented with local or distant recurrence at 33 months' follow-up [98]. Several studies have investigated the effect of SNB after NAC, but most of these did not focus on patients with locally advanced breast cancer. In these studies ALND was performed regardless of sentinel lymph node (SLN) status and pooled SLN identification rate was 90%, with a false negative rate of 12% and an overall accuracy of 94% for SNB after NAC [99].

The appropriate timing of SNB in the neoadjuvant setting in patients with locally advanced breast cancer remains controversial. It seems that performing a SNB before NAC provides higher SLN identification rate and lower false negative rates. Advantage of SNB after NAC is that it only requires one operation. One of the disadvantages is the unknown effect of no ALND in patients whose nodes were downstaged by NAC [99]. There are no published randomised studies on this subject. Based on the above described (non-conclusive) evidence, Fig. 2 presents an algorithm for the treatment of the axilla in patients with locally advanced breast cancer.

Summary

This section is summarised in Box 3.

IV. Surgery in locoregional recurrence

If patients with breast cancer develop recurrence after initial treatment, this can occur locally or regionally,

that is, in the ipsilateral breast or in the regional lymph nodes. Chances of developing local recurrence depend on the stage of the initial disease and age in case of breast-conserving surgery. In case of ductal carcinoma in situ (DCIS), 10–15% of all patients treated with breast-conserving surgery develop a local recurrence within 10 years and 0–4% after mastectomy. Half of these recurrences are invasive [100,101]. In patients with T1–2N0–1 breast cancer, the local recurrence percentage is usually lower in case of modified mastectomy compared to breast-conserving surgery, though the type of surgery has no influence on overall survival [102,103]. Younger age appears to be unfavourable for the chance of local recurrence, especially after breast-conserving therapy (BCT) [102–104]. The risk to develop locoregional recurrence in early breast cancer is 1–5% [105,106]; in pT3 or pN2 patients, it is higher (7–15%) [107,108]. Axillary recurrence after a sentinel node procedure is very rare (0.25%) [109]. In case of a locoregional recurrence, 5-year survival ranges between 40% and 65%. If locoregional recurrence occurs, patients should first be assessed for distant metastatic disease. If no distant metastases are present, the intention of the treatment of an isolated locoregional recurrence has to be curative.

Local recurrence after breast-conserving surgery

Therapy in local recurrence after breast-conserving surgery consists of surgery, and mostly a mastectomy is advised. Research on mastectomy versus breast-conserving therapy in local recurrence demonstrates a significantly worse disease-free and overall survival for patients treated with breast-conserving therapy and radiotherapy [110]. In case of an irresectable local recurrence (18–27%) [107,111,112], radiotherapy with hyperthermia is recommended [113–115].

Local recurrence after (modified) mastectomy

In local recurrence after (modified) mastectomy, surgery should be performed followed by locoregional radiotherapy. The tumour should be removed completely, if possible. Otherwise, surgery is still advised: resection should be performed as complete as possible. Including surgery in the treatment strategy results in an improved local control [116,117]. However, in 20–40% of all local recurrences the tumour appears irresectable [107,116]. If the region has initially been treated with radiotherapy, high-dose radiotherapy cannot be administered, and low-dose radiotherapy with hyperthermia should be used [113–115,118,119].

Treatment of the axilla in local recurrence

Patients who present with local recurrence have all received different initial treatments, and therefore they may have been treated with a sentinel node biopsy. If this SNB was negative, axillary lymph node dissection was not performed, so part of these patients still have axillary lymph nodes. The question is, if these patients develop local recurrence in the breast, what should be done with the axillary lymph nodes? One study analysed 70 patients with previous negative SNB who developed a local recurrence [120]. Thirty-seven patients were treated with ALND and in 13 patients a second SNB was attempted. The SNB was successful in only 5 cases. Overall, positive lymph nodes were detected in 13 of the 50 patients who underwent axillary staging, either by SNB or ALND. The investigators concluded that, considering the high rate of positive axillary lymph nodes in these patients, repeat surgical staging is appropriate, because staging provides useful information about the need for systemic therapy [120]. Further, if tumour cells are present in the axilla, removal can provide improvement of regional control. Other studies as well state that SNB is feasible in patients with local recurrence, but these studies also involve small patient groups [121,122]. If larger studies indicate that SNB is a safe and reliable procedure to replace ALND in patients with local recurrence, this less invasive treatment should be recommended. At this moment such a large observational study is being conducted in the Netherlands: *Sentinel node and recurrence breast cancer* (SNARB). In patients with local recurrence, axillary staging is advised, either by SNB or ALND in previously SNB negative patients. If an ALND has already been performed no further treatment is recommended.

Regional recurrence after breast-conserving surgery or mastectomy

Regional recurrence represent a very diverse group of recurrences, because the location of recurrence can be supraclavicular, axillar, infraclavicular and parasternal. There are no studies about regional recurrences alone; mostly also local recurrences are taken into account [107,108,111,116,123–130]. In case of a regional recurrence without initial locoregional radiotherapy, high-dose radiotherapy should be given, if possible preceded by surgical removal of the recurrence. If at initial treatment locoregional radiotherapy was used, only low-dose radiotherapy with hyperthermia can be given. This could also be preceded by surgical removal of the recurrence.

Box 4. Surgery in locoregional recurrence

Local recurrence after breast conserving surgery
– Surgical treatment: mastectomy

Local recurrence after (modified) mastectomy
– Surgery (if possible complete resection)
– Followed by radiotherapy

Treatment of axilla in local recurrence
– In patients with previous negative SNB: axillary staging (SNB/ALND)
– In patients with previous ALND: none

Regional recurrence after breast-conserving surgery or mastectomy
– Surgery (if possible complete resection)
– Followed by radiotherapy

Summary

This section is summarised in Box 4.

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Conflict of interest statement

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