Review Article on Loco-regional Therapy for Metastatic Breast Cancer

Surgical therapy for breast cancer liver metastases

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Abstract: Breast cancer is the most commonly diagnosed cancer in females worldwide. If diagnosed early, patients generally have good outcomes. However, approximately 20% to 30% of all women diagnosed with breast cancer develop metastatic disease. Metastatic breast cancer is incurable, but there is growing evidence that resection or other local therapy for breast cancer liver metastases (BCLM) may improve survival. We aimed to review indications for and outcomes of perioperative liver resection and other local therapies for BCLM. In this series, we reviewed 11 articles (605 patients) focusing on surgical resection and 7 articles (266 patients) describing radiofrequency ablation (RFA) for BCLM. Median disease-free survival (DFS) after surgical resection was 23 months (range, 14–29 months) and median overall survival (OS) was 39.5 months (range, 26–82 months). One, 3- and 5-year survivals were 89.5%, 70%, and 38%, respectively. The factors favoring better outcomes are hormone receptor positive primary breast cancer status, R0 resection, no extrahepatic metastases (EHM), small BCLM, and solitary liver metastases. On the other hand, the median DFS with RFA was 11 months, median OS was 32 months, and the 3- and 5-year OS were 43% and 27%, respectively. The clinical features that are indications for RFA are smaller tumor and higher EHM rate than those favoring surgical resection (2.4 *vs.* 4.0 cm and 46% *vs.* 27%). The merits of RFA are its high technical success rate, low morbidity, short hospital stay, and that it can be repeated. Although results are as yet limited, in carefully selected patients, resection or other local therapies such as RFA, render BCLM potentially provide prognostic improvement.

Keywords: Breast cancer; liver metastases; surgical resection; radiofrequency ablation (RFA)

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Introduction

Globally, breast cancer is the most frequently diagnosed malignancy in females. In Japan, during the year 2014, according to the Cancer Information Service at the National Cancer Center of Japan, 76,257 breast cancer cases were diagnosed in Japan. In the United States, 266,120 breast cancer cases were diagnosed in 2018. There were 40,920 deaths due to breast cancer in that year (1). Available data suggest that approximately 20% to 30% of all patients with breast cancer will develop metastatic disease (2). The leading sites of distant metastases are bone (41.1%), lung (22.4%), liver (7.3%), and brain (7.3%) (3). While the liver is not the most common initial location of distant metastases, breast cancer liver metastases (BCLM) are the first site of metastatic disease in 5% to 20% of patients and, furthermore, half of patients develop liver metastases at some point during their clinical course (4,5). Metastatic breast cancer, with the exception of local recurrence, is regarded as being incurable. Ten-year overall survival (OS) of patients given systemic therapy is about 5%. Moreover, only 2–3% of patients maintain a complete response for

more than 20 years (6,7).

Recent evidence suggests that improved systemic treatments are resulting in increased progression-free survival (PFS) and/or OS outcomes. Since the 1990s, chemotherapy has improved the outcomes of metastatic breast cancer patients (8). From the 2000s, especially, molecularly-targeted therapies such as anti-human epidermal growth factor receptor type 2 (HER2) agents, including trastuzumab, pertuzumab and T-DM1 (9,10), mTOR inhibitors and CDK4/6 combined hormonal therapy (11-13), immune checkpoint inhibitors (ICI) such as humanized monoclonal anti-PD-L1 antibody (Atezolizumab) (14), and PARP inhibitors have shown efficacy for BReast CAncer gene (BRCA)-positive HER2 negative metastatic breast cancers (15), thereby contributing to better outcomes. Liver metastases have long been regarded as being incurable and patients generally have poor outcomes, such that treatment is palliative, with the goals being improved quality of life and prolonged survival.

Since there are numerous systemic therapy drugs for metastatic breast cancer, surgery for BCLM has been regarded as being too aggressive for many patients. However, there is growing evidence that resection and other local therapies for BCLM may contribute not only to assessing histological information and the subtype (positivity for estrogen receptor, progesterone receptor, HER2) of metastatic tumors, while also providing a survival benefit. Since 2000, number of studies have examined surgical treatment of BCLM (16-30). The prior studies tended, however, to have limited sample sizes, and the patient selection criteria differed among them. However, some clinical benefits were obtained. Moreover, recent results have shown that patients with solitary liver metastases or oligo-metastatic breast cancer might benefit from local therapies (31,32).

We aimed to review the indications and outcomes of perioperative liver resection and other local therapies for BCLM.

Methods

We searched the PubMed database using the terms “breast cancer”, “liver metastases”, and “surgery”. Since the aforementioned major advances in drug therapies (9-11,33) and advancements in surgical techniques, we identified major studies published after 2010 such that this review covers the two decades between 2000 and the present.

Results

Liver resection

This review covers 11 series (34-44), totaling 605 patients. The author, name of the journal, time span of the study, country, and number of patients are listed in Table 1. The studies were published between 2012 and 2018. In nearly all of the series, the study period started around or after 2000, though two series were started in the 1980 which included more than 100 patients in each series (42,43). The median number of patients was 43 (range, 12–131). Six studies (34,35,40-42,44) were prospective and two (38,43) were retrospective. Three were case control studies (36,38,44). Nine were single center analyses (34-42) and two were multicenter analyses (43,44). Five series consisted of patients who had undergone radiofrequency ablation (RFA) (35-39). Several reviews on liver resection have been reported for the last decade (45-51). As the authors investigated, we summarized the data of primary tumor, clinical outcomes, and prognostic factors in this review.

Primary tumor

The major histological type was invasive ductal carcinoma, accounting for a median 83% (range, 12–92%) of cases. TNM stage was used in most studies, with T and N being reported for 7 series (34-36,38,40,43,44). The median percentage of cases with a T1 or T2 primary tumor diagnosis was 83% (54–92%). Approximately half of the total patients (52.5%, range, 28–71%). The M status was reported for only 3 series (34,38,40), with the percentages having distant metastases at the primary diagnosis being 0%, 10%, and 32%. Nine studies (34-40,43,44) included hormone receptor status and seven (34,35,37,38,40,43,44) HER2 receptor status. The median estrogen and progesterone receptor positive rates were 75% (range, 45–82%) and 55% (range, 9–82%), respectively. HER-2 receptor status was positive in 39% (range, 14–55%) of studies assessing this factor.

Clinical outcomes of hepatic resection for BCLM

Table 1 shows the BCLM information. The median time to diagnosis of liver metastases was 34 months (range, 20–60 months) for 8 studies. Eight reports described a median maximal tumor size of 4 cm (range, 1.8–5.2 cm). The median rate of extrahepatic metastases (EHM) was 26.5% (range, 7–45%). Major resection (three or more segments) was performed in 47% (259/556) of patients (median 42.5%,

Table 1 Details and clinical outcomes of BCLM

First author, year published (reference)	Journal	Study period	N	Age (years)	Tumor sizes (cm)	Solitary BCLM	EHM	R0/RR	DFS/OS (mo)*2	Survival rates (1-/3-/5-year)
Abbot, 2012 (34)	*Surgery*	1997–2010	86	NS*1	NS	62%	28%	90%/NS	14/57	NS/81%/44%
Dittmar, 2013 (35)	*J Cancer Res Clin Oncol*	1997–2010	34	53 [32–74]	NS	24%	35%	62%/NS	NS/36	NS/NS/26%
Mariani, 2013 (36)	*Eur J Surg Oncol*	1998–2007	51	46 [29–69]	1.8	65%	7%	82%/NS	NS/NS	NS/73%/50%
Kostov, 2013 (37)	*J Breast Cancer*	2001–2007	42	58 [39–69]	5.1	52%	45%	83%/41%	29/43	85%/64%/38%
Polistina, 2013 (38)	*World J Surg*	2004–2011	12	63 [44–77]	4	42%	NS	92%/NS	22/29	100%/67%/34%
Treska, 2014 (39)	*Anticancer Res*	2000–2013	13	51±9	5.2	67%	25%	NS/NS	NS/26	80%/46%/11%
Bacalbasa, 2014 (40)	*Anticancer Res*	2002–2013	43	52 [31–79]	NS	56%	NS	91%/40%	NS/32	93%/74%/58%
Weinrich, 2014 (41)	*HPB Surg*	2001–2007	24	53 [38–77]	NS	55%	NS	86%/14%	NS/53	86%/NS/33%
Ruiz, 2015 (42)	*Ann Surg Oncol*	1985–2012	120	51±11	NS	39%	NS	53%/40%	NS/35	NS/50%/38%
Margonis, 2016 (43)	*HPB*	1980–2014	131	55 [46–66]	NS	52%	13%	91%/52%	24/53	99%/75%/NS
Ruiz, 2018 (44)	*Eur J Cancer*	2000–2013	49	50±11	3.2	39%	NS	NS/NS	NS/82	NS/81%/69%

*1, ≥50, 60%, <50, 40%; *2, median. BCLM, Breast cancer liver metastases; EHM, extrahepatic metastases; R0, microscopic negative margin; RR, recurrence rate; DFS, disease-free survival; OS, overall survival; NS, not stated.

range 29–69%). The microscopic negative margins (R0) rate was reported for 9 studies, and the median was 86% (range, 53–92%), while the recurrence rate was 42.5% (153/360) with a median value of 40% (range, 14–52%). The median follow-up time was 55 months (range, 22–69 months). Median DFS was 23 months (range, 14–29 months) and median OS was 39.5 months (range, 26–82 months). The 1-, 3-, and 5-year OS rates were 89.5% (range, 80–100%), 70% (range, 46–81%), and 38% (range, 11–69%), respectively. These studies had different numbers of patients, clinical features, selected cohorts, and designs, such that the data must be carefully interpreted. As to systemic therapy, 6 articles described systemic therapies (36,37,40-43), including hormone administration with and without chemotherapy (doxorubicin, taxol, capecitabine, gemcitabine) and/or trastuzumab or lapatinib. Among the patients included in this review, none had received the newer targeted therapies such as pertuzumab, CDK 4/6 inhibitors, ICI, and so on.

Prognostic factors

The factors found to independently impact outcomes after BCLM resection are listed in *Table 2*. Seven studies showed positive hormone receptor status of the primary breast cancer to be associated with better OS after surgical removal of liver metastases (three multivariate and four univariate analyses) (34,36-40,42). Microscopic negative margins (R0) were associated with better OS (two multivariate and two univariate analyses) (35,37,41,43). Three multivariate analyses showed EHM to be associated with poorer OS. BCLM less than 3 cm in maximum diameter was associated with better OS (43), while liver metastases 3.5 cm or larger were associated with poorer PFS (39), according to three multivariate analyses (35,39,40). Univariate analysis also showed BCLM size to be related to outcomes. One report of multivariate and one of univariate analysis showed that patients with solitary liver metastases had better OS (40,42) and that the number of metastases was associated with DFS and OS (38,41). Patients with DFS of 4 years or less had poorer OS and PFS on multivariate analysis, whereas those with DFS of less than 2 years had poorer OS on univariate analysis. Evaluation according to the RECIST criteria showed a lack of response to pre-operative systemic therapy to be associated with progressive disease, and thereby poorer OS (34,37). Abbot *et al.* reported that patients with a partial response to chemotherapy had a median survival of nearly 80 months, as compared to approximately 30 months for patients with a less than partial response (34). The other primary tumor characteristics, i.e., T stage, lymph node metastases and tumor grade also influenced OS.

Oligometastases

According to the 4th ESO-ESMO International Consensus

Table 2 Positive prognostic factors and safety of treating BCLM

First author (reference)	Positive prognostic factors (multivariate analysis/univariate analysis)	Mortality	Complications	Hospital stay (days)*
Abbott (34)	Hormone receptor positive (primary), preoperative SD/DFS interval >2 years	0%	21%	6
Dittmar (35)	R0 resection, no EHM, HER2 expression, age <50 years of age/BCLM <5 cm	0%	24%	NS
Mariani (36)	EHM (bone), N stage (primary)/hormone receptor positive (primary)	0%	18%	NS
Kostov (37)	Hormone receptor positive (primary), R0 resection, BCLM <4 cm, response to nonsurgical treatment, negative portal LN	2%	36%	NS
Polistina (38)	Hormone receptor positive (primary), Number of metastases <3	0%	42%	NS
Treska (39)*	Hormone receptor positive (primary), BCLM <3.5 cm, no EHM, age >50 years of age, DFS interval >4 years	NS	NS	NS
Bacalbasa (40)	Hormone receptor positive (primary)/BCLM <5 cm, number of metastases, N stage (primary)	NS	NS	NS
Weinrich (41)	Low grade (primary)/R0 resection, Number of metastases, T and N stage (primary)	NS	NS	7
Ruiz (42)	Number of metastases/Hormone receptor positive (primary), DFS interval >2 years	5%	32%	11
Margonis (43)	R0 resection, BCLM <3 cm	0%	23%	NS
Ruiz (44)	NS	NS	34%	10

*, median. SD, stable disease; DFS, disease-free survival; R0, microscopic negative margin; EHM, extra hepatic metastases; BCLM, breast cancer liver metastases; LN, lymph nodes; NS, not stated.

Guidelines for Advanced Breast Cancer (ABC 4) (52), "*Oligometastatic disease is defined as low volume metastatic disease with limited number and size of metastatic lesions (up to 5 and not necessarily in the same organ), potentially amenable for local treatment, aimed at achieving a complete remission status.*" In colorectal cancer cases, resection of liver metastases is a well-established treatment (53,54). However, this strategy remains controversial for BCLM, even with oligometastases. More than 50% of the patients in the reports reviewed herein had solitary metastases (34,36,37,39-41,43). Dittmar *et al.* noted that significantly more long-term survivors, with survival reaching 60 months or more in some cases, had solitary tumors (35). In terms of prognostic factors, solitary liver metastases were associated with better OS (40,42) (m1, u1) and the number of metastases was related to both DFS and OS (38,41). Weinrich *et al.*, studying resection of isolated liver metastases (41), found that 16 of 29 female patients (55%) had one BCLM and 6 (21%) had two BCLMs. Median time to diagnosis of BCLM was 55 months (range, 1–77 months) months. The 1-year survival rate was 86% in patients with and 37.5% in those without resection. R0 resection, fewer liver metastases, and a longer interval to diagnosis of BCLM were found to be significant prognostic factors.

Ruiz *et al.* (42) reported a series of patients undergoing "repeat hepatectomy". The single hepatectomy group (N=120) was compared with those who underwent repeat hepatectomy (N=19). The proportion of patients with solitary liver metastases was 39% in the single hepatectomy group and 53% in the repeat hepatectomy group. After the first hepatectomy, patients who received repeat hepatectomy had longer survival than those who had undergone single hepatectomy (95% and 84% *vs.* 50% and 38% at 3 and 5 years, respectively) (P=0.002). Median survivals were 35 and 100 months, respectively. In terms of the number of metastatic tumors, patients with a single BCLM at first hepatectomy had 3- and 5-year OS rates of 76% and 76% compared with rates of 51% and 17% in patients with multiple metastases (P=0.023). Prognostic factors after repeat hepatectomy included a time interval between breast cancer diagnosis and first hepatectomy of more than 2 years, a limited hepatectomy, solitary metastases, positive progesterone receptor status, and chemotherapy following repeat hepatectomy. The results of Ruiz *et al.* suggest that repeat hepatectomy is potentially curative when combined with systemic therapy.

Recent studies demonstrated that subgroups of these heterogeneous patient populations with oligometastatic

disease benefit from additional local or locoregional treatment, with improved survival rates after R0 resection of BCLM, as compared to systemic treatment alone (42,44,55).

Case control study

To date, there have been no reports of prospective randomized trials examining resection of BCLM. Case control studies have been conducted to determine the actual benefits of surgical treatment (36,38,44). Mariani *et al.* (36) reported 51 patients with BCLM who were individually matched with patients receiving systemic treatment only. None had more than 4 BCLM, and most of the cases fewer than 4. The study group was matched with the control patients for age, year of breast cancer diagnosis, time to metastases, TNM stage, hormone receptor status and tumor pathology. The 3-year survival rates of surgically treated and non-surgically treated patients were 80.7% and 50.9% (P<0.0001), respectively. Ruiz *et al.* (44) reported a case-matched comparison of surgical resection versus systemic therapy for BCLM using data from European patients. Matching was based on age, decade when diagnosed, time to metastases, maximum size of metastases, single or multiple tumors, chemotherapy, and hormonal or targeted therapy after diagnosis. Propensity score matching was used to create a subset of patients with similar characteristics and a similar likelihood of undergoing surgery. The median OS of patients receiving systemic treatment combined with liver resection and systemic treatment only were 82 and 31 months (P<0.001), with 3-year OS of 81% and 69% and 5-year OS of 33% and 24%, respectively. Patients who received systemic therapy combined with liver resection lived more than twice as long as those given systemic therapy alone. According to Cox regression results, patients given systemic treatment combined with liver resection were less likely to die than those receiving systemic treatment alone [hazard ratio (HR) 0.28, 95% confidence interval (CI): 0.15–0.52; P<0.001]. Liver resection is thus potentially effective for appropriately selected cases.

Sadot *et al.* (56) also performed a case-control study. The purpose of the study was to compare outcomes in patients with isolated BCLM who underwent surgery and/or ablation to those of patients who received systemic therapy alone. In total, 167 patients were studied, including 69 and 98 given surgery/ablation and medical treatments, respectively, with a median follow-up of 73 months. Patients in the surgical group tended to have estrogen receptor positive tumors and to receive adjuvant chemotherapy and radiotherapy for their primary breast tumor. The hepatic tumor volume was smaller and the time to diagnosis of BCLM was significantly longer (53 *vs.* 30 months) in the surgical cohort. There was no significant difference in OS between the surgical and systemic therapy groups (median OS: 50 *vs.* 45 months; 5-year OS: 38% *vs.* 39%). Although hepatic resection and/or ablation was not associated with a survival advantage, the surgical treatment group had a median recurrence-free interval of 28.5 months, and 10 patients (15%) were recurrence free after 5 years. In summary, surgical treatment of BCLM might be applicable in carefully selected patients in whom the goal is to minimize or avoid systemic chemotherapy.

Mortality and morbidity

Postoperative mortality and morbidity are shown in *Table 2*. Postoperative mortality was 0% in five reports, 2% in one report, and 5% in one report. Median postoperative morbidity was 28% (range, 18–42%). Major complications developed in 3.5–12% of cases (34,42-44) and included multiple organ failure, biliary leakage, both with and without the need for collection of infectious fluid, biliary fistula, infected intra-abdominal fluid drainage, and requiring percutaneous drainage. The median hospital stay was 8.5 days (range, 6–11 days).

Other local treatments: RFA

RFA (57-63), cryoablation (CRA) (64), stereotactic radiofrequency ablation (SRFA) (65), brachytherapy (66), and transarterial chemoembolization (TACE) (67) are among the local treatments available for BCLM.

RFA is particularly safe and effective, and has been widely reported as a local treatment for BCLM. This part covers 7 reports, totaling 225 patients on RFA published from 2007 to 2018. These studies were conducted during the period from 1996 to 2015. The median number of patients is 43 (range, 12–69) and the median number of treated tumors is 87 (range, 13–135), with an average of 1.9 tumors (range, 1.1–2.1) per patient. Two series examined conventional computed tomography-guided RFA and 5 series focused on conventional ultrasound-guided RFA. The mean size of metastases was 2.4 cm (range, 2–3.5 cm). The mean percentage of patients with EHM was 36% (range, 40–83%). The median complete response rate was 86% (range, 67–97%). The median rate of solitary BCLM was 55.5% (range, 26–62%). Median follow-up in these reports was 24 months, the median DFS was 11 months, the median OS was 32 months, and the respective 3- and

5-year OS rates were 43% and 27%. Complication rates were lower than with surgical resection. Four studies had major complication rates of 0% (57,59,60,62), the others of 1.1%, 2.3%, and 6.9% (severe intrahepatic bleeding, injury to the bile duct, thrombosis of the portal branch, sepsis, and cholecystitis.). The median hospitalization period was 2 days (range, 1–5 days).

As to repeat RFA, Sofocleous *et al.* reported a patient who underwent three RFA sessions, achieving intervention-associated local control for 47 months (57). Jakobs *et al.* reported that local tumor progression was observed in 15 of 111 metastases at 3 months of follow-up. Five patients received repeat RFA in their study (58). Meloni *et al.* (59) reported that a BCLM exceeding 2.5 cm in size was related to poor outcomes. Bai *et al.* (63) reported 69 patients with 135 liver metastases. Local tumor progression was observed in 8 of these patients, 4–8 months after RFA. Local tumor progression rates for tumors with a margin of 0–5, >5–10 and >10 mm were 38.9%, 3.6%, and 0%, respectively. Among these 8 patients, 7 required repeat RFA. Fifty-five percent presented with new intrahepatic metastases, among these, 42% (16/38) underwent repeat RFA, while others received chemotherapy or TACE.

As several reviews on RFA reported (51,68,69), the clinical benefits of RFA included smaller tumor size and the higher EHM rate, as compared to surgical resection (2.4 *vs.* 4.0 cm and 46% *vs.* 27%). The merits of RFA include its high technical success rate (58,60,63), low morbidity, short hospitalization (57,59), and that it can be repeated. However, liver resection is indicated for larger tumors.

Future perspectives

BCLM is reported to potentially be effective (or curative) with surgery, which is clinically applicable to highly selected patients. Evidence of circulating tumor DNA (ctDNA) is growing. In early breast cancer, postsurgical levels of ctDNA were found to predict poor outcomes and risk of recurrence (70,71). Moreover, in the metastatic setting, ctDNA may represent a measure of treatment responses (72,73). The important clinical questions regarding surgical resection for BCLM are “when”, “to whom”, “whether or not to continue systemic therapy (and when systemic therapy should be resumed)”, and “whether or not the cancer can potentially be cured”. Although further investigations are needed, the evidence indicates that ctDNA might answer these questions and facilitate selecting the patients who would benefit from surgical resection of BCLM.

On the other hand, cost-utility is also an important issue in cancer therapy. Spolverato *et al.* (74) evaluated the cost-effectiveness of liver resection. Three groups, liver resection followed by postoperative conventional systemic therapy, conventional therapy alone, and newer targeted therapy alone, were compared by applying the Markov model and Monte-Carlo simulation. The authors concluded that liver resection is potentially more cost-effective than systemic therapy alone, especially in patients positive for the estrogen receptor and/or receiving newer systemic therapies. These data add to the broader discussion of how to best treat patients with BCLM.

As for RFA, combinations with other therapies such as ICI may enhance antitumor immunity. Not only radiotherapy (75,76) but also RFA with ICI can trigger a distal antitumor response which would then lead to an abscopal immune-priming effect (77-79). RFA was reported to increase the antigen specific $CD8^+$ T cells at the site of the residual tumor in a murine model with colorectal cancer (80). Adding a PD-1 inhibitor to RFA reduced the tumor volume and prolonged survival. Pre-operative RFA combined with agents targeting the PD-1/PD-L1 axis could be a promising future approach for managing high-risk patients. Although further investigations are needed, adding RFA to ICI appears to provide an effective strategy for BCLM.

Conclusions

The effectiveness of local treatment for BCLM is still controversial. The data reviewed herein were heterogeneous and selection bias is a weakness. A multicenter randomized controlled trial, examined the potential survival benefit of surgical resection for highly selected patients. RFA has the merits of being repeatable, with low morbidity, and high technical success rates, while being applicable to patients with EHM. Furthermore, new interventions targeting molecules such as ctDNA, and strategies combining ICI targeting the PD-1/PD-L1 axis with other treatments, might have benefits when used with surgical treatment or RFA. In terms of cost-effectiveness, selected patients might benefit from these local treatments during their clinical courses. These newer approaches might, in future, answer some of the clinical questions regarding which patients would benefit from surgical resection or RFA of BCLM.

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