Hepatic Metastasis from Breast Cancer

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Abstract

Keywords
► breast cancer
► locoregional
► hepatic metastasis
► ablation
► chemoembolization
► radioembolization

Breast cancer is the most common cancer in women and breast cancer liver metastasis may be associated with poor outcomes. Emerging locoregional therapies can be given in outpatient settings or with short hospital stays, to provide local control, support quality of life, preserve liver function, and potentially prolong survival. This review discusses retrospective studies suggesting potential benefits of locoregional treatment of breast cancer liver metastasis. Future prospective studies are needed to demonstrate efficacy and optimize patient selection.

Breast cancer is the most common cancer in women and the fifth cause of death among men and women overall.[1] In the United States, the lifetime female incidence of breast cancer is 12%.[2] Metastasis develops in approximately half of breast cancer patients, with liver metastasis occurring in at least two-thirds of these patients.[3] Liver metastasis is associated with relatively poor outcomes and may be the cause of 20% or more of the deaths in breast cancer.[2,4]

The goal of systemic therapy in metastatic breast cancer is to support quality of life and extend survival. Systemic therapies include cytotoxic, hormonal, and immunotherapeutic agents.[5] Hormone-based endocrine therapy is designed to target HER2, resulting in metastatic site reduction and long-term stabilization. In hormone receptor-negative breast cancer, treatment entails single-agent chemotherapy or immunotherapy agents.[6] Triple-negative breast cancer is particularly challenging, with a relative paucity of systemic options.[7] When patients develop resistance to systemic therapies, or when few systemic options are available, locoregional therapies may be offered as refractory options. Most commonly, locoregional therapies are offered in the setting of hepatic metastasis, as hepatic lesions are thought to limit survival and may cause symptoms such as pain.[2,3]

This article reviews emerging locoregional therapies for hepatic metastasis due to breast cancer and categorizes approaches based on the extent of hepatic disease. We review these studies and suggest potential areas for future development.

Limited Hepatic Metastases

Oligometastatic breast cancer (OMBC) is defined as five or fewer metastatic sites that may be treated locally with a goal of long-term remission.[8,9] OMBC treatment is typically palliative in nature, involving systemic chemotherapy and hormonal therapies. For patients with OMBC confined to the liver, systemic treatments extend survival to 27 months and achieve a partial response rates of 50 to 60% in retrospective studies.[8,10] Over the past several decades, advances such as surgical resection, external radiation, and percutaneous ablation have emerged (►Table 1). Combined with systemic therapies, locoregional interventions may further extend survival or delay the need to transition to a new line of systemic therapy by controlling local hepatic tumor growth.[11]

Hepatectomy
Surgical hepatectomy involves resection of compromised hepatic segments or lobes. When there are three or fewer sites, a minor resection may be performed; when there are more than three sites, a major or radical resection may be performed.[12,13] Hepatectomies for OMBC are associated with 20 to 40% rates of any adverse events, and hospital admissions of several following surgery (►Table 1). Roughly 60% of patients develop recurrence (►Fig. 1) and median overall survival ranges from 30 to 80 months (►Table 1).[12–14] Findings suggest that locoregional treatment with hepatectomy

Table 1 Locoregional therapies for oligometastatic breast cancer liver tumors

Reference	Year	n	Treatment modality	OS	Other survival outcomes	AE rate
Vlastos et al[47]	2004	31	Resection	63 mo	2-y OS: 86% 5-y OS: 61%	
Adam et al[4]	2006	85	Resection	32 mo	5-y OS: 37%	22% any AE
Caralt et al[13]	2008	12	Resection		1-y OS: 100% 3-y OS: 79% 5-y OS: 33%	17% any AE
van Walsum et al[48]	2012	32	Resection	55 mo	5-y OS: 37%	34% any AE
Abbott et al[49]	2012	86	Resection	57 mo	PFS: 14.2 mo	21% any AE
Mariani et al[50]	2013	51	Resection		3-y OS: 74% 5-y OS: 50%	20% any AE
Kim et al[14]	2014	13	Resection		1-y OS: 83% 3-y OS: 49%	
Margonis et al[51]	2016	131	Resection	53 mo	1-y OS: 99% 3-y OS: 75%	23% any AE
Ruiz et al[12]	2018	139	Resection		7-y OS: 76% 10-y OS: 36%	25% any AE
Ruiz et al[52]	2018	662	Resection	82 mo	3-y OS: 81% 5-y OS: 69%	
Wieners et al[53]	2011	41	SBRT		6-mo OS: 97% 12-mo OS: 79% 18-mo OS: 60%	<2% grade 3 and higher AE
Milano et al[16]	2012	121	SBRT		2-y OS: 50% 2-y PFS: 26% 5-y OS: 28% 5-y PFS: 20%	<1% grade 3 and higher AE
Palma et al[17]	2018	159	SBRT	20 mo	PFS: 15 mo	30% grade 2 and higher AE
Milano et al[16]	2018	48	SBRT		5-y OS: 31% 10-y OS: 17%	
Mahadevan et al[54]	2018	42	SBRT	21 mo	1-y OS: 66%	
Onal et al[55]	2018	22	SBRT		1-y OS: 85% 2-y OS: 57%	
Sofocleous et al[21]	2007	12	RFA	60 mo	3-y OS: 70% 5-y OS: 30%	
Jakobs et al[33]	2008	43	RFA	59 mo		7% major AE
Meloni et al[23]	2009	52	RFA	42 mo	5-y OS: 32%	4% minor AE
Veltri et al[56]	2014	45	RFA		1-y OS: 90% 2-y OS: 58% 3-y OS: 44%	10% any AE
Kümler et al[57]	2015	32	RFA	34 mo		3% grade 3 and higher AE
Barral et al[28]	2016	50	RFA/MWA/Cryoablation		1-y OS: 98% 2-y OS: 96%	
Bai et al[58]	2018	69	RFA	26 mo	1-y OS: 82% 2-y OS: 50% 3-y OS: 25% 5-y OS: 11%	1% grade 3 and higher AE
Ridouani et al[24]	2020	35	RFA/MWA/Cryoablation	70 mo	Time to progression: 11 mo	8% any AE

Abbreviations: AE, adverse event; MWA, microwave ablation; OS, overall survival; PFS, progression-free survival; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.
Notes: Selected studies are presented. Survival reported as median value from time of treatment; n indicates number of breast cancer patients studied.
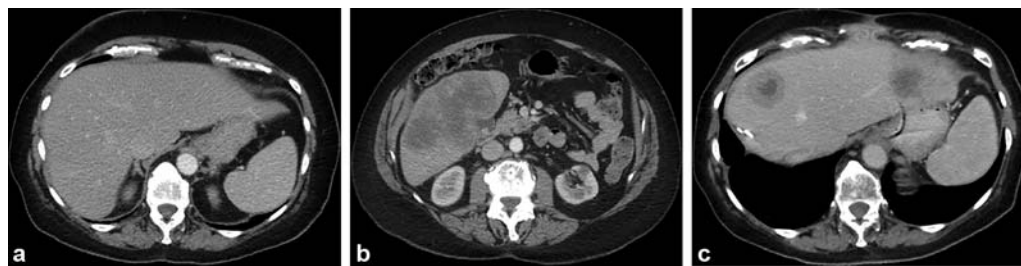
Fig. 1 Liver resection with subsequent progression. Axial images from a contrast-enhanced CT in a 68-year-old woman with triple negative breast cancer demonstrate no tumors in the left lobe (**a**) and a solitary large multilobulated tumor in the right lobe (**b**) that is too large to eradicate with percutaneous ablation. One month later, the right lobe was surgically resected. Six months later, follow-up contrast-enhanced CT shows new tumors in the left hepatic lobe (**c**).

in combination with systemic therapy was associated with a potential 14% cure rate,[12] though prospective studies have not been performed. Compared with less invasive treatment, posthepatectomy care entails hospitalization and extensive follow-up.[14]

External Radiation

Stereotactic body radiation therapy (SBRT) is a localized external radiation treatment for hepatic OMBC that uses imaging guidance to create a three-dimensional model allowing for specific targeting and delivery of high fractional doses of radiation.[15] This is usually done in a varying dosage delivered every 2 days over 2 weeks, to minimize toxicity to healthy tissue.[16] Overall median survival after SBRT has been reported as just over 20 months (►**Table 1**), with 5- and 10-year survival rates of 30 and 17%, respectively.[17,18] One prospective phase 2 study which combined patients with several oligometastatic cancer types including breast cancer, colorectal cancer, and lung cancer demonstrated a trend for prolonged survival in patients who received SBRT to all metastatic sites compared with patients who received chemotherapy alone.[19] However, the patients who received radiation had significantly a higher major adverse event rate compared with the control group (29 vs. 9%), with a nearly 5% rate of SBRT-related deaths. Thus, though it is possible that SBRT may extend survival, nearly a third may experience clinically significant adverse events.

Percutaneous Thermal Ablation

Liver lesions are most commonly treated with heat-based modalities including radiofrequency ablation (RFA) and microwave ablation (MWA) and performed with imaging guidance, usually under general anesthesia. Patient candidates include those with three or fewer lesions, each less than 3 cm in diameter and located away from a critical vessel or other organ such that an adequate margin can be achieved.[20]

Survival outcomes are similar compared with surgical resection, with reported median overall survival ranging from 30 to 70 months (►**Table 1**), though ablation can often be performed on an outpatient basis, or with significantly shorter hospital stays.[21] Ablation is associated with a technical success rate of 95%.[21–23] Most adverse events are mild,[21] and the grade 3–4 adverse event rate is less than 10% (►**Table 1**).[24] One large retrospective case–control study compared patients

who underwent thermal ablation or hepatectomy with patients with liver metastasis who did not undergo locoregional therapy, and found no survival benefit, though locoregional treatment rendered patients without any evidence of disease for long periods.[25] Roughly 15% of patients had no evidence of disease for more than 5 years following locoregional therapy, and over half of patients could refrain from systemic therapy for 2 years. Prospective randomized studies would be necessary to determine whether thermal ablation impacts survival, and future clinical studies could highlight benefits regarding management of systemic therapies as potential important outcome measures.

Local tumor progression after ablation may occur in more than 10% of cases, but can be avoided when margins exceed 5 mm.[24] Given the importance of margin assessment in precluding residual disease and recurrence, advanced imaging techniques are helpful to estimate the ablation margin. Breast cancer liver metastases are typically hypodense, hypoenhancing, and fluorodeoxyglucose- (FDG)-avid.[26] Because ablation zones are also hypodense and hypoenhancing, PET/CT imaging may be helpful to more accurately estimate the ablation zone and margin and assure eradication of tumor (►**Fig. 2**).[27]

Eventually, over half of patients will develop new hepatic lesions despite eradication of targeted tumor.[24,25] These patients may be eligible for additional thermal ablation, or for embolotherapies described later in the "Multifocal Metastases" section.

Radiation Segmentectomy

Radiation segmentectomy, which entails the intra-arterial delivery of radiation doses of 200 Gy or greater to one or two hepatic segments, is an alternative local therapy when percutaneous thermal ablation is not feasible, such as when the lesion exceeds 3 cm or abuts critical structures (►**Fig. 3**).[28] While there are numerous publications regarding the efficacy of radiation segmentectomy for hepatocellular cancer, less is published regarding the use of this approach in metastatic hepatic disease. One study in a small number of patients including one patient with breast cancer suggested low complication rates and high objective response rates on early follow-up imaging.[24] Further research is necessary to delineate the expected outcomes following radiation segmentectomy of breast cancer liver metastasis.
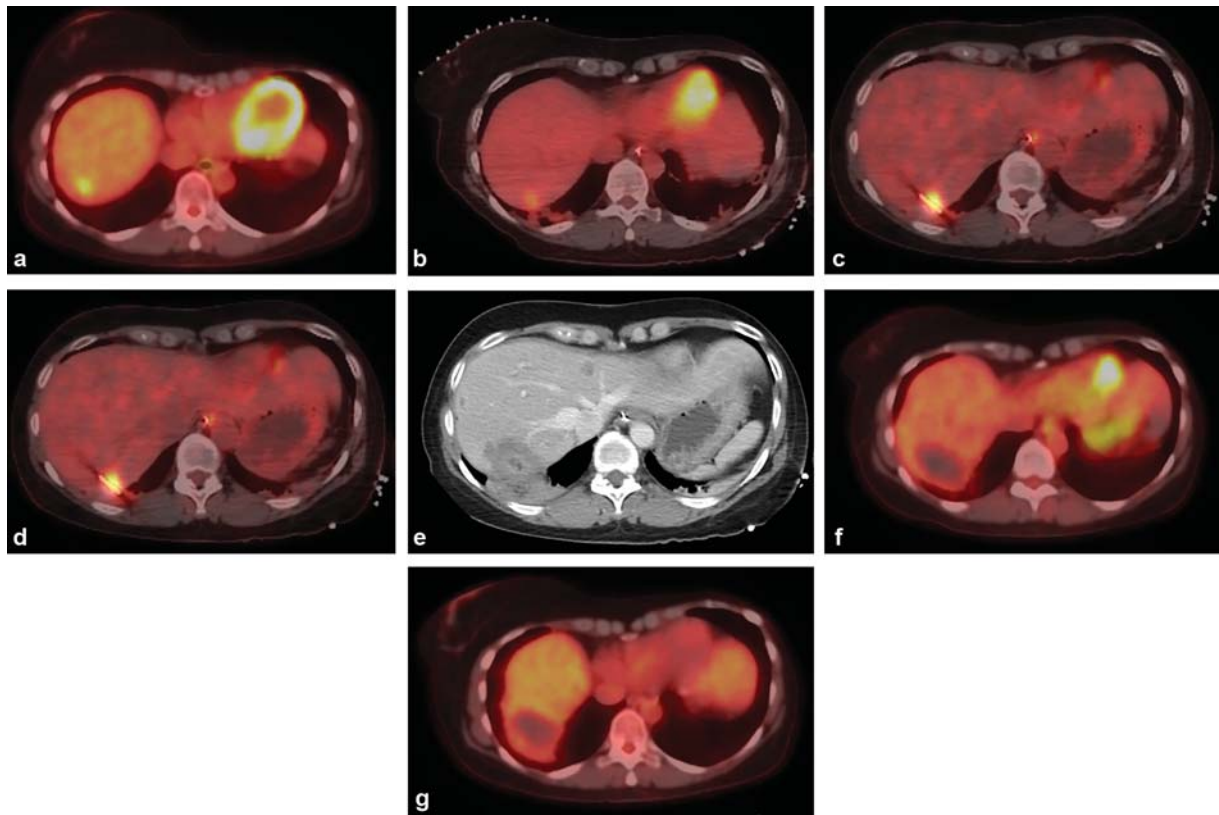
Fig. 2 Percutaneous PET/CT-guided microwave ablation. (**a**) Axial image from a PET/CT in a 48-year-old woman with locally advanced hormone receptor-positive breast cancer shows a solitary FDG-avid liver metastasis in the hepatic dome, which developed 10 years after tamoxifen therapy. (**b**) Intraprocedure preablation PET/CT is obtained after administration of 4 mCi of FDG. (**c**) Once the ablation probe is placed, a repeat PET/CT is obtained to demonstrate positioning of the probe within the tumor. (**d**) Once ablation is complete, an additional 8-mCi FDG is administered and a final intraprocedure postablation PET/CT is obtained to demonstrate eradication of FDG-avid tumor. This imaging is performed 30 minutes after FDG administration; during that period, a contrast-enhanced CT is obtained to demonstrate the ablation zone (**e**). Follow-up PET/CT performed 6 weeks (**f**) and 6 months (**g**) later demonstrate no residual, recurrent, or new hepatic metastasis.
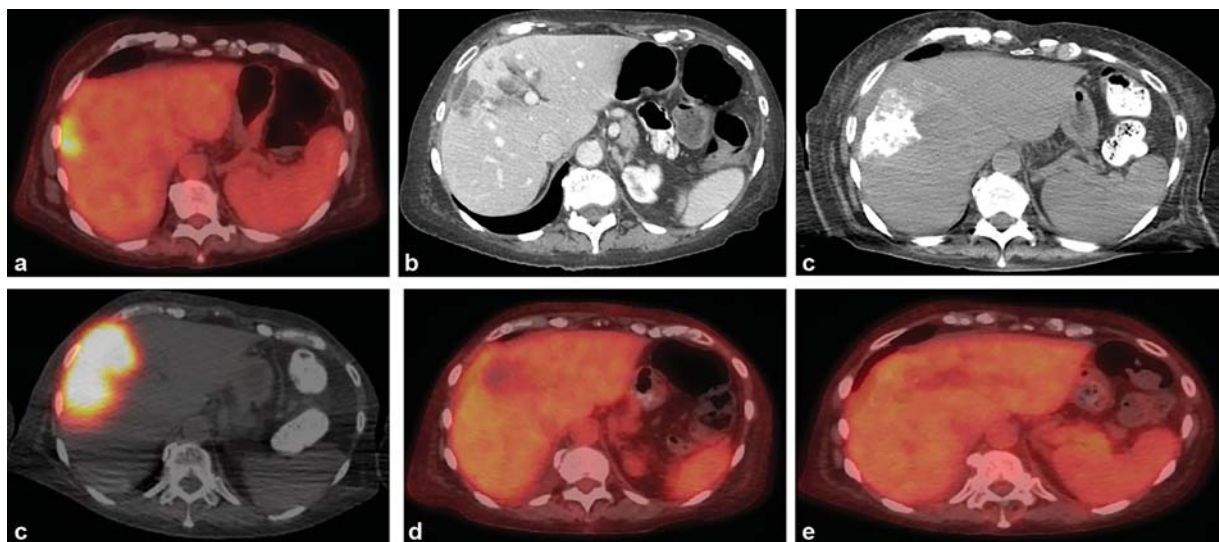

Fig. 3 Radiation segmentectomy for solitary liver metastasis. (**a**) Axial image from PET/CT in a 69-year-old woman with hormone receptor-positive invasive breast cancer shows a solitary liver metastasis. (**b**) Axial image from a contrast-enhanced CT 2 months later demonstrates that tumor grew over 2 months despite systemic therapy. Liver biopsy demonstrated that the liver metastasis was HER2-negative, in contrast to the primary cancer. (**c**) Intraprocedural CTA identified the segmental arteries supplying the tumor, allowing for a segmental treatment. (**d**) Postadministration SPECT/CT demonstrates dense distribution of yttrium-90 within the tumor. Axial PET/CT images at 1 month (**e**) and 4 months (**f**) demonstrate complete response with no residual disease.

Comparing Local Therapies for Oligometastatic Disease

In summary, OMBC confined to the liver may be treated with locoregional therapies including surgical resection, external radiation, thermal ablation, and potentially radiation segmentectomy. No prospective studies have been performed to directly compare modalities. Surgery and ablation are performed in one visit, but surgery is associated with a significantly longer hospitalization. External radiation is delivered over multiple sessions on an outpatient basis over 2 weeks. Morbidity may be similar between approaches. Survival is difficult to compare between approaches, as different studies have reported different survival statistics. For all three treatments, smaller tumor size is associated with better outcomes.[29] The decision to proceed with one or another approach is at this point patient-specific, determined by location and size of tumor, candidacy for invasive therapies, and availability of equipment and advanced techniques.

Multifocal Metastases

Multifocal disease is defined as more than five well-defined metastatic sites that have the potential for extrahepatic spread and are unresectable.[30] Similar to OMBC, treatments for multifocal disease are palliative in nature, and systemic treatments alone may not provide adequate local control, leading to disease progression. Emerging locoregional treatment modalities, including yttrium-90 (^{90}Y) transarterial radioembolization (TARE) and transarterial chemoembolization (TACE), may be offered in the setting of liver-dominant progression to potentially support quality of life, preserve liver function, and prolong survival (►**Table 2**).[31]

Radioembolization

TARE may involve lobar or segmental treatment depending on size, number, and locations of metastases (►**Fig. 4**).[32–34] When performed for breast cancer metastasis, TARE is associated with a less than 15% grade 3 and higher adverse events, including nontarget embolization causing gastroduodenal ulcers and liver failure.[32,33] By RECIST criteria, disease control rates at 1 to 3 months after treatment range from 80 to 100% (►**Table 2**). Overall survival ranges between 6 and 14 months following treatment.[32,34–36] Systemic therapies are most commonly continued before and after TARE, except for bevacizumab which can potentiate vascular complications such as dissection and is held at minimum for 2 weeks, and optimally longer for 4 to 6 weeks.[37]

Optimal imaging follow-up after TARE for breast cancer liver metastasis has not been established, but may entail metabolic imaging. Several studies have demonstrated that imaging response on early follow-up PET/CT 2 to 4 months after TARE is associated with longer survival.[38,39] Furthermore, breast cancer is hypoenhancing,[26] suggesting that response criteria based on enhancement will not be helpful. For other hypovascular tumors such as colorectal cancer metastasis, anatomic/size-based imaging criteria do not reflect posttreatment pathological response.[40] Taken together, findings suggest that PET/CT response assessments may better predict survival and reflect pathologic response com-

pared with size- or enhancement-based strategies, and may therefore be the optimal follow-up imaging strategy. After TARE administered for multifocal breast cancer liver metastasis, complete or partial response is often noted by 1 to 3 months on PET/CT, and endures until approximately 6 months after treatment.[41]

Transarterial Chemoembolization

TACE involves the transarterial administration of chemotherapy drugs, often in a lobar distribution.[42] Chemotherapy is administered with ethiodized oil in the context of conventional TACE, or loaded onto drug-eluting beads containing doxorubicin or other common chemotherapy drugs.[43] TACE may involve a postprocedural hospitalization of 1 or more days.[43] Possible complications include leukopenia (11%), hypochromia (11%), thrombocytopenia (7%), gastrointestinal system reaction (4%), and renal dysfunction (18%).[42] Reported major adverse events rates range from 0 to 35%, and by RECIST criteria, disease control rates at 1 to 3 months range from 40 to 90% (►**Table 2**).[42,44,45] Most retrospective studies evaluating tumor response after TACE for breast cancer liver metastasis have used RECIST; data regarding newer response criteria based on metabolic imaging are limited.

Comparing Embolotherapies

TACE and TARE have similar reported survival outcomes given that they are palliative treatments for patients who typically have refractory disease.[46] A retrospective literature search comparing the two treatment modalities by RECIST imaging response criteria show better disease control rates for TARE (78%) compared with TACE (59%).[46] While survival outcomes are similar and wide ranging in various retrospective studies, one single-center retrospective study comparing both modalities demonstrated a trend for longer survival after TARE compared with TACE.[44]

TARE is associated with fewer adverse events and potentially better quality of life compared with TACE. The single-center retrospective study comparing TACE and TARE reported significantly higher adverse event rates for TACE compared with TARE.[44] In the context of hepatocellular carcinoma, TARE is associated with improved quality-of-life scores, whereas TACE is associated with worsened quality-of-life scores after treatment.[31] It is not clear what drives this finding, though TACE often entails hospitalization for one or more nights,[34] whereas TARE is performed on an outpatient basis. Similar studies have not yet been conducted in the context of breast cancer.

Conclusion

Several locoregional therapies have emerged in the treatment of liver-dominant metastatic breast cancer. In the setting of oligometastatic disease, locoregional therapies including hepatectomy, SBRT, percutaneous thermal ablation, and radiation segmentectomy could potentially prolong survival, particularly when performed in conjunction with systemic therapies. However, prospective studies

Table 2 Embolotherapies for multifocal breast cancer liver metastasis

Reference	Year	n	Treatment modality	OS	Other survival outcomes	Response criteria	Response rate	AE rate
Maes et al[59]	2008	30	Drug-eluting bead TACE	7 mo	PFS: 3 mo	PERCIST	3-mo DC: 44%	20% grade 3 and higher AE
Vogl et al[43]	2010	208	Conventional TACE	25 mo		RECIST	3-mo DC: 64%	0% major AE
Cho et al[60]	2010	10	Drug-eluting bead TACE	26 mo		RECIST	1-mo DC: 50%	70% any AE
Duan et al[61]	2011	44	Drug-eluting bead TACE		1-y OS: 63% 2-y OS: 48% 3-y OS: 28%	RECIST	1–3-mo DC: 84%	77% any AE
Martin et al[42]	2012	40	Drug-eluting bead TACE		PFS: 17 mo	RECIST	1-mo DC: 90%	17% any AE
Nielsen et al[62]	2012	16	Drug-eluting bead TACE	25 mo	PFS: 8 mo	RECIST 1.1	1-mo DC: 50%	13% grade 3 and higher AE
Eichler et al[63]	2013	43	Drug-eluting bead TACE	12 mo		RECIST	3-mo DC: 44%	20% any AE
Damian et al[64]	2013	14	Drug-eluting bead TACE	26 mo		RECIST		
Lin et al[65]	2017	23	Drug-eluting bead TACE	17 mo		RECIST 1.1	3-mo DC: 83%	35% major AE
Li et al[45]	2005	28	Drug-eluting bead TACE	28 mo		WHO	3-mo DC: 71%	0% grade 3 and higher AE
Chang et al[44]	2018	17	Drug-eluting bead TACE	5 mo		mRECIST	3-mo DC: 29%	9% grade 3 and higher, 71% any AE
Haug et al[39]	2012	58	Resin TARE	11 mo		RECIST 1.1	3-mo DC: 66%	
Cianni et al[35]	2013	77	Resin TARE	11 mo		RECIST	2-mo DC: 80%	3% grade 3, 7% grade 1–2 AE
Saxena et al[32]	2014	40	Resin TARE	11 mo		RECIST	3-mo DC: 70%	40% grade 1–2 AE
Gordon et al[66]	2014	75	Resin TARE	7 mo		RECIST	1-mo DC: 98%	8% grade 3 and higher AE
Pieper et al[36]	2016	44	Resin TARE	6 mo		RECIST 1.1	3-mo DC: 82%	2% grade 3 and higher AE
Bangash et al[67]	2007	27	Glass TARE	6 mo		WHO	3-month DC 91%	11% grade 3 and higher AE
Fendler et al[34]	2016	81	Glass and resin TARE	8 mo		PERCIST	3-mo OR: 52%	<10% grade 3 and higher AE
Deipolyi et al[38]	2018	31	Glass and resin TARE	11 mo		PERCIST	3–5-mo OR: 69%	12% major AE
Chang et al[44]	2018	30	Glass and resin TARE	13 mo		mRECIST	3-mo DC: 47%	0% grade 3 and higher, 44% any AE
Deipolyi et al[41]	2019	49	Glass and resin TARE	11 mo		PERCIST	3–5-mo OR: 75%	8% grade 3 and higher AE

Abbreviations: AE, adverse event; DC, disease control including stable disease, partial response, and complete response; mRECIST, modified RECIST; OR, objective response, including partial and complete response; OS, overall survival; PERCIST, Positron Emission Tomography Response Criteria In Solid Tumors; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; WHO, World Health Organization.
Notes: Selected studies are presented. Survival reported as median value from the time of treatment; n indicates number of breast cancer patients studied.

demonstrating survival or quality-of-life benefits, or comparing treatment modalities have not been performed.

For multifocal hepatic metastasis, both TACE and TARE have been applied. Retrospective data suggest that compared with TACE, TARE offers improved imaging outcomes, reduced adverse events, improved quality of life, and potentially longer survival. Variation in follow-up imaging strategies between studies hampers direct comparison between modalities, and prospective comparative studies are needed. Retrospective evidence suggests that metabolic imaging with PET/CT may be the most helpful imaging strategy, given the strong relationship between PET/CT imaging outcomes and survival after TARE.

Additionally, though overall survival and progress-free survival have been traditional outcomes in clinical studies, locoregional therapies may provide other benefits such as delaying changes in systemic therapy or allowing patients to refrain from systemic therapy. These other outcomes warrant future investigation and validation. Finally, there is wide variation between patients in outcomes following liver-directed therapy, and the variables determining these outcomes are not currently known. Delineating factors that predict outcomes after locoregional
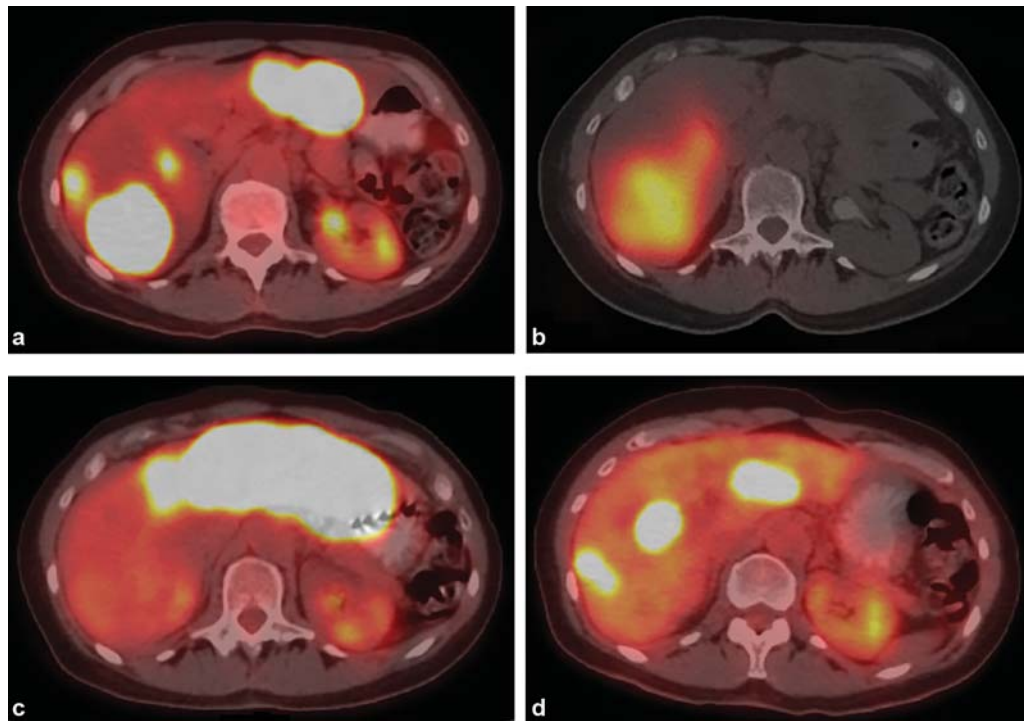
Fig. 4 Radioembolization of multifocal liver metastasis. (**a**) Axial image from PET/CT in a 57-year-old woman with hormone receptor-positive breast cancer shows multifocal bilobar liver metastasis progressing despite several lines of systemic therapy. (**b**) Axial SPECT/CT image obtained immediately following right lobar radioembolization demonstrates distribution of yttrium-90 within right hepatic metastases. (**c**) Axial image from PET/CT 2 months later demonstrates complete response in right hepatic metastases, but progression in left lobar metastases, with subsequent left lobar radioembolization. (**d**) Axial image from PET/CT 2 months after left lobar radioembolization demonstrates partial response in left hepatic metastases, with interval regrowth in the right lobe.

therapies would enable a more personalized approach to treating breast cancer liver metastasis, excluding patients who are unlikely to benefit and avoiding the potential unnecessary risks of invasive procedures. The efficacy of locoregional therapies may also be improved by combination strategies, such as using immunotherapy to generate abscopal effects or radiosensitizers to enhance response to radiotherapies. Much work is needed to justify and expand the application of liver-directed therapy in metastatic breast cancer.

Conflict of Interest

None declared.

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