Review Article on Loco-regional Therapy for Metastatic Breast Cancer

Stereotactic body radiotherapy (SBRT) for oligo-metastatic liver metastases from breast cancer, as an effective and safe alternative to surgery: a review

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Abstract: The liver is a common organ of metastases from most solid malignancies, including breast cancer, and breast cancer with liver metastases (BCLM) has a poor prognosis despite advances in systemic therapies. It has become widely recognized that local treatments for oligometastases with curative intent could improve disease control and survival outcomes under certain conditions. Regarding local therapy for BCLM, surgical resection had been the first choice though its indications were quite limited. Recently, an increasing number of prospective trials on stereotactic body radiation therapy (SBRT) for liver metastases (LMs) were published, reporting excellent tumor control with less toxicity. According to these reports, breast cancer origin is a favorable prognostic factor in SBRT for liver metastasis. Further research on patient selection and optimal dose fractionation will establish SBRT as a safe and feasible alternative treatment for resection and ablation in selected patients with BCLM. This review intends to provide evidence on the background and methods of focal radiation therapy for LMs, especially BCLM, and describes the current and future role of SBRT in the treatment of BCLM.

Keywords: Breast cancer; liver metastases (LM); local control (LC); oligometastases; stereotactic body radiotherapy

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Liver metastases (LMs) of breast cancer

The liver is a common organ of metastases from most solid malignancies, including breast cancer. LM develop in approximately 50% of all patients with metastatic breast cancer, and 5–12% of patients develop LM as the primary site of breast cancer recurrence (1-5). Breast cancer with LM (BCLM) has a poor prognosis of 4–8 months if left untreated, and 18–24 months even with systemic therapies (1,2,6).

Loco-regional treatment for metastatic breast cancer

Systemic hormone- and/or chemotherapy (with or without using local treatment modalities) given with palliative intent had been the only available therapy for the vast majority of patients with advanced breast cancer (4,7-9).

Recently, it has become widely recognized that local treatments for oligometastases with curative intent could improve disease control and survival outcomes under

certain conditions (5,10-14).

Surgical resection has become the first choice offering long-term survival to the patients with limited number of LMs from various primary organs. And patients underwent radical resection have reported 5-year survivals of 30–58% (15-17).

However, resection is possible only in 10–30% of the cases with LM because of medically and technically reasons, such as number and location of tumors (18-20).

In an effort to provide treatments for patients who are not candidates for surgery, the other local ablative techniques such as radiofrequency ablation (RFA), trance-catheter arterial chemoembolization (TACE), cryotherapy, radioembolization (Y90), thermal ablation, and radiotherapy (RT) are being tried (21-33).

Among them, RFA has been the most widely used ablative technique. However, there are several limitations of RFA application in regard to lesion's location and size (≤3 cm), proximity to great vessels, or subcapsular position as in surgery. In addition, local recurrence after RFA is relatively high and has been reported in up to 40% of patients especially if located close to the liver hilum (23,24,31,34).

Stereotactic body radiation therapy (SBRT) for LMs

Previously, the role of RT for liver tumors had been limited due to the high radiation sensitivity of the organ, and it was thought to be difficult to achieve the radiation doses necessary to eradicate metastatic tumors (35).

However, technological advances have made it possible to deliver a very conformal radiation dose to the tumor and a minimal radiation dose to surrounding liver tissues, which allows normal liver tissues to be spared. This technique is known as SBRT, which refers to an ablative RT that focuses high-dose on the tumor in single or several fractions (1 to 6 fractions), in contrast to conventional RT which use low dose per irradiation (usually 1.5–3 Gy) to a larger volume (36-39).

Recently, SBRT has become recognized as non-invasive but curative treatment option for patients with liver oligo-metastases who are not eligible for other radical treatments; such as surgery, RFA, or liver transplantation.

And an increasing number of prospective and retrospective trials on liver SBRT were published, with encouraging results in terms of local control (LC), toxicity and overall survival (OS), though only a few focusing on SBRT for LMs from breast cancer alone (13,14,23,32,36-39).

Indications for SBRT for LMs eligibility criteria

Because SBRT is less constrained by the location of liver tumors than surgery, most SBRT trials have defined their treatment as an alternative therapy or a salvage therapy for inoperable or postoperative isolated LMs (40-43).

The patient selection criteria, and optimal dose fractionation for liver SBRT are still under investigation, leading a significant heterogeneity to the backgrounds in the available literature. The most frequently used indications of SBRT for LM are ≤5 LMs with maximum tumor sizes of 6 cm, controlled or absent extra-hepatic disease, good performance status (Eastern Cooperative Oncology Group 0–1 or Karnosky >70), and adequate hepatic volume and function (28,38,41-47).

Liver function has also been defined in various ways, including adequate baseline hepatic function and ability to spare a critical hepatic volume. Scorsetti *et al.* (41) showed the patient's treatment algorithm, and they used Child-Pugh score (A/B/C) and "free liver volume" (>1,000/<1,000 mL and ≥700/<700 mL) as indicators of liver function to separate patient's suitability for SBRT. Of course, Child class A and >1,000 mL were recommend as good indications for liver SBRT.

To prevent adverse events (AEs), the authors have also referred to the other organs at risk (OARs) in their criteria to have distance of >8 mm from the targets (41). Age has not been included to selection criterions in almost all studies. Indeed, it is one of the reasons why SBRT has been selected for elderly patients, who are often unsuitable for surgery.

Treatment procedure

Liver SBRT is technically challenging due to respiration-related organ motion, requiring highly precise dose planning and delivery, with multiple beams using either coplanar or non-coplanar geometries. Intensity-modulated RT (IMRT), and more recently volume arc radiation therapy (VMAT) and frameless robotic system for radiosurgery (Cyber-Knife®) have achieved a dose distribution that fits the unevenness of the target, reducing OAR exposure (14,28,44,48,49).

The following processes should be added to treatment planning to address respiratory movements (28,48-52).

- Planning computed tomography (CT) scans should be obtained, at least, above and below the region of interest in expiration and inspiration in addition to

free breathing. Recently, it has become recommended that simulations using four-dimensional CT (4D-CT) be performed to more accurately characterize tumor movement for target delineation.

- ❖ Particularly in liver SBRT, which is a solid organ, it is required to fuse magnetic resonance imaging (MRI), and/or 18-fluorodeoxyglucose positron emission tomography (FDG-PET)-CT with contrast-enhanced CT.
- ❖ Image guided radiation therapy (IGRT) should be performed before each daily session to reduce set-up uncertainties. Fiducial markers are employed for target localization in selected patients.

The techniques to reduce respiratory movement itself include oxygen inhalation, abdominal compression, and respiratory arrest (restriction). And in combination with them, as techniques to reduce the influence of respiratory movement, there are the respiratory synchronization and the moving-body tracking (28,44,48-50).

The way of CT imaging and target contouring for treatment planning differs depending on the type of measures for respiratory movement, so it is important to devise an optimal protocol for each facility. Practice guidelines for the performance of SBRT were published in 2010 by ASTRO and ACR (53).

Dose prescription

No standard criteria for prescription dose and fraction have not been established for SBRT of LM, with few large-scale reports and no randomized phase III data. Furthermore, the appropriate regimen would vary depending on the size and location of the tumor and its relationship with OARs, so the prescription for fractionated SBRT will vary between studies, ranging from 25 to 75 Gy in 3 to 6 fractions, most commonly 3 fractions (44,46,54,55). For 3 fractions regimen of SBRT, Chang *et al.* (56) recommended to use a total dose of ≥48 Gy to obtain sufficient LC (1-year LC; >90%). For single fraction SBRT, there are several prospective trial reports, prescribing 14–30 Gy (57,58). We reviewed studies on SBRT of LMs including breast cancer (*Table 1*), with regard to number of patients/number of lesions, number of cases from breast cancer, dose prescription, toxicity and outcome, in terms of LC and OS. Many reports so far have not changed the dose prescription depending on the primary organ or pathology. However, in the future, it might be individualized as the difference in radiation sensitivity and interaction with combination therapy become clear.

Dose constrains

Some previously published papers have shown restrictions on the dose of OAR in liver SBRT. Scorsetti *et al.* (62). described the recommended dose constraints for OAR as shown in *Table 2*. For example, healthy liver volume (excluding cumulative GTV) receiving less than 15 Gy should be at least 700 cm^3. V21Gy (percentage of the volume of an organ receiving 21 Gy) for the duodenum, small bowel, esophagus, and stomach should be less than 1%. The maximum dose delivered to 0.1 cm of the target volume (D 0.1 cm^3) for the spinal cord was limited to less than 18 Gy. There have been several reports of clinical trials performed on slightly different criteria, which can be very helpful (44,47,55,63).

Concomitant therapy

Prolonged prognosis could be expected by adding SBRT to systemic therapy (55).

The sequence and timing of RT and systemic therapy for oligo BCLM patients is still being discussed, but no studies have reported increased AEs with combination of systemic therapy and SBRT (60,62).

Treatment results of SBRT for LM

An increasing number of retrospective and prospective studies have demonstrated the efficacy of SBRT for multi-primary LM including breast cancer.

In general, excellent LC of LM treated by SBRT has been reported. LC rates range from 70% to 100% at 1 year and from 60% to 90% at 2 years (*Table 1*) (28,47,59,63).

In addition, improved LC after liver SBRT would prolong their OS. Median OS after SBRT for LM varied in the wide range from 10 to 48 months (28,38,47,52,63). The differences between published studies is thought to be dependent on the tumor volume and histopathology, prior therapy, RT dose, and fractionation regimens that have been used, and so on.

Some reports of multi-primary LM have indicated breast cancer origin as a good prognostic factor (47,55,58,61,64). Rusthoven *et al.* (47) and Mahadevan *et al.* (61) classified the primary tumor of LM into two groups with favorable

Table 1 Results of current studies on SBRT for liver metastases (including breast cancer origin)

Reference	Study year	Number of patients [lesions]	BCLM patients	Tumor volume (median, cm^3)	Follow up (median, months)	RT dose (Gy/Fr)	Toxicity (Grade 3/≥4)	Survival		Local control (% or median)
								Median, months	%	
Wulf *et al.* (59)	2006	39 [51]	11	NA (CTVmin 9/max 355)	15 [2–85]	26–37.5 Gy/ 1–3 Fr	0/0		72/32 (1 y/2 y)	92/66 (1 y/2 y)
Lee *et al.* (52)	2009	68 [143]	12	75.9	10.8	41.4 (27.7–60) Gy/6 Fr	Acute: 6 (9%)/1 (1%), late: 0/0	17.6	79 (1 y)	71 (1 y)
Rusthoven (47)	2009	48 [63]		NA (diameter 2.7 cm)	16	36–60 Gy/3Fr	G3 1 (2%)	20.5		92/95 (1 y/2 y)
Fumagalli *et al.* (54)	2012	90 [139]	8	28	17	27–60 Gy/ 3–6 Fr	0/0		70.0 (2 y)	84.5/66.1 (1 y/2 y)
Yuan *et al.* (44)	2014	57 [80]	7	27.6	20.5	39–54 Gy/ 3–7 Fr	0/0	37.5	89.6/72.2 (1 y/2 y)	94.4/89.7 (1 y/2 y)
Yamashita *et al.* (49)	2014	51	3	26	475.5 days	30–60 Gy/ 3–8 Fr	0/0		71.9 (2 y)	64.2 (2 y)
Scorsetti *et al.* (55)	2016	33 [43]	33 (100%)	20	24	48–57 Gy/ 3–4 Fr	0/0	48	93/66 (1 y/2 y)	98/90 (1 y/2 y)
Onal *et al.* (60)	2018	22 [29]	22 (100%)		16	54 Gy/3 Fr	NA/0		85/57 (1 y/2 y)	100/88 (1 y/2 y)
Mahadevan *et al.* (61)	2018	427 [568]	42	40	14	45 [12–60] Gy/3 Fr	0/0	22		52 months (median)

SBRT, stereotactic body radiation therapy; BCLM, breast cancer liver metastases; Gy, gray; Fr, fractions; NA, non applicable; y, years.

Table 2 Protocol dose constrains [dose constraints for organ at risks (OARs)]

Organ	Dose-volume limits	Other conditions
Healthy liver (<15 Gy)	>700 cc	Healthy liver volume >700 cc
Spinal cord	D 0.1 cm^3 <18 Gy	
Kidneys (R + L)	V15 Gy <35%	
Stomach, duodenum, small bowel	V21 Gy <1%	GTV >8 mm from the OARs
Heart	V30 Gy <1%	
Ribs	D30 cm^3 <30 Gy	

OAR, organ at risk; Gy, gray; D 0.1 cm^3/30 cm^3, the maximum dose delivered to 0.1 cm of the target volume; V15/21/30 Gy, percentage of the volume of an organ receiving 15, 21, 30 Gy; GTV, gross tumor volume.

and unfavorable based on survival and classify breast cancer with favorable. In addition, Swaminath *et al.* (64) reported, from their data of 81 patients with 142 metastases received liver SBRT, breast cancer subtype was one of the factors influencing the time to local progression.

Though only a few studies focused on BCLM alone, Onal *et al.* (60) combined liver SBRT and systemic treatment in 22 patients with 29 BCLM and reported excellent result (median follow-up time of 16.0 months); 1- and 2-year OS rates 85% and 57%, and the 1- and 2-year LC rates 100% and 88%, respectively. Scorsetti *et al.* (62) had treated lung or liver oligometastases from breast cancer with SBRT and achieved 1- and 2-year OS rates 93% and 66%, and the 1- and 2-year actuarial LC rates 100% and 88%, respectively. The authors of these studies concluded that SBRT may be an effective and safe treatment option in selected patients with BCLM. Chang *et al.* (56) confirmed the better LC for lesion treated with higher prescription dose and suggested the use of a total dose >48 Gy for a 3 fractions regimen of SBRT.

Predictors

Various factors have been reported to be prognostic factors

associated with the effectiveness of liver SBRT. Favorable predictors of LC mentioned in most publications are tumor size, prescription dose, and histology (47,49,55,59-61). And as additional factors related favorable OS, performance status, solitary metastasis, metachronous metastases, and pre-SBRT chemotherapy etc. have been reported (43).

Regarding tumor size, diameter of 30 or 40 mm is frequently used as cut-off value. Yamashita *et al.* (49) reported the maximum tumor diameter >30 *vs.* ≤30 mm had been the only significant factor for LCR. Mahadevan *et al.* (61) reported the results after SBRT of a total of 427 patients with LM from different origin including 42 BCLM patients and claimed smaller tumor volumes (<40 cm^3) are associated with improved LC and OS.

Prescription dose is also an important prognostic factor. Numerous studies on liver SBRT confirmed the correlation between dose prescription and LC. Chang *et al.* (56) reported that total dose (P=0.0015), dose/fraction (P=0.003), and BED (P=0.004) all correlated with LC in their retrospective study. Mahadevan *et al.* (61) and Yuan *et al.* (44) mentioned above, mentioned BED_{10} ≥100 Gy was also associated with improved LC (two-year LC rates; 77.2% *vs.* 59.6%). McCammon *et al.* (65) demonstrated significant improvement in LC with increasing dose, with the 3-year LC rate in their series 89.3% ,59% and 8.1% for those lesions that received 54–60 Gy, 36–53.9 Gy and less than 36 Gy, respectively (P<0.01). Though most reports have not changed the prescribed dose depending on the pathology or primary lesion, Yamashita *et al.* (49) proposed that increasing the dose to metastatic liver tumors appeared to be reasonable since metastatic lung tumors require dose escalation due to relatively low radio-sensitivity.

Toxicity

Severe toxicity associated with liver radiation therapy is rare, especially in hepatic SBRT. Ihnát *et al.* (28) have stated grade 3 side effects would occur in less than 5% of SBRT cases.

First, talking about acute AEs, grade 1–2 gastrointestinal toxicity (nausea, vomiting, abdominal pain, and peptic ulcers) are the most frequent AEs, which are experienced amongst 10–30% of patients (38). And less frequently, depending on the treatment site, chest wall pain, dermatitis, pneumonia, dermatitis, renal dysfunction, etc., could occur.

Radiation-induced liver disease (RILD) is an acute reaction occurring between 2 weeks and 4 months after RT in patients who have received a certain dose to the liver. It is characterized by anicteric ascites with elevation of alkaline phosphatase and liver transaminases and could result in liver failure and death (66,67).

Emami *et al.* (68) had reported doses at 5% risk of RILD as 50, 35 and 30 Gy, for 1/3, 2/3, and the whole liver, respectively. Although this criterion is still widely used, Lawrence *et al.* (69) later stated that with proper restriction of the irradiated area of normal liver, it was possible to administer more than 90 Gy without occurring RILD. Dawson (70) have shown, from 204 patient data, the dose at 5% risk of RILD was 54 and 100 Gy when 2/3 and 1/3 of the liver was irradiated, which was higher than previous reports. From the above, though RILD is the most limiting AE of liver irradiation, its occurrence depends on the volume of the irradiated liver, so it can be prevented by reducing the dose to the normal liver tissue.

After a report by Méndez Romero *et al.* (71) referring to two cases of RILD after SBRT, few cases of RILS have been described in the studies focused on SBRT of LMs. The recent very low incidence of RILD is probably the consequence of extreme accuracy of radiation delivery on target during SBRT.

Late AEs include gastrointestinal ulcers and perforations, bile duct stenosis, pulmonary fibrosis, renal fibrosis, etc., but serious cases about all of which have been rarely reported.

Conclusions

The data from published reports on SBRT for liver oligometastases have shown promising results especially in terms of LC and safety, despite most patients had been determined to be inoperable before treatment. It might be said that SBRT is a safe and feasible alternative treatment to resection and ablation in selected patients with BCLM.

However, the number of cases and observation period of these previous reports are insufficient, and the patient selection criteria and optimal dose and fractionation for liver SBRT are still under investigation. Prospective randomized trials and further studies are required to define appropriate targets and methods for SBRT and establish a role in BCLM.

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