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Clinical Investigation

Lobulated Enhancement Evaluation in the Follow-Up of Liver Metastases Treated by Stereotactic Body Radiation Therapy

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Summary

This study demonstrates the diagnostic value and predictive potential of lobulated enhancement occurrence in assessing local progression of liver metastases treated by stereotactic body radiation therapy. The treatment of patients could be improved by the earlier detection of local progression at a time when the lesion size is still eligible for local salvage treatment.

Objective: The Response Evaluation Criteria in Solid Tumors (RECIST) can have limitations when used to evaluate local treatments for cancer, especially for liver malignancies treated by stereotactic body radiation therapy (SBRT). The aim of this study was to validate the relationship between the occurrence of lobulated enhancement (LE) and local relapse and to evaluate the utility of this relationship for predicting local progression.

Patients and Methods: Imaging data of 59 lesions in 46 patients, including 281 computed tomographic (CT) scans, were retrospectively and blindly reviewed by 3 radiologists. One radiologist measured the lesion size, for each CT and overall, to classify responses using RECIST threshold criteria. The second studied LE occurrence. A third radiologist was later included and studied LE occurrence to evaluate the interobserver consistency for LE evaluation.

Results: The mean duration of follow-up was 13.6 months. LE was observed in 16 of 18 progressive lesions, occurring before size-based progression in 50% of cases, and the median delay of LE detection was 3.2 months. The sensitivity of LE to predict progression was 89%, and its specificity was 100%. The positive predictive value was 100%, the negative predictive value was 95.3%, and the overall accuracy was 97%. The probability of local progression-free survival at 12 months was significantly higher for lesions without LE compared with all lesions: 0.80 (CI 95%: 0.65-0.89) versus 0.69 (CI 95%: 0.54-0.80), respectively. The overall concordance rate between the 2 readers of LE was 97.9%.

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Conclusion: Response assessment of liver metastases treated by SBRT can be improved by including LE. This study demonstrates the diagnostic and predictive utility of LE for assessing local progression at a size still eligible for local salvage treatment.

Introduction

Robotic stereotactic body radiation therapy (SBRT) is a technique that allows delivery of a high radiation dose to a tumor while sparing adjacent normal tissues. This is achieved by using a respiratory tracking system that enables accurate radiation delivery, even while the patient breathes freely (1). This technique is an additional therapeutic option for inoperable liver metastases (2) and has been shown to result in favorable liver tolerance and good response rates (3-6).

Monitoring the response of liver metastases to SBRT with imaging is of utmost importance because the misinterpretation of changes detected by imaging may cause a delayed diagnosis of recurrence or may subject the patient to unnecessary chemotherapy.

Assessment of treatment outcomes in solid tumors is usually determined by Response Evaluation Criteria in Solid Tumors (RECIST) (7) based on 1-dimensional tumor size. However, these criteria have limitations for the evaluation of targeted therapies; for example, imatinib for gastrointestinal stromal tumors (GIST) and bevacizumab for colorectal liver metastasis (8-10) or other local treatments, such as lung tumor SBRT (11), liver radiofrequency ablation (12), and hepatocellular carcinoma treated by SBRT (13). Some authors have suggested that the use of functional imaging allows for earlier and more accurate assessment of response to different treatments when compared with morphologic responses: 18F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET), computed tomographic (CT) perfusion, diffusion-weighted sequences, and contrast ultrasound) (14-17); however, further work is needed to standardize the procedures for widespread use. A previous study, conducted in our center, focused on the posttherapeutic CT imaging features of hepatic metastasis treated by SBRT and identified new criteria of early response and progression by incorporating morphologic changes into a size-based response (18). For progressive lesions, the appearance of a lobulated, irregular, thick, peripheral enhancement was observed. This morphologic pattern, called lobulated enhancement (LE), is easy to identify by contouring the outline of a lesion (Fig. E1, available online at www.redjournal.org).

The aim of this study was to validate the relationship between the occurrence of LE and local response and to evaluate the utility of this relationship in the diagnosis and prediction of local progression.

Patients and Methods

Patients with liver metastases who were ineligible for surgery or radiofrequency ablation and who were referred to our center for SBRT radiosurgery were included. Treatment indication was approved in a multidisciplinary staff meeting that included a hepatic surgeon, a radiation oncologist, a medical oncologist, and an interventional radiologist. The following criteria were used: World Health Organization performance status score less than 3, 4 or fewer hepatic lesions, and initial lesion size smaller than 100 mm. The delivered radiation dose was 40 Gy in 4 fractions initially, then it increased to 45 Gy in 3 fractions.

The inclusion criteria for this study were as follows: patients with liver metastases treated by SBRT with respiratory tracking, target lesion size of at least 10 mm (according to RECIST criteria), and at least a 6-month delay between the first treatment session and the latest follow-up CT scan. CT scans were obtained with a 16-detector row CT scanner (Sensation 16; Siemens AG, Munich, Germany) until 2010 and then with a 128-detector row CT scanner (Somatom Definition AS; Siemens AG).

The exclusion criteria were as follows: lobular shaped lesion at the pretherapeutic CT scan making LE difficult to detect (evaluated during a first review by a senior radiologist) and lack of sufficient follow-up CT examinations (with at least 1 portal phase), including a pretherapeutic CT scan and at least 2 posttherapeutic examinations.

This study was approved by our internal review board, and informed consent was obtained from all referred patients.

A blinded retrospective review of CT examinations was performed by 2 radiologists. One radiologist measured the longest diameter and recorded lesion size in an edited reading grid. The second studied the lesion's shape and recorded lesion morphology in a second edited reading grid using 1 of 3 possible descriptors for each lesion at each CT: LE-present, LE-absent, or LE-doubtful. LE was defined as a thick (>1 mm) peripheral LE that included at least 3 lobulations. A typical LE is shown in Figure 1.

Posttherapeutic local outcome was classified into 4 categories according to the RECIST threshold criteria for each hepatic lesion: local complete response (LCR) with the disappearance of the treated hepatic lesion, local partial response (LPR) with more than a 30% decrease from the baseline of the longest irradiated lesion diameter, local progressive disease (LPD) with more than a 20% increase

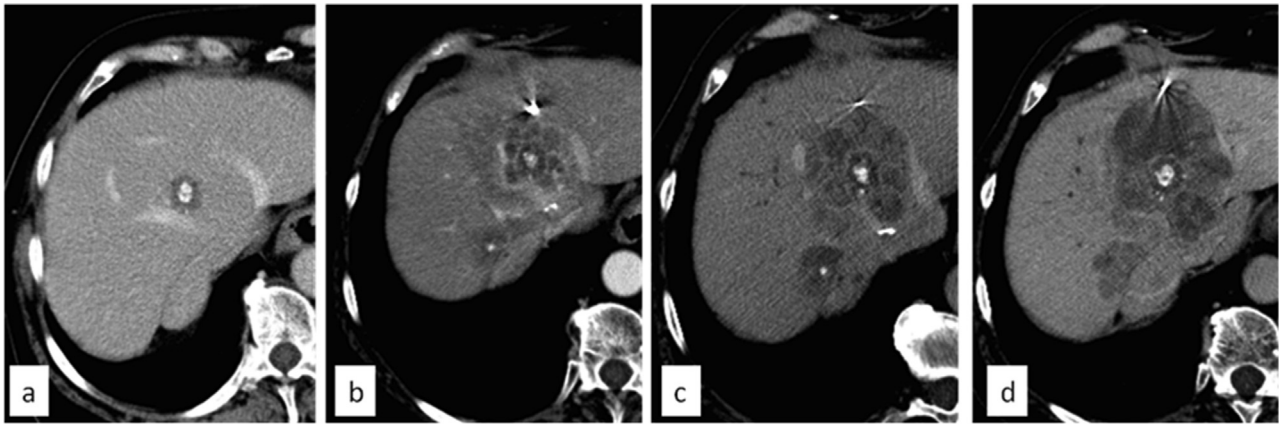

Fig. 1. Enhanced computed tomographic scans at portal phase axial views of a 69-year-old woman with a liver metastasis from colon cancer treated by SBRT. (a) Before treatment. (b) At 3.7 months. (c) At 5.8 months. (d) At 9.3 months after treatment. Typical lobulated enhancement occurred at 3.7 months, with a peripheral thick lobulated enhancement that looked like a daisy (b), with an increased number of lobulations and lesion size on next follow-up scans.

from the nadir of the longest irradiated lesion diameter, or local stable disease (LSD).

The overall response for each lesion was ranked as LPD if this status occurred once during follow-up. Otherwise, it was ranked as best quoted response (LPR, LSD, or LCR) during follow-up.

All of the CT evaluations were assessed independently by another radiologist for the presence or absence of LE. The assessor was blinded to the results of the first evaluation. Statistical analysis was performed with the Stata statistical software package, version 11.2 (StataCorp LP, College Station, TX). The demographics and lesion characteristics are presented as frequencies and percentages.

The association between the occurrence of LE and local response was assessed by Pearson χ^2 test. Initial lesion size was compared between LE-present and LE-absent or LE-doubtful groups and between progression and local control groups by the Mann-Whitney U test. Quantitative variables were compared between predictive LE and non-predictive LE groups by the Mann-Whitney U test.

Local progression-free survival (LPFS) was defined as the time from the start of treatment until the criteria for local progression of an irradiated lesion was met. Lesions that met the criteria for progression were censored at the last follow-up visit. The LPFS rates were estimated by the Kaplan-Meier method. The LPFS curves were analyzed separately for all lesions and lesions without LE to account for the censoring of lesions with LE occurrence at the time of their observation. The impact of LE on LPFS was tested by the use of time-dependent covariates in a Cox proportional hazards model. Response rates are presented with a 95% confidence interval calculated from the binomial distribution. Differences were considered statistically significant when $P<.05$.

Concerning LE concordance, the McNemar test was used to test for symmetry among the discordant pairs, and the κ statistic was used to assess agreement.

Results

Between July 2007 and September 2011, 128 patients were treated by SBRT for liver metastasis; 82 patients were excluded from this study, 80 for lack of sufficient follow-up and 2 for initial lobulated shape. Fifty-nine lesions in 46 patients were analyzed (Table E1, available online at www.redjournal.org). The median age was 65 (range, 23-84 years), and 35% were female. The primary cancer sites were colorectal (63%), breast (9%), and other sites (28%). The median initial lesion size was 30.5 mm (range, 11-83 mm). Thirty-six (78%) patients presented with only 1 lesion.

Two hundred eighty-one CT examinations were reviewed by 2 radiologists: 59 before treatment and 222 after treatment.

Pretherapeutic CT scans were performed 20 ± 14 days before the treatment started. The mean duration of CT imaging at follow-up was 13.6 ± 5.8 months, with a follow-up duration of more than 9 months for 73% of the lesions.

Size-based local response and morphologic features, evaluated after each CT scan, are presented in Table 1.

Table 1 Size-based local response and lobulated enhancement during follow-up

		Size-based local response				
Lobulated enhancement	Initial	LPD	LSD	LPR	LCR	Total
Present	0	27	9	0	0	36
Doubtful	0	1	1	0	0	2
Absent	59	4	92	75	13	243
Total	59	32	102	75	13	281

Abbreviations: LCR = local complete response; LPD = local progressive disease; LPR = local partial response; LSD = local stable disease.

During the follow-up, no LE was observed in lesions classified as partial or complete response. A total of 15 lesions showed a discordant association between LE classification and size-based response. Nine size-based local responses classified as LSD/LE-present included 8 lesions that later had a size-based local progression and thus had a LE classification that was predictive of outcome. Four size-based local responses classified as LPD/LE-absent and 2 classified as LE-doubtful represented 2 lesions from 1 patient that were LE-doubtful at 3.8 months but were not confirmed later when size-based progression occurred. The characteristics of these 2 lesions evolved similarly with a pattern of increase that is associated with nonenhanced lesions and is indicative of total necrosis (Fig. E2, available online at www.redjournal.org).

The overall responses for all lesions are presented in Table 2, where each lesion has an overall response in size ranked as LPD if this status occurred once during follow-up. Otherwise, it was ranked as best quoted response (LPR, LSD, or LCR) during follow-up. LE status is reported for each lesion as well.

The local progression rate was 30.5% (18/59), and the mean delay before progression was 8.5 ± 3.3 months (range, 3.8-19.1 months).

Among the 18 progressive lesions, LE occurred during follow-up in 16 cases (90%). Among these 16 LPD/LE-present cases, LE appeared before size-based progression and thus was predictive of progression in 8 of 16 (50%) of cases. An example is shown in Figure E3 (available online at www.redjournal.org). These 8 predictive cases corresponded to the 9 LSD/LE-present cases in Table 1 (for 1 lesion, LE was observed twice before progression occurred). For the 8 remaining cases, LE appeared at the same time as progression. No LE appeared after local progression. No patient categorized as having a progressive lesion changed their response status after progression occurred. For all lesions with LE present (n = 16), no reversal was observed; however, an increase in the number of lobulations and thickness of enhancement was observed. Two cases of progression without LE were observed in 1 patient, corresponding to the 2 LE-doubtful cases and the 4 LPD/LE-absent cases (Table 1).

Lesions considered as in local control (41/59) included 6 LCR, 26 LPR, and 9 LSD. No LE was observed in these 41 lesions during follow-up. There was no significant difference in initial lesion size between LPD and local control groups ($P = .32$).

There was no significant difference in initial lesion size between groups LE-present and LE-absent or LE-doubtful ($P = .17$).

A significant association between the occurrence of LE and size-based progression (Table 3) was observed. The sensitivity of LE to predict a progression was 89% (16/18), and its specificity was 100% (41/41). The positive predictive value was 100% (16/16), and the negative predictive value was 95.3% (41/43), for an overall accuracy of 97% (57/59). In 50% of progressive lesions (8/16), LE occurred before local size-based progression.

The characteristics of lesions with LE are summarized in Table 4. The median time to LE occurrence was 6.4 months (range, 2.4-19.1 months). The median size at LE occurrence was 38.5 mm (range, 18-96 mm). For predictive cases (n = 8), the median time to LE occurrence was 3.9 months (range, 2.4-9.0 months), the median time of prediction before progression was 3.2 months (range, 1-6.9 months), and the median size at LE occurrence was 32.5 mm (range, 18-52 months).

There was no significant difference between predictive and nonpredictive LE groups for the following variables: lesion size at size-based progression ($P = .96$), initial size ($P = .83$), and time to local progression ($P = .88$).

The delay between the beginning of the treatment and the last CT scan, performed before LPD, was significantly shorter in the predictive LE group than in the nonpredictive LE group ($P = .02$) (Table 4).

The probability of survival without local progression was estimated for 2 groups: all lesions and lesions without LE (lesions were censored when LE occurred) (Fig. 2). A significant difference was found between these groups when LE was used as a time-dependent covariate in a Cox model ($P < .0001$), indicating that progression is more likely to occur when LE appears during follow-up.

The probability of local progression-free survival at 12 months was lower for all lesions compared with lesions without LE: 0.69 (confidence interval [CI] 95%: 0.54-0.80) versus 0.80 (CI 95%: 0.65-0.89), respectively.

For interobserver variability, a total of 275 of 281 assessments were evaluated similarly, leading to an overall

Table 2 Size-based overall response and lobulated enhancement status during follow-up

	Size-based overall response				
Lobulated enhancement	LPD	LSD	LPR	LCR	Total
Present	16	0	0	0	16
Doubtful	2	0	0	0	2
Absent	0	9	26	6	41
Total	18	9	26	6	59

Abbreviations: LCR = local complete response; LPD = local progressive disease; LPR = local partial response; LSD = local stable disease.

Table 3 Contingency table

	Size-based response		
	LPD	Local control (LCR, LPR, SD)	
LE Present before or when LPD	16	0	16
LE Absent or doubtful	2	41	43
	18	41	59

Abbreviations: LCR = local complete response; LE = lobulated enhancement; LPD = local progressive disease; LPR = local partial response; LSD = local stable disease.

Table 4 Characteristics compared according to predictive value of lobulated enhancement pattern

Characteristic	All LE (n=16) Median (min-max)	Predictive LE (n=8) Median (min-max)	Nonpredictive LE (n=8) Median (min-max)
Size, mm			
Initial size	30.5 (16-83)	32 (16-67)	27.5 (16-83)
Size at first LE	38.5 (18-96)	32.5 (18-52)	49 (25-96)
Size at LPD	43.5 (21-96)	42.5 (21-95)	49 (25-96)
Delay, mo			
Time to LPD	8.1 (4.8-19.1)	8.5 (4.8-12.3)	8.1 (6.3-19.1)
Time to first LE	6.4 (2.4-19.1)	3.9 (2.4-9)*	8.1 (6.3-19.1)*
Delay of last CT performed before LPD	3.6 (2.1-12.4)	3 (2.1-4.5)*	5 (2.8-12.4)*

Abbreviations: CT = computed tomography; LE = lobulated enhancement; LPD = local progressive disease; max = maximum; min = minimum.
* $P<.05$.

concordance rate of 97.9%: 4 evaluations initially coded as absent by the first LE assessor were evaluated as present, and 2 evaluations initially coded as present by the first LE assessor were evaluated as absent at the same time point (McNemar, $P=.68$). The κ statistic was equal to 0.91 ($P<.0001$), indicating close to perfect agreement.

Considering the presence of LE for each lesion, there was 100% concordance. The 6 discordant cases concerned only the time to observation of LE that occurred at the previous assessment 1.5, 2.6, 4.7, and 5.3 months earlier (4 lesions) and at the next assessment 2.4 and 4.3 months later (2 lesions) for the second assessor.

Discussion

Because of the high conformity index and the use of a respiratory tracking system, SBRT can deliver a high dose of radiation to a precise target volume. The planning target volume includes the gross target volume and a 5-mm peripheral expansion that represents the microscopic extension of disease (clinical target volume) plus an additional 3-mm expansion to account for positioning uncertainties.

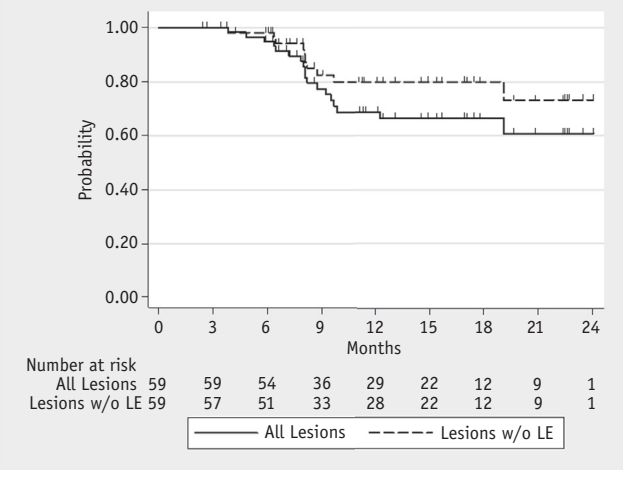

Fig. 2. Local progression-free survival according to the predictive value of the lobulated enhancement (LE) pattern.

The irradiated volume is larger than the tumor volume, creating a region where fibronecrotic scar tissue could form and whose monitoring is not relevant with RECIST criteria because a tumor response may be achieved with a stable target, and conversely recurrence from a residual viable peripheral portion may occur while size criteria achieve stable disease. The challenge for follow-up imaging is to detect as early as possible this viable peripheral tumor portion, which may lead to treatment failure, at a stage when additional local treatment is still possible.

The focus of this study was on the pattern of occurrence of LE, a posttherapeutic morphologic feature of liver metastases treated by SBRT, and the diagnostic and prognostic utility of this pattern.

The RECIST criteria are widely used to assess response to treatment. However, this response assessment has limits, as has already been reported, especially for response assessment of hepatocellular carcinoma and pulmonary lesions treated by SBRT and liver metastases treated by radiofrequency ablation.

Posttherapeutic features of liver metastases treated by SBRT make response assessment with the use of international standardized criteria often inadequate.

In this study, we describe a prospective marker of local progression in liver metastases treated by SBRT. Our results demonstrate a significant association between LE occurrence and size-based progression. The prevalence of local progression in this study is similar to that in other published studies. Our rate of local control at 1 year was 69% compared with the 71% of Lee et al (19), the 72% of Kress et al (5), and the 73% of Dewas et al (20). The sample of lesions included in this study can therefore be considered representative. LE was observed in 90% of progressive lesions. Two false negative LE cases, which occurred in 2 lesions from the same patient, had an increase in size with a doubtful LE at 3.8 months after treatment, but this was not confirmed later. Although progression was considered to be significant according to RECIST criteria cut-offs, these 2 lesions showed no LE, suggesting the presence of total necrosis and a pseudoprogression response. Similar response features have been described with targeted therapies, such as for GIST liver metastases treated by imatinib (21) and colorectal hepatic

metastases treated by yttrium 90 (22). These authors attributed the increased lesion size to a hemorrhagic phenomenon, cystic degeneration, and intratumoral necrosis. Biopsies of the 2 LPD/LE-absent lesions were not performed because of an extrahepatic progression (cerebrum) and the absence of additional therapeutic options for the patient.

No LE occurred during follow-up in local control lesions. For progressive lesions, 5 of 18 were classified as PR at the beginning of follow-up. Therefore, an initial PR at 3 months does not exclude the possibility of later progression. This emphasizes the importance of follow-up and the potential prognostic value of LE occurrence and detection as a predictor of progression, particularly because no biomarker predictive of response is currently in use for liver metastases treated by SBRT. LE was predictive of progression in 50% of cases (8/16), and the median delay of prediction was 3.2 months.

The median delay between the last CT follow-up and the occurrence of progression was significantly shorter in the predictive LE group (3 months) than in the nonpredictive LE group (5 months). This highlights the challenges to having a homogeneous follow-up for all patients, given the potential for geographic breakdown leading to a decentralized follow-up. A heterogeneous follow-up likely affected the percentage of predictive LE, and a more regular follow-up could have maximized the rate of predictive cases. Further studies would help to confirm this.

The median size of lesions when LE was first observed was smaller in the predictive LE group than in the nonpredictive LE group, allowing for additional local treatment to be considered for the predictive LE group. Integrating LE into the imaging evaluation could optimize patient treatment by enabling local salvage therapy at the time when LE is observed, while the lesion is still eligible for local therapy by either reirradiation (23) or radiofrequency ablation (24).

Based on our analysis of the mean delay before progression occurrence (8.5 months) and LPFS curves, adjustments to CT follow-up that include shorter time intervals between follow-up scans (for example, between 3 and 6 months or at 4.5 months) in the first year for patients with LE would ensure detection of recurrences as early as possible.

A limitation of this study was that 80 patients were excluded for lack of sufficient follow-up data. Some of these patients were not followed up in our center, making collection of their data difficult. Centralization of follow-up is a constraint for patients recruited far from the region. Although 25 of the 80 excluded patients had multimodal follow-up, using alternately CT, MRI, or FDG-PET, we chose not to integrate data from multiple modalities to ensure homogeneous data and measurements.

In this study, we excluded lesions with an initial lobulated shape (2 patients) because this would make the detection of LE difficult. For the imaging of those lesions to assess a response, a combination of criteria was used based on a previous study (18): lesion size, LE, and total necrosis. Functional quantitative imaging techniques such as diffusion-weighted sequences, perfusion MRI, or PET could facilitate response assessment in these lesions (14, 16, 25-27).

Although a minimum follow-up time of 6 months seems insufficient for SBRT evaluation, 73% of lesions in this study were followed up for more than 9 months, and the mean duration of follow-up, 13.6 months, was similar to that in published studies (20, 28).

The RECIST criteria were used to evaluate lesions for 2 reasons. First, histopathologic confirmation was unavailable and often was not justified because it would not change patient treatment; second, this response assessment of liver tumors treated by SBRT, which is based on size criteria, has been used in published studies and is currently used in multicenter studies (3, 20, 28).

The use of RECIST criteria for other local treatments, such as radiofrequency ablation (12), is questionable because SBRT destroys a target volume that is larger than the tumor volume and includes a peripheral margin of surrounding "healthy" tissue, resulting in scar tissue that progressively shrinks. Size measurement alone provides insufficient information because it does not include important posttherapeutic changes, such as tumor necrosis, LE, and tumor metabolic changes (25). The use of CHOI, mRECIST, and EASL criteria may be questionable but they seem to be inadequate for early detection of progression in liver metastases treated by SBRT for 2 reasons. First, liver metastases that are eligible for SBRT in our study have already been modified by previous chemotherapy and thus do not show internal enhancement but peripheral and circumferential enhancement whose measurement consists finally in the measurement of the total size of the tumor. Second, monitoring the thickness of peripheral enhancement may not be appropriate in the case of SBRT because it includes the surrounding focal liver reaction related to radiation injury. Thus, the shape of enhancement is an important pattern and could make differentiating recurrence from radiation injury easier (18).

The use of PET FDG CT may be promising if it is borne in mind that radiation injury surrounding the lesion may show an increased uptake. An increase of the standard uptake value during follow-up may be helpful in the discrimination of local progression, but this implies the availability of PET for monitoring liver metastasis after SBRT.

The LE is an easily reproducible sign (concordance rate 97.9%, $\kappa = 0.91$ [$P < .0001$]). The interobserver variability concerned time to observation of LE (earlier for second LE assessor in 4 cases and later in 2 cases compared with the first LE assessor). This variability is explained by the subtlety of LE at the beginning (at least 3 lobulations, thickness >1 mm).

Given the promising potential of LE in the diagnosis and prediction of local progression in liver metastases, it should be incorporated with combined criteria for assessing tumor response after SBRT.

It is concluded that SBRT is an option for the local treatment of unresectable liver malignancies, especially liver metastases. Response assessment using imaging

methods currently relies on the size-based RECIST criteria; as demonstrated in this study, this could be optimized by including an evaluation for LE. This study demonstrates the diagnostic value and predictive potential of LE occurrence in assessing local progression and the high interobserver concordance rate of this sign. Patient treatment could be improved by the earlier detection of local progression at a time when the lesion size is still eligible for local salvage treatment. On the basis of the results of this study, we recommend that additional CT examinations be performed between 6 and 9 months to optimize patient treatment.

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