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Evaluation of response after SBRT for liver tumors

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ABSTRACT

Stereotactic body radiotherapy (SBRT) has developed over the last few years for the treatment of primary and metastatic hepatic tumors. The tumoral and adjacent peritumoral modifications caused by this radiosurgery limit the evaluation of response by anatomic imaging and dimensional criteria alone, such as with RECIST. This suggests that it is of interest to also take into account the residual enhancement and hyper metabolism of these hepatic targets. We have reviewed the English language literature regarding the response of hepatic lesions treated by SBRT, and found that only seven articles were specifically concerned with this problem.

The response of the hepatocellular carcinoma after SBRT has been studied specifically with multiphase enhanced CT-scan. Criteria set by the European Association of Study of the Liver better estimate response at each time point of follow up than RECIST does. Non-enhancement, reflecting tumor necrosis, is additionally an early indicator of response with extended response in time and a best non-enhancement percentage is observed at 12 months. The response after treatment by SBRT of cholangiocarcinoma has not yet generated a specific report.

Use of RECIST criteria is also inadequate in the evaluation of response after SBRT for hepatic metastases. Response of liver metastases to SBRT is better assessed with a combination of size and enhancement pattern. The occurrence of a lobulated enhancement during follow up is efficient to predict local progression in a specific, reproducible, and sensitive way. Patients with FDG-avid hepatic metastases are also better evaluated with PET-CT and functional criteria than routine imaging and metric evaluation alone.

Abbreviations: SBRT, stereotactic body radiotherapy; RECIST, criteria of response in solid tumors; mRECIST, modified criteria of response in solid tumors; CT, computerized tomography; MRI, magnetic resonance imaging; PET, positron-emission tomography; HCC, Hepatocellular carcinoma; PERCIST, PET Response Criteria in Solid Tumors; EASL, European Association of Study of the Liver; FDG, fluorodeoxyglucose; SUV, standard uptake value.

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1. Background

Extra cranial stereotactic body radiotherapy (SBRT) has been shown to be a therapeutic alternative in the ablation of primary hepatic diseases (cholangiocarcinoma, hepatocellular carcinoma) and hepatic metastases.[1,2]

The morphological evaluation of this treatment by routine imaging is a problem. Indeed, the criteria of response in solid tumors (RECIST) is not applicable in the irradiated zone as stated in the revisited RECIST guideline, except in the case of progressive disease.[3] This is due to the compulsory early reorganizations of the irradiated zone which can mask a partial or complete response.[4]

This limitation of the strictly dimensional evaluation of the hepatic lesions was previously identified for other targeted therapies or other ways of percutaneous destruction. Further to its conference of September, 2000, the European Association of Study of the Liver (EASL) recommended to consider the enhancement of the viable portions after percutaneous or endovascular treatment of hepatocellular carcinoma (HCC) in computerized tomography (CT) and magnetic resonance imaging (MRI).[5] Therefore, the RECIST guideline was modified for this particular evaluation in 2008 (mRECIST).[6] Also, changes in CT density were usefully added to size criteria to estimate the response to imatinib of the gastro-intestinal stromal tumor hepatic metastases.[7] The enhancement of hepatic metastases due to colorectal cancer after treatment with bevacizumab has also been taken into account from 2009.[8]

Positron-emission tomography (PET) is a functional imaging modality that logically claims to best evaluate the liver treated by SBRT. Considering the limitations of anatomic imaging alone in assessing the activity of newer cancer therapies that stabilize disease, 18F-FDG PET could be efficient in such cases.[9] From this perspective, standardization is even available to improve reproducibility of the PET Response Criteria in Solid Tumors (PERCIST).[9] Acuteness of FDG-based criteria is shown particularly in the evaluation of patients with Non-Small Cell Lung Cancer treated with SBRT.[10–14]

We bring together in this work articles of English language literature estimating the response of hepatic lesions treated by SBRT.

2. Evaluation of response after SBRT for primary hepatic tumors

Care of HCC often includes local treatments such as radiofrequency and chemoembolization, reshaping targets and leaving scars. This hampers the evaluation of their efficiency by metric criteria. Therefore, learned societies propose criteria to estimate the viable portion enhancing during the arterial phase of the CT or MR imaging.[5,6,15]

SBRT also leads to acute tumoral change and normal tissue regeneration which can distort a purely dimensional evaluation. Herfarth et al. described in 2003 several types of early target modifications after SBRT, changing during follow-up.[4] These reorganizations do not cause, however, a typical arterial enhancement of HCC as seen with multiphase CT-scanning. Moreover, abnormal enhancement of peritumoral liver is seen in most cases by 6 months.[16,17] Nevertheless, these arterial enhancements of healthy liver do not present a typical portal wash out of HCC.

The criteria used in the evaluation of response to SBRT in the management of HCC are heterogeneous in the reported series. Certain works limit themselves to the RECIST criteria.[18–22] Other publications apply recommended EASL or mRECIST criteria.[23–27]

A single article compared the RECIST and EASL criteria in this indication. Price et al. reported in 2012 on a series of 26 patients treated for 29 CHC by SBRT by comparing the morphological evolution according to the RECIST and EASL criteria[16] (Table 1). This evaluation consisted of MRI and CT examinations with dynamic injection quarterly during one year. They observed that the RECIST criteria underestimated response at each time point. In addition, this analysis suggested that tumor non-enhancement, reflecting tumor necrosis, is an early indicator of response. Best non-enhancement percentage is observed at 12 months. Nevertheless, a baseline pattern of those lesions was not described in that work. We may suppose that only HCC with typical enhancement prior to SBRT were included. Moreover, in the cases of mismatch between response estimated by RECIST and EASL criteria, further research is called for. In those cases, a gold standard will consist ideally in a pathologic response in explanted liver.

The evolution of the local response according to mRECIST criteria is extended in time. This aspect was studied in particular in the series published by Sanuki et al. in 2013.[28] They showed, according to mRECIST, that local CR increased over time with a maximum 2-year local control rate of 97%. Two delayed local relapses occurred at 1 and 3 years. The hepatic recurrence outside the treatment volume reached the level of 58%. Sustained follow up is, therefore, warranted until tumor regrowth. It should be noted that only typical enhanced lesions are studied in that cohort.

The interest of the metabolic imaging in this indication is not demonstrated. Huang et al. aimed to determine whether 18F-FDG-PET/CT and combined 18F-FDG with contrast CT parameter could predict tumor control.[29] Even if this study is quiet irrelevant for our issue (*evaluation of response*), it is of interest to pinpoint that SUVmax could be the best indicator regarding local control. SBRT of HCC with baseline SUVmax below 3.2, indeed, enables a better 4y tumor control rate. Nevertheless, we should remember that the sensitivity of 18F-FDG for diagnosis of HCC is low: only 50–55%.[30–32]

To our knowledge, the evaluation of the response after treatment by SBRT of cholangiocarcinoma has not generated scientific report to this day.

3. Evaluation of response after SBRT for hepatic metastases

With the emergence of the concept of *oligo-metastatic state*, techniques of focal ablation, such as SBRT, are proposed to cure hepatic metastases.[1,33,34] For the same reasons as in the case of HCC discussed above, the evaluation of response could be limited with RECIST criteria in these cases.

Table 1 – Main original publications concerning evaluation of response after SBRT for liver tumors. *Abbreviations*: SBRT, stereotactic body radiotherapy; RECIST, criteria of response in solid tumors; mRECIST, modified criteria of response in solid tumors; CT, computerized tomography; MRI, magnetic resonance imaging; PET, positron-emission tomography; EASL, European Association of Study of the Liver; FDG, fluorodeoxyglucose; SUV, standard uptake value.

Study	Liver disease	Purpose	Imaging technology	Criteria	Material and methods	Findings
Jarraya et al.[35]	Liver metastases	Describe post-therapeutic transformations of liver metastases treated with cyberknife	CT	RECIST vs. new set of combined criteria (enhancement pattern and size)	28 patients 40 liver metastases	Use of RECIST criteria may be inadequate. Response of liver metastases to SBRT is better assessed with a combination of size and enhancement pattern.
Jarraya et al.[36]	Liver metastases	Validate relationship between lobulated enhancement occurrence and local relapse to predict local progression	CT	Occurrence of lobulated enhancement	46 patients 59 liver metastases	"Lobulated enhancement" pattern appears efficient to predict local progression In a specific, reproducible, and relatively sensitive way
Solanki et al.[37]	Liver metastases	Evaluate the utility of 18F-PET-CT as an indicator of treatment response in oligo-metastatic patients undergoing SBRT	18F-FDG PET/CT	RECIST vs. visual 18F-FDG uptake and SUV max	9 liver metastases	18F-PET-CT seems to realize a practicable evaluation of response to SBRT in oligo-metastatic disease. It shall allow in particular to recover complete response underestimated by RECIST criteria as stable disease
Stinauer et al.[38]	Liver metastases	Characterize SUV changes of hepatic metastases after SBRT. Evaluate normal tissue regeneration	18F-FDG PET CT	Lesion SUV max and total liver volume	27 patients 35 hepatic metastases	Maximum SUV of controlled lesions decreases to 3.1: similar to median SUVmax of normal liver. The cut-off to define local control failure consists in SUVmax $\geq$ 6. Liver volume after SBRT reached its NADIR (20% less) between 3 and 6 months.
Huang et al.[29]	Liver primary tumors	Determine whether 18F FDG-PET and combined 18F-FDG contrast CT parameter could predict tumor control	18F-FDG PET CT	SUV max, rSUV max, score combining tumor volume and SUVmax	31 patients 41 tumors	Tumor SUVmax is the best indicator regarding local control. SBRT of HCC with baseline SUVmax below 3.2 enables a better 4y tumor control rate.
Price et al.[16]	Liver primary tumors	Compare RECIST and EASL criteria as early indicators of response to treatment	CT and MRI	RECIST vs. EASL	26 patients 29 tumors	Reduced vascularity or nonenhancement (EASL) may be a more useful indicator than size reduction (RECIST) in the first 6–12 months.

Table 1 – (*Continued*)

Study	Liver disease	Purpose	Imaging technology	Criteria	Material and methods	Findings
Sanuki et al.[27]	Liver primary tumors	Describe the long term imaging appearance of small HCC following SBRT using mRECIST	CT	mRECIST	38 patients 42 tumors	According to mRECIST, local CR increases over time with a maximum 2-years local control rate of 97%. 2 local relapses (1 and 3 years). Hepatic recurrence outside treatment volume: 58%. Sustained follow up is warranted until tumor regrowth.

Jarraya et al. began in 2013 by describing post-therapeutic CT transformations of secondary hepatic lesions treated with cyberknife.[35] Following the example of the work by Chun on the hepatic metastases treated by bevacizumab,[8] they described four types of responses according to the evolution in size, the occurrence of a lobulated enhancement or total necrosis. According to that work, the use of RECIST criteria may be inadequate. Response of liver metastases to SBRT is better assessed with a combination of size and enhancement pattern.

That team continued on the same subject by focusing on the occurrence of lobulated enhancement during the follow up.[36] That enhancement was observed in 89% of progressive lesions, occurring before size-based progression in half of the cases, with a median delay of 3.2 months. The sensitivity of Lobular Enhancement to predict progression was 89%, and its specificity was 100%. The probability of local progression-free survival at 12 months was significantly higher for lesions without Lobular enhancement compared with all lesions: 0.80 (95% CI: 0.65–0.89) versus 0.69 (95% CI: 0.54–0.80), respectively. The overall concordance rate between the 2 readers in identifying lobular enhancement was 97.9%. That pattern appears actually efficient to predict local progression in a specific, reproducible, and rather sensitive way.

The cohort reported by Solanki et al. also included some cases of hepatic metastases treated by SBRT and evaluated by 18F-FDG PET-CT.[37] Even if this work was not solely dedicated to hepatic metastases, it suggested the interest of 18F-FDG PET-CT in the evaluation of response to SBRT in oligo-metastatic disease, in particular for the recovery of patients with complete response underestimated by RECIST criteria as a stable disease.

In the same way, Stinauer et al. characterized SUV changes of hepatic metastases after SBRT and evaluated normal tissue regeneration.[38] They found that SUVmax of controlled lesions decreased to 3.1, similar to median SUVmax of normal liver. The cut-off to define local control failure consisted in SUVmax $\geq$ 6. Liver volume after SBRT reached its NADIR (20% less) between 3 and 6 months. It is to be noted that patients with non-FDG avid tumors are excluded from that analysis.

4. Conclusions

Only seven original articles are dedicated to the evaluation of response to liver after SBRT.

Response of hepatocellular carcinoma after SBRT has been studied specifically with multiphase enhanced CT-scan. Criteria of the European Association of Study of the Liver better estimates response at each time point of follow up than RECIST does. Non-enhancement is additionally an early indicator of response with extended response in time and the best non-enhancement percentage is observed at 12 months. The limitations of RECIST criteria remain unresolved for targets with atypical enhancement. The response after treatment by SBRT of cholangiocarcinoma has not yet generated a specific report.

Use of RECIST criteria is also inadequate in the evaluation of response after SBRT for hepatic metastases. Response of liver metastases to SBRT is better assessed with a combination of size and enhancement pattern. The occurrence of a lobulated enhancement during follow-up is useful to predict local progression in a specific, reproducible, and sensitive way. Patients with FDG-avid hepatic metastases may also be evaluated with 18F-FDG PET-CT and functional criteria. Surprisingly, no specific evaluation with MRI functional parameters, such as diffusion-weighted imaging has been proposed on that topic.

Conflict of interest

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REFERENCES

1. Comito T, Clerici E, Tozzi A, D'agostino G. Liver metastases and SBRT: a new paradigm? *Rep Pract Oncol Radiother* 2014 [in press].
2. Rubio C, Morera R, Hernando O, Leroy T, Lartigau SE. Extracranial stereotactic body radiotherapy. Review of main SBRT features and indications in primary tumors. *Rep Pract Oncol Radiother* 2013;**18**(6):387–96.
3. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;**45**(January (2)):228–47.
4. Herfarth KK, Hof H, Bahner ML, et al. Assessment of focal liver reaction by multiphasic CT after stereotactic single-dose radiotherapy of liver tumors. *Int J Radiat Oncol Biol Phys* 2003;**57**(October (2)):444–51.
5. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001;**35**(September (3)):421–30.
6. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008;**100**(May (10)):698–711.
7. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol* 2007;**25**(May (13)):1753–9.
8. Chun YS, Vauthey JN, Boonsirikamchai P, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. *JAMA* 2009;**302**(December (21)):2338–44.
9. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 2009;**50**(May (Suppl 1)): 122S–50S.
10. Clarke K, Taremi M, Dahele M, et al. Stereotactic body radiotherapy (SBRT) for non-small cell lung cancer (NSCLC): is FDG-PET a predictor of outcome? *Radiother Oncol* 2012;**104**(July (1)):62–6.
11. Hoopes DJ, Tann M, Fletcher JW, et al. FDG-PET and stereotactic body radiotherapy (SBRT) for stage I non-small-cell lung cancer. *Lung Cancer* 2007;**56**(May (2)):229–34.
12. Mahasittiwat P, Yuan S, Xie C, et al. Metabolic tumor volume on PET reduced more than gross tumor volume on CT during radiotherapy in patients with non-small cell lung cancer treated with 3DCRT or SBRT. *J Radiat Oncol* 2013;**2**(June (2)):191–202.
13. Takeda A, Kunieda E, Fujii H, et al. Evaluation for local failure by 18F-FDG PET/CT in comparison with CT findings after stereotactic body radiotherapy (SBRT) for localized non-small-cell lung cancer. *Lung Cancer* 2013;**79**(March (3)):248–53.
14. Takeda A, Yokosuka N, Ohashi T, et al. The maximum standardized uptake value (SUVmax) on FDG-PET is a strong predictor of local recurrence for localized non-small-cell lung cancer after stereotactic body radiotherapy (SBRT). *Radiother Oncol* 2011;**101**(November (2)):291–7.
15. Fournier L, Ammari S, Thiam R, Cuenod CA. Imaging criteria for assessing tumour response: RECIST, mRECIST, Cheson. *Diagn Interv Imaging* 2014;**95**(July–August (7–8)):689–703.
16. Price TR, Perkins SM, Sandrasegaran K, et al. Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma. *Cancer* 2012;**118**(June (12)):3191–8.
17. Park MJ, Kim SY, Yoon SM, et al. Stereotactic body radiotherapy-induced arterial hypervascularity of non-tumorous hepatic parenchyma in patients with hepatocellular carcinoma: potential pitfalls in tumor response evaluation on multiphase computed tomography. *PLOS ONE* 2014;**9**(2):e90327.
18. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2011;**81**(November (4)):e447–53.
19. Huang WY, Jen YM, Lee MS, et al. Stereotactic body radiation therapy in recurrent hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2012;**84**(October (2)):355–61.
20. Ibarra RA, Rojas D, Snyder L, et al. Multicenter results of stereotactic body radiotherapy (SBRT) for non-resectable primary liver tumors. *Acta Oncol* 2012;**51**(May (5)):575–83.
21. Katz AW, Chawla S, Qu Z, Kashyap R, Milano MT, Hezel AF. Stereotactic hypofractionated radiation therapy as a bridge to transplantation for hepatocellular carcinoma: clinical outcome and pathologic correlation. *Int J Radiat Oncol Biol Phys* 2012;**83**(July (3)):895–900.
22. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol* 2008;**26**(February (4)):657–64.
23. Facciuto ME, Singh MK, Rochon C, et al. Stereotactic body radiation therapy in hepatocellular carcinoma and cirrhosis: evaluation of radiological and pathological response. *J Surg Oncol* 2012;**105**(June (7)):692–8.
24. Kang JK, Kim MS, Cho CK, et al. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. *Cancer* 2012;**118**(November (21)):5424–31.
25. Kwon JH, Bae SH, Kim JY, et al. Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. Stereotactic radiotherapy for liver cancer. *BMC Cancer* 2010;**10**:475.
26. Louis C, Dewas S, Mirabel X, et al. Stereotactic radiotherapy of hepatocellular carcinoma: preliminary results. *Technol Cancer Res Treat* 2010;**9**(October (5)):479–87.
27. Sanuki N, Takeda A, Mizuno T, et al. Tumor response on CT following hypofractionated stereotactic ablative body radiotherapy for small hypervascular hepatocellular carcinoma with cirrhosis. *Am J Roentgenol* 2013;**201**(December (6)):W812–20.
28. Sanuki-Fujimoto N, Takeda A, Ohashi T, et al. CT evaluations of focal liver reactions following stereotactic body radiotherapy for small hepatocellular carcinoma with cirrhosis: relationship between imaging appearance and baseline liver function. *Br J Radiol* 2010;**83**(December (996)):1063–71.
29. Huang WY, Kao CH, Huang WS, et al. 18F-FDG PET and combined 18F-FDG-contrast CT parameters as predictors of tumor control for hepatocellular carcinoma after stereotactic ablative radiotherapy. *J Nucl Med* 2013;**54**(October (10)):1710–6.
30. Jeng LB, Changlai SP, Shen YY, Lin CC, Tsai CH, Kao CH. Limited value of 18F-2-deoxyglucose positron emission tomography to detect hepatocellular carcinoma in hepatitis B virus carriers. *Hepatogastroenterology* 2003;**50**(November–December (54)):2154–6.
31. Khan MA, Combs CS, Brunt EM, et al. Positron emission tomography scanning in the evaluation of hepatocellular carcinoma. *J Hepatol* 2000;**32**(May (5)):792–7.
32. Trojan J, Schroeder O, Raedle J, et al. Fluorine-18 FDG positron emission tomography for imaging of hepatocellular carcinoma. *Am J Gastroenterol* 1999;**94**(November (11)):3314–9.
33. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995;**13**(January (1)):8–10.

34. Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol* 2011;**8**(June (6)):378–82.
35. Jarraya H, Mirabel X, Taieb S, et al. Image-based response assessment of liver metastases following stereotactic body radiotherapy with respiratory tracking. *Radiat Oncol* 2013;**8**:24.
36. Jarraya H, Borde P, Mirabel X, et al. Lobulated enhancement evaluation in the follow-up of liver metastases treated by stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2015;**92**(June (2)):292–8.
37. Solanki AA, Weichselbaum RR, Appelbaum D, et al. The utility of FDG-PET for assessing outcomes in oligometastatic cancer patients treated with stereotactic body radiotherapy: a cohort study. *Radiat Oncol* 2012;**7**:216.
38. Stinauer MA, Diot Q, Westerly DC, Schefter TE, Kavanagh BD. Fluorodeoxyglucose positron emission tomography response and normal tissue regeneration after stereotactic body radiotherapy to liver metastases. *Int J Radiat Oncol Biol Phys* 2012;**83**(August (5)):e613–8.