Original research article

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.

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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.  

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. This is due to the compulsory early reorganizations of the irradiated zone which can mask a partial or complete response.  

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). Therefore, the RECIST guideline was modified for this particular evaluation in 2008 (mRECIST). 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. The enhancement of hepatic metastases due to colorectal cancer after treatment with bevacizumab has also been taken into account from 2009.  

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. From this perspective, standardization is even available to improve reproducibility of the PET Response Criteria in Solid Tumors (PERCIST). Acuteness of FDG-based criteria is shown particularly in the evaluation of patients with Non-Small Cell Lung Cancer treated with SBRT.  

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.  

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. 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. 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. Other publications apply recommended EASL or mRECIST criteria.  

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 HCC by SBRT by comparing the morphological evolution according to the RECIST and EASL criteria. 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. 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. 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%.  

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. 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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Liver disease</th>
<th>Purpose</th>
<th>Imaging technology</th>
<th>Criteria</th>
<th>Material and methods</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jarraya et al.</td>
<td>Liver metastases</td>
<td>Describe post-therapeutic transformations of liver metastases treated with cyberknife</td>
<td>CT</td>
<td>RECIST vs. new set of combined criteria (enhancement pattern and size)</td>
<td>28 patients 40 liver metastases</td>
<td>Use of RECIST criteria may be inadequate. Response of liver metastases to SBRT is better assessed with a combination of size and enhancement pattern. “Lobulated enhancement” pattern appears efficient to predict local progression in a specific, reproducible, and relatively sensitive way.</td>
</tr>
<tr>
<td>Jarraya et al.</td>
<td>Liver metastases</td>
<td>Validate relationship between lobulated enhancement occurrence and local relapse to predict local progression</td>
<td>CT</td>
<td>Occurrence of lobulated enhancement</td>
<td>46 patients 59 liver metastases</td>
<td></td>
</tr>
<tr>
<td>Solanki et al.</td>
<td>Liver metastases</td>
<td>Evaluate the utility of 18F-PET-CT as an indicator of treatment response in oligo-metastatic patients undergoing SBRT</td>
<td>18F-FDG PET/CT</td>
<td>RECIST vs. visual 18F-FDG uptake and SUV max</td>
<td>9 liver metastases</td>
<td>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.</td>
</tr>
<tr>
<td>Stinauer et al.</td>
<td>Liver metastases</td>
<td>Characterize SUV changes of hepatic metastases after SBRT. Evaluate normal tissue regeneration</td>
<td>18F-FDG PET CT</td>
<td>Lesion SUV max and total liver volume</td>
<td>27 patients 35 hepatic metastases</td>
<td>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 ≥ 6. Liver volume after SBRT reached its NADIR (20% less) between 3 and 6 months.</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>Liver primary tumors</td>
<td>Determine whether 18F FDG-PET and combined 18F-FDG contrast CT parameter could predict tumor control</td>
<td>18F-FDG PET CT</td>
<td>SUV max, rSUV max, score combining tumor volume and SUVmax</td>
<td>31 patients 41 tumors</td>
<td>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. Reduced vascularity or nonenhancement (EASL) may be a more useful indicator than size reduction (RECIST) in the first 6–12 months.</td>
</tr>
<tr>
<td>Price et al.</td>
<td>Liver primary tumors</td>
<td>Compare RECIST and EASL criteria as early indicators of response to treatment</td>
<td>CT and MRI</td>
<td>RECIST vs. EASL</td>
<td>26 patients 29 tumors</td>
<td></td>
</tr>
</tbody>
</table>
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,36 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 ≥ 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

None declared.

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REFERENCES


