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Retrospective Study

Liver EOB-MRI for evaluation of response to treatment after SBRT of HCC

single center experience

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Abstract

BACKGROUND

Although Stereotactic Body Radiation Therapy (SBRT) is increasingly used, its application has not yet been regulated by the main international guidelines, leaving the decision to multidisciplinary teams.

AIM

To assess MRI features of hepatocellular carcinoma (HCC) treated with SBRT, highlighting the efficacy of the treatment, the main aspects of the lesion before and after the procedure.

METHODS

As part of a retrospective study, 49 patients, who underwent SBRT for HCC between January 2013 and November 2019, were recruited. Each patient underwent a pre-treatment MRI examination with hepatospecific contrast agent and a similar follow-up examination within 6 mo of therapy. In addition, 22 patients underwent a second follow-up examination after the first 6 mo.

The following characteristics were analysed: features analysed compared to pre-treatment MRI examination, presence or absence of Infield and Outfield progression, ring-like enhancement, signal hyperintensity in T2-weighted sequences in the perilesional parenchyma, capsular retraction and "band" signal hypointensity in T1-weighted GE Fat Sat sequences obtained hepatobiliary excretion.

RESULTS

Signal hyperintensity in the T2-weighted sequences showed in the post-SBRT first control a statistically significant reduction in the number of lesions ($P = 0.0006$). Signal hyperintensity in DWI-weighted sequences was decrease in MRI first control ($p < 0.0001$). Statistically significant increase of ADC values from a median of 1.01 to 1.38 at the first post-control was found ($p < 0.0001$). Capsular retraction was increased in the

late evaluation ($P = 0.006$). Band-like signal hypointensity in the hepatobiliary phase is present in 94% in late control ($P = 0.006$). The study of the risk of outfield progression *vs* infield progression using the Hazard Ratio is 9.

CONCLUSION

The efficacy of SBRT should be evaluated not in the first 6 mo, but at least 9 mo post-SBRT, when infield progression persists at very low rates while the risk of outfield progression increases significantly.

Key Words: Hepatocellular carcinoma; Stereotactic body radiation therapy; Magnetic resonance imaging; Histopathology; Outcome; Radiology

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Core Tip: As part of a retrospective study, 49 patients, who underwent SBRT for HCC between January 2013 and November 2019, were recruited. Each patient underwent a pre-treatment MRI examination with hepatospecific contrast agent and a similar follow-up examination within 6 mo of therapy. In addition, 22 patients underwent a second follow-up examination after the first 6 mo. The study results show that efficacy of SBRT should be evaluated not in the first 6 mo, but at least 9 mo post-SBRT, when infield progression persists at very low rates while the risk of outfield progression increases significantly.

INTRODUCTION

Although Stereotactic Body Radiation Therapy (SBRT) is increasingly used, its application has not yet been regulated by the main international guidelines, leaving the decision to multidisciplinary teams. Lack of diffusion and standardization of treatment

indications makes the radiological definition of outcome particularly complex and not completely concordant with the main therapy evaluation systems (mRECIST, ² Response Evaluation Criteria in Solid Tumors, and EASL, European Association for the Study of the Liver). By analysing the MRI semeiological characteristics of the HCC lesions treated by SBRT and remaining liver parenchyma, it would be possible to evaluate further evolution over time and changes in the diagnostic process following therapy^[1].

In addition, search of possible correlations between MRI findings and clinical, laboratory and radiotherapy data could help to prevent radio-induced liver damage and to implement customized treatment planning. This has made possible to use this treatment in different stages of HCC, both in patients with early-stage unifocal disease, in patients not eligible for other loco-regional therapies and for palliative purposes^[2,3].

From a technical point of view, number of target lesions as well as their location within the liver are potential limitations in treatment planning and dose distribution. A minimum distance of at least 5 mm of the target HCCs from adjacent hollow viscera is recommended, otherwise dose has to be reduced to match tolerance of neighboring organs.

Semeiotic characteristics of SBRT-treated lesions differ from the imaging of other locoregional therapies: whereas the latter result in immediate devascularization of tumor, radiotherapy leads to histological changes in the lesion and surrounding parenchyma that are gradual over time. Reflecting evolution of histological changes, an acute, subacute and chronic stage can also be distinguished^[4-10].

The main aim of the study is to analyse MRI features of HCC lesions treated by SBRT and remaining liver parenchyma, to monitor how these properties evolve over time and how these aspects may modify subsequent diagnostic course of therapy.

MATERIALS AND METHODS

PATIENT POPULATION

A retrospective observational study was conducted in 49 patients (mean age 64.44 years, range 48.71-84.51), 22 females and 27 males, undergoing radiotherapy between January 2013 and November 2019.

In 29 patients (59%) SBRT was chosen as the first treatment option, in 20 patients (41%) in combination with previous locoregional treatments on the same lesion. Six of these patients (12%) subsequently underwent liver transplantation (bridge therapy).

Sixtyone lesions were treated; among those, 42 were newly diagnosed HCC and 19 were focal lesions that had already undergone previous treatment and were therefore attributable to persistent or recurrent disease.

In the period between January 2013 and June 2020, each patient underwent an MRI examination with hepatospecific contrast agent prior to treatment, and a similar follow-up examination within 6 mo of therapy (mean time 4 mo). In addition, 22 patients (a total of 36 Lesions) underwent a second follow-up after the first 6 mo (mean time 9 mo).

IMAGING PROTOCOL

All MRI examinations were performed with 1.5 T equipment, Philips Achieva, infusing hepatospecific contrast agent (Primovist 0.25 mmol/mL, ¹Bayer Schering Pharma, Berlin, Germany) at a dose of 0.1 mL/kg with a flow rate of 2 mL/sec.

IMAGING ANALYSIS BEFORE TREATMENT

The acquired images were re-evaluated using the PACS system (Synapse PACS, Tokyo, Japan) by a radiologist with 15 years of experience in abdominal MRI.

For each lesion, the following characteristics were analysed and catalogued:

- Newly diagnosed HCC or previously treated HCC (persistence or recurrence of disease);
- Liver segment;

- Centroparenchymal or subcapsular location (distance from glissonian surface ≤ 10 mm);
- Diameter of hypervascularised tissue in arterial phase;
- Diameter of the lesion in basal (T1-weighted in-phase and out-of-phase) sequences;
- Diameter in hepatobiliary excretory phase sequences;
- Average lesion diameter;
- Presence or absence of signal hyperintensity in the T2-weighted sequences, in relation to the surrounding parenchyma;
- Presence or absence of signal enhancement in DWI;
- ADC value (obtained by manually positioned ROI).

RADIOTHERAPIC DATA ANALYSIS

All lesions that did not show an increase in size or contrast-enhancement intensity in the arterial phase were considered free of progressing disease, and therefore treatment was assessed as effective.

- Staging according to BCLC system;
- Pre-treatment Child-Pugh Score evaluation;
- Pretreatment ALBI assessment;
- Occurrence of RILD;
- Child-Pugh Score variation after treatment;
- ALBI change after treatment;
- Total Liver Volume;
- PTV (Planning Target Volume).

IMAGING ANALYSIS AFTER TREATMENT

The following features were analysed in the post-treatment MRI examinations:

- Features analysed on pre-treatment MRI examination;
- Presence or absence of Infield progression: signs of disease progression within the treated field (increase in size and/or increase in intensity of arterial contrast-enhancement);
- Presence or absence of Outfield Progression: signs of disease progression outside the radio-treated field according to mRECIST criteria;
- Presence or absence of ring-like enhancement (altered vascularity of the parenchyma adjacent to the treated lesion);
- Presence or absence of signal hyperintensity in T2-weighted sequences in the perilesional parenchyma;
- Presence or absence of capsular retraction; Presence or absence of "band" signal hypointensity in T1-weighted GE Fat Sat sequences obtained in the perilesional parenchyma;
- T1-weighted sequences obtained during hepatobiliary excretion of irradiated parenchyma;
- Calculation of the volume of "band" area in T1-weighted GE Fat Sat sequences acquired during hepatobiliary excretion by manual segmentation using polygonal ROIs, using the OsiriX DICOM Viewer software.

A retrospective analysis was performed comparing pre-treatment MRI characteristics with subsequent follow-ups.

RESULTS

Almost 55.7% of the treated lesions had a subcapsular location; the distribution in the different hepatic segments is as follows: 3 in S1, 4 in S2, 2 in S3, 8 in S4, 10 in S5, 5 in S6, 9 in S7 and 20 in S8.

The average diameter of the lesions was 17 mm (SD 13-24mm), a value that is significantly reduced both in the first control (10 mm, SD 11-20mm) and in the second follow-up (10 mm, SD 7-15mm) (table 1).

Five lesions out of 61 (8.2%) were hypovascular HCC. The remaining lesions showed typical post-contrast features with a mean diameter of 17 mm (12-24 mm), with a statistically significant reduction at follow-up.

Both the diameter during hepatobiliary phase and in basal T1 weighted sequences underwent size reduction in both controls.

On pre-treatment MRI, signal hyperintensity in the T2-weighted sequences was found in 62% of lesions, in the post-SBRT first control in only 30%, with a statistically significant reduction in the number of lesions ($P = 0.0006$).

Signal hyperintensity in DWI-weighted sequences was found in 68% of lesions and in only 18% in MRI first control ($p < 0.0001$). For both T2 and DWI variations, no statistically significant changes were found between first and second MRI control.

These variations were associated with a statistically significant increase of ADC values, which increased from a median of 1.01 at the pre-treatment examination to 1.38 at the first post-control ($p < 0.0001$).

In most of the lesions, the typical characteristics of the action of SBRT were identified. In particular, at the first MRI examination, 82% of the lesions showed ring-like enhancement and 84% perilesional hyperintensity in T2. These percentages tend to decrease in the second MRI examination (69% and 75% respectively).

Capsular retraction was evident in 33% of cases in the first control, a features that significantly increases to 64% in the late evaluation ($P = 0.006$).

Band-like signal hypointensity in the hepatobiliary phase was present in the first control in 95% of cases and in 94% in late ($P = 0.006$). The mean volume of the area of hypointensity calculated by manual segmentation was 85.47 cm³ (range 15.21-248.16).

Considering the mRECIST criteria for evaluation of response to therapy, at the first examination signs of infield progression were observed in 5% of cases (3 Lesions) and 18% of outfield progression.

At the second MRI check-up only 1 case of infield progression (3%) and 19 cases of outfield progression (28%) were observed.

The study of the risk of outfield progression *vs* infield progression using the Hazard Ratio is 9.

The risk increases as time progresses, with a sharp increase in the cumulative outfield progression hazard of around 9 after the end of therapy, as shown by the Kaplan-Meier curve study.

The time free from progression through the Kaplan Meier curve showed a plateau of onset of infield progression around 9 mo, an interval in which outfield progression tends to increase.

A direct relationship was also found between the area of band hypointensity during hepatobiliary excretion calculated by segmentation and PTV.

The two volumes are linked by a parabolic correlation: up to certain volumes of PTV, the area of hypointensity also increases in a directly proportional manner. For particularly high PTV values (greater than 300 cm³) the hepatic reaction area remains at significantly lower values.

No further statistically significant correlations were found between the available clinical data, the radiotherapy data obtained and the radiological findings.

DISCUSSION

In the acute stage (1-3 mo post-SBRT), typical peripheral hyperarterization can be seen, which persists or subsides in the subsequent post-contrast phases, referred to ring-like enhancement. These changes imply the phenomena of venous congestion and reactive hyperemia in the treated area ^[10].

In the subacute stage (3-6 mo post-SBRT), the parenchyma involved shows relative hypoattenuation in basal and portal acquisitions, with progressive enhancement in the late phase, related to the occlusion of the centrilobular veins and reduced intravenous contrast clearance^[6].

In the chronic stage (more than 6 mo after treatment), imaging will reveal changes caused by radio-induced fibrosis^[6,11].

The study showed the effectiveness of the treatment in controlling local disease, in particular: as already described in the literature, the reduction in the diameters of the lesion assessed (arterial, hepatobiliary and basal sequences) also becomes increasingly marked in the controls following the first^[5,6].

This phenomenon is attributable to microscopic phenomena due to venocclusion that lead to fibrosis and collapse of the liver lobules at a late stage and which a reduced nutrient supply to the lesion and a progressive volumetric reduction of the whole radio-treated parenchyma^[12,13].

In addition to the analysis of the classical criteria for locoregional treatment, the study focused on the analysis of signal intensities in the T2 and DWI weighted sequences.

Both sequences provide information about the nature of the tissue and the cellularity of the lesion and are therefore a useful "sentinel" parameter of treatment outcome.

Signal hyperintensity both in the long TR and DWI sequences tends to decrease at the first control, remaining stable in subsequent controls showing isointensity to the surrounding liver parenchyma^[6,10].

There is a statistically significant increase in the ADC values measured before and after SBRT, probably due to a reduction in the cellularity of the lesions due to necrosis.

As already described by Sanuki and Oldrini *et al*, persistence of arterial enhancement after stereotactic radiotherapy is common. In particular, arterial enhancement persists in our population, but its diameter tends to reduce over time, probably due to progressive and slow necrosis and intralesional giantocellular reaction.

If this hypervascularisation, especially in a short-distance follow-up, was to be assessed in the same way as other locoregional therapies according to mRECIST criteria, it would be considered as a persistence of viable tissue, leading to consider as ineffective^[9,10].

This is in contradiction with what is reported in the literature, attesting to a percentage of complete response to SBRT that tends to progressively increase up to 90% at 12-24 mo after treatment, a figure confirmed by our study in which infield progression at the second control was 3%.

For a correct interpretation of post-procedural imaging, it is essential to recognize features in the peri-injury parenchyma and how they change over time: peripheral hypervascularisation, signal hyperintensity in long TR sequences and band hypointensity in the hepatobiliary excretion phase.

In the context of CT, the imaging characteristics of focal hepatic reaction have been well described. In the immediate post-treatment, early vascular phase is hyperdensity as a consequence of sinusoidal congestion and reduced venous drainage, which gradually subsides in the portal and late phases. This may make it difficult to distinguish any persistence of hypervascularised lesional tissue in the arterial phase.

Over time, as fibrosis sets in, there will be contrastographic impregnation of the closely packed parenchyma closely contiguous to the lesion, included in the field of irradiation in the late stages^[14]

The above contrastographic features, defined as "ring-like" enhancement, are similarly present in the MRI survey of our population.

Associated with this aspect is the signal hyperintensity of the treated areas in the acquisitions with T2-weighted and Fat Sat T2-weighted sequences, which is also an indicator of radio-induced venoocclusive damage, which in the earliest phases is due to oedema and hyperemia, and with time to fibrosis^[15].

This latter factor is particularly evident in the phenomenon of capsular retraction, present in 64% of cases in late follow-up.

All these described elements, confirm the data available in literature on the capability of multiparametric MRI in the evaluation of locoregional hepatic therapy both in terms of post-procedural control and follow-up.

The use of liver specific contrast agent, based on the functional alteration of the hepatocytes, allows precise delineation of the irradiated field, which will appear hypointense during excretion, with a typical "band" configuration^[7,8,16].

This alteration further highlights how radiotherapy-induced structural changes in the liver through veno-venous disease can have a negative impact on the liver's immune system.

We have also found a direct correlation between the focal hepatic reaction volume calculated by segmentation and the PTV programmed by radiotherapy of the parabolic type.

The fact that beyond a certain PTV there is not an equal increase in the volume of focal hepatic reaction area could be explained by two factors, one of which is closely linked to the MRI method, which does not allow adequate quantification of the parenchyma.

The other explanation could be due to the fibrotic response of the liver: greater the fibrosis in absolute terms, consequently the reduction in liver volume will be greater, negatively affecting the quantification of the area of hypointensity.

According to some authors, this association could be exploited from a clinical-radiotherapeutic point of view both to assess the accuracy of centering and possibly modify it by reducing radio-induced damage, and to quantify "in vivo" radiation-induced liver damage and use it as a quantitative biomarker of hepatotoxicity^[17-20] .

Nevertheless, the integration of liver function parameters and MR-quantifiable liver damage might in the future allow further customised dose delivery or provide additional information to the radiologist in the post-therapeutic evaluation, so as to identify possible biomarkers predictive of liver damage.

However, this finding, which can be obtained from the earliest post-treatment controls, underlines the technical accuracy of the procedure.

In our population, no correlation was found between the occurrence of toxicity, the change in blood values and the radiological findings described.

The stability of these characteristics of good response to treatment and frequency of infield progression is concomitant with the rise of the frequency curve of outfield progression, which from the 9th month onwards is 9 times more frequent than local progression.

This finding could lay the basis for a different follow-up timing in patients treated by SBRT.

It is in fact known that histological changes cause long-term radiological effects, therefore delaying the first follow-up in selected patients beyond the usual 6 mo (all too

often not respected) would allow radiologist to express more confidence in the treatment region and at the same time have a greater chance of detecting new liver lesions, thus allowing a better correct staging.

This study showed the effectiveness of treatment in controlling local disease; indeed, while infield progression decreased from 5% to 3% of the population in subsequent controls, while outfield progression tends to increase (from 18% to 28%).

However, although it is increasingly used in clinical practice today, the assessment of its effects by MRI is still lacking.

LIMITATIONS

Limitations of this work are undoubtedly its retrospective nature. This leads both to a lack of systematic planning of the diagnostic procedure of the patients, which sometimes results in an incorrect and non-standardised timing, and to a low population size, since many patients, especially in the follow-ups after the first one, undergo CT scans.

Moreover, given the highly differentiated indications, patients undergoing SBRT are a particularly heterogeneous population including individuals with very different lesion sizes and staging.

It is therefore clear that this does not allow an indicative the impact of the treatment on survival.

In addition, as a treatment that is particularly effective in controlling local disease, it is not possible to create two comparative subpopulations in order to identify any prognostic or predictive indicators of response to treatment.

CONCLUSION

In conclusion, our study emphasized the role of liver MR after SBRT for HCC: a multiparametric approach using liver specific contrast agent provides more information about lesion and liver parenchyma changes compared to conventional CT studies. The

direct correlation between the area of hypointensity in the hepatobiliary phase and the PTV is indicative of the accuracy of the radiotherapy treatment and useful to define the infield and outfield progression disease.

ARTICLE HIGHLIGHTS

Research background

Although SBRT is increasingly used, its application has not yet been regulated by the main international guidelines, leaving the decision to multidisciplinary teams.

Research motivation

Literature is lacking in works assessing the role of liver MRI in the evaluation of HCC treated by SBRT.

Research objectives

To analyse MRI features of HCC lesions treated by SBRT and monitor how these properties evolve over time and how these aspects may modify subsequent diagnostic course of therapy.

Research methods

A retrospective observational study was conducted in 49 patients (mean age 64.44 years, range 48.71-84.51), 22 females and 27 males, undergoing radiotherapy between January 2013 and November 2019.

Research results

The most significant results came from the evaluation of infield and outfield progression. The risk increases as time progresses, with a sharp increase in the cumulative outfield progression hazard of around 9 after the end of therapy, as shown by the Kaplan-Meier curve study.

Research conclusions

A multiparametric approach using liver specific contrast agent provides more information about lesion and liver parenchyma changes compared to conventional CT studies. The direct correlation between the area of hypointensity in the hepatobiliary phase and the PTV is useful to define the infield and outfield progression disease.

Research perspectives

To enlarge the sample of patients and to be able to perform further follow-ups to the patients who have already undergone the first two checks.

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