Contrast Enhanced Ultrasound (CEUS) in the immediate and long term follow-up of patients with Hepatocellular carcinoma (HCC) treated by ablation

Poster No.: C-1471
Congress: ECR 2014
Type: Scientific Exhibit
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Keywords: Cancer, Contrast agent-intravenous, Ablation procedures, Ultrasound, MR, Liver
DOI: 10.1594/ecr2014/C-1471

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Aims and objectives

HCC is the main cause of death among patients with liver cirrhosis. From the time when surveillance programs are applied, a large number of lesions are detected with a size smaller than 3cm and consequently can be treated by ablation.

In our group (BCLC), the treatment of ablation is applied in patients with single or < 3 lesions of HCC small than 3 cm. not candidates to liver transplant. Ablation is also used for very early lesions (< 2cm ) substituting surgery (1) and in the waiting list for liver transplant.

The efficacy of ablation is crucial for the survival of the patients. In fact complete response is associated to increased survival in patients Child A or even in Child B (2). A close control of the treatment of those patients is recommended.

Efficacy of the ablation is evaluated with radiological imaging considering the absence of contrast enhancement as synonymous of complete necrosis. The most common technique used in the follow-up is dynamic CT. (3-4)

In 2006 (5) we report a study comparing CEUS and CT in the immediate response to ablation and in the results obtained at 1 month. The results of this study showed that immediate response can not predict the results obtained at 1 month. In fact the early evaluation was only useful when they were technical problems suggesting that the ablation was uncompleted. At 1 month similar results were obtained with CT or CEUS and since then our patients are controlled at 1 month only with CEUS. If the lesion is not perfectly seen on US, other contrast techniques are used.

CEUS has been used for other authors but comparative data with long term result are not available (6)

The capacity of MRI to detect small associated focal lesions is superior to dynamic CT (7) and for this reason the staging of our patients before ablation is done with MRI as well as the the follow-up after ablation.

The AIM of the present study was to determine the role of CEUS in evaluating long term response of tumor ablation in HCC patients compared to MRI, considering it as the gold standard. A secondary aim was to evaluate the capacity of CEUS compared to MRI in the detection of new focal lesions during the follow-up.
Methods and materials

This is a prospective study with two years of inclusion and one more year of follow-up.

In the two years period, patients submitted to ablation were studied according to the following protocol:

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>1 month after ablation</th>
<th>3 month after ablation</th>
<th>Every 6 months of follow-up</th>
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<tbody>
<tr>
<td>CEUS</td>
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<tr>
<td>MRI</td>
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<tr>
<td>Clinical evaluation</td>
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</table>

At 1 month if a persistence of enhancement was detected on CEUS a new treatment was performed.

Patients with poorly visualized tumors on ultrasound were not included. Also those patients who refused MRI or to participate in the study were excluded.

Retrospectively we also excluded those patients missing a control o with a delay between the two techniques superior to 1 month.

Finally, 68 cirrhotic patients with 76 HCC treated in a period of two years and with a minimal follow up of 1 year, were included.

Ablation: In 20 cases ablation was performed with PEI (percutaneous ethanol injection)
In 46 patients Radiofrequency (RF) was applied and in 2 cases RF+PEI.

At the time of evaluation, complete necrosis was considered when there was absence of enhancement with both techniques.

If hyper-enhancement in arterial phase was detected only in CEUS, a new control was performed after 3 month with both techniques considering as false positive for CEUS.

If hyper-enhancement in arterial phase was detected only in MRI using gadolinium, a new treatment of RF or PEI was performed. In such case a false negative CEUS was
considered. After one month of this second treatment we start again with a 1, 3 and every 6 month control according to the protocol.

As MRI was considered the gold standard we perform a new treatment immediately, so the possibility of false positives for MRI could not be evaluated.

The possibility to perform a biopsy was discarded according to the low capacity of diagnosis expected in that scenario.

The study of the remaining cirrhotic liver was carefully analyzed to detect new lesions during the follow-up.

The results of CEUS or MRI were evaluated by different radiologists unaware of the results obtained by the other technique.

CEUS was performed by using Sequoia (Siemens) equipment, at a MI < 20 and with SonoVue® (Bracco) using the recommended method of administration.

MRI was performed with de 1.5 T (Symphony: Siemens Medical Systems, and SIGNA General Electric) and the contrast used was Gadodiamide (Amersham) at a rate of 0.2 mmol/Kg

Data obtained was analyzed with SPSS-16.0
Results

The evaluation of the 68 patients realized at the first control one month after treatment was not included in the results of this study, as it was not compared with MRI according to the present protocol.

In 27 month mean follow-up, 150 evaluations of the results of ablation with CEUS and MRI could be compared.

A complete response was obtained in 88% of the cases. In tumors smaller than 2 cm (28 cases) complete necrosis was obtained in 93% (1 case had a persistence of focal enhancement).

CEUS and MRI agreed in 146 evaluations (Fig. 1 and 2).

CEUS disagreed with MRI in 4 lesions: 1 false positive at 3 month (Fig 3) and 2 false negative at 3 month (Fig 4) and 1 false negative at 15 month.

Overall sensitivity, specificity, positive predictive value and negative predictive value and overall accuracy for CEUS was: 83.3 %, 99.2 %, 93.7%, 97.8% and 97.3% in relation with MRI.

Overall accuracy at 3, 9 and 15 month was 96.3% (82 comparisons), 100% (40 comparisons) and 94.7% (19 comparisons).

New lesions: during the follow-up, new HCC lesions were present in 17 patients: a single lesion in 14 patients and two lesions in 3 patients. Mean size of the lesions was 17 mm (range: 12 - 25 mm).

In 12 patients CEUS and MRI detected new lesions simultaneously. Five lesions were detected only with MRI (Fig 5 and 6) one at 3 month and 4 between 9 and 15 month.
Fig. 1: Fig 1- HCC patient. One month after treatment the ablation was complete. At 3 month CEUS and MRI showed a small area of enhancement inside the ablated area (arrows). A new treatment was performed.

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Fig. 2: Ultrasound detected a < 2 cm lesion confirmed as HCC at MRI. At 3 month after treatment both techniques disclosed a small area of hyper enhancement (arrows) suggesting local recurrence.

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**Fig. 3:** Fig 3- This is the case of false positive for CEUS at 3 month after ablation. CEUS an MRI before treatment showed low enhancement in arterial phase (arrows). At 3 month control a focal low intensity enhancement in the periphery of the ablated area with a late wash-out was detected on CEUS and considered as persistence of tumour (arrows). MRI performed in few days could not detect any enhancement. At 6 month of follow-up, the complete necrosis of the tumour was confirmed.

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Fig. 4: Complete necrosis at 1 month. At 3 month MRI disclosed a 8 mm enhancement in the periphery of the ablated area, considered as recurrence (arrow). On CEUS, performed shortly before MRI, the lesion was considered with complete necrosis. Irregular limits were related to multiple insertions. A new ablation of the area was performed.

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**Fig. 5:** Initial HCC lesion in the dome of the liver was ablated by RF. At 3 month a 1.5 cm new HCC was detected by MRI in the neighborhood of the ablated area. CEUS was considered negative.

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Fig. 6: New distant lesion detected only by MRI. 1.2 cm lesion in the left lobe with the characteristic behavior HCC: hyper-enhancement in arterial phase and wash-out in portal and late phases.

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Conclusion

CEUS and MRI showed similar results in the control of HCC ablated lesions.

CEUS can be used as a single technique to evaluate the ablated area at 3 month.

After 6 month MRI can provide better detection of new lesions, suggesting the need of MRI follow-up every 6 month in the first two years after ablation.
References


