Therapeutic impact of intraprocedural contrast-enhanced ultrasound (CEUS) in percutaneous radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC)

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Purpose

Radiofrequency ablation (RFA) is nowadays considered as effective as surgical resection for the treatment of small hepatocellular carcinomas (HCCs).

With this technique it is crucial for the treatment to be considered complete to obtain a complete coagulation necrosis of the index tumor with a sufficient ablative margin (a partial necrosis involves needs of future retreatments with increased discomfort for patients, greater technical difficulties, and higher rate of failure and of possible complications).

Targeting and intraprocedural monitoring are generally performed by unenhanced imaging, including Ultrasound (US), Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), while precise assessment of technical success requires the use of contrast enhanced imaging, and is generally performed by contrast-enhanced CT (CECT) and/or MRI (CEMRI) within one week after the procedure.

The use of contrast-enhanced US (CEUS) immediately after the ablation (diagnostic accuracy similar to CECT has been reported) has been proposed to early identify incomplete ablation and allowing for an early retreatment in the same operative session, to allow a reduction of the number of second treatment, with a strong impact on costs and patient outcome.

At our institution CEUS is always performed intraoperatively after ablation procedures, and immediate CEUS-guided targeted retreatment is carried out during the same treatment session when incomplete ablation is depicted.

This study aims at assessing the clinical and economic impact of intraoperative CEUS in patients that underwent percutaneous RFA for HCC.
Methods and Materials

Sample

Approval was obtained by the Institutional Review Board and patients' consent was waived.

We retrospectively reviewed our consecutive series of patients that underwent percutaneous thermal ablation of focal liver tumors at our institution between January 2008 and June 2011.

Exclusion criteria: patients who underwent treatments for metastatic tumors and treatments with microwave ablation; patients with tumors undetectable by ultrasound; patients with tumors larger than 2.5 cm.

Patients with HCC that were treated by RFA and with tumors smaller than 2.5 cm were included in the analysis. In this way we included only patients in which, given the lesion size, a single insertion of the ablative device was preoperatively planned.

Procedure

RFA procedures were performed with patient under general anaesthesia, with US guidance (using a 3.5-MHz probe with an incorporated guide) and a 17-gauge cooled-tip electrode (Cool-Tip, Valleylab, Burlington, MA) with a 3-cm exposed portion. All procedures were performed by two of three interventional radiologists with more than ten years of experience in percutaneous thermal ablations. CEUS was performed using sulfur hexafluoride microbubbles (SonoVue, Bracco, Italy) before and immediately after RFA procedures to monitor and assess the therapeutic result before closing the treatment session. Contrast-specific software (Coherent Contrast Imaging, CCI and Contrast Pulse Sequencing, CPS, Siemens Acuson, USA; ECI, Siemens, Germany; Contrast Tuned Imaging, CnTI, Esaote, Italy) in continuous mode with very low mechanical index (0.01-0.1) was employed for all the examinations.

The first step of the RFA session was pretreatment CEUS examination, in order to reproduce mapping of lesions as shown on CECT/CEMR imaging examinations and to allow real-time lesion targeting. Images and/or movie clips were digitally stored to be compared with the immediate postablation study. Immediate postablation evaluation using CEUS was performed 5-10 minutes after the assumed completion of the RFA session, with the patient still under general anesthesia.
If residual enhancement was found in the ablated mass or volume of avascular area was considered to be too small to achieve a good coverage of the whole tumor and safety margin, the treatment was considered to be incomplete and a new ablation was immediately performed during the same treatment session.

CECT or CEMRI was performed at 24 hours in all cases and used as reference standard for assessing technical success.

**Therapeutic impact**

Patients in which intraoperative CEUS detected an incomplete treatment at the end of the ablation and that underwent a second CEUS-guided ablation in the same operative session were retrospectively evaluated on the basis of the description of the procedure recorded in the operative registry.

Incompletely treated patients at the end of the treatment were evaluated by reviewing the reports of the 24 hour CECT. Patients in which CEUS detected an incomplete ablation and then underwent a second CEUS-guided ablation in the same session who were confirmed to be fully treated at the 24 hour CECT were considered to have avoided a second intervention thanks to the intraoperative use of CEUS.

**Health Technology Assessment (HTA)**

Economic and managerial evaluation was conducted through a HTA approach (Guidelines for the Economic Evaluation of Health Technologies, CADTH, 2006). A cost-effectiveness analysis was conducted along with a budget impact analysis, and analyses of the impacts on the organisation and on equity.

The two comparators taken into account are the surgical intervention described above (performing a CEUS during the intervention) and the same surgical intervention without the aforementioned exam.

The effectiveness parameter taken into consideration to perform the cost-effectiveness analysis was the percentage of patients who avoided a second surgical intervention due to incomplete ablation.

Costs associated with the procedures were collected with a bottom-up approach (Activity Based Costing, Adam et al., 2003). Procedures were divided into single phases and the costs from each phase were evaluated (costs referred to human resources, machines,
surgical instruments, consumption materials, drugs and overheads). All phases, from the pre-admission testing to the discharge of a typical mean pathway of a standard patient without complications were evaluated, using the retrospective data related to the study sample in terms of time necessary for the surgical intervention considering the number of lesions to be treated, and the inpatient days. To assess the costs related to the procedure without intraprocedural CEUS, a differential analysis was performed not considering the time and the resources necessary to perform this exam.

The perspective taken into consideration was that of the hospital. Cost data, provided by the management control service of the hospital, are value added tax (VAT) inclusive and refers to 2011.

A sensitivity analysis was conducted to test the robustness of the results. 1,000 simulations were performed varying each cost category and effectiveness data with uniform distributions as follow: human resources and consumables ±10%; machinery 0, +750% (most of the technologies used for the intervention analyzed completed the amortization period, therefore a high range for sensitivity analysis was considered); laboratory exams, drugs, hotel services and effectiveness ±5%; overheads 0, -5%. The cost variations were the same for the two procedures in each simulation, while effectiveness could have different values for the procedures in the same simulation.

Impact on the hospital budget was calculated considering the annual number of RFA for HCC interventions performed in 2010 in the hospital. Two scenarios were than taken into consideration: 1) to assess the impact of the use of CEUS, using the real number of interventions and reinterventions due to not complete ablations within the period; 2) to assess the impact of the procedure without intraoperative CEUS, considering the interventions and the hypothetical number of reinterventions due to not complete ablations.

The costs of each intervention and reintervention were calculated for both procedures, along with the DRG reimbursement provided by the Regional Healthcare Service of Lombardy Region.

A sensitivity analysis was performed using bootstrapping methodology to simulate 100 different samples, considering a uniform distribution of ±10% in the number patients with of 1 and 2 lesions.

The impact on the organisation was assessed through guided interviews with three experienced radiologists working within the interventional radiology ward of the hospital involved in the study.
The impact on equity was investigated through guided interviews to three experienced radiologists, detecting their perception using a seven point scale concerning the two different processes in terms of adverse events, patient safety, accessibility, waiting lists, usability, invasiveness.
Results

In the considered period 640 liver lesions in 384 patients underwent percutaneous RFA. 148 HCCs in 93 patients met the inclusion criteria and entered our analysis, 59 (63.4%) males, aged 72.3 ± 7.9 years (median: 73.5 years). Treated HCCs had a maximum diameter of 1.86 ±0.57cm (median: 2.0 cm).

<table>
<thead>
<tr>
<th>HCCs per patient</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>62.4%</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>24.7%</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>8.6%</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

Number of HCCs treated per patient

Therapeutic impact

Intraprocedural CEUS detected incomplete treatment in 43/148 (29.0%) lesions in 34/93 (36.5%) patients after the first ablation. All 34 patients underwent additional treatment during the same session until complete absence of vascularisation was demonstrated by intraprocedural CEUS. At 24-hour CE-CT or CE-MRI, complete ablation was found in 143/148 (96.6%) lesions in 88/93 (94.6%) patients. Only 5/93 (5.4%) patients underwent local re-treatment subsequently. Thanks to intraprocedural CEUS a second session of treatment was spared in 29/93 (31.1%) patients.

Health Technology Assessment

The results of the cost-effectiveness analysis are reported in Table 1.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mean cost (€)</th>
<th>Effectiveness</th>
<th>Δ cost (€)</th>
<th>Δ Effectiveness</th>
<th>Cost effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>without intraprocedural CEUS</td>
<td>4,228</td>
<td>64.13%</td>
<td>4,228</td>
<td>64.13%</td>
<td>6,592</td>
</tr>
</tbody>
</table>
The mean cost of RFA without intraprocedural CEUS is 4,228 €, 3.7% less than RFA with intraprocedural CEUS. This difference is due to the longer time of RFA, and to the contrast agent.

Considering effectiveness, the use of intraprocedural CEUS led to a 94.57% value vs. 64.13% when CEUS was not employed. The cost-effectiveness value shows an advantage for the use of intraprocedural CEUS (4,639 vs 6,592) (Figure 1).

| with intraprocedural CEUS | 4,387 | 94.57% | + 159 | + 30.43% | 4,639 |

**Fig. 1**: Incremental Cost Effectiveness plan
The procedure with intraprocedural CEUS proved to be more effective and more expensive, with an Incremental Cost Effectiveness Ratio (ICER) (that represents the cost per effectiveness point gained) of 521.97 per intervention.

The probability of being cost-effective for the use of intraprocedural CEUS is over 50%, with a willingness to pay threshold of 575 €. This represents the willingness to pay of the Health Service to reach a 1 point effectiveness gain.

The budget impact analysis on the activities performed on the sample considered leads to the following results: the use of intraprocedural CEUS allowed a reduction in terms of costs of 21.95% compared to the treatment of the whole sample without intraprocedural CEUS, due to avoided re-treatments. A 25.95% reduction in terms of reimbursement was observed, since the number of re-treatments in the sample considered is higher without intraprocedural CEUS and therefore the considered treatments and DRGs are higher in this scenario.

The mean cost per patient to receive a complete treatment (comprehensive of first and second RFA) is 4,609 € vs. 5,872 € respectively with the use of intraprocedural CEUS and with the standard procedure.

The sensitivity analysis results show a minimum and maximum reduction of costs for the hospital of 19.02% and 23.26% respectively with the use of intraprocedural CEUS.

The analysis of the organisational impact leads to the identification of hypothetic investments necessary for the introduction of CEUS within a Department of Interventional Radiology of less than 11,000 € (update of softwares, training of radiologists and meetings).

The perceived short-term organizational impact results are reported in Figure 2.
In the short term, the introduction of CEUS leads to a medium negative impact on learning time, a low negative impact on training for personnel directly involved in the procedure, and for support personnel, meetings within the Department, and software update. A positive medium impact was assessed for internal processes and appropriateness of requests of diagnostic exams, both leading to a reduction in terms of further interventions or investigations needed for the same patient.

In a medium/long term perspective, the positive impacts remain, while the negative dimensions will not have further impact on the organization.

Considering the impact on equity, the use of intraprocedural CEUS was associated with a highly positive impact for the quality of data related to the investigated diagnostic question, which leads to more precise information to support medical decisions, a medium positive impact since it allows to reduce waiting lists for surgical interventions, avoiding re-treatments, and a low negative impact on usability and invasiveness of the procedure (Figure 3).
Fig. 3: Impact on equity

References: Department of Radiology, Ospedale di Busto Arsizio
Fig. 1: Incremental Cost Effectiveness plan

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Fig. 2: Short term organizational impact

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Fig. 3: Impact on equity

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Conclusion

Intraprocedural use of CEUS can reduce the number of incomplete treatments and consequently the number of re-treatments and the total costs of RFA for HCC.

RFA proved to be effective in the treatment of small HCCs, with results comparable with surgical resection. However, given that the assessment of the completeness of ablation is generally performed after the treatment, often more than one ablation session is required to achieve complete response, with increasing risk of complications for the patient and increasing costs. Accordingly, the achievement of complete response after the first ablation would be extremely important.

Due to CEUS level of accuracy, similar to other contrast-enhanced imaging modalities for the assessment of technical success after RFA, some Authors suggested its use immediately after RFA, in order to be able to perform a re-treatment during the same interventional session when incomplete ablation is detected.

The adoption of this strategy at our institution allowed the detection of incomplete ablations in 29.0% of lesions in 36.5% of patients and to perform an immediate CEUS-guided targeted re-treatment, that led to a complete ablation rate at 24-hour CE-CT or CE-MRI in 94.6% of patients. Thus, a second session of treatment was avoided in 31.1% of patients.

The introduction of intraprocedural CEUS determined a 3.7% increase of costs, compared with the standard procedure. This difference is due to the longer time needed to perform CEUS, and to the cost of the contrast agent. However, the use of intraprocedural CEUS showed a better cost-effectiveness value compared to the standard procedure and a higher probability of being cost-effective with a 575 € threshold of willingness to pay.

From a Hospital perspective, the intraoperative use of CEUS determined a 21.95% reduction of costs, due to a lower number of re-treatments. This would lead to the possibility to perform ablations for a higher number of patients with consequent more effective use of resources and shortening of waiting lists. Moreover, considering from the point of view of the Health Service, the use of intraprocedural CEUS allows a lower cost per patient’s complete treatment, granting savings for the whole Service.

The introduction of intraprocedural CEUS in Centers where CEUS is already employed for other purposes would lead to low organisational impact, but to a relevant positive
impact on equity, since the avoided re-treatments would improve the quality of life of patients, increasing their serenity and reducing the number of hospitalizations.

In conclusion, the intraprocedural use of CEUS in our analysis had a relevant therapeutic impact on percutaneous RFA for HCC, reducing the number of re-treatments and the related costs per patient.

Limits

Even if CEUS has been demonstrated to have diagnostic accuracy similar to CE-CT in the assessment of treatment results a limitation of our analysis is the lack of studies that compare CEUS with other contrast-enhanced modalities immediately after RFA.

The decision to perform a new ablation immediately, in the same session, was taken on the basis of the assessment of the Interventional Radiologists. Thus, the need for immediate re-treatment could have been overestimated.

Being a second-level Center, a higher rate of "complex cases" is referred to our Department from other hospitals compared to the general situation of Departments of Interventional Radiology, with an increased mean technical difficulty of the cases to be treated. Thus, the same analysis performed in a different Hospital might lead to different results.

The absence of a real control group in which CEUS was not performed, led our results to be obtained comparing a real group with an hypothetical one in which CEUS was not performed.
References


