Project no. 610886

Project acronym: ClinicIMPPACT

Clinical Intervention Modelling, Planning and Proof for Ablation Cancer Treatment

Work programme objective: ICT 2011.5.2 Virtual Physiological Human

Instrument: STREP

Deliverable D6.8

Scientific publication on evaluation of the clinical study results

Due date of deliverable: 31/07/2017
Actual submission date: 08/09/2017

Organisation name of lead contractor for this deliverable: MUL

Start date of project: 01/02/2014  Duration: 42 months
Scientific publication below will be submitted to the Journal of Radiology

Clinical Intervention, Modeling, Planning and Proof for Ablation Cancer Treatment (ClinicIMPPACT) Trial – Planning and real-time simulation of hepatic RFA procedures

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Funding information:

This research was funded by the Seventh Framework Program of the European Union (grant number 610886)

Type of manuscript: Original Research. This manuscript was not presented at any RSNA meeting and has not been submitted to any future meeting.

Keywords: RFA; liver; lesion prediction; segmentation; perfusion CT
Abstract

Purpose:

Patient-specific factors as tumor proximity to vessels or tissue perfusion can affect lesion size during radiofrequency ablation (RFA) of liver tumors and lead to both, over- and under treatment. We aimed to clinically validate a comprehensive software tool designed to optimize the planning and simulation of RFA procedures.

Methods and Materials:

In this prospective clinical trial, we included 47 hepatic lesions from 44 patients with different liver malignancies, who underwent multi-phase computed tomography (including quantification of liver perfusion) prior to RFA. The actual RFA-needle position was assessed by intraprocedural CT-scans and registered to a 3D-model created prior RFA. Image computations and thermal simulation allowed real-time processing during the RFA procedure. Size, shape and position of the simulated lesions were compared to the true ablation zones determined by follow-up CT one month after RFA.

Results:

There was a strong correlation \( r=0.71, \rho<0.0001 \) and no significant difference (Wilcoxon \( p=0.49 \)) between the simulated- and segmented lesion volumes. Surface- and volume deviation between the simulated- and segmented lesions were 3.8 mm±2.0 SD (absolute average error, AAE), and 1.1 %±1.2 SD (relative volume deviation). AAE was positively correlated to the duration of the ablation \( r=0.29, p<0.05 \) and the duration of the ablation was an independent predictor of AAE \( (\beta=0.027±0.01 \text{ minutes}, p=0.02) \), after adjustments for tissue perfusion and presence or absence of liver cirrhosis.

Conclusion:

Our software application provided good accuracy for predictions of lesions resulting from radiofrequency ablations in the liver. Implementation into clinical routine may help to improve the safety and success of radiofrequency ablations in the liver.
Introduction

Local thermal ablation techniques such as radiofrequency ablation (RFA) are considered first line treatment options for inoperable patients with early-stage hepatocellular cancer (HCC) (1). With comparable overall survival RFA is also a viable therapeutic alternative for early metastatic liver cancer in inoperable patients (2), and in the presence of poor liver function (3,4).

The percutaneously applied RFA probe induces cell death via coagulative necrosis. Despite precise image guided needle placement (e.g. using computed tomography) RFA can be challenging in terms of sufficiency. This is mainly owed to the complex relationship between applied thermal energy and variable local tissue perfusion, more specifically due to the presence or absence of neighboring cooling venous and portal-venous vessels, which divert heat from the ablation zone (heat sink effect).

Reliable real-time therapy monitoring remains the missing link which would likely reduce discrepancies between the expected and the real lesion, which can only be sufficiently assessed by follow-up imaging once post interventional tissue swelling disappeared but lesion shrinkage has not yet set in, which is usually the case 1 month after RFA. The intraprocedural uncertainty about the volume and shape of the resulting ablation zone leads to over- (up to 9% of major complications) (5), or under treatment (with up to 40% local recurrence) (5,6).

Different approaches to simulate and predict the resulting ablation zone have been described (7–10), however only few groups incorporated important patient specific parameters, i.e. liver perfusion into their models (10,11). Preclinical studies included extensive experiments on cell cultures and animals to create a heat dependent cellular death model, which was implemented into the current simulation algorithm (12,13). The RFA-Guardian software provides a simulator for interventional radiologists (IRs) to plan, review and optimize RFA procedures.

After generating a 3D-model of the liver, the actual needle position is assessed by intraprocedural CT-scans, registered to the 3D-model to simulate the thermal lesion. Image computations and thermal simulation allow real-time processing during the RFA procedure. Size,
shape and position of the simulated lesions are then compared to the true ablation zone as determined by follow-up CT one month after RFA.

In this trial, we collected pilot clinical data to test how precise, as measured by volume and surface deviation, and how efficient, compared to a retrospective control group, newly developed software can provide real-time predictions of resulting lesion sizes during RFA of liver malignancies.

Materials and Methods

Subjects and study design

In this multicenter prospective clinical trial, we invited N=44 (N=14 Turku, Finland; N=3 Graz, Austria; N=12 Nijmegen, Netherlands; and N=15 Leipzig, Germany) patients with pre-diagnosed primary (hepatocellular carcinoma, HCC) or secondary malignant liver tumors (e.g. metastases). One patient from Turku died, within the four weeks between RFA treatment and follow up visit, of reasons unrelated to the treatment and was therefore excluded from the analysis. Four patients presented with N=2 lesions each, which led to N=47 lesions included in this trial. Diseases were diagnosed in two independent imaging modalities or alternatively histologically proven. Decisions on optimal therapies were made, according to AASDL guidelines, by each local tumor board (consisting of radiologists, oncologists and hepatobiliary surgeons), which evaluated options such as resection, liver transplantation, adjuvant or neoadjuvant chemotherapy, or image-guided procedures such as RFA. Resection or other treatment options were not suitable for these patients, who presented with a maximum of 3 lesions and a maximum diameter of 3 cm per lesion.

Furthermore, sufficient coagulation parameters according to European School of Interventional Radiology - guidelines were required. Participants were at least 18 years old and fulfilled standard eligibility criteria for undergoing pre-interventional diagnostic imaging, such as absence of pregnancy or current nursing, dysfunction of the kidney or thyroid gland, and known anaphylactic reaction to iodine/contrast agent. Concurrent participation in other interventional trials as well as splenectomy were exclusion criteria.
Patients gave both verbal and written informed consent and approvals for the trial were granted by the institutional ethics committees at all four clinical sites and the German Federal Office for Radiation Protection.

The study design of this clinical trial is described in great detail elsewhere (14). The main components of the study design are shown in Figure 1 and described in the sections below. Preliminary results with focus on technical aspects have been published earlier (13).

Figure 1. Study design overview

![Flow chart of the ClinicIMPPACT Trial](image)
Imaging

Planning Imaging

Multiphase diagnostic CT imaging of the abdomen was carried out as part of the clinical routine, comprising the parameters shown in Table 1. Patients were fasted at least 4 hours prior to the examination. No oral contrast agent was used. First a non-enhanced scan was performed. Intravenous contrast agent was injected at a flow rate of 3ml/s (contrast agent ≥300mlg/ml) and CT scans were conducted in the arterial, portal venous, and venous contrast phase. Total contrast volume depended on individual body weight. All images were acquired during breath hold in expiration, with arms elevated above the head. Based on the portal venous data set multiple segmentation processes are carried out to segment the liver, vessel trees, and the tumor, and to ultimately create a complete 3D model (10).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Non-enhanced</th>
<th>Arterial phase</th>
<th>Portal venous phase</th>
<th>Venous phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covered Area</td>
<td>Liver</td>
<td>Liver</td>
<td>Liver to Symphysis</td>
<td>Liver</td>
</tr>
<tr>
<td>Delay (s)</td>
<td>-</td>
<td>15</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>Collimation (mm)</td>
<td>(256) × 0.625</td>
<td>(256) × 0.625</td>
<td>(256) × 0.625</td>
<td>(256) × 0.625</td>
</tr>
<tr>
<td>Rotation time (s)</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>mAs</td>
<td>180</td>
<td>220</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>kV</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Reconstruction (mm)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Increment (mm)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 1. Scan parameters for planning CT imaging

Perfusion CT of the liver

Perfusion is a powerful source of tissue cooling and has the potential to affect heat transfer substantially and ultimately influence the size of the induced thermal lesion (15). For example, in liver cirrhosis hepatic artery flow is higher, compared to healthy liver tissue, while portal venous flow is strongly reduced which leads to a lower overall perfusion (16,17). Dynamic CT measurements after contrast administration were used to quantify tissue perfusion in the liver (18).
The IMPPACT project showed that inclusion of patient specific perfusion values in the heat transfer calculation can substantially improve the accuracy of the simulated lesions’ size (19). A dedicated imaging protocol was developed to combine low radiation exposure with adequate image quality (14).

CT perfusion analysis

The clinical partners of the ClinicIMPPACT project used CT scanners from three different manufacturers (Siemens, Philips and Toshiba). The development of a common software tool for standardized CT data analysis was therefore essential (19). Arterial and portal venous perfusions, both measured in ml/min/100 ml, were identified as the most important perfusion parameters related to the microcirculation in non-tumorous parenchyma. The maximum slope (MS) method was chosen due to several specific advantages, e.g. short acquisition time and reduced radiation dose.

Regions of interest (ROI) were visually placed into the according hepatic regions and the spleen, whose peak enhancement generally serves to separate arterial and portal-venous perfusion from hepatic perfusion. Further details about CT perfusion analysis can be found here (19).

CT-guided Radiofrequency ablation

After acquisition of a non-enhanced CT scan, with the patient under full anesthesia, to localize the tumor and plan optimal needle access, the IR inserted the probe using CT guidance. Once the probe (RITA Starburst® XL, AngioDynamics, Latham, NY, USA) was in its final location the hooks were completely deployed and a non-enhanced CT scan (under temporary apnea) was performed. Once the IR confirmed the deployed needles’ proper position the CT data was then transferred to an external PC for fast needle registration, which semi-automatically registers the needle into the 3D model created prior to the intervention (10).

The RFA and computer simulation of the lesion (13) started simultaneously. The employed standard- or modified ablation protocols can be found is provided in table 2. Optional to a standard non-enhanced CT-scan after the ablation, a control CT with contrast agent was performed to evaluate potential residual tumor. If the lesion was not sufficiently treated, needle adjustment and additional
Ablation was performed under CT-guidance. If the ablation result seemed sufficient, the needle was removed under track ablation (14).

<table>
<thead>
<tr>
<th>Deploy to</th>
<th>Target temperature (°C)</th>
<th>Power (Watt)</th>
<th>Duration (min)</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 cm</td>
<td>105</td>
<td>150</td>
<td>15</td>
<td>Heat until target temperature is reached, then deploy to 3 cm</td>
</tr>
<tr>
<td>3 cm</td>
<td>105</td>
<td>150</td>
<td>14.5</td>
<td>Heat until target temperature is reached, then deploy to 4 cm</td>
</tr>
<tr>
<td>4 cm</td>
<td>105</td>
<td>150</td>
<td>14</td>
<td>7 min after target temperature is reached, then deploy to 5 cm</td>
</tr>
<tr>
<td>5 cm</td>
<td>105</td>
<td>150</td>
<td>7</td>
<td>7 min after target temperature is reached, then cool down</td>
</tr>
</tbody>
</table>

*Table 2.* Ablation protocol for a 5 cm ablation using the RITA Starburst®-probe (RITA Starburst® XL, AngioDynamics, Latham, NY, USA)

**Real-time RFA lesion prediction**

Because the 3D model of the liver was generated pre-operatively it was required to register the heat source (i.e., the needle) to the precomputed model during the RFA procedure. We previously designed a needle-registration method that offers both fast computing (< 2 minutes) and accuracy (average absolute error < 5.0 mm).

In the recent IMPPACT project a prototype for RFA simulation was developed (20), that provides state of the art visualization. Compared to others (21,22), the prototype was the first tool to consider cell death instead of simple heat approximations for its simulation (23). The improved, current version of the tool – the RFA Guardian performs all real time computations by using a modern graphics processing unit (GPU) (24,25). A detailed description of the algorithm can be found elsewhere (13).
Follow-up imaging and postprocessing

Follow-up imaging was performed 1 month after RFA via multiphase CT (non-enhanced, arterial, portal venous, venous) for HCC lesions or using mono-phase CT (portal venous) for metastases, both under breathhold in expiration. All CT images, whether pre-, peri- or post-interventional (i.e. follow-up) were evaluated by radiologists with more than 10 years of experience in abdominal imaging, at each participating clinical site.

In a post-processing step the simulated lesion from the intra-procedural CT scan (acquired in apnea under full anesthesia) was co-registered to the semi-automatically segmented true ablation lesion from the follow up CT scan (acquired under breathhold in expiration). Then volume- and surface deviations between the simulated and the segmented lesion were computed (Figure 2). The volumes of the simulated and true RFA lesion were determined by counting the number of matching voxels, i.e. the voxels of simulation and segmented data, sharing the space coordinates, and dividing by the sum of the voxels of the simulated and real lesions (10).
Figure 2. Lesion shift due to registration error of simulated lesion (red, from intra-procedural scan) and segmented lesion (blue, from 1 month post RFA scan).

**Statistical analysis**

Normally distributed data were described using means and standard deviations, skewed variables (simulated- and segmented lesion volumes) were described with medians and interquartile ranges. Initial correlations between simulated- and segmented lesion volumes were determined using Spearman rank correlations ($\rho$). Non-parametric One-Way ANOVA (Wilcoxon Signed-Ranks Test) was used to assess differences between simulated- and segmented lesion volumes.

To analyze primary outcome variables, we employed the following established scores to represent volume- and surface deviation for the registered simulation and simulation alone, respectively: Relative volume deviation (RVD), a ratio between the absolute volume difference to the volume of the actual lesion. Surface deviation is calculated based on the Hausdorff distance formula and represented by the average absolute error (AAE). The secondary outcome variable (workflow efficiency of the intra-procedural software application) was investigated by comparing the durations of the RFA procedures between a sub sample of study population (N=31) and a retrospective control group (N=31), pair-matched for tumor volume. Both, durations and tumor volumes were compared using Student’s t-test. The beginning and end of the RFA procedure were defined as the “time stamp” on the planning- and post procedural CT scans.

Because tissue perfusion can potentially influence the resulting lesion size and because the duration of the ablation can be an indicator of the complexity of the ablation we correlated these variables with AAE and RVD using Pearson rank correlation coefficients ($r$). Significant correlation between these variables were investigated further using multivariate linear regression with ablation time, tissue perfusion and presence or absence of liver cirrhosis included as quantitative variables and AAE and RVD as dependent variables, respectively. Cirrhotic tissue can acts as thermal
insulation, preventing the applied heat to spread beyond the target area and may therefore alter the ablation results (26). Effect sizes of multivariate linear regression models are reported as parameter estimates with [95% confidence limits]. Statistical data analyses were performed using the SPSS software (SPSS Inc., Chicago, Illinois, USA, version 18.0).

Results

Summary measures for continuous variables of the study population and lesions, and the retrospective control group are shown in table 1. In the study group twenty seven patients presented with HCC, seventeen with colorectal carcinoma metastasis, and three with other metastases (from cholangiocellular-, ovarian-, and gastric carcinoma). Liver cirrhosis was present in twenty three patients of the study group. Transarterial chemoembolization (TACE) was performed in seven lesions of the study group prior to RFA.

There was a strong correlation between the simulated- and segmented lesion volume \( r = 0.71, p<0.0001 \), Figure 3) and a Wilcoxon Signed-Ranks Test indicated that the median simulated- and segmented lesion volumes did not differ significantly (Wilcoxon \( p=0.49 \), table 3). When comparing the surface- and volume deviation (AAE and RVD, respectively) between the simulated- and segmented lesion, based on the registration of the intra-procedural CT-scan to the one month post ablation control scan we found an AAE of 6.1 mm \( (+ 3.2 \text{ SD}) \) and RVD of 1.3 % \( (+ 3.4 \text{ SD}) \). By excluding the error that goes along with co-registration through translation of both lesions into the same coordinate system, AAE improved significantly to 3.8 mm \( (+ 2.0 \text{ SD}; p<0.0001) \); RVD: 1.1 % \( (+ 1.2 \text{ SD}; p=0.59) \) when simulated and segmented lesion were compared directly. This actual AAE (aAAE) was positively correlated to the duration of the ablation \( r = 0.29, p<=0.05 \), Figure 5), but not with tissue perfusion \( r = -0.18, p=0.22 \). RVD was not associated with either tissue perfusion \( r = -0.23, p=0.11 \), or with the duration of the ablation \( r =
In a linear model the duration of the ablation was an independent predictor of aAAE ($\beta=0.027\pm0.01$ minutes, $p=0.02$).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lesions in study group (N=47; F=9; M=35)</th>
<th>Volume matched study group (F=7; M=24)</th>
<th>Volume matched retrospective control group (F=7; M=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.2 ± 10.1</td>
<td>67.5 ± 11.2</td>
<td>64.8 ± 9.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.2 ± 4.8</td>
<td>26.6 ± 4.3</td>
<td>26.7 ± 3.6</td>
</tr>
<tr>
<td>Tissue perfusion (ml/min/100 ml)</td>
<td>61.0 ± 24.9</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tumor perfusion (ml/min/100 ml)</td>
<td>39.9 ± 30.9</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tumor volume (cm³)</td>
<td>5.46 ± 5.</td>
<td>6.06 ± 5.6</td>
<td>6.05 ± 5.5</td>
</tr>
<tr>
<td>Simulated lesion volume (cm³)</td>
<td>17.28 [9.09 – 22.2]</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Segmented lesion volume (cm³)</td>
<td>18.09 [7.77 – 22.97]</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of treatment (min)</td>
<td>93.0 ± 43.1</td>
<td>91.4 ± 31.4</td>
<td>77.4 ± 22.2</td>
</tr>
<tr>
<td>Duration of ablation (minutes)</td>
<td>39.4 ± 20.4</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 3. Demographic and anthropometric characteristics of the study population. Median simulated versus segmented volumes did not differ significantly (Wilcoxon $p=.49$). The duration of the treatment did differ significantly between the volume matched study group and the retrospective control group (student’s t-test: $P=0.04$). BMI = body mass index. NA = non applicable.
Figure 3 shows the correlation between simulated and segmented RFA – lesion volumes ($r = 0.71$, $p < 0.0001$, Figure 2). Excluding the two outliers (top right and bottom far right) did not change the results significantly ($r = 0.71$, vs. $r=0.67$, both $p<0.0001$).
Figure 4: Bland-Altman plot showing the limits of agreement (mean and 95% confidence interval) between paired values for simulated and segmented RFA - lesion volumes.

Figure 5: The AAE was positively correlated to the duration of the ablation ($r = 0.32$, $p=0.03$), after exclusion of the registration error.
Discussion

In this first prospective clinical trial for the evaluation of the precision and efficacy of a software application, developed to predict RFA induced hepatic tissue necrosis in patients with liver malignancies, we found that the application predicted lesions with good accuracy and at a high speed, suitable for clinical routine.

We found a rather large registration error, which is best explained by a variation in the position and shape of the liver in the intra-procedural CT-scan (used for the simulation) and the 1 month – control scan (used for true lesion segmentation) (Figure 2). An animal study with 12 ablations in porcine livers found a mean deviation (point-to-mesh error) between predicted and true ablation of 5.3 ± 3.6 mm. The problem is well known in the fields of radiotherapy and nuclear medicine. In stereotactic body radiation therapy, this problem is conquered by the use of implanted markers which act as localizing and tracking devices to optimize tumor targeting (27). In our cases the differences in the position and shape of the liver, as a result of longitudinal or rotational movements related to variations in diaphragm position, are severe because the intra-procedural scan is acquired in end-expiration apnea with the patient under full anesthesia. This includes complete relaxation of the diaphragm, while the 1 month control scan is performed in active expiration with breathhold in the conscious patient. Hence, it was not surprising to find a reduction in surface deviation (AAE) of 37.5% and a reduction in volume deviation of 20.6 % (RVD) after translation of the lesions into the same coordinate system. However, because the simulation is computed based on the real intra-procedural CT scan with the RFA – probe in place this issue is only relevant for this evaluation study but irrelevant towards the accuracy of the simulation algorithm itself.

In a preliminary analysis we found that the surface deviation decreased by 5-10% when including measured perfusion values, rather than estimated CT-perfusion values (13). The importance of hepatic blood flow and the proximity of the tumor to blood vessels is further highlighted when taking a closer look at two outliers indicated in Figure 3. In one case the
segmented (true) lesion was underestimated by ca. 50 cm³, in another case overestimated by roughly 30 cm³. The explanation for the significant underestimation of the resulting ablation zone was due to unpredicted arterial damage in the first case which led to non-perfusion and finally necrosis of a large (unpredicted) tissue areal adjacent to the ablation site. The reason for the significant overestimation of the ablation in the second example is unclear, but most likely due to miscalculations based on the provided perfusion values of the tissue. Especially the first example displays one limitation of the simulation in regards of predicting vessel damage in a highly perfused organ.

Interestingly, duration of the ablation was an independent predictor of surface deviation. A prolongation of the ablation of 37 minutes would lead to one additional millimeter of surface deviation. Consequently, one could argue that larger lesions and lesions in proximity to large vessels, which require longer ablation phases might be less suitable for adequate lesions prediction. The Bland–Altman plot further underlines the fading precision of the lesion prediction with larger volumes.

In regards to efficacy we identified data transfer to be one of the most limiting factors for sufficient implementation of the software application into the clinical workflow. In this study, the software was not connected to the local data networks, due to data security concerns. This led to time consuming data transfer from the CT scanner to the software workstation, via external data drive. This fact explains the average difference in procedure duration of 14 minutes between the trial and a matched retrospective control group. It would therefore be desirable to integrate the system into the local hospital network (in this specific case after FDA approval as medical device) and therefore eliminate this confounder.

In summary, our results indicate good precision and efficacy of a dedicated software solution to accurately predict lesion size and shape after radiofrequency ablation of liver tumors. As mispredictions of true ablation zones can lead to increased tumor recurrence due to under treatment or complications due to overtreatment this tool might be of interest to the interventional
radiology community. It potentially helps treating tumors in close proximity to larger vessels and might support less experienced IR’s to perform RFA with confidence. Further randomized clinical phase II trials are needed to test whether the use of this tool improves patient outcome.

Conflict of interest

The authors declare no conflict of interests.

Acknowledgments

The research leading to these results has received funding from the European Community's Seventh Framework Program under grant agreement no. 610886, project ClinicIMPPACT and grant agreement no. 600641, project GoSmart. Furthermore we would like to thank and name all associated investigators: Martin van Amerongen, Jan Egger, Jukka Ilari, Philipp Stiegler, Horst Portugaller, Dieter Schmalstieg, Mark Dokter, Phil Weir, Nikita Garnov, Tuomas Alhonnoro, Miko Lilja and Bianca Schmerböck.

Abbreviations: BF: blood flow; BV: blood volume; CT: computed tomography; EU: European Union; HCC: hepatocellular carcinoma; IMPPACT: Intervention Modelling, Planning and Proof for Ablation Cancer Treatment; RFA: radio frequency ablation; US: ultrasound.
References


