Selective Internal Radiation Therapy (SIRT) in colorectal liver metastases: Dynamic Contrast Enhanced Ultrasound (DCE-US) assessment of altered liver blood flow can predict responders: A preliminary study

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Aims and objectives

Introduction

The liver is a unique organ with a dual blood supply, the portal vein and the hepatic artery. Up to 75% of the normal liver is supplied by the portal vein. The liver is also one of the most common sites for metastasis. In contrast, the blood supply of liver metastasis is almost entirely arterial.

Selective internal Radiation Therapy (SIRT) is a radio-embolism technique used in treatment of unresectable liver metastases or liver dominant disease. Early evidence has suggested that SIRT is a promising treatment option for extensive liver metastases that are refractory to first and second line chemotherapies (1,2).

Selective Internal Radiation Therapy

SIRT is performed by delivering biocompatible, resin based Yttrium 90-labeled microspheres (SIR-Spheres®, SIRTEx Medical; North Ryde, New South Wales, Australia) to targeted liver tumours via the hepatic arterial supply. These microspheres have a median diameter of 32.5 microns (range 20-60 microns) and are large enough to lodge within the tumour microvasculature. Yttrium 90 emits beta rays but not gamma rays. As such, the maximum range of emissions in tissue is 11mm, with a mean of 2.5mm. This enables the solid tumours to be destroyed, while minimising the damage to the liver. The isotopes have a half-life of 64.1 hours, while 94% of the radiation is delivered in 11 days following administration (3).

Prior to SIRT treatment, a hepatic angiogram is performed to detect and embolise any vessels that may potentially carry the microspheres from the hepatic artery to the bowel vasculature. In the same sitting, Technetium-99m macro-aggregated human (Tc-99m MAA) is administered into the hepatic artery as a tracer. A Tc-99m MAA nuclear medicine SPECT scan is perform one day later to determine the extent of arteriovenous shunting to the lungs and to confirm the absence of collateral flow into the gastric and duodenum before the patient can be accepted for treatment.

Assessment of SIRT Treatment response

Response evaluation criteria in solid tumours (RECIST) has been the standard criteria used in assessing tumour shrinkage after cytotoxic therapy (4). However, SIRT treated tumours generally produce significant tumour necrosis and may sometimes show a paradoxical increase in size. This limits the usefulness of RECIST assessment.
PET/CT imaging with $^{18}$F-FDG has been shown to be more sensitive in evaluating post SIRT response (5), using metabolic indices and/or SUV based parameters (6,7). However, PET/CT imaging is expensive and not widely available.

**Dynamic contrast enhanced ultrasound (DCE-US)- A potential biomarker**

Ultrasound contrast agents (UCA) have been widely used in Europe and Asia for hepatic imaging. Some UCA presently available in the market include Optison® (FS-069, perflutren protein type A microspheres; GE Healthcare, Princeton, NJ), Definity® (MRX-115, perflutren lipid microspheres; Bristol-Myers Squibb Medical Imaging, North Billerica, MA) and Sonovue® (BR-1, sulfur hexafluoride; Bracco International BV, Amsterdam, the Netherlands)

UCA is a pure blood pool agent, which makes it an ideal medium for perfusion imaging. This is thought to be useful for monitoring of anti-angiogenic or anti-vascular cancer therapies (8).

**Aim**

The aim of this study is see if altered liver blood flow readings obtained from DCE-US will predict and monitor response in patients undergoing SIRT treatment for liver metastases.
Methods and materials

Patients

A group of 32 patients were recruited prospectively for this study from April 2011 to September 2013. The local ethics committee approved the study protocol and informed consent was taken.

The patients had a median age of 61.5 years (Range 31-79 years). There were 15 males and 17 females. 19 of the patients received only SIRT while 13 of the patients received a combination of SIRT and chemotherapy.

DCE-US Protocol

All patients were scanned at baseline, after pre-SIRT treatment embolisation and 2 weeks after SIRT treatment.

The patients were fasted for at least 4 hours prior to DCE-US. The contrast agent used was Sonovue®, a 2nd generation microbubble agent which consists of a phospholipid shell and a core of inert sulphur hexafluoride gas. The agent was prepared by mixing 25 mg of the lyophilized powder with 5 mL of saline, in accordance to the manufacturer's directions. A 1mL bolus was injected via an intravenous cannula placed on the patient's wrist or cubital fossa.

All patients were placed in a supine position and imaged using an iU22 ultrasound machine (Philips, Bothwell, USA) with a C5-1 curvy-linear transducer. The contrast-specific US imaging mode (Figure 1) was activated. (A dual-screen view that displays a contrast only image on one side and a low mechanical index B-mode image on the other to aid anatomical guidance.) Power modulation was used with a 1.7-MHz center frequency at a mechanical index of 0.06. The gain was set at 88% (default value) and the dynamic range was set at 50 dB (maximum value available).

2 separate cine-loops of 90 seconds duration were acquired. The first loop focused on the porta-hepatis, to allow depiction of the portal vein and hepatic artery. The second loop focused on an image plane, which would include a tumour (2-4 cm) and normal liver parenchyma. The obtained image-loops were transferred to a personal computer for further analysis (Figure 2) with QLAB software (Philips Healthcare).

Image analysis
In the image loops, region of interests (ROI) were drawn over the hepatic artery (HA), portal vein (PV), normal liver parenchyma (L) and tumour (T) (Figure 3 & 4). Respiratory gating was performed. Frames where the ROI were out of plane were deleted from analysis. Different subsets of frames were used for the different ROIs as the investigated regions could be out of plane at different time points. Active motion compensation was used when necessary to correct motion artefacts.

Time intensity curves (TIC) proportional to the microbubble concentration were plotted for each ROI. The following parameters were obtained: Rise time (RT), Peak intensity (PI), Wash in slope (WIS) and area under the curve (AUC) (Figure 5). Other than the macrovasculature, these parameters had also been shown experimentally to represent flow in the microvasculature (9).

In addition, the flow rates (FR) of HA and PV were defined by PI x WIS. Contrast enhanced hepatic perfusion index (CEPHI) was expressed as a ratio of HA flow rate over PV flow rate.

\[ \text{CEPHI} = \frac{(FR)_{HA}}{(FR)_{PV}} \]

Baseline TIC parameters were correlated with progression free survival (PFS) and overall survival (OS) of the patients.

**RECIST assessment**

All patients had a contrast enhanced CT scan of the abdomen and pelvis (Arterial and porto-venous phases) performed before the start of the treatment, ranging from 1 day before treatment to 7 weeks before treatment. All patients had their first post treatment scan ranging from 3 to 12 weeks post SIRT.

Local evaluation of the liver tumours was performed using RECIST 1.1. In every patient, the combined longest diameter (LD) of the 2 largest and best-marginated lesions was taken for comparison.

The patient was deemed to have:

Complete response (CR) if no more liver lesion was present after treatment. Partial response (PR) if the combined LD was <30% when compared to previous study. Stable disease (SD) if the combined LD did not decrease <30% or increase >20% of previous study. Progressive disease (PD) if the combined LD was >20%. For the purpose of this
study, extra-hepatic disease was not taken into consideration for RECIST grading as treatment response of the liver metastases was the main focus.

Patients with CR, PR and SD were all taken as responders. Patients with PD were taken as non-responders.

<table>
<thead>
<tr>
<th>Responders</th>
<th>Non-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response, partial response and stable disease (CR, PR and SD)</td>
<td>Progressive disease (PD)</td>
</tr>
</tbody>
</table>

**Classification of responders and non-responders**

**Statistical Analysis**

The TIC parameters measured in the hepatic artery, portal vein as well as tumour and normal liver parenchyma at different time points were compared for both responders and non-responders using paired non-parametric Wilcoxon matched pairs signed rank test. Comparison in TIC parameters between responders and non-responders were made using unpaired non-parametric Mann Whitney test (Prism 6.01; GraphPad Software, San Diego, CA). P < 0.05 was considered statistically significant.
Fig. 1: Dual screen contrast specific US mode showing enhancement of a hyper-vascular liver tumor (Right). The tumor is seen as a hypo-echoic lesion on the B-mode ultrasound (Left).

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Fig. 2: DCE-US analysis of a liver tumor in arterial, porto-venous and delayed phases. The derived time-intensity curve (TIC) is in the lower half of the image.

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Fig. 3: ROIs drawn over the portal vein (Yellow) and hepatic artery (Red)

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Fig. 4: ROIs drawn over tumour (Red) and normal liver (Yellow). The ovoid purple marking indicates the position of the diaphragm and is used for the purpose of respiratory gating.

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**Fig. 5:** Time intensity curves (TIC) representations of the hepatic artery (Red) and portal vein (Yellow). Peak Intensity (PI): Maximum local density value. Rise time (RT): time the intensity took to increase from 5% of peak intensity to 95% of peak intensity. Wash in slope (WIS): 0.95 peak intensity - 0.05 peak intensity. Area under the curve (AUC): Quantification of blood volume.

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Results

First post treatment CT scan

By RECIST classification, there were 28 responders and 4 non-responders.

Flow rates

DCE-US flow rates at baseline, post embolisation and 2 weeks post SIRT therapies of responders are shown in Table 1.

In responders, there was a general increase in HA, PV and tumour flow rates post embolisation.

2 weeks post SIRT, the flow rates in HA and PV remained increased. There was however a reduction in tumour flows.

Baseline hepatic artery TIC parameters

The baseline hepatic artery flow rates of responders were significantly higher than non-responders (1428 +/- 529 vs. 20 +/- 12, p= 0.02). TIC parameters such as PI, WIS and AUC were also significant higher (Figure 6).

A baseline high HA flow rate was 89% accurate in predicting responders.

Tumour blood flow TIC parameters

There was no significant difference in tumour flow parameters between responders and non-responders.

Post SIRT portal vein TIC parameters

In responders, there was a significant increase in the portal vein flow rate 2 weeks post SIRT when compared to baseline (74 +/- 28 vs. 2714 +/- 1115, p= 0.02). TIC parameters of PI and WIS also showed significant increase (Figure 7).
CEPHI is the ratio of HA flow rate over PV flow rate. There was a significant reduction in CEPHI for responders 2 weeks post SIRT when compared to baseline (15 +/- 5 vs. 60 +/-23, p=0.04) (Table 2 & Figure 8)

**Predicting survival**

Patients who showed a 10% decrease in CEPHI 2 weeks post SIRT when compared to baseline had significantly prolonged progression free survival (PFS) and overall survival (OS) (Figure 9).

Patients who showed a 30% decrease in total liver flow rate 2 weeks post SIRT when compared to baseline had significantly prolonged OS (Figure 10).
Table 1: DCE-US flow rates of Responders at baseline, post embolisation and 2 weeks post SIRT
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Fig. 6: Graphical representation of Hepatic artery TIC parameters and flow rate (unpaired Mann Whitney test), Responders vs Non-responders
**Fig. 7:** Graphical representation of portal vein TIC parameters and flow rate of responders (Wilcoxon matched pairs), baseline vs 2 weeks post SIRT

<table>
<thead>
<tr>
<th>Flow</th>
<th>Baseline Mean ± SE</th>
<th>Post Embolisation Mean ± SE</th>
<th>2W SIRT Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEHPI</td>
<td>59.9 ± 23.3</td>
<td>62.7 ± 41.4</td>
<td>15.2 ± 4.6</td>
</tr>
</tbody>
</table>

**Table 2:** CEPHI of responders at baseline, post embolisation and 2 weeks post SIRT
**Fig. 8:** Graphical representation of CEPHI in responders (Wilcoxon matched pairs), baseline vs 2 weeks post SIRT

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**Fig. 9:** PFS & OS survival curves based on 10% reduction in CEPHI at 2 weeks from Baseline

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**Fig. 10:** PFS & OS survival curves based on 30% reduction in liver flow rate at 2 weeks from Baseline

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Conclusion

DISCUSSION

A high baseline hepatic artery flow rate accurately predicts 89% of the responders. Metastatic hepatic tumours are supplied almost exclusively by the hepatic artery. We postulate that a high hepatic artery flow rate will translate to a very robust supply to the metastatic lesions and such lesions are more likely to respond better to SIRT treatment. This is supported by the work of Dancey et al. (10), which found that "hot" lesions on a Tc-99m MAA scan responded better than "cold" lesions to radioembolism treatment.

Leen et al. (11) had previously demonstrated the use of Doppler flow rate (DFR) and Doppler perfusion index (DPI) in detecting colorectal metastases. Patients with colorectal liver metastases typically show an increased HA flow, a decrease in PV flow or both (i.e. a raised DPI). We postulate that a significant reduction in tumour burden would reverse this effect. Given that CEPHI is analogous to DPI, the increase in PV flow and decrease in CEPHI of responders seen in our results are interesting but not unexpected phenomena.

DCE-US was not only useful in predicting response before the commencement of SIRT treatment and early into treatment (2 weeks). A reduction in CEPHI and liver flow rate had shown significantly prolonged survival. These results are encouraging and demonstrated the potential use of DCE-US in SIRT treatment response assessment and monitoring.

SUMMARY

Baseline DCE-US measurement of hepatic arterial flow accurately predicts responders to SIRT. Responders shows significantly increased portal vein flow and reduced CEPHI at 2 weeks.

A reduction in CEHPI at 2 weeks correlates with prolonged PFS and OS while a reduction in liver blood flow at 2 weeks correlates with prolonged OS.
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