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## The Liver INSPECTR Trial: Towards improved understanding of liver function following radiotherapy

Nicholas G. Hardcastle

*University of Wollongong, Peter MacCallum Cancer, nhardc@uow.edu.au*

Carol Haddad

*Royal North Shore Hospital*

G Schembri

*Royal North Shore Hospital*

D Bailey

*Royal North Shore Hospital*

B Jones

*Royal North Shore Hospital*

*See next page for additional authors*

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### Abstract

Liver stereotactic ablative body radiotherapy (SABR) is an emerging treatment option for primary liver cancer and liver metastases. Liver SABR can provide high rates of local control however tumour doses are limited by dose to surrounding organs at risk including liver and gastrointestinal structures. Dose limits to liver are based on anatomical liver, without understanding of underlying liver function. This report describes a prospective clinical trial which measures the spatial variance of liver function through Tc-99m Mebrofenin SPECT in the context of liver SABR.

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### Authors

Nicholas G. Hardcastle, Carol Haddad, G Schembri, D Bailey, B Jones, Adam Briggs, George Hruby, and Andrew Kneebone

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# The Liver INSPECTR Trial: Towards improved understanding of liver function following radiotherapy

N Hardcastle<sup>1,2</sup>, C Haddad<sup>3</sup>, G Schembri<sup>4</sup>, D Bailey<sup>4</sup>, B Jones<sup>5</sup>, A Briggs<sup>3</sup>, G Hruby<sup>3</sup> and A Kneebone<sup>3</sup>

<sup>1</sup>Department of Physical Sciences, Peter MacCallum Cancer, VIC, Australia

<sup>2</sup>Centre for Medical Radiation Physics, University of Wollongong, NSW, Australia

<sup>3</sup>Northern Sydney Cancer Centre, Royal North Shore Hospital, NSW, Australia

<sup>4</sup>Department of Nuclear Medicine, Royal North Shore Hospital, NSW, Australia

<sup>5</sup>Department of Hepatology, Royal North Shore Hospital, NSW, Australia

E-mail: [nick.hardcastle@petermac.org](mailto:nick.hardcastle@petermac.org)

**Abstract.** Liver stereotactic ablative body radiotherapy (SABR) is an emerging treatment option for primary liver cancer and liver metastases. Liver SABR can provide high rates of local control however tumour doses are limited by dose to surrounding organs at risk including liver and gastrointestinal structures. Dose limits to liver are based on anatomical liver, without understanding of underlying liver function. This report describes a prospective clinical trial which measures the spatial variance of liver function through Tc-99m Mebrofenin SPECT in the context of liver SABR.

## 1. Introduction

There is an emerging body of evidence suggesting stereotactic ablative body radiotherapy (SABR) is an effective localised treatment modality for primary cancers of the liver and liver metastases. Recent reports suggest SABR results in comparable local control and quality of life outcomes compared with other localised treatment modalities [1]. SABR involves the delivery of a highly conformal high dose of radiotherapy in a small number of treatment sessions, typically 3-6. Dose is minimised to healthy liver to reduce risk of radiation induced liver disease (RILD). Frequency of RILD is low 1-5% with modern constraints however, more relevant is deterioration in liver function, for example by increasing Child-Pugh score by 2 or more which can be in the order of 30% [2]. Liver function end points and their dependence on radiation dose have been measured previously using global liver function tests. Mean liver dose has been linked to liver function decline, as well as dose to 700 ml of liver [3]. These liver function dose-responses however have been derived from anatomical liver [3]. Patients however often have multiple co-morbidities that render sections of the liver non-functional, thus dose-response data is clouded by the fact that the radiotherapy dose may have been delivered to non-functional liver [3].

Tc-99m mebrofenin SPECT imaging procedure allows evaluation of global and local liver function [4]. Mebrofenin, bound to albumin, is taken up by hepatocytes in a similar manner to organic anions such as bilirubin [5]. SPECT imaging with corresponding CT allows visualisation of the local liver function with respect to anatomy [5-8]. Measurement of regional liver function in the context of liver SABR has the potential to further refine dose-volume predictors of RILD and provide insight into liver function deterioration and recovery post-treatment. Moreover, if liver function is known on a

local basis we may be able to spare highly functional liver more than we do currently through advanced optimisation and delivery methods such as volumetric modulated arc therapy (VMAT) [9].

This work describes the results obtained from the first four patients enrolled in a prospective observational trial investigating the role of Tc-99m Mebrofenin SPECT in liver SABR for both measurement of pre-SABR liver function and change of liver function as a result of SABR.

## 2. Materials and Methods

Liver function Investigation with Single Photon Emission Computed Tomography after Radiotherapy (Liver INSPECTR) is a Phase I pilot study investigating Tc-99m Mebrofenin SPECT in the context of liver SABR. The primary endpoint of the study is to evaluate the pattern of local and global liver function as demonstrated on Tc99m mebrofenin SPECT before and after liver SABR. Patients who are to receive SABR for treatment of primary liver cancer or liver metastases are eligible for the study. Participants receive a Tc-99m Mebrofenin SPECT-CT image at time of CT simulation, and at 1 and 6 months post SABR treatment.

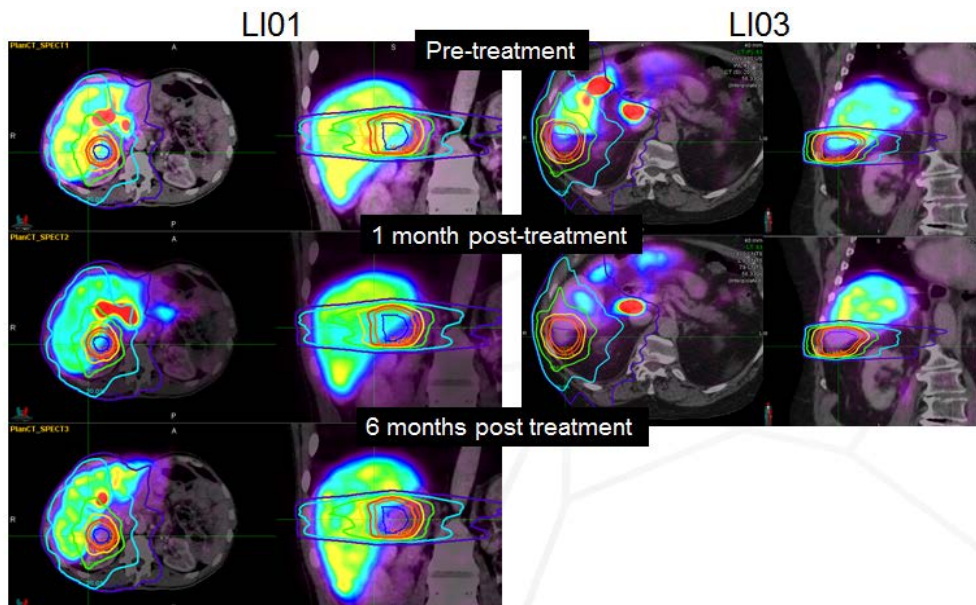
SABR treatment planning 4DCTs were acquired and the treatment plan was performed on the average of the 4DCT, using an internal target volume (ITV) to account for tumour motion due to respiration. A 5 mm ITV-PTV isotropic margin was applied. Treatment planning was performed using VMAT, with an isotoxic prescription regime used; 50 Gy in 5 fractions is prescribed initially. If liver dose constraints were not met, the dose was reduced in 2.5 Gy increments until the liver dose constraints were met. The Tc-99m Mebrofenin SPECT-CT scans were acquired with a low dose 3DCT followed by acquisition of dynamic planar scintigraphy with SPECT on a Siemens Symbia SPECT-CT. For SPECT imaging the radiotherapy treatment planning position was replicated as close as possible to improve spatial correlation between SPECT-CT and radiotherapy treatment planning CT geometry.

The CT component of the SPECT-CT at each time point was rigidly registered to the treatment planning CT based on a best match of anatomical landmarks within the liver and the liver border in the vicinity of the tumour. The same rigid registration was applied to the SPECT image data, to result in SPECT data in the same frame of reference as the treatment planning CT, structures and dose. For each SPECT image, the total SPECT counts in non-tumour liver in each radiotherapy isodose bin from 0-50 Gy in 5-10 Gy increments was measured, and normalised to the total counts in the liver. The relative difference in the contribution to total liver function at each post-treatment time point to the pre-treatment time point was computed.

## 3. Results

Four of a planned 20 patients have consented to participate and have undergone pre-SABR SPECT imaging, ICG and elastography examinations. Two patients have completed 1 month and one patient has completed 6 month post-treatment imaging. Figure 1 shows the pre, and post treatment SPECT images for patients 1 and 3. Visual inspection of the pre and 1 month post-treatment SPECT images show decreased uptake in irradiated volumes at the 1 month time point. The 6 month time point for patient #1 shows slightly increased liver function compared with the 1 month time point in the low dose areas.

The contribution of normal liver receiving 5-50 Gy to the total liver function was analysed for patient #1. Figure 2 shows a decrease in contribution to liver function with increasing dose, the magnitude of which increased at the 6 month time point. A maximum of 41% reduction in liver function was observed at 6 months in the liver receiving 40-50 Gy. A potential compensatory increase in liver function in liver receiving less than 5 Gy was observed. It should be noted the total contribution of these liver volumes to the total liver function in the high dose regions is small; the 40-50 Gy volume contributed only 1.5% of the total liver function pre-treatment. This is a consequence of the SABR treatment technique, which has a very sharp dose fall off outside of the tumour which reduces dose to surrounding non-tumour liver.

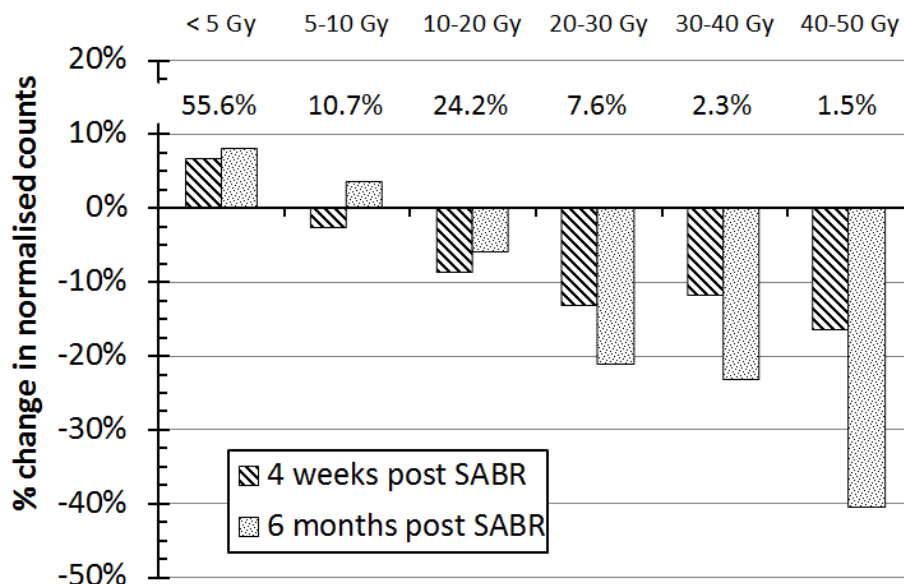


**Figure 1.** Pre-treatment, 1 month and 6 months post treatment  $^{99m}\text{Tc}$  Mebrofenin SPECT scans for patients #1 and #3. Blue contours are the gross tumour volume. From orange to blue, the lines represent the 50, 40, 30, 20, 10 & 5 Gy isodose lines. The colourmap of the SPECT images have been normalised based on total liver counts.

#### 4. Discussion

The current trial aims to improve understanding of liver function prior to and post-SABR by using a nuclear medicine tracer that is almost exclusively taken up by hepatocytes. There is a potential role for Tc- $^{99m}$  Mebrofenin SPECT in liver SABR pre-treatment in both primary liver cancer patients and patients with liver metastases from other cancers. Patients with primary liver cancer typically have heterogeneous liver function. Hepatocellular carcinoma however exhibits no dose response, that is, a high tumour dose is not necessarily required for tumour control [10]. The primary aim is thus to deliver sufficient dose to control the tumour whilst preserving liver function. Functional imaging may provide means to spare the highest quality regions of the liver. Patients with liver metastases will often have good liver function but are often undergoing multiple interventions prior to SABR such as surgery, transarterial-chemo-embolisation or radiofrequency ablation, which can reduce the volume of functional liver. Moreover liver metastases require a high biologically equivalent dose to achieve tumour control [10], and may present with multiple liver metastases. In this case pre-treatment functional imaging may provide a method to ensure sufficient future remnant liver after treatment.

The main limitation in the current workflow is registration uncertainties. The planning CT is an average of a 4DCT acquired on a flat couch top, whereas the CT component of the SPECT-CT is a snapshot on a curved couch-top. Rigid registration is a very good first approximation, given the small volumes involved in SABR planning, but residual uncertainties will still remain due to patient posture and inclusion of some blur due to breathing in the 4DCT. The SPECT image data however is acquired over a longer period of time (10 minutes), thus has respiratory motion blur contained in the image which should match the 4DCT average.



**Figure 2.** The change in contribution to the total liver function of the non-tumour liver receiving 5-50 Gy for patient #1. The percentages above each column pair are the pre-treatment contribution of each volume to the total liver function.

## 5. Conclusion

The Liver INSPECTR trial incorporates novel functional imaging to improve understanding of radiation effects on functional liver in the context of liver SABR. Initial results show reduction of liver function in regions of liver that receive high doses. Future work will further measure patient-specific changes in liver function post-SABR, and determine whether pre-treatment functional imaging can be incorporated into treatment planning to reduce dose to high functioning liver.

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