Short communication: timeline of radiation-induced kidney function loss after stereotactic ablative body radiotherapy of renal cell carcinoma as evaluated by serial 99mTc-DMSA SPECT/CT

Price Jackson1, Farshad Foroudi2,3, Daniel Pham4, Michael S Hofman5, Nicholas Hardcastle1,6, Jason Callahan5, Tomas Kron1 and Shankar Siva2,3*

Abstract
Background: Stereotactic ablative body radiotherapy (SABR) has been proposed as a definitive treatment for patients with inoperable primary renal cell carcinoma. However, there is little documentation detailing the radiobiological effects of hypofractionated radiation on healthy renal tissue.

Findings: In this study we describe a methodology for assessment of regional change in renal function in response to single fraction SABR of 26 Gy. In a patient with a solitary kidney, detailed follow-up of kidney function post-treatment was determined through 3-dimensional SPECT/CT imaging and 51Cr-EDTA measurements. Based on measurements of glomerular filtration rate, renal function declined rapidly by 34% at 3 months, plateaued at 43% loss at 12 months, with minimal further decrease to 49% of baseline by 18 months.

Conclusions: The pattern of renal functional change in 99mTc-DMSA uptake on SPECT/CT imaging correlates with dose delivered. This study demonstrates a dose effect relationship of SABR with loss of kidney function.

Keywords: Stereotactic radiation, Renal cell carcinoma, Primary kidney cancer, Functional imaging, Single photon emission tomography

Findings
Introduction
Stereotactic ablative body radiotherapy (SABR) is an emerging treatment option for inoperable primary renal cell carcinoma (RCC) in both preclinical [1,2] and early clinical trials [3]. Local control rates above 90% have been reported [4–7] and side effects are usually well tolerated [4,8–10]. It is believed that treatment delivered in a single fraction may deliver potent dose effects due to radiation-induced vascular damage, which may prove valuable in the control of radioresistant tumour strains [11]. This effect may have equal consequence in both malignant and healthy tissue; of particular concern for functional renal cells where protracted vascular damage due to ionising radiation may have a significant latent period before manifesting the effects of injury.

There is limited prospective data of renal impairment after SABR to the kidney [3]. Dose–response relationships in this context have been thought to be mitigated by the precision delivery of radiation which may largely spare substantial amounts of renal parenchyma [12,13]. However, no report to date has reported follow-up with accurate functional imaging assessment of both global kidney function using calculated glomerular filtration rate (GFR) and regional kidney function (using DMSA SPECT/CT).
This study presents a preliminary assessment methodology to identify radiation dose effects to renal tissue for a patient receiving single-fraction SABR to a patient with a solitary kidney with primary renal cell carcinoma. Local dose effects to healthy renal tissue are tracked through serial functional SPECT/CT imaging and correlated with radiation dose prescription from treatment planning. This data represents a detailed report of local radiobiological changes following this form of hypofractionated therapy where dose effects are evaluated not just on biochemical markers (GFR & serum creatinine) but through measures of tissue function in 3-dimensional nuclear medicine studies.

Methodology
As part of an independent research board approved prospective clinical trial (clinicaltrials.gov ID NCT01676428), a 42 year old patient was enrolled with an incidentally discovered enlarging primary left renal RCC in a solitary kidney. This patient had been previously treated with orchiectomy, retroperitoneal lymph node dissection and BEP chemotherapy at the age of 19 for a non-seminomatous germ cell tumour. In 2007, he subsequently underwent a right nephrectomy removing two T1a RCCs. In 2012, the new left solitary kidney mass was biopsy confirmed as clear cell carcinoma, measured $38 \times 34 \times 30$ mm on CT imaging, and was situated in the midpole. This patient had renal impairment with an eGFR of 48 ml/min (creatinine 149 $\mu$mol/L). The patient was otherwise fit, ECOG performance status of 0, and continued to work full time and exercised daily. A partial nephrectomy was thought not to be technically achievable, and a total nephrectomy would have necessitated immediate dialysis. The lesion was located adjacent to the renal pelvis in contact with renal vessels and ureter, and thought not suitable for radiofrequency ablation. In 2012, he was enrolled as a study participant and underwent a single fraction of SABR (26 Gy) for his solitary left kidney RCC. The radiotherapy plan was generated using a 3D conformal technique with only co-planar beams in the same axial plane in order to avoid beams entering and exiting the superior and inferior poles of the kidney and spare this renal parenchyma (Figure 1). The dose was prescribed to the 80% isodose, ensuring that prescription dose encompassed 99% of the target volume. Radiotherapy was delivered on a Varian Clinac 21iX linear accelerator (Varian Medical Systems, Palo Alto, United States) incorporating vacuum immobilisation with an Elekta BodyFIX device (Elekta Medical Intelligence, Stockholm, Sweden) as previously published [14,15]. Serial nuclear medicine assessments were performed.

SPECT imaging & glomerular filtration rate
$^{99m}$Tc-DMSA SPECT/CT images (200 MBq injected activity) and GFR by $^{51}$Cr-EDTA plasma clearance were recorded concurrently at baseline (1 month pre-treatment), and at 2-weeks, 3-, 12-, & 18-months post SABR. Regional renal function was quantified based on measured GFR and total counts in the volume-of-interest comprising the kidney on SPECT imaging. Each voxel’s contribution to total renal function [GFR: (ml/min) per ml tissue] was then calculated based on that scaling factor. The quantified voxel values were compared between baseline and follow-up scans in order to calculate change in local renal function according to prescribed isodose region from the radiotherapy treatment plan.

SPECT images were coregistered to the pre-therapy planning CT and dose prescription image sets. Fused SPECT/CTs were aligned by deformable registration of anatomical, CT volumes with the MIM software package (version 6.1, MIM Software Inc, Cleveland OH, USA). Planning structures were utilised for segmentation of healthy renal tissue [Kidney minus Internal Target Volume (ITV)] [16]. Healthy renal tissue was then differentiated based on radiation isodose zone in 1 Gy increments to record mean counts and volume per zone and identify a dose/response relationship.

Results
At 18 months post treatment, the patient’s disease is controlled after single-fraction ablative radiotherapy. The positioning of treatment fields within the axial plane permitted the sparing of substantial volumes of renal tissue at the superior and inferior limits of the kidney volume. $^{99m}$Tc-DMSA SPECT/CT scans indicate that renal cortical function is spared to regions with prescribed radiation doses.

Figure 1 Axial images of renal carcinoma a) on baseline planning CT, b) pre-therapy T2-weighted MRI, & c) T2 MRI at 18 months post-SABR.
absorbed dose values below approximately 13 Gy (50% of the prescription dose). In this patient, 60% of tissue was spared appreciable deterioration in regional function, in line with the 13 Gy isodose volume as seen in Figure 2. A modest decline in $^{99m}$Tc-DMSA uptake is observed at 2-weeks & 3 months post-therapy for high-dose regions. It is apparent from late follow up scans, however, that evidence of radiation induced injury may be delayed for up to a year (Figure 3). Ongoing evolution of dose dependent loss in renal perfusion is demonstrated at 12 months post treatment. At 12 & 18 months the pattern of tracer uptake closely matches the spared dose zones from treatment planning. Minimal decline in perfusion and GFR were observed beyond one year and at a rate that is consistent with the trajectory of progressive chronic kidney disease as previously described by Demirjian et al. [17], (Figure 3b).

From a clinical perspective, the patient continues to work full-time, has an ECOG performance status of 0, and continues to lead a productive lifestyle. He is asymptomatic from his decline in renal function with no significant clinical toxicity.

Discussion
In this study we find both imaging and biochemical data suggest that dose effects to healthy renal tissue continue to evolve beyond three months after SABR but may stabilise at approximately one year post treatment. In spite of this patient’s previous nephrectomy, platinum-based chemotherapy, and retroperitoneal surgery which contributed to pre-treatment renal dysfunction, the delivery of hypofractionated ablative radiotherapy to the centrally-located tumour in remaining kidney has spared a sufficient volume of functional tissue for the patient to remain free from dialysis.

It is evident that functional nuclear medicine imaging can be informative for assessing normal tissue effects in ablative radiotherapy for renal cell carcinoma. In this instance, DMSA perfusion has been utilised as a surrogate for local renal function. 3-dimensional $^{99m}$Tc-DMSA SPECT/CT images have indicated that function loss occurs primarily to regions receiving an absorbed dose $>13$ Gy which corresponds to 50% of the prescription dose and higher in this instance. Whether functional loss within the...
intermediate to high dose region is clinically consistent across a broader population of patients is yet to be confirmed.

Conclusion
Single fraction SABR shows promise as viable treatment option for inoperable primary RCC with significant sparing of renal parenchyma in a patient treated with a solitary kidney, although longer-term follow-up is awaited. For the patient reported in this case study, a single-fraction threshold of <13 Gy results in preserved local renal function, with a significant dose/effect relationship at intermediate to high dose ranges (13–25 Gy). This finding requires further validation from multiple patients to confirm the radiation tolerance of renal parenchyma.

Abbreviations
DMSA: Dimercaptosuccinic acid; ECOG: Eastern Cooperative Oncology Group; EDTA: Ethylenediaminetetraacetic acid; GFR: Glomerular filtration rate; ITV: Internal target volume; RCC: Renal cell carcinoma; SABR: Stereotactic ablative body radiotherapy.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
PJ carried out analysis of functional images. FF & SS oversaw patient management and study design. DP was involved with treatment planning and analysis of dose response. MH evaluated functional images and aided in semi-quantitative methodology for analysing SPECT data. NH validated and analyzed the data. WJ carried out analysis of functional images. All authors read and approved the final manuscript.

Author details
1Department of Physical Sciences, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia. 2Department of Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia. 3Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, VIC, Australia. 4Department of Radiotherapy, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia. 5Department of Cancer Imaging, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia. 6Department of Oncology, University of Melbourne, Parkville, VIC, Australia. 74Department of Physical Sciences, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia. 8Department of Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia. 9Department of Cancer Imaging, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia. 10Centre for Medical Radiation Physics, University of Wollongong, Wollongong, NSW, Australia.

Received: 6 June 2014 Accepted: 5 November 2014
Published online: 26 November 2014

References
1. Walsh L, Stanfield JL, Cho LC, C-H C, Forster K, Kabbani W, Cadeddu JA, Hsieh JT-T, Chey H, Timmerman R, Lotan Y: Efficacy of ablative high-dose-per-fraction radiation for implanted human renal cell cancer in a nude mouse model. Eur Urol 2006, 50:795–800.
2. Porsky LE, Crowner RL, Rosen MJ, Rodebaugh RF, Castillo EA, Brainard J, Cherullo EE, Novick AC. Initial evaluation of cyberknife technology for extracorporeal renal tissue ablation. Urology 2003, 61:408–501.
3. Siva S, Pham D, Gill S, Corcoran NM, Foroudi F: A systematic review of stereotactic radiotherapy ablation for primary renal cell carcinoma. BJU Int 2012, 110(E737–E743).
4. Wersäll PJ, Blomgren H, Lax J, Källkner K-M, Lindner C, Lundell G, Nilsson B, Nilsson S, Näslund I, Pisa P, Svedman C. Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma. Radiother Oncol 2005, 77:88–95.
5. Wersäll PJ, Blomgren H, Pisa P, Lax J, Källkner K-M, Svedman C. Regression of non-irradiated metastases after extracranial stereotactic radiotherapy in metastatic renal cell carcinoma. Acta Oncol 2006, 45:493–497.
6. Teh B, Bloch C, Galli-Guevara M, Doh L, Richardson S, Chiang S, Yeh P, Gonzalez M, Lunn W, Marco R, Jac J, Paulino A, Lu H, Butler E, Amato R: The treatment of primary and metastatic renal cell carcinoma (RCC) with image-guided stereotactic body radiation therapy (SBRT). Biomed Imaging Interv J 2007, 3:e6.
7. Nomiyi T, Tsuji H, Hirasawa N, Kato H, Kamada T, Mzzo J, Kishi H, Kamura K, Wada H, Nermoto K, Tsuji H: Carbon ion radiation therapy for primary renal cell carcinoma: initial clinical experience. Int J Radiat Oncol Biol Phys 2008, 72(8):828–833.
8. Svedman C, Karlsson K, Rutkowski E, Sandström P, Blomgren H, Lax J, Wersäll P: Stereotactic body radiotherapy of primary and metastatic renal lesions for patients with only one functioning kidney. Acta Oncol 2008, 47:1578–1583.
9. Svedman C, Sandström P, Pisa P, Blomgren H, Lax J, Källkner K-M, Nilsson S, Wersäll P: A prospective Phase II trial of using extracranial stereotactic radiotherapy in primary and metastatic renal cell carcinoma. Acta Oncol 2008, 45:870–875.
10. Hartke O, Porsky L: Renal radiotherapy. In New Technologies in Urology. Volume 7. Edited by Daigle P, Fitzpatrick J, Kirby R, Gill I. London: Springer; 2010:155–159 (New Techniques in Surgery Series).
11. Song CW, Cho LC, Yuan J, Dusenbery KE, Grilli RJ, Levitt SH: Radiobiology of stereotactic body radiation therapy/stereotactic radiosurgery and the linear-quadratic model. Int J Radiat Oncol Biol Phys 2013, 87:18–19.
12. Dawson LA, Kavanagh BD, Paulino AC, Das SK, Mitten M, Li XA, Fan C, Ten Haken RK, Schultze TJ: Radiation-associated kidney injury. Int J Radiat Oncol Biol Phys 2010, 76:5108–5115.
13. Lo SS, Sahgal A, Chang EL, Mayr NA, Teh BS, Huang Z, Schefter TE, Yao M, Machty A, Slotman BJ, Timmerman RD: Serious complications associated with stereotactic ablative radiotherapy and strategies to mitigate the risk. Clin Oncol 2013, 25:378–387.
14. Pham D, Thompson A, Kron T, Foroudi F, Kolsky MS, Devereux T, Lim A, Siva S: Stereotactic ablative body radiation therapy for primary kidney cancer: a 3-dimensional conformal technique associated with low rates of early toxicity. Int J Radiat Oncol Biol Phys. Advanced online publication. doi:10.1016/j.ijrobp.2014.07.043.
15. Pham D, Kron T, Foroudi F, Siva S: Effect of different breathing patterns in the same patient on stereotactic ablative body radiotherapy dosimetry for primary renal cell carcinoma: a case study. Med Dosim 2013, 38:304–308.
16. Morgan-Fletcher SL: Prescribing, recording and reporting photon beam therapy (Supplement to ICRU Report 50), ICRU Report 87. ICRU, pp. ix+52, Springer; 2010:155–159 (New Techniques in Surgery Series).
17. Inclusion in PubMed, CAS, Scopus and Google Scholar
18. Thorough peer review
19. No space constraints or color figure charges
20. Immediate publication on acceptance
21. Research which is freely available for redistribution

Cite this article as: Jackson et al.: Short communication: timeline of radiation-induced kidney function loss after stereotactic ablative body radiotherapy of renal cell carcinoma as evaluated by serial 99mTc-DMSA SPECT/CT. Radiation Oncology 2014 9:253.
Author/s:
Jackson, P; Foroudi, F; Pham, D; Hofman, MS; Hardcastle, N; Callahan, J; Kron, T; Siva, S

Title:
Short communication: timeline of radiation-induced kidney function loss after stereotactic ablative body radiotherapy of renal cell carcinoma as evaluated by serial Tc-99m-DMSA SPECT/CT

Date:
2014-11-26

Citation:
Jackson, P., Foroudi, F., Pham, D., Hofman, M. S., Hardcastle, N., Callahan, J., Kron, T. & Siva, S. (2014). Short communication: timeline of radiation-induced kidney function loss after stereotactic ablative body radiotherapy of renal cell carcinoma as evaluated by serial Tc-99m-DMSA SPECT/CT. RADIATION ONCOLOGY, 9 (1), https://doi.org/10.1186/s13014-014-0253-z.

Persistent Link:
http://hdl.handle.net/11343/263455

File Description:
Published version

License:
CC BY