CyberKnife for inoperable renal tumors: Canadian pioneering experience

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Introduction: *Stereotactic ablative body radiotherapy (SABR) is currently under study regarding its clinical application in management of patients with kidney tumors. CyberKnife can accurately deliver ablative tumor radiation doses while preserving kidney function. We report Canada's first use of CyberKnife SABR system in treating primary kidney tumors.*

Materials and methods: *Between January 2011 and February 2012, we treated three patients with renal tumors using CyberKnife SABR. Two patients had tumors in solitary kidney. The third patient had a recurrent tumor after two previous radiofrequency ablation treatments. Platinum seed fiducials were used for real time tumor tracking. Magnetic resonance imaging registration was used for tumor delineation in all cases. The patients were followed with regular renal scans and renal function tests.*

Results: *The mean age was 79 years. Mean tumor size was 21.3 cm^3. A dose of 39 Gy in 3 fractions was delivered. The post treatment follow up times were 15 months, 13 months and 12 months. Local control was obtained in all three patients. No acute or chronic toxicity was reported. Kidney functions remained unaffected after treatment.*

Conclusion: *CyberKnife is technically feasible for treatment of medically inoperable renal tumors or tumors in a solitary kidney.*

Key Words: CyberKnife, kidney tumors

Introduction

One in 59 Canadian men and 1 in 92 Canadian women have a life time probability of developing kidney cancer.[1] The overall incidence of renal cell carcinomas (RCCs) has been steadily increasing by 2% per year, partly due to improved detection modalities like computed tomography (CT) and magnetic resonance imaging (MRI) scanning.[2,3] The main stay of treatment for RCCs is surgery.[4,5] For patients who are medically inoperable due to comorbidities, or in extremes of age, the options are limited. Recent statistics show that the number of patients in this subset is increasing and is projected to increase for the next few decades.[6] For these patients, both surveillance and the less invasive ablative modalities such as radiofrequency ablation (RFA), cryoablation (CA), high-intensity focused ultrasound (HIFU) have been used as alternatives to surgery. The evidence and experience with each of these ablative techniques is evolving. Tumors near the renal vessels and collecting system are relative contra-indications for these treatments due to the potential for injury to these normal tissues.

Conventional radiation techniques and doses are used as palliative therapy in RCC. Conventional radiation is not used as a curative treatment for RCC. This practice has stemmed from the knowledge that renal parenchyma and perirenal tissues have low radiation tolerance and also that RCCs are traditionally considered to be radioresistant. But clonogenic survival assays performed at Stanford using RCC cell lines show that the cell lines showed an exponential decrease in survival at doses above 6 Gy.[7] The same tumor response were also seen in cancer patients who were treated by high dose stereotactic radiosurgery (SRS) for RCC brain metastasis with local control of > 90%.[8-13] Stereotactic ablative radiotherapy (SABR), also known as stereotactic

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body radiotherapy (SBRT) is an external beam radiation therapy method used to precisely deliver a high dose of radiation to an extra cranial target within the body, using either a single dose or small number of treatment fractions. SABR is currently under study regarding its clinical application in managing patients with renal tumors. CyberKnife based SABR has the potential to deliver accurately ablative radiation doses to kidney tumors using real time tumor tracking (RTTT) while preserving function of the remaining kidney tissue. We report the first Canadian experience regarding the technique, preliminary efficacy and safety in treating primary kidney tumors using CyberKnife SABR system.

Materials and methods

Between January 2011 and February 2012, the CyberKnife program at the Ottawa Hospital Cancer Centre has treated three patients with renal tumors using CyberKnife SABR. Two patients were medically inoperable and had tumors in a solitary kidney. The third patient was medically inoperable and had a recurrent renal cell carcinoma close to renal pelvis which had recurred after two previous radiofrequency ablation treatments.

SABR simulation, target delineation, treatment planning and delivery

In all three cases, 3 or more platinum fiducials were implanted around the tumors under ultrasound guidance for RTTT on CyberKnife treatment. In one case, CT guidance was required to insert 2 more fiducials to increase targeting accuracy. There were no complications related to the fiducial procedure in all three patients. The CyberKnife program at our center use in-house designed and fabricated platinum fiducials which are better visualized on treatment planning MRIs than gold based fiducials.[14] These fiducials are approved by Health Canada for in-house use only. Treatment planning CT (TP-CT) and MRI (TP-MRI) images were acquired at least 1 week after implantation. One week delay for treatment planning image acquisition was to allow fibroblastic reaction to develop around the fiducials to ensure the fiducials do not migrate between treatments.[15] In all cases, gadolinium enhanced TP-MRI images were registered with TP-CT scans using platinum fiducial-to-fiducial registration. Gross tumor volume (GTV) was delineated as the gross tumor visible from the CT/MRI images. A 5 mm margin was created around the GTV to generate a Planning Target Volume (PTV). The organs at risk volumes delineated included uninvolved kidney (kidney minus GTV minus RFA cavity), liver, spinal cord, large and small intestines, renal vessels, and aorta. All the SABR planning and QA

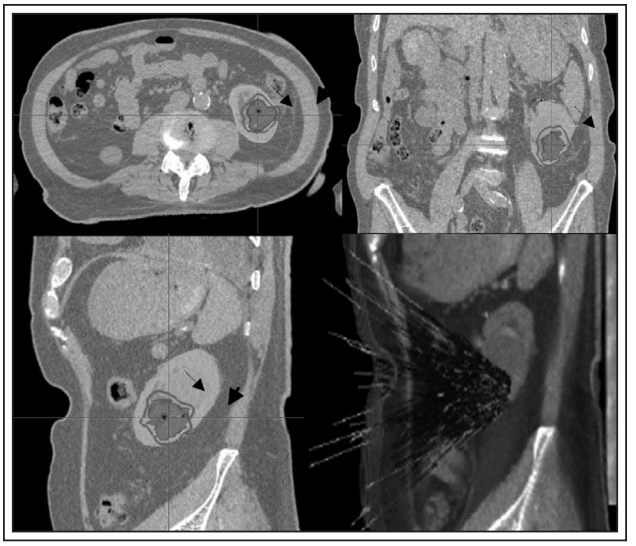

Figure 1. Nephron sparing using robotic stereotactic body radiotherapy using CyberKnife: **a)** GTV (thick arrow) covered by prescription isodose (dotted arrow); **b)** Thin radiation beams converging on the target volume, sparing the healthy kidney.

was done by two board certified physicists. Thirty-nine Gy/3 fractions was delivered to the PTV. In all patients at least 95% of the PTV received full prescription dose, Figure 1 and 2. Table 1 demonstrates the dose volume parameters used in our plans.

All three patients underwent CyberKnife treatment in 3 fractions delivered within 1 week. None of the patients received any premedication. The Synchrony® Respiratory Tracking System which are components of the CyberKnife Robotic Radiosurgery system (Accuray Inc., Sunnyvale, CA, USA), acquires multiple x-rays during the course of treatment to ensure accurate SABR to the tumor. The Cyberknife moves continuously with the tumor during the respiratory cycle to allow ablative doses of radiation to the tumor while sparing uninvolved

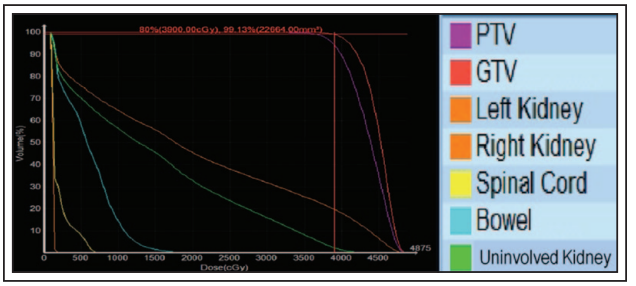

Figure 2. Dose volume histogram showing 99% coverage to the GTV and 94% coverage to PTV with good sparing of the uninvolved ipsilateral kidney.

TABLE 1. **Stereotactic ablative body radiotherapy dose volume parameters used for treatment planning**

Structure	**Dose volume constraints**
PTV	100% of PTV to receive > 95% of Rx dose Max dose to be within PTV and not within any OARs
Organ at risks (OARs)	
Liver	At least 700 mL receives < 15 Gy Mean total healthy liver dose < 15 Gy
Duodenum	Dmax 30 Gy, D (5 cc) ≤ 15 Gy
Stomach	Dmax 30 Gy, D (10 cc) ≤ 15 Gy
Small bowel	Dmax 30 Gy, D (5 cc) ≤ 16.2 Gy
Large bowel	Dmax (1 cc) 30 Gy, D (20 cc) ≤ 20.4 Gy
Healthy kidney	Right kidney V (15 Gy) < 35%;
(Kidney volume – (PTV+ RFA volume)	Total kidney V (15 Gy) < 35%
Esophagus	Dmax 27 Gy, D (5 cm^3) ≤ 21 Gy, D (10 cc) ≤ 16.2 Gy
Spinal cord	Dmax 12 Gy

PTV = planning target volume; RFA = radiofrequency ablation

normal renal tissues. The treating radiation oncologist and medical physicist were both present to ensure the most optimal image guidance with kV-stereoscopic images overlaid on the digitally reconstructed radiograph before each SABR fraction. The patients were followed with CT scans and renal function tests every 3 months, except for one patient who was on dialysis pre SABR. The recorded toxicity was assessed as per the Common Toxicity Criteria for adverse events (CTCAE) v.4.03. We also estimated the glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula in order to observe the relative changes in eGFR over time post treatment.[16] Local control was defined as radiologically stable disease or having partial or complete response as defined by the RECIST criteria.[17]

Results

The mean age was 79 (71, 82 and 87) years. Two were renal cell carcinomas and one was a transitional cell carcinoma of the right pelvis. Age adjusted Charlson's comorbidity index (CMI) of the 3 patients were 5, 6 and 6 respectively.[18] Mean GTV size was 21.3 cm^3 (GTV sizes 17.1 cm^3, 22.9 cm^3, 23.1cm^3). A dose of 39 Gy in 3 fractions was delivered for all three patients. The treatment times were 38, 46 and 25 minutes and number of beams were 123, 167 and 94 respectively. SABR treatment was well tolerated by all 3 patients. One patient experienced grade 1 nausea. There were no other acute side effects of treatment.

The post treatment follow up times were 15 months, 13 months and 12 months. Local control, defined as radiologically stable disease or partial/complete responses, was obtained in all three patients. Two patients had stable disease and one patient achieved partial response. The pre-treatment and post treatment imaging and tumor response is shown in Figure 3. No chronic toxicity was reported during the follow up period. Kidney function remained unaffected after treatment. No abnormality in serum creatinine levels and eGFR levels were noted after more than 1 year of follow up, Figure 4.

Discussion

The definitive treatment of localized RCC is surgical resection. There is increasing evidence regarding use of parenchymal sparing surgeries like partial nephrectomy for RCCs. There is less published data regarding the use of SABR in RCC patients who are unable to undergo surgery due to their comorbidities or patients with contra-indications to other ablative techniques like RFA, Table 2.[19-21]

The CyberKnife system deploys a linear accelerator mounted on an agile robot and directed under image guidance along with RTTT for stereotactic radiotherapy using non-isocentric beam delivery. Robotic SABR has the advantage over linac based SABR of providing RTTT during SABR which corrects for tumor motion during respiration by repositioning the radiation beam to the location of the moving target. In our center, RTTT is performed using Synchrony Respiratory Tracking System which is a component of the CyberKnife Robotic

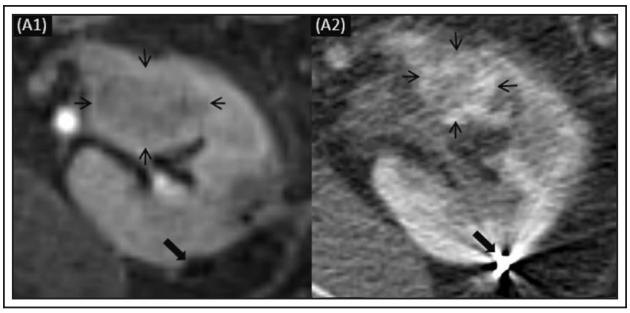

Figure 3a. Partial response demonstrated in post CyberKnife CT scan (A2) dated Nov 2012 versus pre-treatment MRI scan (A1) Feb 2011 (tumor dimensions; 18 mm x 23 mm versus 28 mm x 25 mm). Platinum fiducials indicated by thicker arrows.

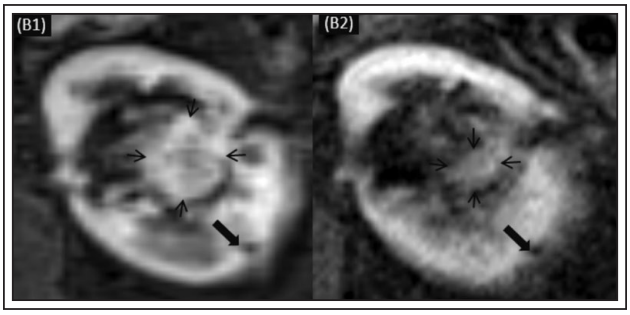

Figure 3b. Post CyberKnife CT scan of another patient dated Nov 2012 (B2) showing reduction in tumor size (tumor dimension; 8 mm versus 24 mm x 22 mm) when compared to pre-treatment MRI dated May 2011.

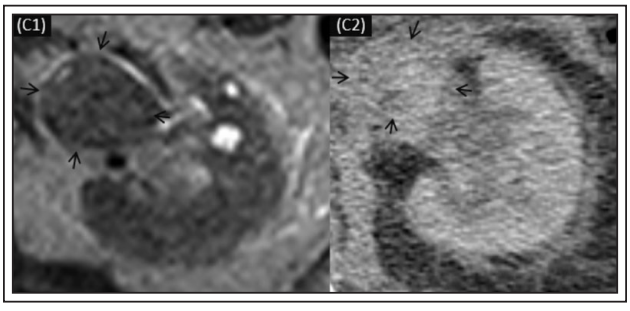

Figure 3c. Figures C1, C2 showing stability of the hilar tumor in the pre-treatment MRI dated May 2011 (C2) and post treatment (C1) CT scan dated October 2012.

Radiosurgery system (Accuray Inc., Sunnyvale, CA, USA). Using these techniques, the relationship between fiducial markers implanted in the vicinity of the tumor and the center of the tumor is identified by a CT scan in advance of treatment. Tracking is based on a measured

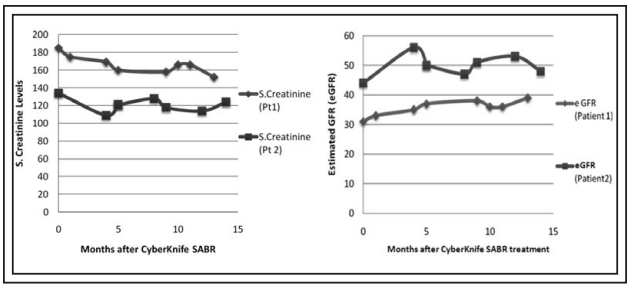

Figure 4. Post CyberKnife SABR treatment serum creatinine levels and eGFR levels showing no abnormal change after treatment.

correspondence model between internal tumor motion and external (chest/abdominal) marker motion. During treatment, using repeated x-ray imaging the position of the markers will be automatically extracted and their locations in space would be calculated prior each treatment. The Synchrony system correlates tumor motion with respiratory motion and constantly updates its correlation model with each new x-ray image, automatically correcting for any changes in the patient's breathing pattern. This continual assessment of tumor motion combined with the CyberKnife System's automatic correction for movement in real time leads to repositioning the radiation beam to the location of moving target ensuring accurate delivery of radiation doses to the target.[22]

Despite being called relatively radioresistant, brain mets from RCCs have achieved a local control rate of 96% with stereotactic radiotherapy.[13,23] Even though RCC tumor cells are resistant to low doses of conventional radiotherapy, they are responsive to high ablative doses of stereotactic radiation. Walsh et al observed marked cytological changes and sustained decrease in tumor volume in nude mouse model with human RCC cells treated using ablative hypofractionated radiotherapy to a dose of 48 Gy in 3 fractions (1 per week).[24]

Both retrospective and prospective phase I-II studies have shown high rates of local control for primary and metastatic renal cell cancers (range of 87.5%-100%) treated using ablative doses of radiation to the kidney tumor. Hypofractionated radiation therapy with less than ablative doses is associated with low tumor control rates. In our cohort, the dose rates where higher than most of the previously reported studies. There are encouraging reports of dose escalation and intensification using SABR resulting in high local control rates in RCC.[25] These studies show that the side effects were generally mild in the treated patients and the treatments were well tolerated.

Our results are in agreement with the study by

TABLE 2. **Literature review stereotactic body radiotherapy (SABR)**

Study	Design	Total dose	Fractionation	Number of patients	Outcome	Follow up
Ponsky et al[33]	Retrospective	16 Gy	4 x 4 Gy	3	33% p CR	12 mo
Beitler et al[23]	Retrospective	40 Gy	5 x 8 Gy	9	8/9 LC	26 mo
Wersall et al[35]	Retrospective	40 Gy	5 x 8 Gy	8	87.5% LC	58 mo
Svedman et al[26]	Retrospective	30-40 Gy	3-4 x 10 Gy	7	100% LC#	49 mo
Qian et al[36]	Retrospective	40 Gy	8 x 5 Gy	74	93%	10 mo
Svedman et al[37]	Prospective	20-50 Gy	Various (5-15 Gy x 2-5)	10	98%	52 mo
Kaplan et al[27]	Prospective*	21-39 Gy	3 x (7-13 Gy)	12	11/12 LC	N/A

#4 out of 7 patients died of metastatic disease
*included tumors near renal pelvis, vessels or ureter

Svedman et al regarding the role of SABR in treatment patients with RCC having only one kidney. The study showed a local control rate of 6 out of 7 patients, with mild or no change in kidney function in all patients. In two patients, the creatinine level remained moderately elevated at approximately 160 micromol/L post treatment.[26] Preliminary data from phase I studies show that SABR kidney is feasible in medically inoperable tumors with favorable tumor control rates.[27] An ongoing multi-institutional non-randomized clinical trial which studies the efficacy of CyberKnife in unresectable renal cell tumors in underway.[28]

Animal studies have shown that in the first few weeks after treatment, the tumors can grow in size temporarily (pseudo progression), however they subsequently decreased progressively to less than 30% of their initial volume. The animal data is consistent with the findings in the post-treatment CT or MRI acquired within the first 3 months following treatment, and is also noted in SABR to other sites such as liver, lung etc.[29,30] Pseudo-progression results from massive tumor cell destruction and a resultant inflammatory response. This phenomenon is not seen in all treated cases and may depend on the delivered dose and timing of the imaging scan. The post SABR response evaluation after kidney SABR has to be evaluated keeping this in mind. Also the use of dynamic multiphase imaging for response evaluation post SABR, similar to liver SABR response evaluation has to be studied further to differentiate this phenomenon with a tumor progression.[31]

Another less understood role of SABR is the possible immunomodulatory effect (abscopal effect) of this dose fractionation which leads to spontaneous regression of non-treated metastasis. Further studies are needed to elucidate this clinical phenomenon.[32]

We present the first Canadian experience in using CyberKnife SABR to treat RCCs with good sparing of adjacent ipsilateral renal parenchyma. This technique is feasible even in patients with renal tumors in solitary kidney. Despite using a high dose per fraction than most publications, the treatment was well tolerated by patients with medically inoperable RCCs, due to comorbidities or in extremes of ages. In our cohort two out of three tumors were located in solitary kidneys. The third tumor was a recurrence near the renal pelvis after two previous RFA treatments. Real-time tumor tracking using fiducials have enabled tight PTV margins and accurate delivery of ablative doses of radiation to the target with maximum sparing of surrounding organs. The use of fiducial-to-fiducial registration of CT and MRI images improve the quality of MRI based target delineation and also in defining the renal parenchyma better. The post treatment eGFR was well maintained even in patients with chronic renal dysfunction. CyberKnife SABR is also feasible in tumors approximating the renal pelvis and vasculature which is a contra-indication for RFA treatments.

Conclusion

Robotic SABR using CyberKnife is technically feasible for treatment of medically inoperable primary or metastatic renal tumors. This can also be used for treatment of patients with renal tumors located in a solitary kidney and tumors adjacent to or involving the renal pelvis. In view of the acceptable toxicity observed, a prospective phase II study is being designed at our center to study the efficacy of this technique with escalated ablative doses. The trial will include patients with renal malignancies who refuse surgery, have solitary kidneys or are medically inoperable. □

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