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Stereotactic ablative body radiotherapy for primary renal cell carcinoma in non-surgical candidates: initial clinical experience
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Abstract

Aims: To report the outcomes of a cohort of patients with renal cell carcinoma (RCC) treated using stereotactic ablative body radiotherapy (SABR).

Materials and methods: Patients treated with SABR for primary RCC from 1 January 2012 to 1 April 2015 were retrospectively reviewed. Patients were non-surgical candidates treated with doses ranging from 30 Gy to 40 Gy in 5 fractions. The tumour sizes and serum creatinine were compared between the pre-treatment assessment and subsequent follow-up assessments. The worst acute and late grade ≥2 toxicity rates were recorded.

Results: 16 patients were included in this study. The median follow-up was 19 months (range 7 – 30). 11 patients had stable disease, 4 had partial responses, and none had progressive disease, indicating a local control rate of 100%. One patient had grade 2 acute nausea, and two patients had grade 4 renal toxicities (two patients with pre-existing stage 4-5 chronic kidney disease required dialysis following SABR). Four out of four patients with pre-SABR symptoms (pain and / or haematuria) had symptomatic relief following SABR.

Conclusion: SABR for RCC is safe, the toxicities are minimal, and the local control is excellent at early follow-up. This technique should be further evaluated in prospective clinical trials.

Keywords:

Carcinoma, Renal Cell

Stereotactic Body Radiotherapy

Radiotherapy, Intensity-Modulated

Introduction

Kidney cancers, primarily renal cell carcinomas (RCCs) are the tenth most common malignancy in Canada, with 6200 estimated new cases in 2015 [1]. The greatest numbers occur in the 60 – 69 year old age group, however a significant number of patients are diagnosed at an older age [2].

The standard treatment of RCC in those with localised disease is surgery, which is curative in the majority of patients. However, elderly patients and those with significant comorbidity may not be surgical candidates. These patients are usually considered for active surveillance [3]. Large series have demonstrated the safety of active surveillance in the management of small renal masses (SRMs), showing that the majority of SRMs grow slowly, and have low rates of metastasis [3]. However, a pooled analysis demonstrated certain risk factors being associated with a higher risk of progression to metastasis while on active surveillance, including increased age, greater initial tumour dimension, and higher growth rate [3]. Additionally, SRMs represent a heterogeneous entity, with up to 20% being benign

masses, which undoubtedly contributes to the low rates of progression noted in the active surveillance studies [3].

Patients with progressing or symptomatic tumours who are not surgical candidates are often considered for local ablative therapies. These approaches include radiofrequency ablation, cryoablation, and stereotactic ablative body radiotherapy (SABR). Radiofrequency ablation and cryoablation are limited by low control rates with tumours larger than 3-4 cm, the fact that there is a high risk of complications in treating tumours in the hilum or central collecting system, and that both are still invasive procedures that require either percutaneous or laparoscopic access to the tumour [4,5].

SABR offers a completely non-invasive approach that may potentially overcome many of the limitations of the other local ablative therapies. SABR refers to the precise delivery of highly conformal and image-guided hypofractionated external beam radiotherapy, delivered in few fractions with doses at least biologically equivalent to conventional radical courses of radiotherapy [6]. SABR allows highly conformal dose distributions with high doses delivered to the target, and steep dose gradients beyond the target such that doses to surrounding organs at risk (OARs) are minimized [6]. Previous studies of conventionally fractionated radiotherapy in RCC have demonstrated that RCC is relatively radioresistant [7]. However, subsequent studies of SABR delivered to RCC metastases have shown excellent rates of local control, indicating that SABR can potentially overcome this resistance [7].

SABR in primary RCC is still a new field, with limited published experience at this stage [8]. We have reported on the outcomes achieved in an initial cohort of patients treated with SABR for RCC in non-surgical candidates.

Materials and Methods

Patients

This was a retrospective review of patients with RCC treated with SABR to the primary tumour from 1 January 2012 to 1 April 2015, with at least 6 months of follow-up data. This study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board. Patients who received prior surgery or ablative therapy to the primary site but had recurred/progressed at the primary site, and patients with regional nodal and/or distant metastatic disease were also included in this analysis, as long as the primary tumour was treated with SABR.

A diagnosis of RCC was made either by biopsy or radiological appearances (where biopsy was not possible). All patients were first assessed by a urologist and deemed not to be surgical candidates before being considered for SABR.

At baseline, all patients were assessed with CT scans of the abdomen and pelvis, and blood tests including serum creatinine. Other investigations including MRI scans of the abdomen and nuclear medicine scans for differential renal function and glomerular filtration rate (GFR) were ordered at the treating physician’s discretion in some of the patients.

Patients with poor baseline renal function were cautioned about the risk of requiring dialysis after having SABR.

Radiotherapy technique

The patients were immobilized using the BodyFIX (Elekta AB, Stockholm, Sweden) dual vacuum immobilization device. Four-dimensional CTs were acquired with phase-binning algorithms for image reconstruction. The treating radiation oncologist delineated the gross tumour volume (GTV) on the 0% (peak inspiratory) and 50% (peak expiratory) image sets. These volumes were combined by Boolean addition to generate the internal target volume (ITV), and then expanded by 5 mm to generate the planning target volume (PTV). The average image dataset was used for radiotherapy dose calculation.

Radiotherapy planning was performed on the Pinnacle 3 (Phillips Medical Systems, Madison, WI) treatment planning system. Earlier patients were treated using step-and-shoot intensity-modulated radiotherapy (IMRT), whereas recent patients were treated using volumetric-modulated arc therapy (VMAT). The prescription dose was 40 Gy in 5 fractions. However, the prescription dose was lowered as required to meet OAR constraints, to a minimum prescription dose of 30 Gy in 5 fractions. The target coverage objectives were ITV V100% ≥ 99%, PTV V95% ≥ 99%, and PTV V110% < 1%. The dose constraints for the organs at risk (OARs) are listed in Table 1. The majority of these dose constraints were derived from the American Association of Physicists in Medicine Task Group 101 (AAPM TG 101) report [9]. A typical dose distribution is demonstrated in Fig 1.

Treatment was delivered on alternate days using an Elekta Synergy (Elekta AB) linear accelerator equipped with the Elekta Synergy Beam Modulator (high resolution 4 mm multileaf collimator), a kilovoltage cone beam CT (CBCT) image-guidance system, and the Hexapod (Elekta AB) robotic couch permitting 6 degrees of freedom patient positioning. Prior to the delivery of each fraction, patients were imaged using CBCT, and by comparing these images with the planning CT scan, patient positioning was corrected in 6 degrees of freedom using the Hexapod robotic couch. After the patient positioning was adjusted, a verification CBCT was acquired to confirm position as required. If accurate patient positioning was confirmed, the treatment was initiated, or else the above procedures were repeated.

Follow-up

Patients were followed up every 3 to 4 months for the first 2 years. After that, follow-up was decreased to every 6 months. Prior to each follow-up appointment, patients had CT scans of the abdomen and pelvis, and blood tests including serum creatinine.

Outcomes

Primary tumour response was assessed using Response Evaluation Criteria In Solid Tumours (RECIST) criteria [10]. Local control was defined as complete response, partial response, or stable disease. The worst acute and late toxicities grade 2 or greater were recorded for each patient according to Common Terminology Criteria for Adverse events version 4.0 [11]. The serum creatinine was recorded at each follow-up visit, and then used to estimate the GFR

using the Modified Diet in Renal Diseases formula [12]. Each patient was then classified by chronic kidney disease (CKD) stage as per the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [13]. The number of patients who had troubling symptoms attributable to the primary RCC at baseline and at follow-up was recorded.

Results

A total of 16 patients were included in this study. The median follow-up was 19 months (range 7 – 30 months). The patient baseline characteristics are listed in Table 2. Four patients (25%) received the top dose of 40 Gy; nine patients (63%) received 35 Gy; one patient (6%) received 32.5 Gy; and one patient (6%) received 30 Gy. Three patients were treated with step-and-shoot IMRT, and the remainder were treated with VMAT. Dose/volume metrics for OARs are listed in Table 3.

Eleven patients had stable disease, and five had partial responses. No patient had either complete response or progressive disease. This translated to a local control rate of 100% as previously defined. Six out of 14 patients (43%) with evaluable scans at 3 months post SABR had a transient increase in tumour size, followed by reduction in tumour size on the subsequent scan. The overall change in tumour size between the pre-radiotherapy scan and the final follow-up scan was a decrease by 12.5% (standard deviation 23.7%). The spider plot in Fig 2 demonstrates the changes in tumour sizes over the length of follow-up. An example case showing partial response on serial imaging is demonstrated in Fig 3.

Eleven patients (69%) had overall deteriorations in eGFR by the end of the study period, however only one patient changed CKD stages between baseline and last follow-up (dialysis was initiated, increasing the patients' CKD stage from 4 to 5). The mean change in eGFR over the entire length of follow-up was a decline of 14.4%. The spider plot in Fig 4 demonstrates the changes in eGFR over the length of follow-up, with the most extreme deteriorations noted in the patients with baseline stage 4-5 CKD.

Two patients with pre-existing stage 4-5 CKD had deteriorations in their kidney function following SABR such that they later required dialysis. These patients are technically classified as having grade 4 toxicities. Both patients were counselled on the high likelihood of requiring dialysis after SABR. One was a 73-year-old lady with a left sided renal mass discovered incidentally on imaging, with a baseline creatinine of 296 µmol/L (eGFR 13 ml/min, stage 5 CKD). She was determined not to be a surgical candidate at the time the mass was discovered, and therefore observed for 2 years. At that stage, the mass had grown to 4.5 cm, and she was therefore referred for arterial embolisation followed by percutaneous RFA. The RFA was attempted twice and aborted both times due to patient discomfort. The mass had grown to 5.3 cm by the time she was referred for SABR. The other patient was a 76-year-old lady with diabetic nephropathy with a baseline creatinine of 236 µmol/L (eGFR 17ml/min, stage 4 CKD), and a biopsy-proven clear cell carcinoma of the left kidney. Her urologist's opinion was that a nephrectomy would result in an immediate requirement for dialysis, and was therefore referred for SABR. She did not have any other interventions prior to SABR.

Other patients with deteriorations in renal function were not classified as having toxicities because they did not change CKD stages compared to their baseline stage. One patient developed acute grade 2 nausea and vomiting following SABR, however this resolved with antiemetics. There were no other recorded grade ≥ 2 toxicities.

Four patients (27%) were symptomatic with flank pain and/or hematuria prior to SABR. All of these patients' symptoms resolved after SABR. Of the ten patients who had localized disease at the time of SABR, none developed regional or distant metastases at the time of the last follow-up. Two patients died following SABR, both of whom had metastatic disease at the time of SABR. One patient died at 15 months and the other at 23 months after SABR.

Discussion

We have described the successful delivery of SABR in an initial cohort of 16 patients with RCC who were not surgical candidates. SABR for primary RCC is a new and evolving technique, and as such, our study is among the first to describe early outcomes [8].

At early follow-up, we have demonstrated an excellent local control rate of 100%. This result is consistent with previous publications. Ponsky et al. performed a Phase I dose-escalation study on 19 patients with RCC [14]. They treated groups of 3-6 patients at increasing dose levels ranging from 24 Gy to 48 Gy in 4 fractions. Their median follow-up was 13.7 months. By examining the imaging using RECIST criteria, they also had a local control rate of 100%. Post-SABR biopsies were performed on 11 of these patients (at a median of 9 months post-SABR), 7 of which were positive. One of the initially positive patients had a second biopsy, which turned negative without further therapy. The significance of these biopsy results is questionable. There currently is no data to guide how to interpret these biopsies in the setting of RCC, post SABR. Multiple studies of post-radiation biopsies in various other malignancies including prostate and head and neck cancer have demonstrated that initially positive biopsies may become negative on subsequent biopsies (possibly due to the cell-cycle-specific nature of radiation injury) [15,16]. As a result of this, it has been proposed that post-radiation prostate biopsies not be performed within 18 months of radiotherapy [15]. Furthermore, radiation atypia in benign tissue may make the interpretation of biopsies difficult [15]. In prostate cancer, post-radiotherapy biopsies done after an appropriate delay have been shown to have some prognostic significance, however are still not accurate enough for predicting outcomes [15]. As such, it is uncertain whether all of these patients with positive biopsies would fail without further therapy. It would be interesting to correlate these patients with positive biopsies with clinical outcomes on long-term follow-up.

McBride et al. performed a Phase I dose escalation study on 15 patients with RCC [17]. They treated patients at increasing dose levels ranging from 21 Gy to 48 Gy in 3 fractions. The median follow-up was 36.7 months. They reported two local failures at 30.7 months and 31.2 months, both in patients in the low dose cohorts (21 Gy and 27 Gy).

Siva et al. performed a systematic review of 10 publications (including 126 patients) of SABR for primary RCC [8]. The weighted local control reported was 94%.

We have demonstrated low toxicity rates with one grade 2 acute toxicity and two grade 4 late toxicities (both cases of which were expected renal toxicities in patients with underlying CKD). This result is also consistent with previous publications. Ponsky et al.'s study (described above) reported one grade 4 acute duodenal ulcer, two grade 3 renal toxicities, one grade 2 urinary incontinence, and one late grade 4 duodenal ulcer [14]. McBride et al.'s study (described above) had one patient with grade 3 renal dysfunction [17]. Siva et al.'s systematic review (described above) reported 3.8% grade 3 or higher toxicities [8].

We also demonstrated deteriorations in renal function in 11 patients, with the overall change in renal function in the whole cohort over the whole duration of follow-up being a decline of 14.4%. At the current follow-up, this is less than the 33% decline noted in McBride et al.'s study [17], however these numbers may deteriorate further with time.

Interestingly, we demonstrated that all four patients with symptoms including pain and/or haematuria prior to SABR experienced symptomatic relief following SABR. As such, patient-reported quality of life should be explored in future prospective clinical trials.

We also observed that 43% of patients had a transient small increase in tumour size on the first post-SABR scan followed by reduction on subsequent imaging. This is consistent with the literature about SABR for liver metastases [18] and stereotactic radiosurgery for brain metastases [19] showing transient increases in tumour size.

A wide range of dose and fractionation schedules has been reported in the literature for SBRT of primary RCC, and it is unclear at this stage which schedule is optimal [8]. We chose the five-fraction schedule because it is one of the schedules that has been successfully employed in past publications [8], and because of our extensive institutional experience with using this schedule for the treatment of liver and central lung tumours [20].

Our study does have a number of limitations. Biopsies were not obtained in all of the patients. Some of these patients were referred for SABR because they were very frail and would not have been able to tolerate a biopsy. Even though the non-biopsied tumours were noted to have increased in size over time on serial imaging, it is possible that some of them were not malignant. The follow-up period is short at this stage, and as such, there may not have been enough time to document local failures or all potential late toxicities. RCC has been demonstrated to have slow growth in active surveillance studies [3], and McBride et al.'s study [17] demonstrated local failures after 30 months of follow-up. Furthermore, late toxicities such as declining renal function may continue to worsen over time. As such, with longer follow-up, we may find more cases of local failures and higher rates of late toxicities. Also, the small sample size limits our ability to draw conclusions from these results. Lastly, as with all retrospective studies, potentially not all toxicity data has been captured. We aim to address the above limitations by performing a prospective multicentre trial [21].

In conclusion, SABR for primary RCC can be delivered safely, with minimal toxicity, and demonstrates excellent local control at early follow-up. This technique is extremely promising in the patient population with RCC that cannot tolerate surgery, and its use should be further evaluated in large prospective clinical trials.

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Fig. 1. An example case of the dose distribution achieved for a patient treated using volumetric-modulated arc therapy. The isodose lines are shown with dose legend on the top right corner of the figure.

Fig. 2. Change in size of the primary tumour after SABR over the follow-up period

Fig. 3. An example case of serial CT scans of the abdomen (axial scans zoomed in on the left kidney tumour) before and after SABR for biopsy-proven RCC. The maximum tumour dimensions were: 4.5 cm 2 months before SABR (A), 4.9 cm 3 months after (B), 4.6 cm 6 months after (C), 4.2 cm 9 months (D), 4.0 cm 12 months after (E), 3.2 cm 30 months after (F), 3.1 cm 35 months after (G), and 2.9 cm 42 months after SABR (H).

Fig. 4. Change in estimated glomerular filtration rate after SABR. Dotted lines represent patients with baseline stage 4-5 chronic kidney disease

Table 1. Planning dose constraints

Organ at risk	Constraint
Renal cortices	Volume receiving less than 17.5 Gy >200 ml [9]
Renal hilum (ipsilateral)	V23Gy < 67% [9]
Combined kidneys	V16.8Gy < 67%*
Spinal cord + 5mm	Dmax <25.3 Gy [22]
Stomach	Dmax <32Gy [9]
	V18Gy <10cc [9]
Duodenum	Dmax <32Gy [9]
	V18Gy <5cc [9]
Small bowel	Dmax <35Gy [9]
	V19.5Gy <5cc [9]
Large bowel	Dmax <38Gy [9]
	V25 <20cc [9]
Chest wall	Dmax <105% [23]
Skin	Dmax < 39.5Gy [9]
	V36.5Gy<10cc [9]

* in-house constraint

Table 2. Patient baseline characteristics

Median age (range)	73 (51-90)
Median tumour size (range)	4.0 cm (1.0-14.6cm)
Characteristic	Number of patients (%)
Sex	
Male	11 (69%)
Female	5 (31%)
CKD stage	
1 (eGFR >=90)	1
2 (eGFR 60-89)	7
3 (eGFR 30-59)	5
4 (eGFR 15-29)	1
5 (eGFR <15 or dialysis)	2
Histology	
Clear cell	6 (38%)
Papillary	2 (13%)
Chromophobe	1 6%)
Not biopsied or information not available	7 (44%)
T-category	
T1	12 (75%)
T2	0 (0%)
T3	2 (13%)
rT1	2 (13%)
N-category	
N0	14 (88%)
N1	2 (13%)
M-category	
M0	10 (63%)
M1	6 (38%)
Tumour laterality	
Left	8 (50%)
Right	8 (50%)
Prior treatment	
Nephrectomy	2 (13%)
Radiofrequency ablation	1 (6%)
Tyrosine kinase inhibitor	1 (6%)

Table 3. Dose/volume metrics for organs at risk

Organ at risk	Metric	Mean (range)
Renal cortices	Volume receiving < 17.5Gy (ml)	238 (109-548)
Renal hilum	V23Gy (%)	37.0 (0-84.1)
Combined kidney	V16.8Gy (%)	24.1 (0-181.4)
	Mean dose (Gy)	7.6 (1.4-15.9)
Ipsilateral kidney	Mean dose (Gy)	16.3 (7.35-28.7)
Contralateral kidney	Mean dose (Gy)	3.3 (0.7-13.3)
Spinal cord + 5mm	Dmax (Gy)	12.2 (3.2-23.7)
Small bowel	Dmax (Gy)	23.3 (3.0-34.2)
Large bowel	Dmax (Gy)	26.7 (10.7-40)