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Tumor Control Outcomes Following Hypofractionated and Single-Dose Stereotactic Image-Guided Intensity-Modulated Radiotherapy for Extracranial Metastases from Renal Cell Carcinoma

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Abstract

Purpose—To report tumor local progression-free outcomes following treatment with single-dose image-guided intensity-modulated radiotherapy (SD-IGRT) and hypofractionated regimens for extracranial metastases from renal cell primary tumors.

Methods and Materials—Between 2004 and 2010, a total of 105 lesions from renal cell carcinomas were treated with either SD-IGRT to prescription doses of 18–24 Gy (median, 24 Gy) or hypofractionation (3 or 5 fractions) with prescription doses ranging between 20 and 30 Gy. The median follow-up was 12 months (range, 1–48 months).

Results—The overall 3-year actuarial local progression-free survival (LPFS) for all lesions was 44%. The 3-year LPFS for those who received high single-dose (24 Gy; $n = 45$), low single-dose (< 24 Gy; $n = 14$), and hypofractionation regimens ($n = 46$) were 88%, 21%, and 17%, respectively (high single dose versus low single dose, $p = 0.001$; high single dose versus hypofractionation, $p < 0.001$). Multivariate analysis revealed the following variables as significant predictors of improved LPFS: dose of 24 Gy compared with lower dose ($p = 0.009$), and single dose versus hypofractionation ($p = 0.008$).

Conclusion—High-dose SD-IGRT is a non-invasive procedure resulting in high probability of local tumor control for metastatic renal cell cancers, generally considered radioresistant according to classical radiobiological ranking.

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Conflict of Interest Statement

The authors have no conflict of interest to disclose.

Keywords

Image-guided radiotherapy; Single fraction; Hypofractionation; Renal cell cancer; Metastases

INTRODUCTION

With the emergence of image-guided radiotherapy (IGRT) and stereotactic radiosurgery, it has become possible to permanently ablate tumors with high radiation doses to limited target volumes with surprisingly minimal morbidity. Using these treatment techniques, high rates of durable local tumor control are achievable in both primary and oligo-metastatic tumors in the lung, liver, and bone, and these outcomes represent a significant improvement compared with historical controls treated with conventionally fractionated regimens. The surprisingly favorable local control rates for metastatic deposits with ultrahigh dose levels (> 20 Gy per fraction) are probably associated with a unique radiobiological mechanism of tumor response recently described.(1, 2) Genetic studies using experimental mouse tumor models revealed that ultra-high dose exposure induces concomitantly DNA double-strand breaks in parenchymal tumor cells and DNA damage-independent endothelial apoptosis in the stromal microvasculature. The ensuing microvascular dysfunction is linked to tumor stem cell clonogen lethality which is required for local tumor cure.(1, 2) While the precise mechanism of the microvascular engagement in parenchymal tumor cell response is still being explored, preliminary studies suggested that it regulates tumor-cell stem cell clonogen lethality *via* attenuating the repair of radiation-induced DNA double-strand breaks.(1) Early clinical studies demonstrated that the high single doses effect is actuated irrespective of tumor histology, favorably affecting the response of tumors classically categorized as radioresistant.(3–6)

Since 2004 we have used stereotactic IGRT techniques to deliver ultrahypofractionated and single-dose regimens in patients with limited metastatic disease. We have previously reported advantages of the high single-dose approach for spinal and non spinal osseous and soft-tissue oligo-metastatic disease (2, 7). Our preliminary observations were notable for excellent control rates observed irrespective of the histology of the tumor type treated. In the current report we focus on the response of metastatic renal cell carcinoma, classically regarded as extremely resistant to fractionated radiotherapy (8).

PATIENTS AND METHODS

Between February 2004 and February 2010, 105 extracranial metastatic lesions from renal cell primaries underwent IGRT using a hypofractionated regimen ($n = 46$) or single-dose irradiation ($n = 59$) according to the discretion of the treating physician. Dose levels and fractionation schemes are summarized in Table 1. Patients in the hypofractionated group were treated in either 3 or 5 fractions with cumulative doses ranging between 24 Gy and 30 Gy (i.e., $6 \text{ Gy} \times 5$ to $8 \text{ Gy} \times 3$). For patients treated with single-dose IGRT, the prescription doses ranged between 18 Gy and 24 Gy (median, 24 Gy). Patients were initially treated to dose levels of 18–20 Gy and, beginning in 2006, a phase I dose-escalation study was activated at 22 Gy with intent to determine the maximally tolerated dose of single-fraction

high-dose extra-cranial IGRT. Once 20 patients were treated at this dose level with a minimum follow-up of 6 months, subsequent eligible patients were accrued to the next dose level of 24 Gy. While the phase I trial is currently accruing patients at the 26 Gy level, the present report includes patient treated with dose ranges of 18–24 Gy until February 2010. The study was internally approved by the Memorial Sloan- Kettering Cancer Center Research Board and all patients signed informed consent forms. No patient had undergone surgical resection of the lesion of interest or prior radiotherapy to this region and adequate cross-sectional imaging was acquired prior to treatment. The decision to utilize a hypofractionated versus a single-dose regimen was at the discretion of the treating physician.

The clinical characteristics of the patients treated are summarized in Table 2. Planning target volume (PTV) sizes between the single-fraction and the hypofractionated groups were compared. The mean PTV in the hypofractionation group was 232.1 cm³ (median 127.8 cm³, range 12.9–1461 cm³). The mean PTV in the single-dose group was 121.4 cm³ (median 76.3 cm³, range 12.9–1151 cm³). The difference in PTV sizes between the two groups was statistically significant ($p = 0.03$).

Treatment Planning

The techniques utilized for treatment planning and delivery of IGRT at our institution have been previously described.(2, 9) All patients were immobilized in a customized cradle developed at our institution for IGRT to prevent any inadvertent patient motion. Before simulation, if deemed necessary, the patient underwent implantation of radioopaque fiducial markers in the vicinity of the target lesion to ensure target localization prior to treatment delivery. Patients were simulated in the cradle using 2 mm slice thickness CT images. During treatment, patient movement was monitored with infrared stereoscopic cameras, and if any motion was noted the treatment was temporarily stopped and only continued when movement was no longer observed.

Treatment planning was performed on in-house software using an inverse treatment algorithm. The dose was prescribed to the 100% maximum isodose line that completely encompassed the PTV. The PTV was created with a 2 mm expansion around the clinical target volume. Dose constraints of < 12 Gy were set as the maximum allowable dose to the spinal cord contour and of 16 Gy to bowel, rectum, bladder, and other identified relevant normal tissue structures. This was determined using a standardized best-fit inverse optimization process that takes into account normal tissue constraints, clinical target volume, and PTV coverage. Typically, seven to nine coplanar fields (6 or 15 MV photons) were set to a single isocenter utilizing dynamic multileaf collimation.

IGRT Technique

Image verification was performed by creating digitally reconstructed radiographs from the simulation studies for each field's beam's eye view, which were used as the gold standard of comparison. Linear accelerator on-board cone-beam computed tomography (CT) was used for verification. These images were digitally overlaid with the reference images to calculate isocenter corrections. The calculated corrections were then verified for each field prior to

actual treatment. Intra-fraction motion was monitored with infrared stereoscopic cameras. Four spherical infrared reflectors were placed on the patient above and below the treated region to track intra-fractional motion. If motion > 2 mm was detected, the treatment was temporarily stopped and the position was verified again with both two-dimensional kilovoltage and three-dimensional beam CT imaging for accurate repositioning.

Endpoints

Patients were generally examined 8 weeks after treatment. Repeat diagnostic CT, magnetic resonance imaging, and positron emission tomography/CT scans were acquired at approximately 3–4 month intervals to assess local control for the first 2 years. The median follow-up was 12 months (range, 1–48 months). No patient has been lost to followup.

Local response to treatment was scored as complete response, stable disease, or failure based on a thorough assessment of all cross-sectional imaging/metabolic studies available. Local failure was scored as an event if a lesion increased in size by ≥ 20% according to the Response Evaluation Criteria in Solid Tumors and whenever persistence of disease was confirmed pathologically.⁽¹⁰⁾ Estimates of local relapse-free survival (LRFS) were calculated using the Kaplan-Meier method.⁽¹¹⁾

RESULTS

The overall 3-year actuarial local progression-free survival for all treated lesions was 44%. Among patients who developed a local failure, the median time to relapse within the irradiated region was 2 months (range 0–25 months). The 3-year LRFS for those who received high single-dose (24 Gy; n = 46), low single-dose (<24 Gy; n = 14), and hypofractionation regimens (n = 46) were 88%, 21%, and 17%, respectively ($p = 0.001$). Patients treated with a single dose had significantly lower risk of local relapse compared to the hypofractionated-treatment group ($p = 0.01$) (Figs 1 and 2). It is also interesting to note that among the size ranges of treated planning target volumes (median, 92 cm³; range, 12.9 cm³–1462 cm³) no differences in tumor control were noted for larger (PTV >100 cm³) versus smaller volumes.

Multivariate analysis was performed using the Cox proportional hazards multiple regression model with fractionation regimen (single dose vs. hypofractionation), prescription dose (24 Gy vs. < 24 Gy), and PTV size as covariates. As shown in Table 3, single-dose compared to hypofractionation ($p = 0.01$) was associated with a significant improvement in LRFS. The additional significant predictor of improved LPFS was noted to be single-dose delivery of 24 Gy ($p = 0.01$).

Toxicity

Treatment was well tolerated both in the single-fraction and hypofractionated groups. Overall, grade 2 radiation-induced dermatitis was observed in two cases treated with single-fraction dose of 24 Gy. Four patients developed fractures post-RT treatment (2 in the hypofractionated group, and 2 in the single-dose group of 24 Gy). One single-fraction patient treated at 24 Gy developed a grade 4 erythema on treated skin, which required debridement.

DISCUSSION

Despite the inherent radioresistance of renal cell tumor histologies, we observed excellent tumor control rates with high-dose single-fraction regimens for treated metastatic lesions. Our data also serve as preliminary evidence that high-dose single-fraction IGRT delivered to metastatic deposits is associated with superior tumor control rates compared with hypofractionated regimens. Among patients treated with high-dose single-fraction regimens (24 Gy), the local control within the irradiated region was 88% compared with 17% when using a hypofractionated regimen of 6–8 Gy per fraction ($p = 0.0002$).

In this study, the excellent long-term LRFS rates (80%) observed with high SDIGRT for renal cell histologies defy standard linear-quadratic model predictions. In fact, it has been disputed that the linear-quadratic model overestimates cell killing at high single doses.(12) Experimental models and emerging clinical data consistently show that significantly lower single exposures can achieve high local control rates, leading to the hypothesis that the underlying mechanisms of tumor-cell killing may be different from fractionated radiotherapy.(13, 14)

The mechanism of this enhanced tumor response after single-dose radiotherapy has been postulated to be different from what may be relevant for conventional fractionated radiotherapy and may explain the apparent superior control rates we observe with a high-dose single-fraction regimen. Studies by Fuks and Kolesnick(15) indicate that single high-dose radiation exposure (> 8–10 Gy) engages a microvascular apoptotic component in tumor response, by inducing vascular collapse within the endothelium. In several types of mammalian cells, radiation has been shown to rapidly activate the cell membrane enzyme acid sphingomyelinase (ASMase) that hydrolyses sphingomyelin to generate the pro-apoptotic second messenger ceramide, thus initiating trans-membrane signaling of apoptosis. (16, 17) Due to the presence of a dose threshold at 8–10 Gy for the endothelial component of this response, this pathway does not appear to be engaged in fractionated regimens where individual doses are too low to invoke this apoptotic stimulus on endothelial cells. While the mechanism by which endothelial damage and microvascular dysfunction confer tumor stem cell clonogen lethality is currently being investigated, these observations support the notion that the mechanisms of tumor cure by single high-dose are distinct, and raises the question whether hypofractionation is necessary when excellent control can be achieved with stereotactic SD-IGRT.

Recent studies have suggested that tumor stem cells reside in niches where specific micro-environmental conditions, including hypoxia, provide critical signals to support and maintain their undifferentiated phenotype.(18) Large radiation doses may be potentially more effective in overcoming the inherent radioresistance of stem cells found in metastases. Consistent with this notion, traditional linear-quadratic formalism indicates that radioresistant tumor histologies with low alpha-beta ratios may respond more favorably to large fraction sizes, where irreparable lethal damage associated with the linked endothelial-stem cell mechanism of tissue damage may be the predominant method of tumor stem cell kill. Therefore, following high-dose irradiation, similar clinical outcomes are to be expected

regardless of the histological phenotype of the primary tumor, as, indeed, the present series appears to indicate.

Metastatic renal cell tumors are characterized as radioresistant tumors according to classical radiobiological sensitivity ranking. Therefore, surgical extirpation, ablative procedures, or systemic therapies have been preferred to conventional radiotherapy approaches. Our present report, however, indicates that the delivery of high-dose single fraction regimens via image-guided stereotactic approaches appears to overcome the inherent radioresistant nature of these tumors. Indeed, when we analyzed the control rates among patients treated to dose levels of 24 Gy using a single fraction, outcomes were excellent.

Using tight margins of 2 mm, these treatment regimens can be delivered accurately with low morbidity rates with stereotactic image-guided techniques using intensity modulated treatment planning. Despite the high dose utilized, we have noted a low incidence of treatment-related complications using stereotactic SD-IGRT both in the single-fraction and hypofractionated groups with minimal treatment-induced chronic toxicity. Grade 2 neuropathy was observed in only one case in the hypofractionated group (30 Gy in 3 fractions) compared to five cases in the single-dose group (at 22–24 Gy). While we observed only one case of treatment-induced vertebral body fracture, there exists a documented risk for this complication after single-dose IGRT to the spine. Rose et al. reported that among patients who received high-dose single-fraction IGRT, the incidence of post-treatment fracture was 39%.⁽¹⁹⁾ Multivariate analysis showed that CT appearance, lesion location, and percent vertebral body involvement independently predicted fracture progression. Lytic disease involving more than 40% of the vertebral body and location at or below T10 conferred a high risk of fracture. Most patients who developed a fracture, however, were effectively palliated with kyphoplasty. These data highlight the potential limitations of using single-dose regimens for spine tumors despite the higher likelihood of improved tumor control. At the present time we are initiating a randomized trial where we will compare tumor control rates and long-term toxicity outcomes between single fractions of 24 Gy to a hypofractionated regimen of 27 Gy in 3 fractions for spinal and osseous metastases from radioresponsive and radioresistant tumor histologies.

Especially for radioresistant tumors such as renal cell carcinoma, we believe that there exists an important potential for radiosensitization of stereotactic image-guided radiotherapy for metastatic deposits using targeted therapies such as sunitinib or bevacizumab. Reported response rates using anti-angiogenic agents alone or in combination with interferon for patients with metastatic renal cell cancers have ranged between 20% and 40%.^(20–23) Recently, clinical data for the use of anti-angiogenic agents (sunitinib, sorafenib, and bevacizumab) as first-line monotherapy agents in metastatic renal cell carcinoma have been reported^(24, 25) from investigators at the Dana Farber Cancer Center.⁽²⁶⁾ Overall objective response rates were 37%, 9%, and 13% for sunitinib, sorafenib, and bevacizumab, respectively. Patients experienced significant adverse effects, which led to modifications and interruptions of therapy (18% of cases). It is likely that using stereotactic IGRT in conjunction with targeted anti-angiogenic therapies could improve the percentage response and its duration for treated lesions, even with drug-dose adjustment to accommodate improved tolerability. The use of anti-angiogenic agents may also be expected to increase

the response to SD-IGRT within renal cell tumors via an enhancement of the apoptotic response with the vascular endothelium. It is plausible, therefore, that using radiotherapy in conjunction with targeted systemic therapies may produce synergistic effects and result in more durable responses with reduced treatment-related toxicities. This has been already shown in pre-clinical models and will need to be studied in prospective clinical trials, which are underway at our institution.

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Fig 1. Actuarial local control (Kaplan-Meier method) as a function of fractionation regimen (single fraction vs. hypofractionation). Y axis represents local relapse-free survival (%; $p = 0.01$).

Fig 2.

Actuarial local control (Kaplan-Meier method) as a function of prescription regimen for renal cell cancer ($p = 0.001$). Y axis represents local relapse-free survival (%).

Table 1

Distribution by Prescription Dose (all lesions, n = 105)

Prescription Dose	n
Single Fraction	59
18 Gy	2
21 Gy	9
22 Gy	3
24 Gy	45
Hypofractionated	46
3 Fractions	14
24 Gy	12
27 Gy	1
30 Gy	1
5 Fractions	28
20 Gy	3
22 Gy	1
30 Gy	23
60 Gy	1
>5 Fractions	4
24 Gy	1
30Gy	2
37.5Gy	1

Table 2

Lesion Characteristics (all lesions, n = 105)

	All lesions (n=105)	Hypofractionated (n=46)	Single Dose (n=59)	Total
Male		36	47	83
Female		10	12	22
Treatment site (n=105)				
Bone		(n=45)	(n=59)	104
Pelvic		11	11	22
Femur		8	1	9
Spine		20	39	59
Other		6	8	14
Lymph node		1	0	1

* Pelvic: includes sacrum, iliac, pubic ramus, acetabulum, symphysis.

† Femur: femoral head and femur.

Table 3

Cox Regression Analysis of Predictors of Local Progression Survival

Factor	Coefficient	95% Confidence (±)	Standard Error	P	Hazard Exp (Coefficient)
Single dose vs hypofractionation	-1.262	0.928	0.473	0.008	0.283
Volume PTV (cm ³)	0.001	0.001	0.001	0.417	1.001
Dose 24 vs <24	-1.328	0.994	0.507	0.009	0.265