enal cell carcinoma (RCC) has been traditionally considered radioresistant. Radioresistance may have implications both in the laboratory and the clinic. Clinically, it typically refers to tumors poorly controlled with conventionally attainable radiotherapy schedules. In the lab, it more precisely refers to characteristics of the clonogenic survival curve. Survival curves have been measured for many human cell lines in culture. They describe the ability of cells to maintain the functional machinery to form colonies on growth media (in vitro) after variable doses of radiation exposure. The classic measure of radiosensitivity is the surviving fraction after 2 Gy exposure (SF$_{2Gy}$), which was chosen because it is the conventional daily dose exposure used in radiation oncology clinics. In the case of RCC, tumor cells appear to be radioresistant to this 2 Gy exposure by both clinical (poor tumor control) and laboratory (high SF$_{2Gy}$) criteria.

Ning and colleagues$^1$ at Stanford University performed clonogenic survival assays with 2 human RCC cell lines: Caki-1 and A498. The cells were irradiated with 0 to 15 Gy and surviving fractions were calculated. Survival curves of both cell lines exhibited a small decrease in survival from 0 to 6 Gy (called the “shoulder” region) followed by an exponential decrease in survival at radiation doses above 6 Gy. As shown in Figure 1, while cell survival for RCC is only modestly effected at 2 Gy (ie, the cells are radioresistant at 2 Gy), the effect of radiation is fairly profound at doses over 6 Gy.

In the linear quadratic mathematical representation of the survival curve, there are 2 components of cell survival: one is proportional to the dose ($\alpha$) and the other is proportional to the square of the dose ($\beta$). As such, this $\alpha$ component contributes a proportionally larger effect on decreasing cell survival in the low dose range, ie, at the 2 Gy conventional dose range. The dose at which both components of cell killing are equal is known as the $\alpha/\beta$ ratio. Generally, cell lines with a high $\alpha/\beta$ ratio ($\geq$10) are considered radiosensitive, again mostly related to more effective killing in the low-dose range.

In the above study, the $\alpha/\beta$ ratio for the Caki-1 cell line was 6.9 versus 2.6 for the A498 cell line, which indicates radioresistance. RCC has a broad shoulder to the survival curve and relates biologically to more effective repair of radiation injury, at least in the lower dose range.

Ultimately, cell death occurs by a variety of mechanisms. Tumor cells with a high level of radiation-induced apoptosis (programmed cell death) tend to be relatively sensitive to radiation, whereas tumor cells with a low level of radiation-induced apoptosis are relatively resistant to radiation.$^2$

Conventionally fractionated radiotherapy is rarely used to treat primary renal tumors. Limited radiation tolerance of the normal kidneys and the surrounding tissues along with the feeling that the tumor is radioresis-
There are several technologies available for delivery of SBRT to the target volume.

Stereotactic body radiotherapy is now an increasingly prevalent ablative treatment strategy in radiation oncology clinics both at academic and community centers. Treatments generally include delivery of more than 8 Gy per fraction in 1 to 5 fractions, over a period of 1 to 2 weeks. In contrast, conventionally fractionated standard radiotherapy typically uses 1.8 to 2.0 Gy per fraction delivered over a period of 5 to 6 weeks. The main advantage of high dose per fraction radiotherapy is a higher biological potency that results in better local control and tumor response rate. The main disadvantage relates to more pronounced injury to any normal tissues receiving the same potent dose.

Today, SBRT is increasingly being used to treat inoperable early stage primary non–small-cell lung cancer as well as metastatic disease in the lungs and liver from other primary malignancies with a local control at 2 years of over 90% for lung and liver metastases, respectively.\(^\text{10,11}\) Patients who have a limited number of metastatic deposits within their body, so-called oligometastases, may be potentially cured if their oligometastases are completely eradicated.\(^\text{14}\) While surgical metastatectomy still remains the standard of care in operable patients, SBRT, as a non-invasive approach, is increasingly being used. Stereotactic body radiotherapy can be delivered on an outpatient basis in a short time frame, which allows patients a quick recovery, and return to daily activities.

Renal cell carcinoma has been considered radioresistant. This belief prevails despite the impressive clinical effectiveness of stereotactic radiosurgery used for years in the management of brain metastases from RCC with local control ≥90%.\(^\text{15-20}\) Perhaps a similar clinical paradigm exists in extracranial sites. This article provides a critical literature review of SBRT in the management of primary and metastatic RCC. An attempt was made to collect evidence to answer the following questions: Is a high SF\(_{2\text{Gy}}\), implying radioresistance, predictive of radioresistance at higher dose per fraction radiotherapy achievable by SBRT? Can cells deemed to be radioresistant at 2 Gy be simultaneously radiosensitive at higher dose?

**Materials and Methods**

PubMed was searched for English-language publications up to December 2010 on SBRT for primary and metastatic RCC outside the brain. The search was performed using the following key words: renal cell carcinoma, kidney cancer, radiosurgery, stereotactic radiosurgery, stereotactic body radiation therapy, extracranial stereotactic body radiotherapy, metastatic renal cell carcinoma, and spinal metastases. Ten reports of SBRT for primary and metastatic RCC were identified, and full articles were obtained. Treatment experiences were divided into spinal metastases versus nonspinal metastases (including primary RCC).

**Figure 1.** Survival curves for 2 human renal cell carcinoma lines, Caki-1 and A498, are shown. Cells were irradiated at a dose rate of 430 cGy per minute using a cesium-137 irradiator, and an in vitro clonogenic assay was performed. The surviving fraction is shown as a function of dose. Data points represent the mean ± standard deviation. The survival curves are fitted by the linear-quadratic model. Tumors with radiation survival curves characterized by a steep initial slope and small shoulder tend to be relatively more sensitive to radiation than tumors with a flat initial slope and large shoulder. Reproduced with permission from Ning et al.\(^\text{1}\)
The primary goal of this study was to evaluate the safety and efficacy of SBRT. The study included 30 patients with a mean age of 64 years. Lung and mediastinal metastases were the most commonly treated tumors. The majority of patients received no prior systemic therapy. Primary RCC was treated in 10 patients. The same follow-up strategy was used as previously reported by Wersall and colleagues. With a median follow-up of 52 months, local tumor control was 79%, and median overall survival was 32 months. Adverse effects were mild, mostly limited to grade I-II toxicities, such as cough, fatigue, and skin rash with local pain.

The Karolinska University group subsequently reported on 2 additional small studies. One study included patients who demonstrated an immunomodulatory effect (also known as abscopal effect) of SBRT in non-irradiated metastases. This effect, characterized by a regression of non-irradiated metastases was seen in 4 out of 28 (14%) patients following SBRT. The authors speculated that radiation therapy might be able to cause a release of tumor antigens, which are recognized by the dendritic cells. These cells, as antigen presenting cells, migrate to the draining lymph nodes and present antigens to T cells with a subsequent immune response. The other study included 7 patients with primary or metastatic RCC with only 1 functioning kidney. In this study, 3 out of 7 patients were alive with a median follow-up of 49 months, and none of the patients developed hypertension or kidney failure that required dialysis.

In the United States, 2 studies in patients with primary and metastatic RCC have been reported. Qian and colleagues reported their experience with 74 patients with the majority of patients treated for metastatic disease. With a median follow-up of 10 months, local tumor control was 92% for patients with metastases, and 93% for patients with primary RCC. Beitler and colleagues published their experience with 9 patients with primary biopsy-proven RCC treated with SBRT. During the median follow-up of 26 months 4 out of 9 patients were alive. Stereotactic body radiotherapy was well tolerated: 2 out of 9 patients experienced nausea and vomiting and 1 out of 9 patients experienced weight loss following SBRT.

Table 1. Differences Between Stereotactic Body Radiotherapy and Conventional Radiotherapy

<table>
<thead>
<tr>
<th>Potency</th>
<th>Stereotactic body radiotherapy</th>
<th>Conventional radiotherapy</th>
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<tbody>
<tr>
<td>Very potent, ablative</td>
<td>Typically nonablative, and used in the adjuvant setting to address microscopic disease; it can be ablative if high dose is delivered for a definitive treatment</td>
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<table>
<thead>
<tr>
<th>Dose per fraction</th>
<th>High dose per fraction (≥ 8 Gy)</th>
<th>Low dose per fraction (1.8-2.0 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall treatment time</td>
<td>1-5 treatment fractions over 1-2 weeks</td>
<td>5-9 weeks, for instance, definitive radiotherapy for prostate cancer in 44 fractions (each fraction 1.8 Gy) over 9 weeks</td>
</tr>
</tbody>
</table>

| Treatment volume definition | Minimal amount of normal tissue may be included in the treatment volume to account for set-up error and tumor motion; there is very limited normal tissue DNA damage repair due to ablative dose | Minimal amount of normal tissue should be included to minimize treatment toxicity; however, low dose per fraction allows normal tissue DNA damage repair |

| Application | Early stage medically inoperable non–small-cell lung cancer*, lung, and liver metastases from different primary malignancies including kidney cancer, primary small medically inoperable kidney cancer, prostate cancer† | The majority of disease sites in radiation oncology |

*SBRT is now the standard of care for early stage medically inoperable non-small cell lung cancer.
†For definitive therapy of prostate cancer, the standard of care in radiation oncology is still conventional radiotherapy, while SBRT is currently used in the setting of a clinical trial only.

Results

SBRT for primary and metastatic RCC (excluding spinal metastases)

Table 2 presents a summary of published SBRT data for primary and metastatic renal cell carcinoma. In 2005, Wersall and colleagues at Karolinska University Hospital reported a retrospective experience in 58 patients with primary and metastatic RCC. The majority of patients underwent nephrectomy, subsequently presented with lung metastases, and received no prior systemic therapy. Primary biopsy-proven RCC was treated in 8 patients. Follow-up strategy included CT every 3 months for 2 years, and then every 6 months. With a median follow-up of 37 months, local tumor control was 90%. The treatment was well tolerated with grade I-II toxicities, such as cough, nausea, and pain; 5 out of 58 patients developed radiation pneumonitis, and only 1 out of 58 patients had grade V toxicity (gastric hemorrhage).

In 2006, the Karolinska University group reported a phase 2 trial of SBRT in patients with primary and metastatic RCC. The primary goal of this study was to evaluate the safety and efficacy of SBRT. The study involved 58 patients out of 5-20 toxicity (gastric hemorrhage).
SBRT for spinal metastases from RCC

Table 3 summarizes published data on SBRT for RCC spinal metastases. Several retrospective studies in the United States reported on SBRT outcomes in patients with spinal metastases secondary to RCC. Gerszten and colleagues,27 at the University of Pittsburgh, reported their experience with 48 patients and 60 treated spinal metastases with 20 Gy in a single fraction. With a median follow-up of 37 months, pain control was 89%. In a larger study that included spinal metastases from different primary tumors, the same group treated 393 patients with 500 spinal metastatic lesions out of which 93 spinal metastases were in patients with RCC histology.28 During the median follow-up of 21 months, utilizing 20 Gy in a single fraction, local spinal tumor control was 94% and pain relief was 87%.

Yamada and colleagues,29 at Memorial Sloan-Kettering Cancer Center, reported their experience with 24 Gy in a single fraction. A total of 93 patients with 103 spinal metastases were treated; 21 out of 103 patients had spinal me-tastases secondary to RCC. With a median follow-up of 15 months, local spinal tumor control and pain relief were 90%. Recently, Nguyen and colleagues30 at the MD Anderson Cancer Center published their experience with SBRT in patients with spinal metastases secondary to RCC only. Most of the spinal metastases were treated with 21 Gy in 3 fractions. In 48 patients with 55 spinal metastases secondary to RCC during the median follow-up of 13 months, local spinal tumor control was 82% and pain relief 52%.

Discussion

Renal cell carcinoma is considered radioresistant, and this belief prevails despite our experience with stereotactic radiosurgery in patients with brain metastases from primary RCC. While perhaps RCC is radioresistant to 2 Gy fractions, several clinical studies from the United States and Europe reported excellent local control of brain metastases in patients with RCC treated with >10 Gy fractions delivered with stereotactic radiosurgery.15-20 Reported local control is ≥90% and the majority of patients die of extracranial disease progression.

Laboratory evidence also challenges the labeling of radioresistance. Efficacy of high-dose-per-fraction radiotherapy for implanted human RCC in a mouse model was shown in a study at the University of Texas Southwestern Medical Center.31 Nude mice were injected subcutaneously with A498 human RCC cells and the animals were subsequently irradiated with 48 Gy in 3 fractions while untreated animals served as controls. Treatment with high-dose-per-fraction radiotherapy resulted in a sustained decrease in tumor volume, and marked cytological changes with extensive tumor necrosis.
Regression of non-irradiated metastases following SBRT indicates a possible immunomodulatory effect (also known as abscopal effect) of SBRT in non-irradiated metastatic deposits.\textsuperscript{23} Further studies are necessary to elucidate this clinical phenomenon.

The available phase 2 and retrospective data for primary and metastatic RCC that showed that SBRT yields high local control have been presented. Stereotoxic body radiotherapy as a treatment modality should be considered in patients with medically inoperable early stage primary RCC and patients with oligometastases from this malignancy. Patients with local recurrence after other therapies may also be candidates for SBRT. Further prospective clinical trials and dose escalation studies are necessary to clearly establish the role of SBRT in patients with primary RCC.

**Conclusions**

Available data indicate that RCC, which is considered radioresistant to conventionally fractionated radiation therapy, shows response to SBRT and local control no worse than other histologies. Radioresistance to conventionally fractionated RT, does not necessarily imply radioresistance to high dose fractions. Stereotoxic body radiotherapy is a reasonably safe and effective treatment for controlling gross disease from RCC.

**References**


