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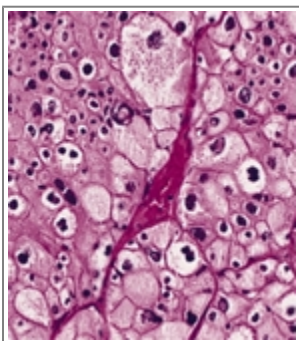
Integrating Innovative Therapeutic Strategies Into the Management of Renal Cell Carcinoma

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ABSTRACT: Three emerging trends have occurred recently in renal cell carcinoma (RCC). First, over the last several decades there has been a marked increase in the diagnosis of RCC, with a corresponding decrease in the typical tumor size, resulting in an increased interest in less invasive approaches to primary tumor treatment. Second, while conventional radiotherapy plays a limited palliative role due to the relative radio-resistance of RCC, advances in immobilization and image guidance have led several investigators to consider stereotactic radiotherapy techniques (SRT) to overcome this resistance, with impressive results in the metastatic setting. In addition, preliminary use of SRT to treat the primary RCC tumor is underway. Thirdly, although RCC is resistant to conventional chemotherapy agents, exciting recent advances have emerged in the treatment of clear cell RCC, with the development of targeted agents in addition to immunotherapy-based treatments. In the current critical review we discuss these emerging trends in localized and systemic treatment as well as possible interesting combinations of the two modalities. Finally, we discuss the role of the new systemic agents in non-clear cell RCC.

Introduction



Renal cell carcinoma, chromophobe cell type: The tumor cells vary from pale and transparent to acidophilic and granular.

In the United States, kidney cancer is the third most common genitourinary tumor and the seventh most common cancer.[1] The incidence of renal cell Carcinoma (RCC) has been increasing at a rate of 2% to 4% per year since 1975.[2] There has been a decrease in the size of tumors at diagnosis, which is likely due to increased use of abdominal imaging and higher incidental detection rates of asymptomatic tumors.[3] More than 80% of cancers of the kidney are adenocarcinoma, and another 10% are derived from the renal pelvis, a urothelial cancer related to bladder cancer and treated with bladder cancer regimens.

This discussion will focus on the nonurothelial carcinomas.

Standard Therapeutic Modalities in the Management of RCC Primary Tumors

Surgical treatment

Standard treatment for nonmetastatic RCC is complete resection of the tumor by either a radical or partial nephrectomy, which can be done as an open procedure or laparoscopically.[4-6] The relative merits of the various surgical approaches to management of RCC are beyond the scope of this review but are well summarized by Touijer et al.[7] Two randomized trials have shown that, in the context of receiving systemic interferon alfa or [interferon alfa-2b](#)([Drug information on interferon alfa-2b](#)), even many patients with metastatic disease should undergo nephrectomy, with reported survival benefits of 10 and 3 months in trials by the European Organisation for Research and Treatment of Cancer (EORTC) and the Southwest Oncology Group (SWOG), respectively.[8,9] Whether this benefit still applies in the context of current systemic therapies is uncertain.

Less invasive ablative modalities

Radiofrequency ablation (RFA), cryoablation (CA), and high-intensity focused ultrasound (HIFU) have been used as treatment options that are less invasive than radical or partial nephrectomy. RFA and CA are accomplished by introducing needle(s) or probe(s) into the tumor and delivering the ablative treatment. These procedures can be performed percutaneously, using image guidance to place the needles/probes, or they can be performed intraoperatively, usually via laparoscopic surgery.[6,10] They usually are performed with the patient under conscious sedation or anesthesia, take about 2 to 3 hours, and often require an overnight stay in the hospital.

Gervais et al conducted a careful assessment of tumor response in a series of 100 RCC patients, with a mean follow-up of 2.3 years (range, 3.5 to 6 years). They reported achieving a tumor ablation rate of 90%. The most common complications were hemorrhage, occurring in 5% of patients, and ureteral stricture or injury, occurring in 3%; one-third of patients required a hospital admission of at least one night following the procedure. The same group of investigators reported on post-radiofrequency ablation syndrome, which consists of a low-grade fever and flu-like symptoms, and which has been shown to occur in approximately 30% of patients.[11]

TABLE 1

Study	Year	Technique	Number of Patients	Technique
Reichel et al [12]	1979	WBRT	46	Median OS: 10.5 mo
Landwehr et al [13]	1979	WBRT	76	Median OS: 10.5 mo (95% CI, 8.8-12.2 mo)
Reichel et al [14]	1979	WBRT	15	5-yr OS: 10.5 mo (95% CI, 8.8-12.2 mo)
Landwehr et al [15]	1979	WBRT	154	Median OS: 8.8 mo
Reichel et al [16]	1979	WBRT	15	Median OS: 10.5 mo (95% CI, 8.8-12.2 mo)
Landwehr et al [17]	1979	WBRT	154	Median OS: 10.5 mo (95% CI, 8.8-12.2 mo)
Reichel et al [18]	1979	WBRT	15	Median OS: 10.5 mo (95% CI, 8.8-12.2 mo)
Landwehr et al [19]	1979	WBRT	154	Median OS: 10.5 mo (95% CI, 8.8-12.2 mo)
Reichel et al [20]	1979	WBRT	15	Median OS: 10.5 mo (95% CI, 8.8-12.2 mo)
Landwehr et al [21]	1979	WBRT	154	Median OS: 10.5 mo (95% CI, 8.8-12.2 mo)

Treatment of RCC With Radiofrequency Ablation, Cryotherapy, and HIFU

Park et al reported on a prospective study of RFA in patients with RCC. A total of 94 tumors were treated in 78 patients. At a median follow-up of 25 months, the authors reported an initial RFA success rate of 98% and a recurrence-free rate of 97%. The rate of minor complications was 10% and that of major complications was 3%.[12] Percutaneous cryoablation of renal masses has been reported by Atwell et al in a retrospective series of 115 patients. Seventy-nine percent of these masses were biopsy-proven RCC or other malignancy; the other lesions were presumed malignant based on imaging. The authors reported a 100% local control rate in patients undergoing follow-up of 3 months or longer. However, local control was not defined in this paper. Six percent of patients experienced grade 3 toxicity, the most common being bleeding/hematoma, and 12% of patients required a hospitalization of two or more nights.[13] Although the results of RFA and cryotherapy are encouraging, the follow-up in most series is short, most of the studies are retrospective, and the procedures are still invasive. The only truly noninvasive modality is HIFU; however, this technique lacks a substantial evidence base, having been investigated mostly in small series of patients. Results of these modalities are summarized in [Table 1](#).

Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiotherapy (SBRT) in Metastatic and Primary RCC

Deschavanne and Fertil reviewed the radiosensitivity of 694 cell lines in vitro. In their study, the cells were exposed to irradiation at doses up to 12 Gy and their response showed that RCC cells were the most radiation-resistant cells.[14] The clinical results of standard fractionated radiotherapy (RT) for RCC mimic this in vitro work with relatively poor results. For example, results of several studies of whole-brain radiotherapy (WBRT) for brain metastases from RCC have been poor, showing a median survival after WBRT of only 2 to 4.4 months.[15-18] A poor outcome is seen even in patients with a good recursive partitioning analysis class who receive higher radiation doses.[17,18]

TABLE 2

Study	Year	Technique	Number of Patients	Technique
Reichel et al [12]	1979	WBRT	46	Median OS: 10.5 mo
Landwehr et al [13]	1979	WBRT	76	Median OS: 10.5 mo (95% CI, 8.8-12.2 mo)
Reichel et al [14]	1979	WBRT	15	5-yr OS: 10.5 mo (95% CI, 8.8-12.2 mo)
Landwehr et al [15]	1979	WBRT	154	Median OS: 8.8 mo
Reichel et al [16]	1979	WBRT	15	Median OS: 10.5 mo (95% CI, 8.8-12.2 mo)
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Landwehr et al [21]	1979	WBRT	154	Median OS: 10.5 mo (95% CI, 8.8-12.2 mo)

Results of Conventional and Stereotactic Radiotherapy for Treatment of Brain Metastases of RCC

Compared with reported results of standard fractionated RT, the techniques of SRS and SBRT have demonstrated good responses in an experimental animal model and in clinical studies of patients with RCC.[19] A prospective trial was conducted by Hoshi et al involving 42 patients with brain metastases from RCC who underwent Gamma Knife (Elekta, Stockholm, Sweden) radiosurgery (GKS). Twenty of the 42 cases had multiple brain metastases. Neurological symptoms, seen in 40 patients, were rapidly improved in 80% of these patients after GKS. MRI evaluation after GKS in 32 patients showed the

disappearance of brain tumor in 28%. The median survival time was 12.5 months, with an overall local control (LC) rate of 80%. [20] Several retrospective studies have shown similar findings (Table 2).

TABLE 3

Study	Year	Patients	Response	LC	Median Survival (mo)
DiBiase et al [21]	1997	114	50%	80%	12.5
Shaw et al [22]	2007	30	100%	97%	52

Results of Standard Radiotherapy and SBRT for Metastatic RCC to Extracranial Sites

Similar improved results with SBRT compared to conventional treatment are also seen for other metastatic sites. DiBiase et al reported results of palliative RT using standard fractionation in 114 patients and showed a 50% pain relief rate. [21] On the other hand, others have shown significantly better response rates and excellent LC rates with SBRT. In a prospective study of 30 patients with 82 lesions (metastatic and inoperable primary RCC) who underwent SBRT at doses of 8 Gy \times 4, 10 Gy \times 4, 15 Gy \times 2, or 15 Gy \times 3, after a median follow-up of 52 months, local progression was seen in only 2% of patients. [22] Results of standard and SBRT treatment of extracranial sites are summarized in Table 3.

TABLE 4

Study	Year	Patients	Response	LC	Median Survival (mo)
Kaplan et al [23]	2011	10	100%	100%	30
Shaw et al [24]	2007	10	100%	100%	30
Shaw et al [25]	2007	10	100%	100%	30
Shaw et al [26]	2007	10	100%	100%	30
Shaw et al [27]	2007	10	100%	100%	30

Results of Stereotactic Radiotherapy Techniques for Treatment of Primary RCC Tumors

With these encouraging results in the metastatic setting, treatment of the primary renal tumor with SBRT is beginning. The only prospective therapeutic trial has recently been reported by Kaplan et al. This prospective phase I dose-escalation study of SRS for primary RCC used CyberKnife (Accuray, Sunnyvale, California) and gold fiducials for image guidance in medically inoperable patients. The dose-level range (21, 28, 32, or 39 Gy) was delivered in three fractions. Tumors up to 5 cm in diameter were included. The investigators reported minimal toxicity; only two patients with chronic renal failure had worsening of their renal function during follow-up. Only one patient treated at a dose of 21 Gy developed local progression. [23] These results, along with results of other retrospective series, are summarized in Table 4. SBRT should continue to be studied prospectively and may play an important role in management of RCC in the future.

Immunotherapy

Immunotherapy with interferon alfa and interleukin-2 has been used for treatment of metastatic clear cell RCC (mRCC) for more than 20 years and is currently the only treatment for this disease that has the potential for a durable complete response (CR). [24-28]

Both interferon alfa and interleukin-2 are components of innate and adaptive immune responses, and function to alter biologic pathways. Interferon alfa modulates a number of proteins, and is noted for its activation of dendritic cells. It also has antiproliferative effects on hematopoietic cells and potentially direct effects on tumor cells. [29] Interleukin-2 was previously named T-cell growth factor, and its major initial effect is expansion and activation of populations of tumor-directed killer cells, along with a cascade of pro-inflammatory cytokines. Clinically it is administered in supra-physiologic doses in an attempt to activate killer cells and overwhelm the tumor-induced immunosuppressive component of the immune system (regulatory T cells and immunosuppressive cytokines). The utilization of these

treatments has been limited by the complexity and intensity of treatment, requiring specialized centers to administer this therapy. Nevertheless, with an outcome that includes decades-long response, interleukin-2 remains in the armamentarium for mRCC.

Recent reports of new immunotherapeutic agents have aroused interest once again in immunotherapy for cancer. One such agent, ipilimumab (Yervoy), is an anti-CTLA-4 monoclonal antibody reported to have activity in mRCC.[30] This agent removes the “brake” from immune activation, leading to an anti-tumor response and auto-immune adverse events.[31,32] The degree and durability of its anti-tumor activity in RCC is still undergoing evaluation. In addition, the PD-1/PD-L (programmed death–1/programmed death–1 ligand) pathway is being investigated because it is directed toward reversing the immunosuppression that tumors are able to induce. This pathway regulates T-cell activation as a mechanism for down-regulation of cytotoxic lymphocytes in the tumor environment, allowing tumor evasion of host immunity.[31]

Radiation and immunotherapy

There has been long-standing interest among radiation biologists in the potential for radiation to induce immune responses. Studies have demonstrated induction of inflammatory cytokines (such as tumor necrosis factor, interleukin-1, and type I interferon[32-34]) and alteration in expression of major histocompatibility (MHC) antigens from exposure to radiation, and thus potential for activation of cellular immunity.[35,36] Clinical studies are needed to assess the role of a combination of immune modulators and RT in patients with cancers such as RCC, in which the immune system plays an important antitumor role.

Targeted Therapy

Within the past 7 years, seven new agents have been approved for the treatment of mRCC. Five of these targeted therapies are specifically focused on anti-angiogenesis, targeting the vascular endothelial growth factor (VEGF)-mediated pathway and impeding new blood vessel growth by the tumor.[37] The interest in anti-angiogenesis treatment and mRCC is predicated on the highly vascular nature of these tumors and the inactivation of von Hippel-Lindau (vHL) gene in the majority of patients with clear cell RCC, with resultant elevated levels of hypoxia-inducible factors (HIFs) and VEGF.[38] Therefore, this seemed the most likely tumor to prove the concept of an antitumor effect of inhibition of VEGF. While this approach on the surface would also appear to be most effective in clear cell mRCC with its associated up-regulation of HIF proteins, there is also definite activity in the non-clear cell subtypes of mRCC. The two additional approved agents for mRCC are directed toward inhibition of the mammalian target of rapamycin (mTOR) and have a multitude of downstream effects, including anti-angiogenesis, antimetabolism, and impairment of protein synthesis.[39]

These seven agents are all administered as outpatient therapies, and five are oral agents. While they target similar pathways, there are also drug-specific effects, so distinguishing between the different agents and developing algorithms of treatment has become complicated. There are questions regarding sequencing of these drugs and their role, if any, in combination therapy or combined with immunotherapy.

TABLE 5

Agent	Regimen	ORR (%)	PFS (months)	OS (months)
Bevacizumab	Bevacizumab + IFN-α	31	10.2	24
Sunitinib	Sunitinib	13	5.4	10
Sorafenib	Sorafenib	13	5.4	10
Pazopanib	Pazopanib	13	5.4	10
Everolimus	Everolimus	13	5.4	10
Axitinib	Axitinib	13	5.4	10
Temsirolimus	Temsirolimus	13	5.4	10
Ipilimumab	Ipilimumab	13	5.4	10
Nivolumab	Nivolumab	13	5.4	10
CheckMate 010	CheckMate 010	13	5.4	10
CheckMate 013	CheckMate 013	13	5.4	10
CheckMate 014	CheckMate 014	13	5.4	10
CheckMate 015	CheckMate 015	13	5.4	10
CheckMate 016	CheckMate 016	13	5.4	10
CheckMate 017	CheckMate 017	13	5.4	10
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CheckMate 098	CheckMate 098	13	5.4	10
CheckMate 099	CheckMate 099	13	5.4	10
CheckMate 100	CheckMate 100	13	5.4	10

Phase III Agents for Treatment of Metastatic RCC

The initial anti-angiogenesis study by Yang using [bevacizumab](#) ([Drug information on bevacizumab](#)) (Avastin) in mRCC showed marked decline in rates of tumor growth, and even tumor shrinkage.[40] Two subsequent phase III studies, one in Europe (AVOREN [Avastin and Roferon in Renal Cell Carcinoma]) and one in the United States (CALGB [Cancer and Leukemia Group B]) compared bevacizumab plus interferon alfa to interferon alfa alone. The overall response rate (ORR) doubled with the addition of bevacizumab, with ORRs of 31% vs 13%[41] and 25% vs 13%, [42] respectively; there was also a significant improvement in progression-free survival (PFS) with the combination (with PFS results of 10.2 vs 5.4 months[41] and 8.5 vs 5.2 months, [42] $P < .0001$, respectively). The oral anti-angiogenesis agents have also demonstrated antitumor activity in mRCC in terms of improved PFS following cytokines (sorafenib [Nexavar], sunitinib [Sutent], pazopanib [Votrient]), in comparison with interferon in previously untreated patients (sunitinib, bevacizumab), and following treatment with other anti-angiogenesis tyrosine kinase inhibitors (TKIs; axitinib [Inlyta]).[41-46] The mTOR inhibitors have been shown to have activity in poor-risk mRCC patients, in non-clear cell mRCC (temsirolimus [Torisel]), and following treatment with anti-angiogenesis TKIs (everolimus [Afinitor]).[47,48] All of these agents produce a plateau of PFS, and when given as single agents sequentially, they appear to extend overall survival (OS) for patients with mRCC. The median survival of mRCC patients with intermediate risk, entered into recent trials in which crossover to other active agents is permitted, is now approaching 24 months (compared with 10 months prior to the availability of multiple agents).[39] [Table 5](#) summarizes phase III data from trials of new approved agents for mRCC.

Non-Clear Cell Renal Cell Carcinoma

Non-clear cell RCC includes a broad spectrum of histologies, from adenocarcinomas with papillary and chromophobe histology, to tumors arising more distally, such as collecting duct and medullary renal cell carcinoma. Additionally the translocation RCC found in young people seems to be a distinct entity, with a distinct Xp translocation. There is also sarcomatoid de-differentiation that is seen arising from clear cell or papillary RCC.

There have been substantial investigations in recent years of the different subtypes of renal cancer, initially by histologic appearance—that is, clear cell, papillary, chromophobe, or collecting duct tumors—and more recently by recognition of molecular and gene expression profiles characteristic of different subtypes, which perhaps will eventually direct therapy.[49,50] The distinction between clear cell and non-clear cell types of renal cancer lead to the observation that clear cell renal cancer is more likely to be responsive to immunotherapy than non-clear cell.[24] This is the most definitive distinction with an impact on current treatment choices.

Non-clear cell RCC in general is not thought to be sensitive to immunotherapy, although anecdotal responses are reported in patients with papillary and chromophobe subtypes.[51] In addition, the initial clinical trials of anti-angiogenesis agents were restricted to patients with clear cell carcinoma. However, in the expanded-access trials of [sorafenib](#) ([Drug information on sorafenib](#)) and sunitinib that were opened to allow broader patient access prior to commercial availability, the eligibility criteria were greatly expanded. Approximately 10% of patients in these trials of 5000 patients each had non-clear cell

histologies.[52,53] While strict response evaluation was not completed due to the rapid availability of the commercial drug, the overall impression was that there was no difference in outcome for those with non-clear cell histologies, in terms of response or toxicity. Additionally, in the phase III trial of temsirolimus vs interferon, about 10% of the RCC patients had non-clear cell histologies, mainly papillary histology, reported by the treating institutions. In a specific analysis, patients with non-clear cell RCC did as well—or better—with temsirolimus as they did with interferon (due in part to the lack of efficacy of interferon in this RCC subtype).[54] These data, therefore, have led to the use of targeted therapies in mRCC of non-clear cell histologies, albeit with no further formal study.

At the other end of the spectrum, collecting duct and medullary RCC are very aggressive subtypes, are more similar to urothelial cancers, and on the basis of anecdotal evidence are treated with chemotherapy regimens used for urothelial cancers, but with no specific regimen identified as optimal. Reports of treatment for these subtypes include therapy with taxanes, [cisplatin](#)([Drug information on cisplatin](#)), [carboplatin](#)([Drug information on carboplatin](#)), and [gemcitabine](#)([Drug information on gemcitabine](#)) (Gemzar). These variants are so uncommon that clinical trials have not been accomplished. Medullary RCC is associated with sickle cell trait; is seen in younger patients; usually presents with widespread metastatic disease; and is treated with chemotherapy or targeted agents, with limited success.[55] RCC with a large component of sarcomatoid features is the most aggressive classification, with very rapid growth of metastatic disease. We have reported some success with a chemotherapy regimen of [doxorubicin](#)([Drug information on doxorubicin](#)) and gemcitabine, including complete responses, some of which have been durable.[54] An ongoing Eastern Cooperative Oncology Group study is evaluating sunitinib alone compared with sunitinib plus gemcitabine in patients with tumors that have sarcomatoid features. The Cleveland Clinic has reported some success with anti-VEGF targeted therapies in this variant, but with responses seen only in patients who have clear cell RCC with less than 20% sarcomatoid features.[56]

Conclusions

The treatment of RCC has been enhanced in recent years. Several newer agents have been introduced, generally targeting the angiogenesis pathways; these have significant antitumor effects and have become part of the routine care of this disease, resulting in improved disease control and survival. Immunotherapy continues to play an important role and can induce long-term remissions. In addition, although conventional RT continues to play a role, particularly in bone metastases, SBRT appears superior to conventional treatment in the metastatic setting and should be considered when feasible. Finally, use of stereotactic techniques to treat the primary RCC tumor is under study and may come to play an important role in the management of RCC in the future.

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