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Adjuvant Therapy in Renal Cell Carcinoma

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Abstract Renal cell carcinoma (RCC) is characterized by (a) lack of early warning signs, which results in a high proportion of patients with metastases at the time of diagnosis; (b) protean clinical manifestations; and (c) resistance to radiotherapy and chemotherapy. The estimates of new diagnoses and deaths from kidney cancer in the United States during 1996 are 30,600 and 12,000, respectively. RCC occurs nearly twice as often in men as in women. The age at diagnosis is generally older than 40 years; the median age is in the midsixties. The incidence of RCC has been rising steadily. Between 1974 and 1990, there was a 38% increase in the number of patients who had a diagnosis of RCC. This increase was accompanied by a significant improvement in 5-year survival. Both trends are likely the result of improved diagnostic capability. Newer radiographic techniques, including ultrasonography, computed tomography, and magnetic resonance imaging, are detecting kidney tumors more frequently and at a lower disease stage, when tumors can be resected for cure. Surgical treatment is the only curative therapy for localized RCC. Radical nephrectomy remains the mainstay of surgical management, but techniques are being modified. These modifications include partial nephrectomy and resection of vena caval thrombi. In highly selected cases, surgical resection of locally recurrent RCC or of disease at a solitary metastatic site is associated with long-term survival. Metastatic RCC is highly resistant to the many systemic therapies that have been extensively investigated. A minority of patients achieve complete or partial response to interferon, interleukin-2, or both. Response can be dramatic but is rarely durable. Because most patients do not achieve response, these agents are not considered effective treatments for RCC, but the response in some patients indicates the need for continued research on their use. Identification of new agents with better antitumor activity against metastases remains a high priority in clinical investigation of therapy for this refractory disease.

Keywords: *Renal Cell Carcinoma, RCC, Therapy*

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1. Introduction

Renal cell carcinoma (RCC) is common among men and women worldwide [1]. Due to widespread use of computed tomography and renal ultrasound, the incidence of RCC has been increasing over the past three decades [1,2]. While there has been a significant increase in the incidence of RCC, survival for patients with local, regional, and distant disease has only modestly improved over the past several decades. From 2000 to 2011, 5-year cancer-specific survival for RCC was 94% for localized disease, 71% for regional disease, and 12% for distant disease [3]. In the metastatic setting, most recent data from contemporary phase 3 studies demonstrate a 5-year overall survival of 48% for patients with intermediate and poor risk RCC being treated with ipilimumab and nivolumab and 3-year overall survival of 63% for patients with RCC receiving pembrolizumab and axitinib [4]. For patient with localized disease, the standard of care continues to be radical or partial nephrectomy. Despite definitive surgical resection, a subset of patients with localized disease go on to develop distant metastases and lethal RCC.

Outcomes for patients with localized RCC are heterogeneous. According to one systematic review of contemporary data, 5-year recurrence free survival varied from 42% to 98% [5]. In this review, we highlight scoring models and algorithms to aid in risk stratification for patients with localized RCC. There have been a multitude of agents that have been tested in the adjuvant setting including cytokine based treatments, targeted therapies, and most recently checkpoint inhibitors. Despite the volume of agents tested, there still remains a very limited number of treatments which have demonstrated clinical efficacy in the adjuvant setting. In this review, we discuss the role of adjuvant immunotherapy in RCC.

2. Risk Stratification

Given the heterogeneous outcomes in terms of cancer

recurrence and metastasis after nephrectomy for localized RCC, risk stratification tools have been developed to identify patients at increased likelihood of adverse outcomes. The TMN staging system, which takes into account tumor size and disease extension as estimated by T stage, is an important prognostic tool in RCC. This staging system has also been incorporated with a number of prognostic factors into nomograms (Table 1). The local and distant recurrence rates at a mean follow-up of 56 months was 0% and 4.4% for T1; 2.0% and 5.3% for T2, 8.2% and 11.5% for T3a, 10.6% and 14.9% for T3b, respectively [6]. Possibly due to relatively low frequency of lymph node dissection in RCC, the frequency of node positive disease is low but when present is associated with poor prognosis [7]. In addition to TNM staging, tumor grade has been historically shown to be associated with tumor recurrence independent of tumor stage [8]. For example, for T1 tumors, 5-year cancer-specific survival for grade 1, 2, 3, and 4 histology was 91%, 83%, 60%, and 0% [8]. The TNM staging system has been incorporated with several other factors potentially associated with recurrence such as histologic features, performance status, Fuhrman grade, tumor size, tumor necrosis, presence of symptoms, and margin status. These risk factors are reflected in several nomograms developed for disease prognostication in the setting of localized disease (Table 1). These nomograms vary either in their input clinical or pathologic characteristics or their computed outcomes, for example disease-free survival, cancer specific survival, or overall survival.

In addition to patient clinical and pathologic characteristics, several studies have investigated biomarkers for predicting post-surgical disease recurrence [9,10]. Several molecular assays have been developed. ClearCode34, a 34-gene classifier was developed to sub-stratify clear cell RCC to estimate recurrence-free survival and overall survival [11]. In contrast, the cell cycle proliferation (CCP) score is an RNA assay characterizing expression of cell cycle proliferation genes [12]. On multivariable regression analyses, CCP was significantly associated with recurrence and disease-specific mortality after radical nephrectomy in localized clear cell, papillary, and chromophobe RCC [12]. Moreover, long non-coding RNA signature has also been shown to exhibit potential utility in disease prognostication in RCC [13]. There is a great deal of ongoing interest in utilization of molecular markers for risk stratification, disease prognostication, and potentially guiding neoadjuvant or adjuvant systemic therapy in advanced RCC. Currently, however, there exists no validated criteria beyond clinical information and histopathology for risk assessment.

3. Adjuvant Cytokine Therapy

Cytokine therapy was first among many classes of therapies to be investigated in the adjuvant setting after nephrectomy. Beginning in the 1980s, seven key studies investigated the role of adjuvant cytokine-based treatment post nephrectomy. These were the first trials to test immunotherapy strategies in the adjuvant setting. One of the earliest trials by Trump et al. and Porzolt et al. utilized adjuvant lymphoblastoid interferon (IFN) and recombinant IFN-2a in RCC with perinephric fat, renal vein, or inferior vena cava involvement [14,15]. These therapies did not improve disease-free survival. From the 1990s to 2000s, additional studies evaluated the efficacy of IFN-α2b (rIFNα2b) and IFN-NL; both these trials were negative [16,17].

Interleukin 2 (IL-2) was evaluated in the 2000s as a potential adjuvant therapy in RCC. In a randomized phase III clinical trial, Clark et al. evaluated high dose bolus IL-2 in patients with high-risk RCC post resection [18]. The primary endpoint of 30% improvement in 2-year disease-free survival was not met [18]. Additional trials investigated IFN in comparison to IL-2 and chemotherapy and all failed to improve outcomes for patients and were associated with increased toxicity [19,20]. The adjuvant cytokine trials are summarized in Table 2. Currently, there is no role for adjuvant cytokine-based treatments in RCC.

4. Adjuvant Targeted Therapy

After these negative cytokine trials, there was a hiatus in exploring adjuvant therapy in localized RCC. During this time, tyrosine kinase inhibitors and mammalian target of rapamycin (mTOR) inhibitors began to show efficacy for metastatic RCC. Thus, the next rationale was to test these agents in the adjuvant setting. The adjuvant targeted therapy studies, summarized in Table 3, have produced mixed results. These trials tested the efficacy of adjuvant sunitinib, sorafenib, pazopanib, axinitib and everolimus with the primary endpoint of disease-free survival [21,22,23,24,25,26,27]. Of the trials discussed in this domain, the ASSURE and S-TRAC trials are most frequently highlighted in the literature [21,23,24,25,26,27]. The ASSURE trial was a phase III randomized, double-blind, placebo-controlled study evaluating sunitinib, sorafeninb, and placebo in patients with non-metastatic RCC (including non-clear cell histologies) after complete resection [26]. It was the largest of the adjuvant studies to date. The primary endpoint, disease-free survival, was not met among the treatment arms [26]. Furthermore, subgroup analyses in patients with only clear cell histology or those with pT3 or pN1 disease showed no benefit to treatment [22].

The S-TRAC trial was the only positive trial of the targeted therapy studies. It was a phase III randomized, double-blind, placebo-controlled study evaluating sunitinib in patients with locoregional high-risk clear cell RCC [23]. The trial was carefully designed and more specific in its patient selection. Unlike the ASSURE trial, which included patients with lower risk tumors, the S-TRAC trial selected for patients with only clear cell histology and high-risk locoregional disease (tumor stage 3 or higher, regional lymph-node metastasis, or both) [23,26]. The primary endpoint of disease-free survival was longer in the sunitinib treatment arm (median 6.8 vs 5.6 years, Hazard Ratio [HR] 0.76, 95% Confidence Interval [CI] 0.59–0.98; $p=0.03$) [23]. However, sunitinib did not result in improvement in overall survival and was associated with increased incidence of grade 3 and 4 adverse events and decreased quality of life [23]. Ultimately, sunitinib was approved by the Food and Drug Administration in the United States [28]. The European

Medicines Agency, however, did not approve adjuvant sunitinib. In clinical practice, adjuvant sunitinib is not routinely administered and requires careful shared decision making with patients regarding the risks and benefits of treatment.

Several explanations have been proposed to examine the reasons behind the failures of the adjuvant TKI trials. One, these negative trials were potentially weakened by inclusion of lower risk patients. For example, 34–35% of patients in the treatment arms of ASSURE were AJCC stage I or II [26]. Two, toxicity of TKI required several trials to lower the starting dose of TKI, potentially decreasing efficacy. In SOURCE, only 13% of patients received the full starting dose [21]. Three, it is possible that from a mechanistic standpoint, TKIs alone lack the capability to eradicate micrometastatic disease given the lack of overall survival benefit in these trials. This finding is mirrored in the metastatic setting; for example in poor risk metastatic RCC treated with sunitinib compared to IFN-α, median PFS and OS did not significantly differ between the arms HR=0.660 (95% CI, 0.360 to 1.207) [29].

Table 1. Models for prognostication in localized renal cell carcinoma

Model	Parameters	Outcome	Type
UISS	TNM, grade, ECOG PS	OS	KM analysis
Leibovich	TNM, pN+, tumor size, grade, tumor necrosis	MFS	Algorithm
SSIGN	TNM, pN+, pM+, tumor size, grade, tumor necrosis	CSS	Algorithm
MSKCC	TNM, tumor size, grade, tumor necrosis, symptoms	RFS	Nomogram
Kattan	TNM, tumor size, histology, symptoms	RFS	Nomogram
Yaycioglu	Tumor size, symptoms	RFS	Formula
Karakiewicz	TNM, age, sex, + margin, tumor size, symptoms	CSS	Nomogram
Cindolo	Tumor size, symptoms	RFS	Formula

UISS=University of California Los Angles Integrated Staging System, SSIGN=Stage, Size, Grade and Necrosis Score for Renal Cell Carcinoma; MSKCC=Memorial Sloan Kettering Cancer Center Nomogram, ECOG=Eastern Cooperative Oncology Group, PS=Performance Status, pN+=pathologically confirmed nodal metastasis; pM+=pathologically confirmed distant metastasis, + margin=positive margin, OS=overall survival, MFS=metastasis-free survival, CSS=cancer-specific survival, RFS=recurrence-free survival, KM=Kaplan-Meier.

Table 2. Adjuvant cytokine therapy trials in renal cell carcinoma

Trials	Population	Arms	N	Primary	Hazard Ratio Confidence Interval
Trump et al. (1987)	pT3-4aN0 or pTxN1-3	L-IFN vs. Observation	294	Recurrence	No Difference. Hazard Ratio NA
Porzsolt et al. (1988)	pT3-4N0 or pTxN1-3	IFN-α vs. Observation	270	TTF/Survival	No Difference. Hazard Ratio NA
Clark et al. (1990)	pT3b-4Nx or pTxN1-3	IL-2 vs. Observation	138	2-year DFS	No Difference. Hazard Ratio NA
Pizzocaro et al. (2001)	pT3-4aN0 or pTxN1-3	IFN-a vs. Observation	247	5-year OS	1.040 (95% CI, 0.671–1.613) p=0.861
Messing et al. (2003)	pT3-4aN0 or pTxN1-3	IFN-α vs. Observation	283	5-year OS	1.35 (95% CI 0.98–1.36) p=0.09
Atzpodien et al. (2005)	pT3b-4Nx or pTxN1-3	IL-2/IFN-a/5-FU vs. Observation	203	2-year DFS	p=0.2398. Hazard Ratio NA
Aitchison et al. (2014)	pT3b-4Nx or pTxNa-2 or +margins/vascular invasion	IL-2/IFN-a/5-FU vs. Observation	309	3-year DFS	0.87 (95% CI 0.61–1.23) p=0.428

+ margin=positive margin, NA=not available, IFN-α=interferon alpha, L-IFN=lymphoblastoid interferon, IL-2=interleukin 2, 5-FU=5 fluorouracil, TTF=time to treatment failure, DFS=disease-free survival, OS=overall survival, vs=versus.

Table 3. Adjuvant tyrosine inhibitor trials in renal cell carcinoma

Trial	Arms	Years	N	Primary Endpoint	Clear Cell Only	Eligibility	Hazard Ratio Confidence Interval
ASSURE	Sunitinib vs. Sorafenib vs. Placebo	1	1943	DFS	No	pT1bG3-4N0, pT2-4GxN0, TxGxN +	Sunitinib –1.02 (97.5% CI 0.85–1.23), p=0.8038 Sorafenib –0.97 (97.5% CI 0.80 – 1.17), p=0.7184
S-TRAC	Sunitinib vs. Placebo	1	615	DFS	Yes	pT3-4GxN0-x, TxGxN1-2	0.76 (95% CI 0.59–0.98), p=0.03
PROTECT	Pazopanib vs. Placebo	1	1538	DFS	Yes	pT2G3-4N0, pT3-4N0, pTxN1	0.86 (95% CI 0.70–1.06), p=0.165
ATLAS	Axinitib vs. Placebo	1–3	724	DFS	Yes	pT2-GxN0, pTxN1	0.870 (95% CI 0.66–1.147), p=0.3211
SORCE	Sorafenib vs. Placebo	1–3	1711	DFS	No	Leibovich scores 3–11	1.01 (95% CI 0.83–1.23), p=0.95

EVEREST	Everolimus vs. Placebo	1	1545	RFS	No	pT1bG3-4N0 to pT3a G1-2N0, pT3aG2-4 to pT4 G1-4 or N1	0.85 (95% CI, 0.72 –1.00); 1-sided p=0.0246, not significant because p greater than one-sided significance level of 0.022.

DFS=disease-free survival, RFS=recurrence-free survival, G1-4=grade 1 to 4, CI=confidence interval, vs=versus.

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