Adjuvant Therapy for High-risk Renal Cell Carcinoma Patients

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Current Urology Reports 2007, 8:19–30
Current Medicine Group LLC ISSN 1527-2737
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For most cases of renal cell carcinoma (RCC), the standard of care is surgical resection as monotherapy or as part of a multimodal approach. In patients with early localized disease, radical nephrectomy is associated with a favorable prognosis, whereas patients with advanced disease are rarely cured. A significant number of patients undergoing surgery for localized RCC experience recurrence, suggesting that there are some individuals in whom surgical excision is necessary but insufficient. In these patients, the development of effective adjuvant strategies is imperative. In this article, we review the prognostic variables and comprehensive staging algorithms for identifying patients at high risk for disease recurrence. Additionally, we review data from completed adjuvant RCC trials and highlight relevant ongoing trials.

Introduction

Kidney cancer accounts for 3% of all malignancies with an estimated 36,160 new cases and approximately 12,660 deaths annually, making renal cell carcinoma (RCC) the most lethal of all genitourinary tumors [1].

Like most malignancies, RCC is a heterogeneous disease. This heterogeneity is reflected in its presentation, pathology, molecular biology, and clinical course. Patients may exhibit a variety of symptoms at presentation, including any of the classic triad of flank pain, hematuria, and a palpable abdominal mass [2]. Other nonspecific presenting symptoms include fatigue, weight loss, or anemia [2], though some patients may be completely asymptomatic. The widespread use of body imaging modalities has led to increased detection of incidental renal masses over the past two decades [3]. Pathologic heterogeneity is illustrated by several distinct histologic subtypes, which exhibit varying degrees of biologic aggressiveness [4•], and by variations in tumor grade (nuclear/nucleolar size, shape, and content) [5]. Emerging data from molecular analyses indicate that RCCs express a variety of molecular tumor markers and unique patterns of gene expression [6,7]. Clinically, the disease behaves quite heterogeneously, with courses ranging from indolent to highly aggressive. Although relatively few data exist regarding the natural history of untreated RCC, a recent meta-analysis demonstrates that most small renal tumors exhibit slow albeit variable growth kinetics [8].

For most cases of RCC, surgery alone or as part of a multimodal approach remains the standard of care. In patients with early, localized disease, radical nephrectomy is associated with a 5-year cancer-specific survival (CSS) as high as 97% for pT1a lesions and 87% for pT1b tumors, whereas nephron-sparing surgery is associated with 5- and 10-year CSS of 96% and 90%, respectively, for tumors 4 cm or smaller [9,10]. Early data regarding laparoscopic partial nephrectomy is similarly favorable, with 100% CSS at 3-year median follow-up [11]. Additionally, minimally invasive ablative technologies are emerging as potential treatment options for localized RCC with excellent initial outcomes [12].

Unfortunately, 20% of patients at presentation have either locally advanced or node positive (N+) RCC, whereas another 22% have metastatic RCC (mRCC) [1]. Figure 1 depicts 5- and 10-year survival rates for patients presenting with localized, regionally advanced, and mRCC. Unlike the outcomes in early localized disease, survival rates for N+ patients are 11% to 35% at 5 years [4•], and patients with N+ mRCC are rarely cured despite aggressive multimodal therapy. Cytoreductive nephrectomy with systemic therapy in mRCC is associated with few cures and poor CSS outcomes with median survivals of 12 to 24 months [13–17]. Moreover, only 5% to 20% of patients with mRCC respond to biologic drugs such as interferon (IFN) and/or interleukin (IL) [18–20]. The use of oral tyrosine kinase inhibitors in mRCC has improved overall response rates to 10% to 42%, with disease stabilization in another 26% to 74% [21••,22••].

Between the extremes of early incidental RCC and mRCC exists a gradation of risk. Twenty to 40% of patients undergoing surgical resection for localized RCC experience recurrence [4•], suggesting that there are some individuals in whom surgical excision is necessary but
insufficient. In these patients, the development of effective adjuvant strategies is imperative. The use of adjuvant therapies to treat patients with high-risk malignancies has been explored for many different solid tumors. These efforts seek to eradicate micrometastatic disease that has escaped surgical control using systemic therapies. There have been relatively few adjuvant studies in RCC due to ineffective systemic therapies for mRCC, a high toxicity profile for most immune modulators, and difficulty recruiting to multi-institutional and cooperative group adjuvant trials for RCC.

In this article, we review the prognostic variables and comprehensive staging algorithms for identifying patients at high-risk for disease recurrence after surgery for RCC. Additionally, we review data from completed adjuvant RCC trials and highlight relevant ongoing trials.

Defining Risk in RCC

Patterns of disease recurrence

Integral to designing an appropriate adjuvant strategy is a fundamental understanding of patients who are at risk for recurrence, when and in what area disease recurs in these patients, and what the important prognostic variables in RCC are. Approximately one third of patients presenting with localized RCC will experience a recurrence after surgery [4•,23•]. Most common are recurrences in the lung, liver, bone, and brain. Local or contralateral recurrence is uncommon but may be higher in some patients treated with nephron-sparing surgery [24]. Surveillance studies are conducted after resection of localized disease to detect recurrence in sites in which treatment may prolong survival or improve palliation. From 52% to 84% of recurrences are discovered during laboratory and/or radiographic surveillance [25]. As stated, survival for patients with mRCC is poor, with a median survival of less than 1 year [26]. Patients who relapse usually succumb to distant metastases as a consequence of the historically ineffective systemic therapy for mRCC. Prognostic algorithms have been developed to quantitate the risk of recurrence after surgery and are discussed later [27–31].

The majority of recurrences after surgical extirpation occur within 3 years. Reports indicate that median recurrence times are 1.7, 1.6, 1.5, and 2.5 years for abdomen, chest, bone, and brain, respectively [32]. Patients with a higher stage or grade at presentation are at proportionally higher risk and tend to experience recurrence within the first 2 to 4 years [32]. Alternatively, patients with lower grade and stage disease have a more gradual decrease in recurrence-free survival and may experience recurrences even after 5 years [32]. Consequently, most surveillance strategies are stage and grade specific.

The most common site of RCC metastasis is the lung, with an incidence among 3% to 16%. Solitary pulmonary recurrence can often be treated with surgical resection. Among patients who develop metastatic disease, 29% to 54% have a pulmonary recurrence [25]. Sixteen to 27% of all patients with recurrent disease have metastasis to the bone, which usually presents with bony pain and is generally treated with palliative measures [25]. Brain metastasis occurs in 2% to 10% of those with recurrent disease, representing less than 2% of RCC patients [25]. Liver metastases have been reported in 1% to 7% of cases and generally carry a poor prognosis, though long-term survival after resection may be possible [25]. Local recurrence after radical nephrectomy is relatively rare, occurring in 5% to 27%; though these rates are confounded by the inclusion of patients with locally advanced or lymph node positive disease [25].

Prognostic variables in RCC

Accurate prognostic methods allow for the identification and selection of patients most likely to benefit from adjuvant therapies. Clinical, anatomic, histologic, and molecular variables in RCC have been shown to be associated with patient outcomes after surgical resection (Table 1).

Important clinical prognostic characteristics for patients with RCC include the presence of symptoms at presentation, performance status, cachexia, and several laboratory parameters. Patients with symptoms attributable to the primary tumor on presentation appear to have a significantly worse prognosis than those with incidentally detected tumors, though this difference may be lost when controlling for stage [33]. Overall health status, determined by the Karnofsky scale or Eastern Cooperative Oncology Group performance status (ECOG-PS), has been closely correlated with survival. Patients with an ECOG-PS greater than or equal to one have a 5-year survival rate of 51% compared with the 81% 5-year survival for patients.

![Figure 1. Relative survival rates by stage at diagnosis for kidney cancer.](Data from the National Cancer Institute [73].)