Renal cell carcinoma is an important malignancy accounting for approximately 3% of all adult cancers [1]. The incidence of renal cell carcinoma has been steadily and significantly increasing over the past two decades, with worldwide mortality expected to exceed 100,000 [2]. A significant proportion of patients with localized disease can be cured by nephrectomy; however, at presentation approximately 50% of patients have locally advanced or metastatic disease [3]. The outlook for these patients remains poor, with a 5-year survival of less than 10% [2].

Renal cell carcinoma is an inherently chemoresistant tumor. There have been many trials of single agent and combination chemotherapy regimens; however, response rates are low and characteristically of short duration. Yagoda and colleagues [4], in a review of 4093 adequately treated patients in 83 phase II chemotherapy trials published between 1983 and 1993, showed an overall response rate of only 6%. Thus, there is no role for chemotherapy alone in the treatment of renal cell carcinoma, but there have been improvements in survival as a result of the development of cytokine therapy.

Prognostic Factors

Metastatic renal cell carcinoma encompasses a heterogeneous group of patients, and it is important to identify prognostic factors that predict survival. Assessment of these factors can assist in decisions regarding patient management as well as categorizing patients in clinical studies, thus aiding trial interpretation. The initial analysis of these factors was carried out by Elson and colleagues [5]. This retrospective study looked at 610 patients treated in the Eastern Cooperative Group (ECOG) phase II trials for advanced renal cell carcinoma between 1975 and 1984. They identified the following risk factors (see below), which enabled them to stratify patients into appropriate risk groups (Table 17.1):

1. ECOG performance status (performance status 1, 2, and 3 counting as one, two, and three risk factors respectively)
2. Recent diagnosis (<1 year)
3. More than one metastatic site
4. Recent weight loss
5. Prior cytotoxic chemotherapy

Other studies analyzing prognostic factors in patients with metastatic renal cell carcinoma have defined different parameters, but consistently performance status and a measure of disease extent appear to be important indicators of survival [6–8].

A retrospective study by Motzer and colleagues [9] looked at the relationship between pretreatment clinical features and survival in 670 patients with advanced renal cell carcinoma treated in Memorial Sloan-Kettering Cancer Center clinical trials between 1975 and 1996. The
following five pretreatment features were associated with a shorter survival in the multivariate analysis:

1. Low Karnofsky performance status (<80%)
2. High serum lactate dehydrogenase (≥1.5 times upper limit of normal)
3. Low hemoglobin (less than the lower limit of normal)
4. High corrected serum calcium (≥10 mg/dL)
5. Absence of prior nephrectomy

Using these factors the authors stratified patients into three separate risk groups (Table 17.2). A recent study from the same group has analyzed prognostic factors in previously treated patients with metastatic renal cell carcinoma [10]. More patients are entering second-line trials of therapy, and thus stratification of these patients is becoming increasingly important. A total of 251 patients treated in 29 consecutive trials between 1975 and 2002 were analyzed. Median survival for the 251 patients was 10.2 months and differed according to the year of treatment, with patients treated after 1990 showing longer survival. The median overall survival for this group was 12.7 months.

The purpose of this study was to establish prognostic factors for this group of patients, who had all received prior cytokine therapy (interferon and/or interleukin-2), and thus establish prognostic factors for current clinical trial design. Pretreatment features associated with a poorer prognosis in the multivariate analysis were low Karnofsky performance status (<80%), low hemoglobin (less than the lower limit of normal), and high corrected serum calcium (≥10 mg/dL). Although these and the previously mentioned prognostic factors are useful in aiding management decisions and subsequently in interpreting trial results, they are not prescriptive, and each patient should be assessed individually.

It is also important to be aware that histologically renal cell carcinoma is a diverse group of tumors, including clear cell, papillary, chromophobe, collecting duct and unclassified cell types. Of these, clear cell is the most common subtype, accounting for approximately 70% of cases. The importance of distinguishing between these different histologies is shown by the fact that metastatic non–clear cell carcinoma is characterized by an increased resistance to systemic therapy and poorer survival [11].

### Immunotherapy

The immune system has evolved to detect and destroy molecules or pathogens that are recognized as “non-self” but not to react to host tissues. Manipulation of the immune system for cancer treatment attempts either to make the tumor appear more foreign when compared to normal tissues or to magnify host immune responses to tumors. The variable natural history of metastatic renal cell carcinoma, and occasional observed spontaneous regression

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Risk factors</th>
<th>Percent of patients</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>0</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1–2</td>
<td>53</td>
<td>10</td>
</tr>
<tr>
<td>Poor</td>
<td>3 or more</td>
<td>22</td>
<td>4</td>
</tr>
</tbody>
</table>

From Motzer et al. [9].