Renal cell carcinomas include a group of epithelial neoplasms, such as clear-cell and papillary carcinomas, that continue to pose significant management challenges in patients with either localized or advanced disease. The article by Wolchok and Motzer describes the current status of therapy for patients with advanced neoplasms.

The authors discuss the issue of stage migration, and they postulate that earlier detection may be responsible for some of the improvements in survival that have been noted during the past 20 years. A recent study by Chow et al.[1] investigated this issue to determine whether earlier-stage patients who are diagnosed incidentally are responsible for this increase in incidence. The results of this investigation indicated that both patients with metastatic disease and those with incidentally discovered renal masses have contributed to the overall increased incidence of this tumor.

The surgical management of renal cancer involves total nephrectomy. More conservative approaches, which are discussed in this article, are relevant for patients with small tumors or abnormal renal function.

Newer approaches to the management of localized renal cancer involve the use of laparoscopy and, more recently, cryoablation of tumors under laparoscopic guidance. These approaches are still under evaluation but may be useful in selected circumstances.

**Role of Immunosuppression**

Wolchok and Motzer discuss the role of immunosuppression in renal cancer. They indicate that there is no definitive evidence of immunosuppressive activity in the primary tumor; thus, removal of the tumor for this purpose may not be relevant.

A recent study by Uzzo et al.[2] investigated T-cell abnormalities in the peripheral blood of patients with both localized and advanced renal cell cancer. This group demonstrated that 60% of patients with the primary tumor in place had abnormal NFkB activation in peripheral blood T-cells, which could revert to a normal pattern following removal of the primary tumor. This transcription factor plays a role in the induction of a series of immune-related genes, such as interferon-gamma. The nature of the immunosuppressive factor produced or associated with the primary tumor was not identified; however, the findings did demonstrate the presence of immune dysfunction in patients with primary renal neoplasms in place.

**Management of Metastatic Disease**

Finally, the management of metastatic renal cell carcinoma continues to represent a significant challenge. The histologic variety of renal cancers, such as clear-cell carcinoma, granular cell carcinoma, papillary carcinoma, or undifferentiated neoplasm, may be a relevant issue in the frequency of response. It is unclear whether papillary tumors respond in a manner similar to clear-cell cancers. This kind of data, which hopefully will be available in the future, will help guide the selection of treatments for these individuals.

Wolchok and Motzer correctly point out that chemotherapy is inactive in renal cell carcinoma. The use of immunotherapy, in the form of systemic administration of cytokines, has assumed a significant role in the treatment of this malignancy. Interferons exhibit some antitumor activity, and, as noted by the authors, recent reports have indicated an improvement in median survival utilizing recombinant interferon-alfa (Intron A, Roferon-A).

Some new developments in interferon therapy include the evaluation of other interferon subtypes and the evaluation of a pegylated form of recombinant interferon-alfa (PEG Intron). The latter preparation appears to have the advantage of less frequent administration and the potential for less toxicity; early studies have reported responses to this preparation in patients with renal cell carcinoma.[3]

The use of monoclonal antibody therapy has also has been pursued by investigators. Trastuzumab
(Herceptin), a monoclonal antibody targeting cells overexpressing HER-2/neu, is of interest given the presence of this protein in selected renal tumors. The frequency of HER-2/neu overexpression is uncertain, but it does appear that selected renal tumors express this protein.

**New Therapeutic Approaches**
The findings of mutations in the von Hippel-Lindau (VHL) gene in clear-cell carcinoma of the kidney, along with the functions of the VHL protein, suggest therapeutic strategies that involve inhibition of angiogenesis. The uncontrolled expression of vascular endothelial growth factor may be related to the presence of mutated VHL protein[4]; this observation provides a rationale for the exploration of this class of agents.

One antiangiogenesis inhibitor under investigation is a vascular endothelial growth factor monoclonal antibody. Other agents that may inhibit the receptors for vascular endothelial growth factor, as well as nonspecific inhibitors of angiogenesis (such as the interferons and thalidomide [Thalidomid]), are also under study.

**Conclusions**
Current therapy for metastatic renal cell carcinoma remains of limited value. Conventional therapy with cyto-kines, although useful in selected patients, produces few complete, durable responses. The present article correctly states that preclinical and clinical investigation of novel agents and new approaches to the treatment of metastatic renal cell carcinoma is required. In addition, a better understanding of the relationship of histology to therapeutic outcome, along with identification of patients who are more likely to respond via prognostic factor analysis, will be of potential value.

**References:**


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