1. Introduction

Cancer of the kidney and renal pelvis is expected to account for an estimated 38,890 new cases and 12,840 deaths in 2006 in the United States [1] and 2% of new cancer cases worldwide. Many patients are likely to either have metastatic disease at diagnosis (20–30%) or develop metastases subsequent to surgery (approximately 50% of those who have a nephrectomy) [2]. The majority of these patients need systemic therapy [3], but treatment options are limited. Despite recent therapeutic advances, response rates with biologic and immunologic therapies are low at 15–25% [4]. Therefore, effective drugs, and accurate staging and prognostication are essential to ensure the best possible management of renal cell carcinoma (RCC).

RCC is a heterogenous disease with diverse pathophysiology. Four subtypes of RCC have been established: clear cell, papillary, chromophobe, and collecting duct [5]. These subtypes differ in terms of originating cell type and growth pattern [6,7].
Papillary RCC can be further divided into subtypes, each associated with very different prognoses. Type I papillary RCCs are low-grade tumours with a chromophilic cytoplasm and a favourable prognosis, and type II are generally high-grade tumours with eosinophilic cytoplasm and are associated with a higher risk of metastatic progression and poor prognosis [3].

Recent studies have led to the identification of a number of interesting tumour markers that may be predictive of response and have advanced our understanding of molecular signalling pathways involved in RCC. In addition the introduction of targeted agents, such as sorafenib (Nexavar®; Bayer Healthcare, West Haven, CT, USA) and sunitinib (Pfizer Inc, New York, NY, USA), into clinical practice has provided much needed new treatment options for patients with advanced RCC, and further agents are being investigated [8]. Integration of the validated markers and histologic profiles of tumours into staging systems may improve prognostication and help urologists tailor treatment strategies to appropriate patients. This approach may be particularly relevant in this new era of targeted therapies for RCC.

As the range of therapeutic options for patients with RCC broadens and our understanding of tumour characteristics improves, there is an increasing potential for urologists to select the most appropriate therapy for individual patients and optimise their long-term prognosis. This paper reviews the systems currently used for the staging and prognostication of RCC, and discusses recent advances, including the identification of molecular markers, and the clinical implications of these developments in an era of targeted therapeutics.

2. Staging and prognostication systems for RCC

Staging systems for RCC use tumour characteristics to stratify patients into clinically meaningful categories; these stratifications can provide information on prognosis, treatment, and eligibility for clinical trials. Currently, the most widely used staging system for RCC is the tumour–node–metastases (TNM) system developed by the American Joint Committee on Cancer and the International Union Against Cancer (Table 1) [5]. On the basis of the observation that patients with organ-confined disease generally have better long-term outcomes than those with nodal involvement or metastatic disease, the TNM system, in its early form, used tumour characteristics and pathology to stratify patients into clinically meaningful categories correlating with patient survival. However, over the last decade, the TNM system has been systematically revised to reflect increased understanding of disease outcome on the basis of tumour size [4,9].

2.1. Comprehensive staging systems for RCC

In recent years, a variety of anatomic, histologic, and clinical prognostic factors have been identified. These include tumour grade, histologic subtype, presence of sarcomatoid features, histologic necrosis, performance status, and localised symptoms (Table 2). Consequently, there has been a move towards more comprehensive staging systems. Elson et al [10] and Motzer et al [11] have both developed models to stratify patients with metastatic disease, and a number of models have been designed to predict outcome postnephrectomy.
including the Kattan postoperative prognostic nomogram [12] and the Stage, Size, Grade and Necrosis (SSIGN) system [13]. More recently, the University of California, Los Angeles (UCLA) Integrated Staging System (UISS) has been developed to include survival of patients with both localised and metastatic disease [14].

The UISS was developed to enable the prediction of outcomes for patients with localised or metastatic RCC and has been validated in ~5000 patients with RCC to date. The UISS takes into account tumour size, grade, stage and type, invasion of surrounding tissues and structures, and Eastern Cooperative Oncology Group Performance Status [15,16]. In addition, at UCLA, the presence and extent of tumour necrosis, invasion to collecting system, and presence of molecular markers are determined; in addition, ancillary analyses such as cytogenetics are routinely carried out. The UISS was originally designed to stratify patients to low-, intermediate- and high-risk categories. However, it was subsequently modified to include separate stratification of metastatic and nonmetastatic cases (Fig. 1) [16]. The UISS predicts postoperative outcome and provides a tool for risk assignment and outcome analysis, thus assisting the determination of appropriate follow-up regimens and evaluation of patient eligibility for clinical trials. The model has been externally validated in an international, multicentre study [17] of 4202 patients, which confirmed that this system is an accurate predictor of survival for patients with localised RCC (Fig. 2), and may also be useful for patients with metastatic disease.

### Table 2 – Anatomic, histologic, and clinical prognostic factors for outcomes for patients with renal cell carcinoma [4]

<table>
<thead>
<tr>
<th>Anatomic prognostic factors</th>
<th>Histologic prognostic factors</th>
<th>Clinical prognostic factors</th>
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<td>Tumour size</td>
<td>Tumour grade</td>
<td>Performance status</td>
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<td>Venous involvement</td>
<td>Histologic subtype</td>
<td>Cachexia</td>
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<td>Lymph node involvement</td>
<td>Sarcomatoid features</td>
<td>Localised symptoms</td>
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<td>Distant metastases</td>
<td>Collecting system invasion</td>
<td>Platelet count</td>
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#### 3. Incorporating molecular markers as prognostic factors for RCC

In recent years, the increased understanding of molecular signalling pathways involved in the pathogenesis of RCC has led to the identification of molecular markers [18] that indicate disease status and may predict response to treatment. This greater understanding of the underlying biology of RCC has also led to the development of targeted therapies directed towards molecular components of signalling pathways involved in tumour growth and angiogenesis. For example, molecular components of the hypoxia-inducible pathway may provide new therapeutic targets for small-molecule inhibitors, vaccines, and gene and antibody therapies. Such new markers need to be incorporated into staging systems to enable accurate prognostication and to allow targeted therapies to be directed towards appropriate patients.
Ongoing work at UCLA is directed at identifying and incorporating relevant molecular markers into the UISS using tissue microarray analysis [4,19]. The most promising molecular markers identified with the use of tissue microarray analyses are shown in Table 3, and include carbonic anhydrase IX (CA IX) and members of the vascular endothelial growth factor (VEGF) family of proteins and receptors.

3.1. Carbonic anhydrase IX

CA IX is a member of the carbonic anhydrase family of enzymes. It is absent in most normal tissues, but is thought to play a role in the regulation of intracellular pH during periods of hypoxia. A recent study [20] reported that 94% of clear cell RCC tumour samples stained positive for CA IX using a specific monoclonal antibody. In addition, multivariate analysis using a prognostic model showed that CA IX (along with vimentin and p53) is a significant predictor of tumour cell survival regardless of T stage, metastatic or performance status, or tumour grade [4], making this an attractive marker for incorporation into an integrated, standardised staging system.

Importantly, CA IX expression also appears to predict likely response to interleukin-2 (IL-2) therapy. Bui and co-workers [20] reported that high levels of CA IX expression were associated with response to IL-2 therapy and that all patients who experienced complete response with IL-2 therapy (8%) also had high levels of CA IX staining (>85%) in their primary tumour. In another study [21] of 66 patients with RCC, response to IL-2 was twice as likely in patients with high levels of CA IX expression compared with patients with low levels of CA IX expression. Overall survival was also significantly longer in patients whose tumours expressed high levels of CA IX compared with patients whose tumours expressed low levels ($p = 0.03$, Fig. 3). In all, 21 of 27 (78%) patients who responded to IL-2 had high CA IX–expressing tumours compared with 20 of 39 (51%) patients who did not respond ($p = 0.04$).

Taken together, these findings may begin to explain why some patients with clear cell RCC appear to respond better to IL-2 therapy than those with other types of RCC, and suggest that analysis of CA IX status could be used to guide the selection of patients who may benefit from IL-2–based therapy [20,21]. Indeed, a recent RAND/UCLA Appropriateness Panel concluded that CA IX expression is a very promising biomarker for response to IL-2, which should be studied further to determine whether it is also predictive of response to targeted therapies [22].

3.2. The VEGF family of proteins and receptors

The VEGF family of proteins and receptors play an important role in angiogenesis and lymphangiogenesis, and have therefore received particular attention as potential prognostic markers for RCC. Leppert and co-workers [23] recently reported results of a tissue microarray analysis to investigate the expression of VEGF-A, VEGF-C, VEGF-D, VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3 in samples of clear cell ($n = 340$) and papillary ($n = 42$) RCC (Fig. 4). Compared with clear cell RCC, samples from papillary RCC tumours had higher mean expression of VEGF-A and VEGFR-2. However, samples from clear cell tumours had higher mean expression of VEGF-D, VEGFR-1, VEGFR-2, and VEGFR-3 within tumour-associated endothelium than papillary tumours. In addition, expression of individual proteins in the VEGF family

<table>
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<tr>
<th>Table 3 – Proposed molecular markers for renal cell carcinoma (adapted from Lam et al 2005 [4])</th>
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<tr>
<td><strong>Hypoxia-inducible</strong></td>
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<td>CA IX</td>
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<td>CXCR4</td>
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<td>VEGF</td>
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CA = carbonic anhydrase; CXCR4 = chemokine receptor 4; IGF = insulin-like growth factor; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor.
Fig. 4 – VEGF-A (panel A), VEGFR-1 (panel B), and VEGFR-2 (panel C) expression in clear cell and papillary renal cell carcinoma [23]. (VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor.)
may provide a profile of kidney cancer metastases [24]. For example, expression of VEGFR-1 and -2 has been demonstrated to predict the presence of distant metastases, whereas VEGFR-3 expression by tumour-associated endothelium may specifically predict lymph node metastases [24].

The results of these studies demonstrate that profiles of expression of VEGF and VEGFR can be useful indicators of tumour subtype and disease stage. These profiles may help to direct targeted therapies to the appropriate patient population. For example, patients with papillary RCC may benefit from therapies targeting the VEGF-A pathway, whereas patients with clear cell RCC may be more likely to benefit from inhibitors targeting VEGFR-3.

4. Conclusions

Staging systems for RCC are useful tools to define subtypes of RCC, stratify patients according to risk, and predict response to targeted therapies. Integrated prognostic systems that include histological and clinical profiles perform better than historical staging systems based solely on tumour characteristics and pathology. As a result, they allow more accurate stratification of patients into sophisticated risk categories. Methodologies to assess the expression of molecular tumour markers such as CA IX and the VEGF family look set to be the next step forward in staging and prognostication of RCC. Integrating these markers into comprehensive prognostic systems may be particularly useful in selecting patients for treatment with targeted therapies, and in the future may even drive the development of new treatments. Ultimately, integrated staging systems for RCC may enable urologists to select the appropriate patient population for a particular targeted therapy, thus improving treatment success and maximising survival.

Conflicts of interest

Arie S. Belldegrun: speaker and investigator for Pfizer and Bayer.

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