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Prognostic factors in renal cell and bladder cancer

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Introduction

Prognostic markers include factors measurable in serum or tissue specimens using an assay; quantitative or qualitative changes from a defined baseline level are correlated with prognosis. Ideally, a prognostic marker should have high specificity, sensitivity and reproducibility. It should be organ- and cancer-specific, and have the power to predict the prognosis. Furthermore, its assessment should be practical, easy and cost-effective. A prognostic marker should be useful in patient management and clinical-decision making, resulting in improved clinical outcome.

However, the ideal prognostic marker has not been discovered for any of the urological malignancies. Few markers are routinely used in clinical decision-making or have been studied in clinical trials. In this review, we discuss the clinical use of tissue-related prognostic factors in RCC and bladder cancer, and review the published literature on experimental prognostic markers.

Renal cell cancer

Radical surgical extirpation of a kidney tumour remains the only effective means of curing localized RCC, despite alternative forms of therapy which have been proposed over the last decade. Patients with metastatic RCC have a poor prognosis, with a median survival of approximately 8 months [1] and limited therapeutic options; RCC is resistant to most conventional cytotoxic agents [2]. More recently, the use of biological response modifiers, especially IL-2 and IFNα, has lead to some responses in patients with metastatic disease [3,4].

The clinical course of metastatic RCC is variable. To obtain an insight into the clinical and biological behaviour of RCC the identification of new prognostic factors is vital. Eventually, the use of these factors should facilitate the choice of optimal treatment for individual patients. Investigators have attempted to identify pathological and morphological features within the tumour that correlate with survival in patients with RCC. Tumour stage remains the most important factor predictive of survival in RCC [5–8]. In addition, tumour size [7], histological pattern [9], cell type [9], nuclear grade [7], DNA content [10] and nuclear morphometry [11] have been reported as prognosticators for survival. Additionally, variables such as performance status [12], weight loss, time to progression, number and type of metastases [13], vascular invasion [14] and several laboratory values, e.g. haemoglobin level, ESR and alkaline phosphatase levels, have been studied in relation to prognosis [13]. Increasing knowledge of cytogenetic abnormalities and the role of oncogenes and tumour suppressor genes in RCC is critical, but the study of molecular mechanisms underlying RCC is still in its infancy; future studies will have to provide information on the implications for the prognosis of patients with RCC.

Stage

The TNM system, which explicitly defines the anatomical extent of disease, is the most commonly used staging system. Several studies have shown that stage is the most consistent single prognostic factor to influence survival [5–8,15]. Survival is inversely correlated with pathological stage as patients with tumours confined to the kidney have significantly better disease-specific survival rates than patients with metastatic RCC [16]. The significance of invasion into the renal vein, vena cava, renal pelvis, perinephric fat and lymph nodes has been the subject of much debate [12]. Most studies do not regard renal vein invasion as a factor that reduces survival [6,9,17]. Tumour penetration into the renal pelvis was thought to reflect tumour stage rather than biological behaviour and is therefore not an independent prognosticator [16]. Data addressing the issue of inferior vena cava invasion are conflicting. Several large series found that invasion of the vena cava minimally affected survival, as long as the tumour thrombus could be totally removed [18,19]. Patients with RCC invading the renal capsule and perinephric fat have a worse survival than those with organ-confined disease [20,21]. Lymph node invasion is an ominous prognostic sign and has a significant impact on survival [9,22]. From these retrospective studies it is uncertain if patients with positive lymph nodes would benefit from lymph node dissection. Whether extended lymphadenectomy improves the survival of patients with RCC may be answered by the ongoing EORTC 30881 randomized trial. Patients with metastatic RCC have a poor prognosis, with 5- and 10-year survival rates of 5–10% and 0–7%, respectively.

Despite great effort to challenge metastatic disease with adjuvant treatments, the overall survival of patients has not been improved. Survival probably depends on the biological aggressiveness of the tumour and not on the site(s) of metastatic lesions, although pulmonary metastases appear to be associated with a better prognosis. In selected cases, excision of solitary lesions may improve the duration of overall survival [23]. In retrospective analyses, nephrectomy in patients with systemic disease did not alter the subsequent disease course [17]. Only a select group of patients who were relatively more suitable to undergo surgery and had a few surgically resectable metastases may have benefited from nephrectomy with extirpation of metastatic lesions. With the development of modern immunotherapy, this issue needs to be re-addressed. In an EORTC study (protocol 30947) patients with metastatic RCC are randomized to either immunotherapy alone or tumour nephrectomy followed by immunotherapy. This important study should shed further light on the role of nephrectomy in metastatic RCC and may well change current attitudes towards how we treat this condition.

Grade

The grading of RCC has proved to be difficult; Skinner *et al.* [6] and Fuhrman *et al.* [24] developed grading systems based on nuclear morphometry of RCC cells. Several studies reported the independent prognostic value of grade in predicting long-term survival [6,17,24,25]. Tumour cell type (i.e. clear granular, spindle or mixed) also appears to influence survival. Tumours with spindle cells are significantly more malignant than the other cell types [6,26]. Although nuclear grade is an independent prognosticator, it is usually only second to stage in significance, as lack of uniformity and inherent subjectivity of grading systems have prevented their widespread application.

Nuclear morphometry

Morphometric analysis of renal carcinoma cells appears to predict survival, as shown in several studies [27–29]. In one study, the 5-year survival rates were significantly poorer if the nuclear area was $>35\ \mu m^2$ [27]. Further studies are necessary with larger groups of patients to confirm the value of nuclear morphometry as a prognostic factor.

DNA content

Several groups have reported that tumour DNA content as measured by flow cytometry may have prognostic value in patients with RCC [10,30,31], with aneuploid tumours being associated with a less favourable outcome. However, most studies did not account for tumour stage, histological grade or tumour heterogeneity, and there were too few patients in these studies to draw definite conclusions about this potential prognosticator.

Cytogenetic findings

Cytogenetic analysis has shown a close correlation between certain recurrent chromosomal rearrangements and several RCC subtypes [32]. Clear cell carcinomas have deletions or translocations involving the short arm of chromosome 3, with breakpoints proximal to 3p22. Papillary tumours have allelic losses of 17p or trisomies of chromosomes 7, 16 and/or 17. Chromophobic cell carcinomas have hypodiploid chromosome numbers, oncocytomas have deletions ($-$Y and -1) and collecting duct carcinomas have been characterized by deletions -1, -6, -14, -15 and -22. Some tumours with predominantly papillary/chromophilic histology and translocations in Xp11.2 have been reported [33]. It has been suggested that RCC may be subdivided into different groups based on genetic abnormalities and that these cytogenetic aberrations may be of prognostic importance [33,34]. Other authors found no correlation between cytogenetic changes and prognosis [35–37]. In a recent study, Elfving *et al.* [32] evaluated the prognostic impact of cytogenetic findings in RCC in 50 patients. Patients with more than five cytogenetic findings had a significantly worse prognosis than patients with fewer changes. Patients with deletions (8p)/-8, $+12$ and $+20$ had a significantly worse prognosis. However, grade was the most reliable independent prognosticator for recurrent disease in this study. Further studies, involving more patients, are needed to evaluate the implications of karyotypic changes in RCC.

Vascular invasion

In a recent study, the correlation between microscopic vascular tumour invasion and disease-free interval after surgery for RCC was examined [14]. Compared with classical tumour stage, grade and tumour diameter, microvascular invasion was found to be the single most relevant prognosticator after presumed curative radical nephrectomy for RCC. In patients undergoing radical nephrectomy for clinically nonmetastatic RCC with microvascular invasion but without lymph node involvement or macroscopic vascular invasion, the chance of disease progression was estimated at 45% within one year.

Clinical and laboratory variables

The overall survival rate among young adults with RCC is similar to that of older patients [38] and hence age does not appear to have prognostic significance. The adverse impact of male gender in RCC has been suggested [38] but several large studies, using multivariate analysis, did not confirm male sex as a prognostic factor [17,39]. Most differences in survival between the sexes are related to differences in stage and grade of tumours. Several authors have reported the prognostic importance of different signs and symptoms. Weight loss [17,26,38,40,41] and performance status [13,40] are important, but are also associated with advanced stages.

Various laboratory results may be adversely related to prognosis. Using univariate analysis, Citterio *et al.* [13] reported that anaemia at diagnosis predicted a poor outcome of metastatic RCC, as well as hypercalcaemia, hypoalbuminaemia and high serum alkaline phosphatase. The ESR has also been related to a poor prognosis [42]. Serum levels of erythropoietin correlate with tumour stage and grade, and may provide prognostic information [43].

Conclusion

Identification and use of prognostic factors will become increasingly important in defining subgroups of patients with RCC who have a poor prognosis. This will allow better selection and evaluation of treatment, leading to improved management of patients with RCC and of the design and analysis of clinical trials in RCC.

Bladder cancer

TCC of the bladder can be classified into two groups with distinct behaviour and prognosis; low-grade tumours (papillary and usually noninvasive) and high-grade tumours (papillary or nonpapillary and often invasive). TCC of the bladder consists of noninvasive tumours (Ta, Tis and T1) for 75–85% of patients and invasive (T2, T3, T4) or metastatic tumours in 15–25%. Of the patients with noninvasive bladder cancer, >70% will have one or more recurrences after initial treatment and in a third progressive disease will develop. Primary therapy is based on clinical staging and morphological assessment. However, tumours may behave differently despite morphological similarity. It is of great importance to identify patients with noninvasive tumours who are likely to develop recurrent or progressive disease; tumour markers may contribute to this goal. Recent developments in molecular and genetic techniques have contributed to our understanding of bladder cancer tumour biology. Biological markers and new bladder cancer detection methods are being developed in an attempt to identify and monitor those patients with noninvasive bladder cancer who are at risk of developing recurrent or progressive disease. Patients with muscle-invasive disease may benefit from the use of markers that predict a tumour's metastatic potential and the outcome of therapy. We will discuss the available prognostic markers, of which relatively few have confirmed clinical utility. Nevertheless, in the near future, the increased use of new prognostic factors may modify the way we manage patients with TCC of the bladder.

Stage

The selection of initial therapy currently depends on clinicopathological variables. Tumour stage, reflecting depth of invasion, remains the most common prognosticator for progression. Several studies have shown that the risk for progression is significantly greater in T1 than Ta tumours [44].

Grade

The grading system involves three classes and is based on the degree of anaplasia. Several studies have shown the power of grade in predicting muscle invasion [45].

DNA ploidy

An increase in nuclear DNA content is regarded as a sign of genetic instability associated with potential malignant behaviour. DNA ploidy in cells obtained from bladder washings was correlated with progression to invasion and metastasis, and poor prognosis in flow cytometric studies [46,47]. However, it is questionable whether ploidy provides additional information to tumour grade and stage [11,48]. Cellular DNA content may be of prognostic value only in grade 2 TCC, as most grade 1 tumours are diploid and most grade 3 tumours are aneuploid [49].

Stöckle *et al.* [50] using paraffin-embedded bladder carcinoma tissue from radical cystectomy, found that in case of noninvasive tumours, DNA cytometry identified potentially invasive tumours. Monosomy of chromosomes 13 and 22 was correlated with a poor prognosis and trisomy of chromosomes 7 with a favourable prognosis [51]. However, bladder cancers consist of cell populations heterogeneous in ploidy. A 'non-tetraploid' DNA aneuploidy in a bladder washing specimen is considered to be recurrent tumour in patients with noninvasive bladder cancer treated by TUR. DNA aneuploidy ⩾ 6 months after intravesical treatment of noninvasive tumours is a good prognosticator for treatment failure and progression [49]. The prognostic value of

DNA ploidy in muscle-invasive TCC remains debatable. The routine use of flow cytometry and image analysis of morphonuclear variables requires further clinical studies and standardization of techniques.

P53 tumour suppressor gene

The tumour suppressor gene *p53* is located on chromosome 17p13–1 and codes for a 53-kDa nuclear phosphoprotein. The role of p53 is critical to cell cycle control, resulting in cell cycle arrest to allow DNA repair or induction of apoptosis in the event of irreparable DNA damage. Inactivation of *p53* by deletion and/or mutation results in loss of tumour suppressive function. Bladder cancer, especially of the invasive type, is associated with a high frequency of *p53* mutations. Several immunohistochemical studies have confirmed that altered expression of the protein product(s) of mutated *p53* is associated with tumour progression in patients with T1 bladder cancer [52,53]. Patients with p53-positive nuclear staining had a significantly shorter disease-free interval. The frequency of p53 mutations may thus predict clinical aggressiveness. In contrast, a further study, this time of invasive tumours, applying PCR-SSCP to assess the mutational status of p53, found no significant association with survival [54]. This may reflect the discrepancy between p53 mutation analysis and p53 immunohistochemistry. In another study of patients with TCC confined to the bladder, an accumulation of p53 in the tumour-cell nuclei predicted a significantly increased risk of recurrence and death, independently of tumour grade, stage and lymph-node status [55]. In two recent studies, p53 nuclear reactivity did not indicate the outcome of chemotherapy for metastatic disease [56,57]. Large prospective studies are needed to evaluate the nuclear overexpression of p53 protein as a prognostic marker in bladder cancer.

Retinoblastoma gene

Loss of heterozygosity at chromosome 13q14, the site of the retinoblastoma (*Rb*) gene, occurs in bladder cancer with a wide range of incidence [58]. *Rb* is a tumour-suppressor gene whose protein product has a function in cell-cycle control. Loss of Rb function may result in increased genetic instability and can occur in both noninvasive and invasive bladder tumours, most commonly in the latter. Several immunohistochemical studies have shown that decreased expression of Rb protein is associated with more aggressive biological behaviour and a decreased life expectancy [59,60]. A recent study, evaluating the expression of Rb in bladder tumours from patients who had undergone cystectomy, reported that both cases with undetectable Rb and high Rb expression had a significantly higher recurrence rate and lower survival rate than cases with moderate Rb expression [61]. In the same study, patients with tumours showing both altered p53 and Rb expression had significantly increased rates of recurrence and decreased survival. The authors concluded that bladder tumours highly expressing Rb showed no tumour-suppressor effects of the protein and that alterations in both p53 and Rb may act together or synergistically to promote tumour progression.

E-cadherin

Decreased expression of E-cadherin may play a role in tumour invasion and metastasis, as E-cadherin-mediated cell-cell adhesion appears to play a critical role in epithelial integrity [62]. Loss of E-cadherin expression may be an important prognostic factor. Decreased E-cadherin immunoreactivity was shown to correlate with both increased grade, stage and poor prognosis in patients with bladder tumours [63–65]. Another study reported an inverse relation between recurrence-free survival and E-cadherin expression in bladder cancer biopsies [66]. Using multivariate analysis, E-cadherin expression had no independent prognostic significance over grade and stage. Otto *et al.* [67] showed that down-regulation of E-cadherin in association with an increase in gp78, an autocrine motility factor receptor, was associated with a poor prognosis. The combined application of these two antigens may identify patients with high-risk bladder cancer and influence treatment decisions.

Epidermal growth factor receptor (EGFR)

An immunohistochemical study in patients with noninvasive TCC (pTa, pT1) showed that overexpression of EGFR, the product of the c-*erb*B-1 gene, was correlated with a significantly higher recurrence rate, shorter time to recurrence and higher tumour progression [68]. EGFR-positive patients with muscle-invasive disease showed no difference in survival.

Overexpression of the c-*erb*B-2 gene product, a transmembrane growth factor receptor with significant sequence homology to EGFR, correlated with tumour grade and survival [69]. Its expression was an independent prognosticator in a multivariate analysis. However, conflicting results have been published in a study reporting no additional prognostic power over tumour grade, DNA aneuploidy and proliferative activity (reviewed in [70]). EGFR overexpression can be used as a prognosticator in noninvasive bladder cancer. The prognostic value of the c-erbB-2 oncoprotein needs further evaluation.

Angiogenesis

Bladder cancer is dependent on angiogenesis to grow progressively and metastasize efficiently [71]. In patients with muscle-invasive disease, microvessel density (MVD) is strongly correlated with lymph node metastases [72], disease recurrence and reduced survival [73,74]. However, other investigators found no correlation between prognosis and MVD, but the patient group examined had a relatively low risk of metastasis [75]. Future studies should provide additional proof of the utility of MVD as a prognosticator in bladder cancer.

Conclusion

The identification of patients with TCC of the bladder at risk of recurrent or progressive cancer at an early stage is important to provide an optimal treatment for these patients. Prognostic markers may be the tools to accomplish this and much effort has been put into research on such markers. Many potential markers have been reported; unfortunately, few of them seem to have true potential prognostic value and their precise clinical utility needs to be studied more intensively. Hopefully, new clinically valuable prognostic markers may evolve from a better understanding of the molecular events involved in bladder cancer progression, leading to the identification of patients with potentially recurrent or progressive disease.

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MCQs

1. Which statement is correct?
(a) the most important area in TCC tissue marker development would be to predict which superficial tumours are likely to recur and/or to progress
(b) molecular markers have a higher prognostic power than tumour morphology, stage and grade in predicting tumour progression
(c) DNA aneuploidy after intravesical treatment of superficial tumours has good prognostic features in TCC
(d) P53 immunohistochemistry is accepted to be inversely correlated to prognosis in TCC
(e) Lack of retinoblastoma tumour suppressor gene expression is found in most invasive TCC lesions
2. Which statement is correct?
(a) the inverse correlation between E-cadherin expression and prognosis in TCC may pose practical problems in standardising the assay for clinical application
(b) epidermal growth factor receptor expression is positively correlated with prognosis in patients with muscle-invasive TCC
(c) microvessel density is an independent prognosticator in bladder cancer
(d) expression of the C-*erb*B-2 gene product is a stronger prognosticator than tumour grade, DNA aneuploidy and proliferative activity
3. Which statement is correct?
(a) tumour grading in bladder carcinoma is not well suited for predicting progression to muscle invasion
(b) determination of DNA ploidy in muscle-invasive bladder carcinoma reflects the true metastatic potential
(c) patients with p53-positive nuclear staining have a significantly shorter disease-free interval in T1 bladder cancer
(d) tumour heterogeneity does not influence the predictive value of flow cytometry in bladder carcinoma
4. Which statement is correct?
(a) expression of retinoblastoma tumour suppressor gene in TCC of the bladder correlates well with aggressive biological behaviour and decreased life expectancy
(b) E-cadherin expression in bladder carcinoma is not an independent prognostic factor over grade and stage
(c) gp 78, an autocrine motility factor receptor, has independent prognostic value in bladder carcinoma
(d) invasive bladder carcinoma is associated with a low frequency of p53 mutations
5. Which statement is correct?
(a) cytogenetic abnormalities have been shown to be the strongest prognosticators in RCC
(b) the expression of chemoresistance genes in RCC has a negative prognostic value
(c) overall, the TNM staging system is the most widely used prognosticator in clinical decision-making for RCC

(d) renal capsular invasion and perinephric fat invasion indicates a worse prognosis than microscopic vascular invasion in RCC

6. Which statement is correct?

(a) grading, nuclear morphometry and DNA content are well established prognosticators in clinical decision-making for RCC

(b) allelic losses of 17p have prognostic value in clear cell carcinoma

(c) the age at diagnosis is an important prognosticator in RCC

(d) microvascular invasion is of prognostic significance in organ-confined RCC

7. Which statement is correct?

(a) deletions in the short arm of chromosome 3 are common in papillary RCC

(b) female patients with RCC may show elevated PSA levels in 22–25% of cases

(c) when compared with each other, venous micro-invasion conveys a better prognosis than a large tumour volume in RCC

(d) hereditary forms of RCC carry a worse prognosis than sporadic cases

8. Which statement is correct?

(a) the recommended laboratory evaluation in the follow-up after curative surgery for RCC includes measuring the haemoglobin level, ESR and alkaline phosphatase

(b) RCC, apart from testicular cancer, has a good prognosis compared with other urological malignancies

(c) prognostic factors have established value in the optimal treatment for metastatic RCC

(d) tumour penetration of RCC into the renal pelvis is thought to be an independent prognosticator

9. Which statement is correct?

(a) Surgical tumour debulking improves response rates under immunotherapy for metastatic RCC

(b) Resection of metastasis improves overall survival in stage M+RCC

(c) The tumour cell type does not influence the prognosis of RCC

(d) Anaemia at diagnosis may predict a poor outcome of metastatic RCC

10. Which statement is correct?

(a) overall, men with RCC have a poorer prognosis than women with RCC

(b) oncocytomas commonly have deletions in the Y chromosome

(c) RCCs are commonly seen from age 20 to age 85 years with a peak incidence in the fourth decade

(d) nuclear morphometry is established in the clinical decision-making for RCC