Prognostic Value of MCM2 Immunoreactivity in Stage T1 Transitional Cell Carcinoma of the Bladder

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Abstract

\textbf{Objective:} Due to the heterogeneous biologic behavior of stage T1 bladder carcinomas, there is a need for new markers allowing to assess the prognosis more accurately. To our knowledge, there are no reports on studies investigating minichromosome maintenance protein 2 (MCM2) expression in bladder carcinomas. Thus, we investigated the prognostic value of MCM2 immunoreactivity in stage T1 bladder tumors.

\textbf{Methods:} Fifty-four tumors were analyzed using Biochip microarrays. Also p53 and Ki67 antigen expression were examined. Immunohistochemical scores were compared with the clinical outcome.

\textbf{Results:} During a median follow-up of 43 months, tumor recurrence was registered in 43 and progression to stage T2 in 19 patients. Kaplan–Meier curves demonstrated that high-level MCM2 expression was significantly associated with early tumor recurrence when using a cutoff of 60\% (p = 0.0035 by log-rank test), and with early tumor progression when using a cutoff of 20\% (p = 0.0454). There was no relationship (p = 0.604) between MCM2 and p53, but a tendentious relationship (p = 0.082) between MCM2 and Ki67 antigen expression. MCM2 (p = 0.006), Ki67 antigen (p = 0.035) and p53 expression (p = 0.049) as well as tumor grade (p = 0.026) and age (p = 0.025) were found significantly associated with recurrence-free survival by univariate Cox regression analysis, among which only Ki67 antigen expression (p = 0.015) and age (p = 0.019) proved to be of independent predictive value by multivariate analysis. Concerning tumor progression, MCM2 expression was identified as the only predictive parameter by log-rank test, but it was not of independent predictive value by multivariate analysis (p = 0.101).

\textbf{Conclusion:} Our data suggest that MCM2 expression may bear some prognostic relevance in stage T1 bladder carcinomas.

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Keywords: Bladder cancer; Immunoreactivity; MCM2; Proliferation; Prognosis

1. Introduction

The management of T1 bladder carcinomas, i.e. of tumors that infiltrate the submucosal stroma, is complicated by their variable biologic behavior. The therapeutic options include transurethral resection alone, postoperative instillation of bacillus Calmette-Guérin (BCG) or cytotoxic agents, radical cystectomy, and radiation therapy. While conservative treatment would be appropriate for tumors that remain superficial, a radical cystectomy is regarded the best treatment for patients with tumors that progress to higher stages. Since the distinction between these two groups is problematic, there is a need for parameters helping to assess the prognosis of an individual patient more accurately. In this regard, many studies have investigated proliferation-associated markers as potential candidates for prognostic factors. Concerning superficial bladder carcinomas (i.e. tumors of stage Ta and/or T1), some authors have reported a predictive value...
for the mitotic index [1], S phase fraction [2], thymidylate synthase activity [3] as well as for Ki67 antigen [1,4–6], proliferating cell nuclear antigen (PCNA) [7,8], Cyclin E [9], Cyclin D1 [10,11], and p21WAF-1 immunoreactivity [12].

Minichromosome maintenance (MCM) proteins represent highly conserved proteins that are essential for initiating and regulating eukaryotic DNA replication by forming part of the prereplicative complex. They are regarded as markers of proliferation, and assessment of their immunoreactivity is suggested to have potential clinical value in some malignant tumors [13]. Thus, a prognostic significance has been reported for MCM2 protein expression in prostatic cancer [14], non-small-cell lung cancer [15], and oligodendrogliomas [16]. Concerning bladder cancer, detection of MCM5 has been described as a valuable diagnostic tool in urine specimens [17], but to our knowledge, no studies investigating the prognostic value of any MCM protein in bladder tumors have been published. Therefore, we examined a series of superficial bladder carcinomas for a potential relationship between MCM2 immunoreactivity and tumor recurrence or progression in this study. Since there are considerable biologic differences between papillary bladder carcinomas of stage Ta and T1 [18], we focussed exclusively on T1 tumors to avoid any stage-related influence on the clinical outcome of the patients. Moreover, we compared MCM2 expression with other prognostically relevant factors like tumor grade, p53 and Ki67 antigen immunoreactivity.

2. Materials and methods

2.1. Patients and clinical follow-up

Fifty-four patients with stage T1 papillary transitional cell carcinomas of the bladder primarily diagnosed at the Department of Urology of the University of Lübeck between 1987 and 1997 were included. In all of these patients, a complete transurethral resection of the tumor had been performed, and the initial histopathological diagnosis was papillary transitional cell carcinoma of stage T1. This stage was generally confirmed in an independent review made by two pathologists (S.K. and C.T.). Grading was performed by the same pathologists according to the World Health Organization (WHO) criteria [19]. Thus, 28 tumors were assigned as G2 and 26 tumors as G3 in our collective of tumors.

The series of patients consisted of 46 men and 8 women (male-to-female ratio, 5.8:1). The median age was 68 years (range 37–85 years). All but eight patients received instillation therapy with bacillus Calmette-Guérin (BCG). Patients were followed with urinary cytology and cystoscopy every 3 months during the first 2 years following primary diagnosis and every 6 months thereafter. Tumor recurrence or progression had to be histologically confirmed. Patients without recurrence were censored at the time of the last cystoscopic examination. Recurrence-free and progression-free survival were defined as the interval between initial tumor diagnosis and tumor recurrence or tumor progression, respectively. Only patients with a minimum follow-up of 1 year were included in the study. Thus, a medium follow-up of 43 months was achieved (range 12–108 months).

2.2. Immunohistochemistry

Immunohistochemistry was done on Biochip arrays, which represent a high throughput technique allowing the simultaneous investigation of a large number of specimens on one slide. Biochip arrays were purchased from Euroimmun Medizinische Labordiagnostica, Lübeck, Germany, and modified in cooperation with two of the authors (W.S. and E.M.-K.). The Biochips were produced as

Fig. 1. Aspect of a Biochip after immunohistochemical staining (only a part of the slide is shown). Representative specimens of tumor tissue (size: 2 mm × 2 mm, respectively) are arranged in lines and rows.
described previously [20,21]. They contained up to 45 tumor specimens (sizes 2 mm × 2 mm) which were arranged in lines and rows on the slide (Fig. 1).

Immunohistochemical stainings were performed according to a standard three-step immunoperoxidase technique with diaminobenzidine (DAB) as chromogen. The sections were pretreated with a high temperature antigen unmasking technique and proteinase K digestion. The following antibodies were used: mouse monoclonal anti-MCM2, clone ccr2.1 (dilution 1:10); mouse monoclonal anti-p53, clone pAb1801 (dilution 1:50; both antibodies purchased from Novocastra, Newcastle, UK); mouse monoclonal anti-Mib-1, clone Ki67 (dilution 1:20; purchased from DAKO, Hamburg, Germany). In all staining runs, negative controls were included by omitting the primary antibody or by substituting the primary antibody by appropriate concentrations of non-immune mouse immunoglobulin. Paraffin sections from tonsils were used as positive controls for the MCM2 and Ki67 antigen staining, whereas sections from a colorectal adenocarcinoma with known high p53 immunoreactivity proven in previous experiments were used as positive controls for p53 staining.

2.3. Evaluation

The evaluation of the immunohistochemical preparations was performed by two of the authors (S.K. and C.T.) independently and without knowledge of the clinical outcome. Since the Biochips used in this study contained 2 mm × 2 mm-sized tumor specimens with a quite heterogeneous amount of tumor cells (ranging from about 50 to more than 2000 cells), we did not count a defined number of tumor cells in each case, but rather performed a semiquantitative analysis. Due to the considerable variation in cutoff levels reported for MCM2 immunoreactivity (10% in a study on prostatic adenocarcinoma [14], 25% in a study on non-small cell lung cancer [15]), we first identified which semiquantitative model of categorization fitted best to our study. For this purpose, we performed a statistical analysis on different data-sets by comparing four different models of categorization (Kuczyn et al. [22]: 0–20%, 21–40%, 41–60%, 61–80%, or 81–100%; Gardiner et al. [23]: 0%, 1–10%, 11–25%, 26–50%, 51–75%, and 76–100%; Friedrich et al. [24]: 0–4%, 5–19%, 20–49% and 50–100%; Leisner et al. [12]: 0%, 1–20%, 21–50%, 51–80%, and 81–100%). Among these, the model of Kuczyn et al. [22] was chosen because it proved to be the most effective in our collective of patients by yielding the lowest p-values in the statistical survival analyses.

There was generally an excellent interobserver agreement regarding tumor categorization. In the few cases with initial disagreement, consensus was reached using a multireader microscope. In agreement with previous studies [25–27], we considered tumors with a labeling index of ≥20% as positive for p53. With regard to Ki67 antigen immunoreactivity, the median level represented the cutoff for tumor categorization.

2.4. Statistical analysis

All statistical calculations were done using the SPSS statistical software package (SPSS Inc., Chicago, USA). The relationship between categorized parameters (immunoreactivity scores, tumor grade, age and sex) was assessed using contingency table methods and tested for significance using the Pearson’s χ² test. The MCM2 expression of G2 and G3 carcinomas was compared by the Mann–Whitney U-test. Kaplan–Meier curves were plotted from recurrence and progression-free survival data, and the log-rank test was used to analyze differences between groups. Patients who were lost to follow-up without having experienced tumor recurrence or progression were treated as censored data in the survival analyses. Univariate and multivariate survival analysis was performed using the Cox Proportional Regression Hazard Model. In multivariate analysis, all variables were selected in a stepwise fashion (forward and backward selection of covariates) to evaluate the predictive power of each variable independent of the others. A p-value of 0.2 was adopted as the limit for entering and removing covariates. Of the prognostic factors that contributed significantly to the model, the effect was calculated in terms of relative risks (RR) and the associated 95% confidence intervals. A statistical significance was assumed at a p level of <0.05.

3. Results

3.1. Immunohistochemical results

Immunohistochemical stainings of the Biochip arrays for MCM2, Ki67 antigen and p53 were generally successful and showed significant nuclear reactivity of the tumor cells, respectively. The aspect of an immunohistochemical MCM2 staining is illustrated in Fig. 2. The immunohistochemical scores for all markers are listed in Table 1. A tendentious correlation was found between MCM2 and Ki67 antigen expression (p = 0.082), while no association existed between MCM2 and p53 expression (p = 0.604). When analyzing the relationship between MCM2 expression and tumor grade, a significant difference (p = 0.004) was registered inasmuch as G3 tumors displayed a higher MCM2 immunoreactivity (median, 40–60%) than G2 tumors (median, 0–20%; Table 2). Additionally, MCM2 expression was tendentially higher in men than in women (p = 0.072; medians in both groups: 21–40%; data not listed in the table). No significant

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Immunoactivity for MCM2, Ki67 antigen and p53 in stage T1 papillary transitional cell carcinomas of the bladder (n = 54)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Markers</th>
<th>0–20%</th>
<th>21–40%</th>
<th>41–60%</th>
<th>61–80%</th>
<th>81–100%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>MCM2</td>
<td>22</td>
<td>40.7</td>
<td>13</td>
<td>24.1</td>
<td>9</td>
</tr>
<tr>
<td>Ki67 antigen</td>
<td>6</td>
<td>11.1</td>
<td>21</td>
<td>38.9</td>
<td>21</td>
</tr>
<tr>
<td>p53</td>
<td>28</td>
<td>53.8</td>
<td>7</td>
<td>13.5</td>
<td>13.5</td>
</tr>
</tbody>
</table>

A tendentious correlation exists between MCM2 and Ki67 antigen expression (p = 0.082 by Pearson’s χ² test), but there is no relationship between MCM2 and p53 reactivity (p = 0.604).

p53 available only in 52 cases since no representative tumor tissue was present on the Biochip in two cases.
association was observed between MCM2 expression and age \( (p = 0.791; \) data not shown).

### 3.2. Survival analyses

The clinical course of the 54 patients was characterized by tumor recurrence in 43 cases after a median interval of 15 months and by progression to stage T2 in 19 cases after a median interval of 31 months. Kaplan–Meier curves demonstrated that high-level MCM2 expression was significantly associated with early tumor recurrence when categorized at a cutoff of 60\% \( (p = 0.0035 \) by log-rank test; Fig. 3), while other cutoffs did not reach the level of statistical significance (data not shown). Kaplan–Meier curves of other potentially relevant parameters revealed that also tumor grade \( (p = 0.0217 \) by log-rank test), age \( (p = 0.0197) \), Ki67 antigen \( (p = 0.0283) \) and p53 immunoreactivity \( (p = 0.0425) \) were significant predictors of recurrence-free survival (not illustrated). These results are reflected in Table 3, in which the data of a univariate Cox regression analysis are listed. A multivariate analysis demonstrated that age \( (p = 0.019) \) and Ki67 antigen expression \( (p = 0.015) \) were the only independent prognosticators with regard to recurrence-free survival (Table 4).

When examining the progression-free survival of our patients, MCM2 expression—categorized at a cutoff of 20\%—was identified as the only parameter with significant predictive value \( (p = 0.0454 \) by log-rank test; Fig. 4). Other cutoff levels were not prognostically relevant (not illustrated). In univariate Cox regression analysis, however, the level of statistical significance was not reached by any of the parameters, even not by MCM2 expression \( (p = 0.059) \); Table 3). Correspondingly, no independent prognosticator of tumor progression could be identified by multivariate analysis in our series (Table 4).

### Table 2

<p>| Immunoreactivity for MCM2 with regard to tumor grade in 54 stage T1 bladder carcinomas |
|---------------------------------|--------|--------|--------|--------|--------|</p>
<table>
<thead>
<tr>
<th></th>
<th>0–20%</th>
<th>21–40%</th>
<th>41–60%</th>
<th>61–80%</th>
<th>81–100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCM2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 ( (n = 28) )</td>
<td>17</td>
<td>60.7</td>
<td>7</td>
<td>25.0</td>
<td>2</td>
</tr>
<tr>
<td>Grade 3 ( (n = 26) )</td>
<td>5</td>
<td>19.2</td>
<td>6</td>
<td>23.1</td>
<td>7</td>
</tr>
</tbody>
</table>

A significant difference exists between G2 carcinomas (median, 0–20\%) and G3 carcinomas (median, 41–60\%; \( p = 0.004 \) by U-test).
Fig. 3. Kaplan–Meier curve for recurrence-free survival of 54 stage T1 bladder carcinoma patients with regard to MCM2 expression (cutoff: 60%). Low-level expressers are indicated by a dotted line, high-level expressers by a solid line, and censored data by squares, respectively. A significant difference in survival exists between these two groups ($p = 0.0035$ by log-rank test).

Fig. 4. Kaplan–Meier curve for progression-free survival of 54 stage T1 bladder carcinoma patients with regard to MCM2 expression (cutoff: 20%). Low-level expressers are indicated by a dotted line, high-level expressers by a solid line, and censored data by squares. A significant difference in survival exists between these two groups ($p = 0.0454$ by log-rank test).

### Table 3

Univariate Cox regression analysis on the contribution of various potential prognostic factors to recurrence-free and progression-free survival of 54 patients with stage T1 papillary transitional cell carcinoma of the bladder.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recurrence-free survival</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Age (≤68 years vs. &gt;68 years [median])</td>
<td>2.09</td>
<td>1.10–4.00</td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
<td>0.97</td>
<td>0.42–2.23</td>
</tr>
<tr>
<td>Tumor grade (G2 vs. G3)</td>
<td>2.05</td>
<td>1.09–3.85</td>
</tr>
<tr>
<td>MCM2 expression (≤20% vs. &gt;20%)</td>
<td>1.68</td>
<td>0.89–3.18</td>
</tr>
<tr>
<td>MCM2 expression (≤60% vs. &gt;60%)</td>
<td>2.93</td>
<td>1.36–6.33</td>
</tr>
<tr>
<td>Ki67 antigen expression (≤40% vs. &gt;40%)</td>
<td>2.31</td>
<td>1.06–5.05</td>
</tr>
<tr>
<td>p53 expression (≤20% vs. &gt;20%)</td>
<td>1.88</td>
<td>1.00–3.53</td>
</tr>
</tbody>
</table>

RR: relative risk; CI: confidence interval.

### Table 4

Multivariate Cox regression analysis on the contribution of various factors to recurrence-free and progression-free survival of 54 stage T1 bladder carcinoma patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recurrence-free survival</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Age (≤68 years vs. &gt;68 years [median])</td>
<td>1.15–4.42</td>
<td>2.25</td>
</tr>
<tr>
<td>Tumor grade (G2 vs. G3)</td>
<td>0.99–3.76</td>
<td>1.93</td>
</tr>
<tr>
<td>MCM2 expression (≤60% vs. &gt;60%)</td>
<td>0.67–4.21</td>
<td>1.68</td>
</tr>
<tr>
<td>Ki67 antigen expression (≤50% vs. &gt;50%)</td>
<td>1.22–6.18</td>
<td>1.14</td>
</tr>
<tr>
<td>p53 expression (≤20% vs. &gt;20%)</td>
<td>0.54–2.40</td>
<td>1.15</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>0.37–3.41</td>
<td>1.13</td>
</tr>
<tr>
<td>Tumor grade (G2 vs. G3)</td>
<td>0.83–8.02</td>
<td>2.58</td>
</tr>
<tr>
<td>MCM2 expression (≤20% vs. &gt;20%)</td>
<td>0.64–4.83</td>
<td>1.76</td>
</tr>
<tr>
<td>p53 expression (≤20% vs. &gt;20%)</td>
<td>0.64–4.83</td>
<td>1.76</td>
</tr>
</tbody>
</table>

Only parameters with a $p$-value of <0.2 in univariate analysis were entered in the analysis. RR: relative risk; CI: confidence interval.
4. Discussion

The evaluation of tumor markers that identify proliferating cells is a widely used approach to increase the amount of prognostic information in malignant tumors. In this regard, antibodies to proteins involved in the regulation of chromosomal replication may be of special interest. In all eukaryotic cells, chromosome duplication is tightly regulated and coupled to progression through the cell cycle (reviewed in [28]). The formation of prereplicative complexes by replication initiation factors like the origin recognition complex (ORC), the Cdc6 protein and the minichromosome maintenance (MCM) proteins represents the first key event during the G1 phase of cell cycle. In a second step, other effectors coordinate unwinding of replication origins and the establishment of bi-directional replication forks to control entry into the S phase. In detail, MCMs form a hexameric DNA helicase at the replication forks, while Cdc6, by interacting with ORC, acts as a clamp-loader required to assemble the MCMs around the DNA. On the other hand, when mammalian cells exit the cell cycle into the quiescent, differentiated and senescent states, the Cdc6 and MCM components of the replication initiation pathway are downregulated [29]. It has been demonstrated that dysregulated expression of these proteins is a characteristic feature of dysplasia in cervical squamous intraepithelial neoplasia [30] and also in urothelial neoplasia of the bladder [17]. Thus, abnormal expression of Cdc6 and MCM proteins may be a hallmark of cell cycle dysregulation, which is supposed to be a key event in the development and progression of bladder carcinomas.

In the present study, we examined the expression of the MCM2 protein in papillary bladder tumors of stage T1, i.e. in locally invasive tumors that have already passed the phase of tumor initiation. In contrast to normal urothelium, which showed no MCM2 expression in preceding experiments (data not shown), MCM2 immunoreactivity—although to a varying degree—was observed in the vast majority of carcinomas. While MCM2 expression was found not associated with p53 immunoreactivity, it showed a tendentious correlation with Ki67 antigen expression (Table 1). The Ki67 antigen is currently used as a widespread proliferation marker in tumor tissues, although its functional significance is still unclear [31]. Recent data suggest that it may be involved in ribosome biosynthesis required during cell proliferation [32], and there is evidence that the molecule is not inevitably essential for cell proliferation [33]. Therefore, antibodies to proteins which regulate chromosomal replication have been proposed to offer a potentially more accurate means of determining the proliferation fraction within a tumor [34].

A main scope of our study was to examine the prognostic relevance of MCM2 expression in bladder cancer. In our series of stage T1 bladder carcinomas, high-level MCM2 immunoreactivity was found significantly associated with early tumor recurrence when using a cutoff of 60% and with early tumor progression when using a cutoff of 20%. The different cutoff levels point to a biologic significance inasmuch as exclusively tumors with high proliferative activity may be prone to tumor recurrence, whereas tumor progression to a muscle-invasive stage may already be performed by tumors showing moderate proliferative activity and presumably other additional characteristics not evaluated in this study.

When comparing the predictive power of MCM immunoreactivity with that of p53 and Ki67 antigen in a multivariate analysis (Table 4), the latter parameter was identified as the only immunohistochemical factor with independent predictive value concerning the assessment of tumor recurrence. This finding confirms the view that Ki67 expression is one of the best markers of tumor recurrence in superficial bladder carcinomas [1,6]. The prognostic value of age found in our study has also been described by others [1]. With regard to grading, we found a significant predictive power only by univariate, but not by multivariate analysis. The role of grading as a prognostic factor is controversially discussed in literature. Some studies investigating exclusively stage T1 carcinomas have reported a significant predictive value of grading [35–37], while others did not register any prognostic significance [38–40]. This discrepancy may be possibly due to varying proportions of G3 tumors included in these studies (ranging from 23 [38] to 59% [39]; mean value of all six studies: 35%), for it is well known that T1, G3 tumors form a special subgroup of T1 tumors revealing a different biological behavior [36,41] and a higher number of genetic alterations compared to G2 tumors [42]. In the present study, G3 tumors were included at a relatively high percentage of 48% (26/54 tumors), and this fact may have a potential impact on the results reported. However, when analyzing the prognostic value of MCM2 and other immunohistochemical markers in G2 or G3 tumors alone, no significant associations were found, which is presumably caused by the low numerical strength of these subgroups. The question whether MCM2 has a predictive power in T1, G3 tumors alone should be elucidated in a future study comprising a larger number of tumors.

In contrast to prognosticators of tumor recurrence, the number of parameters with predictive power con-
cerning tumor progression was relatively scarce in our analyses: MCM2 expression was identified as the single factor that significantly correlated with progression-free survival by log-rank test \((p = 0.0454)\). However, the level of statistical significance \((0.05)\) was missed in a univariate Cox regression analysis \((p = 0.059)\). This finding may be regarded an artifact caused by inherent statistical features of the Cox regression analysis, which is known to yield generally higher \(p\) values compared with the log-rank test. Nevertheless, the predictive power of MCM2 immunoreactivity in assessing tumor progression was—regardless of the statistical test—generally superior to that of tumor grade, age, Ki67 antigen and p53 expression. The fact that MCM2 expression showed a significant correlation with progression-free survival by log-rank test and a tendentious correlation by univariate \((p = 0.055)\) and multivariate Cox regression analysis \((p = 0.101)\) suggests that MCM2 expression may potentially bear some prognostic power concerning tumor progression and may therefore be used as an additional tool to identify high-risk patients within the heterogeneous group of T1 bladder carcinoma patients. This issue should be validated in a prospective study.

The tissue microarray technique used in this study provides an accurate means of investigating a high number of tumors immunohistochemically. Although this technique analyzes only small fractions of tissue from tumors that potentially display intra-tumor heterogeneity, it has been recently documented that the analysis of tissue microarrays is highly representative and yields similar results compared with the conventional analysis of larger tumor sections [43]. Based on the experiences made in the present study, we regard the tissue microarray technique an easy and cost-effective measure that may be suitable for the investigation of large numbers of cancer specimens and therefore can be generally recommended for immunohistochemical studies as presented here.

In conclusion, the present study is, to our knowledge, the first to examine MCM2 expression immunohistochemically in bladder tumors. Our data demonstrate that MCM2 immunoreactivity is a proliferation-dependent phenomenon showing significant associations with the biological behavior of stage T1 bladder carcinomas. Hence, MCM2 may be—in addition to already established prognostic factors—another criterion helping to assess the prognosis and to define the therapeutic strategy in an individual patient.

References


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