Clinical importance of independent prognostic factors for renal parenchymal carcinoma and a possibility of predicting the treatment outcome

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ABSTRACT

Aim To determine the influence of independent predictors (nuclear grade, patient’s general condition, tumor size) on survival of patients suffering from renal cancer.

Methods The study included 158 patients treated for renal parenchymal carcinoma in the period between 01. 01. 1998 and 31. 12. 2011. The patients’ general condition was evaluated using the ECOG staging system. Nuclear grade (NG) was assessed by the Fuhrman criteria. Prognostic factors were tested applying the Cox regression analysis and based on the significance independent predictors were determined.

Results The total survival rate of patients with renal parenchymal carcinoma was 81.2% after one year, 77.6% after 5 years and 70.4% after 10 years. In patients with NG 1 the survival rate after 5 years was 100%, whereas the survival in patients with NG 2, 3 and 4 was 98%, 48% and 0%, respectively. The survival rate in patients with ECOG 0 and 1 after 5 years was 100%, while in patients with ECOG 2 and 3 stage of the disease the survival rate was 68% and 25%, respectively. In patients with a tumor node less than 40 mm, ten-year survival rate was 100%, whereas the ten-year survival rate in patients with the tumor node sized 40 to 70 mm was 87%, and in patients with the tumor node over 70 mm ten-year survival rate was 66%.

Conclusion Multivariate analysis has established that the size of the tumor node, patient’s general condition and nuclear grade are independent predictors of disease outcome.

Key words: renal cancer, survival, predictors.
INTRODUCTION
Renal cell carcinoma (RCC) is ranked the ninth in Europe according to its prevalence, with 66,000 newly detected cases, and 39,000 fatal outcomes annually (1). Determining prognostic factors of survival for patients with RCC would be valuable in directing therapy and interpreting results of clinical trials. Clinical trials that include survival as an end point must account for prognostic factors to assure that treatment outcomes can be ascertained (2). Also, an assessment of patients’ survival benefits both patients and physicians in clinical management (2).

According to a retrospective epidemiological study of renal cancers conducted in Zenica-Doboj region during the 1998-2011 period (3), we investigated if manner of detection, clinical stage and histopathological type of the tumor met the criteria for independent predictors for the prognosis of renal cancer outcome, and negative result was found. In this paper we analyzed a correlation of tumor node size, nuclear grade (NG), and ECOG stage of patients with survival rate and determined the role of these parameters as criteria for independent predictors.

PATIENTS AND METHODS
The research was conducted in Cantonal Hospital Zenica, Bosnia and Herzegovina (B&H), a large 913-bed secondary hospital that serves 400,000 inhabitants of Zenica-Doboj Canton, as well as the patients from other cantons as required. This retrospective study included 202 patients with diagnosed renal cancer in the period between 01. 01. 1998 and 31. 12. 2011. The study included 158 patients with renal parenchymal carcinoma confirmed by histopathological diagnosis, who regularly reported for control examinations. Forty-four patients whose death was not related to the cancer, those who had been treated with immunotherapy and chemotherapy, and patients with inadequate documentation were excluded.

The patients’ average age was 57.5±11.1 years. There were 90 (57%) male, and 68 (43%) female patients. In 90 patients laparotomy was used as a surgical procedure, whereas 68 patients underwent lumbotomy. Total survival of patients with renal parenchymal carcinoma was 97.5% after one year, 89.5% after 5 years and 80.6% after 10 years. Median follow-up was 87 months.

The study was approved by the Director of the Zenica Cantonal Hospital.

All the patients included in the research were divided based on the cancer type and nuclear grade. All histopathological tests were performed at the Pathology Department of Cantonal Hospital Zenica, using the standard methods applied in histopathology, i.e. conventional processing using immunohistochemical methods and detection of tumor markers on an assay of the removed kidney, according to the protocols of the European Association of Pathologists i.e. the percentage of positive tumor cells as a criterion, in accordance with the ASCO/CAP (2). In case of ambiguous chromophobetype of cancer, immunohistochemical analyzes were performed: cytokeratin, EMA, CD-10, E-Cathearin (Roche Diagnostics, Deutschland).

The Eastern Cooperative Oncology Group (ECOG) Performance Scale was used to assess the patients’ performance status, evaluating a status of patients’ ability with grades 0-5, where zero means a fully active patient able to carry on all pre-disease performance without restriction, and grade five means death.

Classification of RCC into four categories according to nuclear size and the presence of nucleoli, as reported by Fuhrman (1982), is currently the most widely used grading protocol in North America and Europe (4-6). Fuhrman grading schema is an assessment based on the microscopic morphology of a neoplasm stained with haematoxylin and eosin. The system categorizes renal cell carcinoma with grades 1-4 based on nuclear characteristics: size and irregularity of appearance.

From the disease history the following laboratory parameters were analyzed: values of hemoglobin and erythrocyte sedimentation rate, patient’s general condition at admission and histopathological findings. At the control examination the patient’s general condition was determined, and control chest x-ray, ultrasound examination of abdomen and retroperitoneum and CT scan were performed to establish the presence or absence of the disease. Controls were performed as per the European Association of Urologists (EAU) protocols. The first control was carried out after 6 months, and the following ones once a year. After the fifth year, controls were scheduled according to the individual risk profile.

Prognostic factors were tested using the Cox regression analysis, and based on significance indepen-
dent predictors were determined. Multivariate Cox regression factors were used to develop prognostic nomograms. Internal validation was conducted on 200 bootstrap resampling. Predictive accuracy was assessed with ROC curve, which is obtained from the area under the curve (AUC). Statistical significance was tested at the level $p \leq 0.05$. Based on analyzed data a nomogram was created for prediction of outcome, and comparison was made with the model of logistic regression.

**RESULTS**

The total survival rate of patients with renal parenchymal carcinoma was 154 (97.5%) after one year, 141 (89.5%) after 5 years and 127 (80.6%) after 10 years. In 68 (43.1%) patients the general condition evaluated according to ECOG was 0, ECOG 1 was found in 74 (46.8%) patients, ECOG 2 in 12 (7.6%) patients, and 4 (2.5%) patients had ECOG 3. There were no patients with ECOG 4.

The average size of the primary tumor node was $65.9 \pm 29.9$ mm. The tumor nodes of size up to 40 mm were found in 38 (24.1%) patients, tumor size between 40 and 70 mm was found in 104 (65.8%) and in 16 (10.1%) patients the node size was larger than 70 mm.

Having analyzed the nuclear grade according to Fuhrman, grade 1 was found in 75 (47.5%), grade 2 in 70 (44.3%), grade 3 in 11 (6.9%) and grade 4 was found in two (1.3%) patients.

As far as the general condition is concerned (Log rank $p < 0.0001$), we found that the patients’ survival was significantly different. In the group of patients with ECOG 0 and ECOG 1, the survival rate of over 90% after 5 years was determined. As expected, the survival rate was shorter for patients with a higher ECOG score (Table 1).

Further analysis found that the survival length of patients was significantly different in relation to the nuclear grade (NG) (Log rank $p < 0.0001$) (Table 3). It was not possible to perform an analysis for the group of patients with the confirmed NG4, as there were only two patients in this group.

**Table 2. Survival rate of patients according to the size of tumor node**

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>1-year</th>
<th>5-year</th>
<th>10-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 mm</td>
<td>38 (100.0)</td>
<td>38 (100.0)</td>
<td>38 (100.0)</td>
</tr>
<tr>
<td>40-70 mm</td>
<td>103 (98.6)</td>
<td>93 (89.4)</td>
<td>90 (87.0)</td>
</tr>
<tr>
<td>&gt; 70 mm</td>
<td>15 (94.0)</td>
<td>13 (82.4)</td>
<td>11 (65.9)</td>
</tr>
</tbody>
</table>

Multivariate analysis established that the nuclear grade, patient’s general condition and tumor size category (up to 40 mm, between 40 and 70 mm and over 70 mm) were independent predictors of disease outcome, where as other analyzed factors did not meet the requirements for independent predictors (Table 4).

**Table 3. Determined length of one-year, five-year and ten-year survival rate of patients according to nuclear grade (NG)**

<table>
<thead>
<tr>
<th>NG</th>
<th>1-year</th>
<th>5-year</th>
<th>10-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72 (98.6)</td>
<td>68 (91.3)</td>
<td>66 (88.0)</td>
</tr>
<tr>
<td>2</td>
<td>67 (98.6)</td>
<td>64 (92.1)</td>
<td>56 (80.7)</td>
</tr>
<tr>
<td>3</td>
<td>9 (81.8)</td>
<td>7 (65.5)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

**Table 4. Multivariate analysis of independent prognostic factors**

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>p</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear grade</td>
<td>0.5501</td>
<td>0.2940</td>
<td>&lt;0.0001</td>
<td>0.05</td>
</tr>
<tr>
<td>General condition</td>
<td>1.7377</td>
<td>0.3072</td>
<td>&lt;0.0001</td>
<td>0.05</td>
</tr>
<tr>
<td>Size category</td>
<td>0.8348</td>
<td>0.4410</td>
<td>&lt;0.0001</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Disscussion**

Most recent studies mention laparoscopy as a surgical approach, especially in patients with T1 and T2 stages of the disease (7). Unfortunately, in our conditions laparoscopy is not performed due to very limited resources.

According to ECOG analysis of the patients, our results are comparable with Bamias et al. study (8), as the assessment of the condition was subjective and the distinction between the two categories was not exact. Regardless of the aforementioned, most patients (around 90%) were fully physically active.
Tumor nodes size in our study was very different to tumor nodes sizes found by Santana-Rios et al; <40 mm found in 24.1% vs 11%, 40 to 70 mm in 65.8% vs 23% and >70 mm in 10.1 vs 66%, respectively (9). The explanation for this discrepancy could be in the fact that in our setting ultrasound was very popular and inexpensive diagnostic tool, so the disease was diagnosed in an early phase.

Compared to a study by Tastekin et al, we found more patients with lower grades: 47.5% vs 18% for NG1, 44.3% vs 41% for NG2, 6.9% vs 26% for NG3, and 1.3% vs 15% for NG4 (10). The nuclear grade is a direct indicator of cancer’s malignant potential. For this fact, it may be concluded that the malignant disease of the examined sample is of a significantly weaker malignant potential.

According to our study a higher ECOG score was connected with a shorter survival. Verhoesta et al. research involving 1124 patients in 5 referral centers in Europe proved that the performance status was an independent predictor (11), and most patients had the performance status 0 or 1, which was also the case in our research.

A size of the primary node in our study did not correlate with the survival rate. The same results were obtained by Jorns et al. (12). Interestingly, none of the studies have investigated the location of the tumor in relation to vascular structures, which could have larger impact on the development of the disease. That would explain why the tumor of the same characteristics generates metastases in some patients, while in others it does not, even in case of very small tumors (13).

The division of patients into the groups according to the size of tumor node has shown a significant difference in the survival rate. Steiner et al. have found a difference in the survival rate among the patients (the size of 40 mm was taken as a borderline), and in the group of patients with the tumor node less than 40 mm, ten-year survival was 100% (14). Similar data have been shown in recent studies, which point out that distant metastases very rarely occur in patients with the primary node less than 3 cm (15), while Igarashi et al. did not find them at all (16). In our study we proved that the patients with smaller tumor survived longer, for the tumor node smaller than 40 mm, survival rate after 10 years was 100%. Also, Steiner et al. pointed out that the survival rate was significantly lower in patients if the borderline value was 70 mm, 177 vs. 237 months (14).

Further analyses found that the survival rate was significantly different as compared with nuclear grade, lower NG, longer survival. The analysis for NG4 was not possible because there were only two patients in the group. Nuclear grade as a direct indicator of malignant potential is an important predictor. It is particularly important to monitor patients with sarcomatoid component or a high nuclear grade. Although our research practically did not include patients with NG4, when comparing patients with NG1 or NG2 with patients having NG3, there was a significant difference. It is true that the everyday practice pays little attention to this factor, and more attention is given to the size of the tumor node, although it was proven that the tumor size itself is not a predictor.

Multivariate analysis has established that the nuclear grade, patient’s general condition and size are independent predictors of the disease outcome. As opposed to univariate model, which tests only one variable, multivariate model includes multiple factors and tests them among each other and a degree of their individual participation in the model. Multivariate model is more potent than the prediction model, as it includes more factors and reflects the real situation better than the univariate model.

After the multivariate analysis, variables were tested in the model of logistic regression, and the exact prediction of treatment outcome was determined in 91.8% of patients. In patients who survived for 10 years from the time of surgery the prediction accuracy is 97.8%. In patients who did not survive this period the prediction is accurate in 50%. Studies showing prognostic models are contradictory; some underline the importance of the manner of detection (17-19), whereas there is an increasing number of nomograms which include tumor size, histopathological type, nuclear grade and clinical stage (17,20,21).

In conclusion, we found that the patients’ general condition, size of the tumor node and nuclear grade are independent predictors of the renal cell carcinoma outcome.

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TRANSPARENCY DECLARATIONS
Competing interests: none to declare.
REFERENCES

Klinički značaj neovisnih prediktora kod bubrežnog karcinoma i mogućnost predikcije ishoda

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SAŽETAK

Cilj Odrediti utjecaj neovisnih prediktora (nuklearni gradus, opće stanje bolesnika, veličina tumora) na preživljavanje kod oboljelih od karcinoma bubrega.


Rezultati Stopa preživljavanja bolesnika s karcinomom bubrežnog parenhima iznosila je 81,2% nakon jedne godine, 77,6% nakon 5 godina i 70,4% nakon 10 godina. Kod bolesnika koji su imali NG 1 stopa preživljavanja iznosila je 100% nakon 5 godina, dok je petogodišnja stopa preživljavanja pacijenata s NG-om 2, 3 i 4 iznosila 98%, 48%, odnosno 0%. Stopa preživljavanja bolesnika s ECOG-om 0 i 1, nakon 5 godina, iznosila je 100%, dok je u pacijenata s ECOG-om 2 i 3 stadijem petogodišnja stopa preživljavanja iznosila 68,2%, odnosno 25%. U bolesnika s tumorskim čvorom manjim od 40 mm, desetogodišnja stopa preživljavanja iznosila je 100%, dok je u bolesnika s tumorskim čvorom veličine 40 do 70 mm iznosila 87%. Međutim, u bolesnika s tumorskim čvorom većim od 70 mm, desetogodišnja stopa preživljavanja iznosila je 65,9%.

Zaključak Multivarijantnom analizom utvrđeno je da su veličina tumorskog čvora, opće stanje bolesnika i nuklearni gradus neovisni prediktori ishoda bolesti.

Ključne riječi: karcinom bubrega, preživljavanje, prediktori.