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External Validation of the Mayo Clinic Stage, Size, Grade, and Necrosis (SSIGN) Score for Clear-Cell Renal Cell Carcinoma in a Single European Centre Applying Routine Pathology

Richard Zigeuner[a,*], *Georg Hutterer*[a], *Thomas Chromecki*[a], *Arvin Imamovic*[a], *Karin Kampel-Kettner*[a], *Peter Rehak*[b], *Cord Langner*[c], *Karl Pummer*[a]

[a] *Department of Urology, Medical University Graz, Austria*
[b] *Department of Surgery, Division of Biomedical Engineering & Computing, Medical University Graz, Austria*
[c] *Institute of Pathology, Medical University Graz, Austria*

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Abstract

Background: The stage, size, grade, and necrosis (SSIGN) score has been created as an outcome prediction tool for clear-cell renal cell carcinoma (ccRCC) using review pathology.
Objective: We evaluated the prognostic accuracy of the SSIGN score model using routine pathology records.
Design, setting, and participants: We retrospectively evaluated pathology records of 1862 consecutive ccRCC patients with complete data including follow-up who had been operated between 1984 and 2006.
Intervention: Surgical treatment of patients with ccRCC.
Measurements: TNM stage, largest tumour diameter, tumour grade, and presence of histologic tumour necrosis were recorded. ccRCC were categorised according to the SSIGN-score algorithm as 0–15. Cancer-specific survival (CSS) was assessed using the Kaplan-Meier method for individual SSIGN-score categories (scores 0–1 and $\geq$10, respectively, were combined). For evaluation of the prognostic impact of stage, size, grade, and necrosis regarding CSS, a multivariate analysis using a Cox regression model was performed, and for assessment of prognostic accuracy, Harrell's concordance index was performed.
Results and limitations: Median tumour diameter was 5.0 cm (range: 0.6–22 cm). Tumour necrosis was noted in 607 tumours (32.6%). Median follow-up was 72.5 mo (range: 0–281 mo); 359 of 1862 patients (19.3%) died of RCC. Ten-year CSS rates for respective SSIGN scores in our study ranged from 96.5% (scores 0–1) to 19.2% (scores $\geq$10). pT categories, lymph-node status, distant metastases, high tumour grade (size $\geq$5 cm), and necrosis were each independent predictors of CSS. The Harrell's concordance index was 0.823. Limitations included smaller sample sizes in higher risk categories and limited numbers of patients at risk after 10 yr.
Conclusions: Outcome prediction with the SSIGN score using routine pathology records was comparable to the original data based on review pathology. Combining scores into five categories improved discrimination. Our data support the routine use of the SSIGN score in clinical practice with regard to follow-up decisions and patient selection for adjuvant trials.

* Corresponding author. Department of Urology, Medical University Graz, Auenbruggerplatz 7, A-8036 Graz, Austria. Tel. +43 316 385 81967; Fax: +43 316 385 3550.
E-mail address: richard.zigeuner@meduni-graz.at (R. Zigeuner).

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1. Introduction

Renal cell carcinoma (RCC) is the third most common urologic cancer, with >54 000 new cancer cases and 13 000 cancer-related deaths estimated in the United States in 2008 [1]. Despite recent advances in medical treatment [2–7], metastatic RCC (mRCC) is an incurable disease in the majority of cases, with median survival times ranging from 4 mo to 20 mo depending on risk-group stratification [8].

Several prognostic models for patients with clear-cell RCC (ccRCC) have been developed [9–11]. Some have been updated by the same institutions [12–14], and for others an external validation has been performed [15–18]. Currently evidence-based follow-up guidelines for RCC patients are lacking [19].

One model is the stage, size, grade, and necrosis (SSIGN) score developed by the Mayo Clinic to predict cancer-specific survival (CSS) of patients with ccRCC [9]. The model had been based on pathology review by one uropathologist. It has been validated by Ficarra et al [18] using a smaller sample size of 388 patients and a review pathology which is not routinely available. Thus, we performed an external validation of the SSIGN score with a single-centre dataset based on routine pathology reports.

2. Methods

2.1. Patient selection and pathologic features

Data from consecutive patients undergoing radical or partial nephrectomy for RCC between 1984 and 2006 were retrieved from the database of the Institute of Pathology at the Medical University of Graz, Graz, Austria. No pathology review was performed. Routine pathologic diagnoses of RCC specimens are based upon a minimum of three paraffin blocks per tumour at our institution. During the observation period, 28 pathologists, mainly general pathologists, were involved. The pathology reports were evaluated regarding pT categories, tumour grade, tumour size, histologic subtype, and presence of histologic coagulative tumour necrosis. Lymph-node status was recorded if available. Since the TNM classification system for RCC changed twice during the observation period, for the present study pT categories were adjusted to the TNM classification of 1997 [20] which had been implemented in the original SSIGN-score algorithm [9].

Tumour grade was assessed according to the following criteria: Four nuclear grades were defined in order of increasing nuclear size, irregularity, and nucleolar prominence. Grade 1 tumours have small, round nuclei with inconspicuous nucleoli. Grade 2 tumours show round to slightly irregular nuclei with finely granular chromatin and mildly enlarged nucleoli. Grade 3 tumours are characterised by round to irregular nuclei with prominent nucleoli, whereas Grade 4 tumours display marked nuclear hyperchromasia and polymorphism including giant cell formation.

Tumour size was recorded as the largest diameter (cm) described in the pathology report. Only patients with ccRCC were included. Tumour necrosis was recorded as either present or absent but was not assessed quantitatively. If necrosis was not mentioned, it was regarded as absent. Regressive changes such as fibrosis, hyalinisation, or cystic transformation were not considered to be necrosis.

In accord with Frank et al [9], patients with synchronous bilateral tumours were excluded. In patients with bilateral metachronous RCCs, only the first tumour was chosen for analysis. Pathologic features of resected metachronous tumours were recorded and compared with the primary contralateral RCC.

All procedures were carried out in accord with the ethical guidelines established by our institution.

2.2. Clinical parameters and outcome

Assessment of patient-related features included age, gender, date and type of surgery, tumour side, bilateral tumours, metastatic disease at presentation, and histologically confirmed secondary malignancies other than RCC diagnosed at any time in the patient's history. Lymphadenectomy was performed only in presence of enlarged nodes.

Follow-up was performed according to the following scheme: For imaging during follow-up, chest X-ray and abdominal ultrasound were predominantly used, especially in patients with a low risk for relapse (pT1 G1–2), whereas computed tomography (CT) or magnetic resonance imaging (MRI) were performed in all other patients or to further clarify suspicious findings. This follow-up regimen has recently been confirmed by the guidelines of the European Association of Urology [21]. Follow-up evaluations were performed every 6 mo for 5 yr and annually thereafter in locally advanced tumour stages. In organ-confined cancers, imaging was performed twice in the first year after surgery and annually thereafter. No adjuvant treatment was given.

If a secondary malignancy was indicated in the patient's history and metastases were diagnosed, a histologic verification of metastases was obtained to confirm the origin of metastatic disease and to define the direction of further treatment.

Survival data were mainly retrieved from the electronic patient records of our institution. Missing data were retrieved using letters and telephone interviews with patients and/or family doctors. For deceased patients, dates and causes of death were obtained from the central Austrian Bureau of Statistics. Death was assessed as either cancer-related or unrelated. All deaths of patients who had confirmed mRCC at any time were considered to be cancer-related. Follow-up time was calculated in months from the date of surgery to the last medical check or death.

2.3. Statistical methods

Differences regarding clinicopathologic features between our study population and the Mayo Clinic series were evaluated using the chi-square test or the Fisher exact test for all clinicopathologic parameters as described above.

The SSIGN score was calculated for each patient according to the original scoring algorithm [9]. Details of the algorithm are listed in Table 1. The scores ranged from 0 to 15 with 0 representing the most favourable outcome. CSS was assessed using the Kaplan-Meier method and the log-rank test was used for the individual scoring categories. According to the original publication by Frank et al, scores of 0–1 as well as scores of 10 or greater, respectively, were pooled together, resulting in 10 subgroups [9]. In a second step, a summary analysis of scores 0–2, 3–4, 5–6, 7–9, and 10 or greater, respectively, was performed according to Ficarra et al [18].

Associations between CSS and the assessed clinicopathologic parameters were evaluated using univariate and multivariate Cox proportional hazards regression models including hazard ratios (HR) and 95% confidence intervals (CI). Like the original publication by Frank et al, the concordance index (*c* index) described by Harrell et al [22] was used for assessment of the prognostic ability of the model in univariate and multivariate Cox regression analyses. To compare estimated survival data between the Mayo Clinic study and our study at each of the time intervals, reverse life table analyses and the Fisher exact test were used.

All reported *p* values were two-sided. Statistical analyses were performed using NCSS (NCSS, Kaysville, UT, USA), SPSS (SPSS Inc.,