available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Kidney Cancer

Application of the Stage, Size, Grade, and Necrosis (SSIGN) Score for Clear Cell Renal Cell Carcinoma in Contemporary Patients

William P. Parker[a], *John C. Cheville*[b], *Igor Frank*[a], *Harras B. Zaid*[a], *Christine M. Lohse*[c], *Stephen A. Boorjian*[a], *Bradley C. Leibovich*[a], *R. Houston Thompson*[a,*]

[a] *Department of Urology, Mayo Clinic, Rochester, MN, USA;* [b] *Department of Pathology, Mayo Clinic, Rochester, MN, USA;* [c] *Department of Health Services Research, Mayo Clinic, Rochester, MN, USA*

Article info

Article history:
Accepted May 25, 2016

Associate Editor:
Giacomo Novara

Keywords:
Partial nephrectomy
Prognosis
Radical nephrectomy
Renal cell carcinoma
Survival

Abstract

Background: The tumor stage, size, grade, and necrosis (SSIGN) score was originally defined using patients treated with radical nephrectomy (RN) between 1970 and 1998 for clear cell renal cell carcinoma (ccRCC), excluding patients treated with partial nephrectomy (PN).
Objective: To characterize the original SSIGN score cohort with longer follow-up and evaluate a contemporary series of patients treated with RN and PN.
Design, setting, and participants: Retrospective single-institution review of 3600 consecutive surgically treated ccRCC patients grouped into three cohorts: original RN, contemporary (1999–2010) RN, and contemporary PN.
Intervention: RN or PN.
Outcome measurements and statistical analysis: The association of the SSIGN score with risk of death from RCC was assessed using a Cox proportional hazards regression model, and predictive ability was summarized with a C-index.
Results and limitations: The SSIGN scores differed significantly between the original RN, contemporary RN, and contemporary PN cohorts ($p < 0.001$), with SSIGN ≥ 4 in 53.5%, 62.7%, and 4.7%, respectively ($p < 0.001$). The median durations of follow-up for these groups were 20.1, 9.2, and 7.6 yr, respectively. Each increase in the SSIGN score was predictive of death from RCC (hazard ratios [HRs]: 1.41 for original RN, 1.37 for contemporary RN, and 1.70 for contemporary PN; all $p < 0.001$). The C-indexes for these models were 0.82, 0.84, and 0.82 for original RN, contemporary RN, and contemporary PN, respectively. After accounting for an era-specific improvement in survival among RN patients (HR: 0.53 for contemporary vs original RN; $p < 0.001$), the SSIGN score remained predictive of death from RCC (HR: 1.40; $p < 0.001$).
Conclusions: The SSIGN score remains a useful prediction tool for patients undergoing RN with 20-yr follow-up. When applied to contemporary RN and PN patients, the score retained strong predictive ability. These results should assist in patient counseling and help guide surveillance for ccRCC patients treated with RN or PN.
Patient summary: We evaluated the validity of a previously described tool to predict survival following surgery in contemporary patients with kidney cancer. We found that this tool remains valid even when extended to patients significantly different than were initially used to create the tool.

* Corresponding author. Department of Urology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel. +1 507 266 9968; Fax: +1 507 284 4951.
E-mail address: thompson.robert@mayo.edu (R. Houston Thompson).

http://dx.doi.org/10.1016/j.eururo.2016.05.034
0302-2838/

1. Introduction

The tumor stage, size, grade, and necrosis (SSIGN) score was reported in 2002 based on patients treated with radical nephrectomy (RN) between 1970 and 1998 for clear cell renal cell carcinoma (ccRCC) [1]. It was developed due to the limited prognostic ability offered by the TNM staging system to predict death from renal cell carcinoma (RCC) following RN, specifically for ccRCC. As such, the SSIGN score incorporates several pathologic features (tumor size, grade, and presence of coagulative necrosis) beyond TNM stage that are predictive of survival following nephrectomy [2–4]. Since its original description, the SSIGN score has been externally validated [5–8], compared favorably with other prognostic models [5], been included in guidelines [9], and is now being utilized to stratify patients for therapeutic clinical trials and assess the role of biomarkers in predicting survival for RCC patients [10–15].

However, the original description and subsequent validations may not reflect current clinical practice. Important changes have influenced survival for RCC patients since the initial publication of the SSIGN score including significant stage migration [16] and the introduction of targeted agents for metastatic RCC [17]. In addition, the utilization of partial nephrectomy (PN) for localized RCC has dramatically increased in the past decade [18], a procedure excluded from the SSIGN score development. Finally, the original description of the SSIGN score, and the subsequent validations, lacks long-term follow-up data and an assessment of the competing risk of death from non-RCC causes.

Given the changes in the landscape of RCC management since the inception of the SSIGN score and its ongoing utilization in validating new biomarkers, we sought to reassess the originally described cohort to evaluate the SSIGN score with longer follow-up, investigate the competing risk of non-RCC death, and evaluate the predictive ability of the SSIGN score in contemporary patients managed with both RN and PN.

2. Materials and methods

2.1. Patient selection

Following institutional review board approval, we queried the Mayo Clinic Nephrectomy Registry to identify the 1801 patients treated with RN for sporadic unilateral ccRCC between 1970 and 1998 who were used to develop the Mayo Clinic SSIGN score [1]. Of these patients, 6 declined use of their medical records for research, leaving 1795 patients for analysis. We also identified 1038 patients treated with RN and 767 patients treated with PN for sporadic unilateral ccRCC between 1999 and 2010 to serve as contemporary RN and PN cohorts.

2.2. Clinicopathologic features

Clinical features assessed included age at surgery, sex, symptoms at diagnosis, smoking history, preoperative estimated glomerular filtration rate (eGFR; in ml/min per 1.73 m^2), Eastern Cooperative Oncology Group (ECOG) performance status, Charlson Comorbidity Index (CCI) score, and body mass index (BMI; in kg/m^2). Patients with a palpable flank or abdominal mass, discomfort, gross hematuria, acute onset varicocele, or constitutional symptoms (rash, sweats, weight loss, fatigue, early satiety, and/or anorexia) were considered symptomatic at presentation.

All pathologic specimens were reviewed by one urologic pathologist (J.C.C.) blinded to patient outcome for identification of histologic subtype, tumor size, 2010 TNM classification [19], 2016 World Health Organization/International Society of Urological Pathology grade (identical to the nuclear grading system used for the Mayo Clinic Nephrectomy Registry and the development of the SSIGN score [1,20,21]), coagulative necrosis, and sarcomatoid differentiation. The original SSIGN score was developed using the 1997 TNM classification, which has since been updated [19]; all patients have been restaged to reflect the current system, and the SSIGN scores are reflective of this change (Supplementary Table 1). For example, patients with level 0 tumor thrombi were originally classified as pT3b in the 1997 system and are now classified as pT3a. Because 2 points are added to the SSIGN score for all pT3 tumors, this did not result in a change in the calculated SSIGN score. Similarly, 2 points are added to the SSIGN score for both pN1 and pN2 tumors from the 1997 system, which are now both classified as pN1 in the 2010 system [1].

2.3. Patient outcome

Vital status for patients in the Nephrectomy Registry is updated yearly, with the most current follow-up utilized for analysis. For patients who died within the previous year, the cause of death is determined by death certificate review. If patients visited our institution for metastatic RCC within 6 mo of death, they are considered to have died of RCC. If the death certificate does not support this conclusion, the medical history is reviewed by an attending urologist to determine cause of death, which may include verification with the patient's local physician.

2.4. Statistical methods

Continuous features were summarized with medians and interquartile ranges (IQRs); categorical features were summarized with frequencies and percentages. Comparisons of features between patients in the original and contemporary RN cohorts and between patients in the contemporary RN and PN cohorts were evaluated using Wilcoxon rank sum and chi-square tests. Cancer-specific survival (CSS) was estimated using the Kaplan-Meier method, with duration of follow-up calculated from the date of surgery to the date of death or last follow-up. Associations of the SSIGN score with death from RCC were evaluated using univariable Cox proportional hazards regression models and summarized with hazard ratios (HRs) and 95% confidence intervals (CIs). The predictive ability of the SSIGN score was summarized with a bootstrap-corrected C-index. Additional multivariable models assessed the effect of cohort assignment, M stage, and SSIGN score on outcome within the RN cohorts. A separate analysis accounting for the competing risk of non-RCC death was performed by calculating the adjusted cumulative incidence of death from RCC [22]. Proportional subdistribution models were used to assess associations of the SSIGN score with the adjusted cumulative incidence of death from RCC and were summarized with HRs and 95% CIs. Statistical analyses were performed using SAS v.9.3 (SAS Institute Inc., Cary, NC, USA) or R v.3.1.1 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two sided with p values < 0.05 considered significant.

3. Results

3.1. Cohort characterization

Table 1 summarizes the clinicopathologic features of the 3600 patients stratified by cohort. Comparing the original

Please cite this article in press as: Parker WP, et al. Application of the Stage, Size, Grade, and Necrosis (SSIGN) Score for Clear Cell Renal Cell Carcinoma in Contemporary Patients. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.034