Original Paper

Current Urology

Curr Urol 2020;14:98–104
DOI: 10.1159/000499252

Received: April 1, 2019
Accepted: June 19, 2019
Published online: June 23, 2020

Predictive Ability for Disease-Free Survival of the GRade, Age, Nodes, and Tumor (GRANT) Score in Patients with Resected Renal Cell Carcinoma

Alessio Cortellini[a,b] Sebastiano Buti[c] Melissa Bersanelli[c] Katia Cannita[a] Giada Pinterpe[a] Olga Venditti[a] Lucilla Verna[b] Giampiero Porzio[a,b] Clara Natoli[d] Nicola Tinari[d] Luca Cindolo[e] Luigi Di Clemente[f] Antonino Grassadonia[d] Michele De Tursi[d] Corrado Ficorella[a,b]

[a]Medical Oncology Unit, St. Salvatore Hospital, L'Aquila; [b]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila; [c]Medical Oncology Unit, University Hospital of Parma, Parma; [d]Department of Medical, Oral and Biotechnological Sciences, University G. D'Annunzio, Chieti; [e]Department of Urology, ASL 2 Abruzzo, Hospital "S. Pio da Pietrelcina", Vasto; [f]Department of Urology, St. Salvatore Hospital, L'Aquila, Italy

Key Words
GRANT • Renal cell carcinoma • Disease-free survival • Kidney • Predictive model

Abstract
Background: Recently, the GRANT (GRade, Age, Nodes, and Tumor) score was validated through an adjuvant trial population. ***Methods:*** This retrospective study evaluated the performance of the GRANT score as a prognostic model for disease-free survival (DFS), compared to the University of California Los Angeles Integrated Staging System (UISS) score, in a "real-life" population of early renal cell carcinoma patients. A uni-/multi-variate analysis of DFS was also performed, to weigh the roles of baseline clinical factors. ***Results:*** From February 1998 to January 2018, 134 consecutive patients were enrolled, of which 85 patients (63.4%) had a favorable GRANT score, 49 (36.6%) an unfavorable GRANT score, and 21 (15.7%), 84 (62.6%), and 29 (21.6%) patients had a low, intermediate, or high risk of recurrence according to the UISS score, respectively. The median follow-up was 96 months. The median DFS of the overall study population was 53.7 months (95% CI: 38.4–87.8). Only bilateral renal cell carcinoma (p = 0.0041), Fuhrman grade 3/4 (p = 0.0008), pT3b–4 (p = 0.0324), and pN1–2 (p = 0.0303) pathological status were confirmed as independent predictors of a shorter DFS by the multivariate analysis. The median DFS of patients with favorable and unfavorable GRANT scores were 84.9 (95% CI: 49.8–129) and 38.4 months (95% CI: 24.4–87.8), respectively, with a statistically significant difference (p = 0.0147). The median DFS of patients with low, intermediate, and high risk of recurrence according to the UISS score were 92.3 (95% CI: 18.1–153.9), 51.7 (95% CI: 36.2–87.8), and 49.8 months (95% CI: 31.3–129), respectively, without statistically significant differences (p = 0.4728). DFS c-statistic values were 0.59 (95% CI: 0.51–0.67) and 0.51 (95% CI: 0.42–0.60) for the GRANT and the UISS scores, respectively. ***Conclusion:*** The GRANT score might be a useful tool that is user-friendly and easy to perform in clinical practice.

Introduction

Renal cell carcinoma (RCC) is the 9th most common cancer in men and the 14th in women worldwide [1]. Complete surgical resection, with partial or total nephrectomy, is the only curative treatment, but approximately 20–40% of patients radically treated, will have

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.com
www.karger.com

Alessio Cortellini
Medical Oncology Unit, St. Salvatore Hospital
Department of Biotechnological and Applied Clinical Sciences
University of L'Aquila, Via Vetoio
IT–67100 L'Aquila (Italy)
E-Mail alessiocortellini@gmail.com

a recurrence of the disease after a disease-free interval [2–4]. To date, no adjuvant treatment has been proven to be clearly effective, although results with immune checkpoint inhibitors are eagerly awaited [5]. A well-aimed prediction of the risk of recurrence is crucial for good post-surgical management, for the personalization of follow-up procedures, and a proper selection of patients who could be candidates for adjuvant clinical trials. Several clinical and pathological factors (e.g. TNM staging and Fuhrman grade) have been used to design prognostic models/nomograms. Among them the Mayo Clinic Stage, Size, Grade, and Necrosis (SSIGN) [6], the Leibovich score [7], and the University of California Los Angeles Integrated Staging System (UISS) [8], should be mentioned. The UISS score is a validated prognostic model that includes the Eastern Cooperative Oncology Group performance status (ECOG-PS), Fuhrman's histological grade, and the TNM anatomical staging system. With these variables, the score identifies 3 prognostic categories (low, intermediate, and high risk) which correlate with the post-nephrectomy outcome (recurrence). Despite being mainly based on routine factors, these models/nomograms have not become common clinical practice and are currently only used in clinical trials. Recently, the GRade, Age, Nodes, and Tumor (GRANT) score developed from explorative sub-analyses performed in an adjuvant trial with interleukin-2 and interferon-α [9], was validated through the ASSURE adjuvant trial population [10], showing its efficiency in predicting disease-free survival (DFS) and overall survival (OS) [11]. The GRANT score is based on 4 easy-available features: Fuhrman grading, patient's age, nodal status (pN or cN), and pathological tumor stage (pT). Each factor is worth 0 or 1 and they are summed into 2 risk categories: favorable (0–1 factors) and unfavorable (≥ 2).

Here we report a retrospective study, which evaluated the performance of the GRANT score as a prognostic model for DFS, compared to the UISS score, in a "real-life" population of early RCC patients.

Patients and Methods

Study Design

In this multicentre retrospective study, we included consecutive RCC patients who underwent curative surgical treatment. The referral centers were medical oncology departments of university hospitals of L'Aquila and Chieti. The aim of the study was to evaluate the predictive ability of the GRANT score and the UISS score regarding the risk of recurrence in a "real-life" population. As data were collected during a period of about 20 years, patients' survival has progressively improved after the advent of both targeted therapy and immunotherapy in relapsed (metastatic) disease. In our cohort, the estimation of OS with (post-surgical) predictive models could be flawed by post-progression treatments, so we decided to focus our attention on DFS, in order to avoid these biases. Furthermore, to properly weigh the roles of baseline clinical factors, we planned a uni-/multi-variate analysis of DFS.

Only patients with a histologically confirmed diagnosis of RCC, aged 18 years, and successfully treated with nephrectomy (radical or partial) were considered eligible for the analysis. During the follow-up, patients were monitored with hematological and radiological exams in clinical practice, as indicated according to physicians' choice, but at least every 6 months. Being a retrospective observational update, this collection was not considered a clinical trial. Therefore, approval by institutional review boards was not required, although a notification was sent (normative ref. Gazzetta Ufficiale della Repubblica Italiana n. 76 of 31-3-2008). The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. The study was conducted following the rules about personal data protection of the local bioethical committee competent on human experimentation (Comitato Etico per le province di L'Aquila e Teramo).

Statistical Analysis

DFS was defined as the time from surgical treatment to the first evidence of recurrence of disease or to the last contact in recurrence-free cases. OS was defined as the length of time between the surgical treatment and death from any cause or to the last contact for patients still alive. Tumor staging was assessed according to the American Joint Committee on Cancer (AJCC 6th edition) [12]. Clinic-pathological features used as covariates were: age (≤ 60 vs. > 60 years old), ECOG-PS (0–1 vs. ≥ 2), Fuhrman grade (1–2 vs. 3–4), pathological lymph node status (pN0–x vs. pN1–2), pathological T status (pT1–3a vs. all others), side (left vs. right tumors), and histology (clear cell carcinoma vs. papillary/chromophobe cells vs. others).

The median period of follow-up was evaluated according to the reverse Kaplan-Meier method, the median DFS and median OS were computed with Kaplan-Meier survival analysis, and the log-rank test was used to compare the median DFS among different risk subgroups by GRANT and UISS scores, and to evaluate hazard ratios (HRs) for each comparison [13]. Cox proportional hazard regression was used for uni-/multi-variate analyses of DFS. The concordance index (c-statistic) for each score was computed to evaluate the ability of the GRANT score and the UISS score to discriminate recurrence probability. The data cut-off period was May 2018. All statistical tests were two-sided with a level of significance set at $p < 0.05$. All statistical analyses were performed with MedCalc Statistical Software version 18.10 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

Results

Patients' Characteristics

From February 1998 to January 2018, 134 consecutive patients were enrolled. The median age was 59 years (range 29–84 years), the male/female ratio was 93/41,

Table 1. Patients' characteristics

	Overall population	GRANT favorable	GRANT unfavorable
Patients, n (%)	134	85 (63.4)	49 (36.6)
Age, years	59.1 (29–81)	54 (84–29)	65.5 (41–81)
≤ 60, n (%)	70 (52.2)	63 (74.1)	7 (14.3)
> 60, n (%)	64 (47.8)	22 (25.9)	42 (85.7)
Gender, n (%)			
Male	93 (69.4)	60 (70.6)	33 (67.3)
Female	41 (30.6)	25 (29.4)	16 (32.7)
ECOG-PS, n (%)			
0–1	127 (94.8)	79 (92.9)	48 (97.9)
≥ 2	7 (5.2)	6 (7.1)	1 (2.1)
Side, n (%)			
Right	60 (44.8)	39 (45.9)	21 (42.8)
Left	71 (53)	44 (51.8)	27 (55.1)
Bilateral	3 (2.2)	2 (2.3)	1 (2.1)
Histology, n (%)			
Clear cells	105 (78.4)	69 (81.2)	36 (73.5)
Papillary/chromophobe cells	15 (11.2)	8 (9.4)	7 (14.3)
Others	14 (10.4)	8 (9.4)	6 (12.2)
Fuhrman grade, n (%)			
1–2	67 (50)	55 (64.7)	12 (24.5)
3–4	67 (50)	30 (35.3)	37 (75.5)
T, n (%)			
1–3a	105 (78.4)	81 (95.3)	23 (46.9)
3b–4	29 (21.6)	4 (4.7)	25 (53.1)
N, n (%)			
0–x	119 (88.8)	84 (98.8)	35 (71.4)
1–2	15 (11.2)	1 (1.2)	14 (28.6)
UISS score, n (%)			
Low risk	21 (15.7)	19 (22.3)	2 (4.1)
Intermediate risk	84 (62.6)	42 (49.4)	42 (86.7)
High risk	29 (21.6)	24 (28.2)	5 (10.2)

Table 2. Cox proportional-hazards regression: uni- and multi-variate analysis of DFS

Variable (comparator)	DFS, Cox proportional hazard regression			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age (> 60 vs. ≤ 60 years)	1.19 (0.77–1.84)	0.4268	–	–
Sex (male vs. female)	1.34 (0.83–2.16)	0.2266	–	–
ECOG-PS (≥ 2 vs. 0–1)	0.85 (0.31–2.34)	0.7620	–	–
Side (left)				
Right	0.79 (0.50–1.26)	0.3301	0.97 (0.58–1.61)	0.9197
Bilateral	9.5 (2.78–32.7)	0.0003	6.59 (1.81–23.9)	0.0041
Histology (clear cell)				
Papillary/chromophobe	0.58 (0.23–1.46)	0.2549	0.50 (0.19–1.29)	0.1530
Others	2.44 (1.24–4.81)	0.0094	1.59 (0.74–3.39)	0.2277
Fuhrman grade (3–4 vs. 1–2)	2.09 (1.34–3.26)	0.0011	2.21 (1.39–3.51)	0.0008
T (3b–4 vs. 1–3a)	1.65 (1.01–2.69)	0.0437	1.73 (1.04–2.87)	0.0324
N (1–2 vs. 0–x)	3.16 (1.68–5.92)	0.0003	2.23 (1.07–4.63)	0.0303

and 70 patients (52.2%) were ≤ 60 years old. Seven patients (5.2%) had ECOG-PS ≥ 2 and 3 (2.2%) had bilateral synchronous RCC. The majority of the patients (78.4%) had clear cell histology, 11.2% papillary/chromophobe cells and 10.4% others histologies, and 50% of the patients had tumors with 1–2 Fuhrman grade. The majority of the patients had a pT1/3a and pN0/x pathological status (78.4 and 88.8%, respectively). A total of 85 patients (63.4%) had a favorable GRANT score, 49 (36.6%) an unfavorable GRANT score, and 21 (15.7%), 84 (62.6%), and 29 (21.6%) patients had a low, intermediate, or high risk of recurrence according to the UISS score, respectively. All the patients' features are listed in detail in table 1. Among patients with a favorable risk according to the GRANT score, 22.3, 49.4, and 28.2% had low, intermediate, or high risk according to the UISS score, respectively. On the other hand, among patients with an unfavorable risk according to the GRANT score, 4.1, 86.7, and 10.2% had low, intermediate, or high risk according to the UISS score, respectively.

Survival Analysis

The median follow-up was 96 months (range 1.7–287.1 months) and 39 patients (29.1%) had a follow-up of less than 36 months. The median DFS of the overall study population was 53.7 months (95% CI: 38.4–87.8; 58 censored patients) and the median OS was 118.5 months (95% CI: 85.5–174.5; 76 censored patients). Table 2 summarizes uni- and multi-variate analysis of DFS. Bilateral RCC (p = 0.0041), Fuhrman grade 3/4 (p = 0.0008), pT3b–4 (p = 0.0324), and pN1–2 (p = 0.0303) pathological status were confirmed as independent predictors of a shorter DFS.

DFS by Risk Group according to GRANT and UISS Scores

The median DFS of patients with a favorable GRANT score was 84.9 months (95% CI: 49.8–129; 36 censored patients), while the median DFS of patients with an unfavorable GRANT score was 38.4 months (95% CI: 24.4–87.8; 13 censored patients) (fig. 1). The difference between the subgroups was statistically significant (p = 0.0147) and HR was 0.58 (95% CI: 0.34–0.89). The median DFS of patients with a low risk of recurrence according to UISS score was 92.3 months (95% CI: 18.1–153.9; 9 censored patients), the median DFS of intermediate risk patients was 51.7 months (95% CI: 36.2–87.8; 30 censored patients), while the median DFS of patients with a high risk of recurrence according to the UISS score was 49.8 months (95% CI: 31.3–129; 13 censored patients) (fig. 1). The differences between the subgroups were not statistically significant (p = 0.4728). HRs were: 0.68 (95% CI: 0.34–1.38) between low and intermediate risk UISS scores, 0.68 (95% CI: 0.34–1.38) between low and high risk UISS scores, and 0.99 (95% CI: 0.55–1.77) between intermediate and high risk UISS scores. DFS c-statistic values were 0.59 (95% CI: 0.51–0.67) for the GRANT score and 0.51 (95% CI: 0.42–0.60) for the UISS score.

Discussion

Our epidemiological data are aligned with what was already reported: median age and patients' distribution among age subgroups [14], the very low frequency of bilateral aggressive forms [15], the prevalence of patients with a good PS at the moment of surgical resection [16], the balanced distribution of the Fuhrman grade [17], and the stratification among different classes of risk by the UISS score [8] and the GRANT score [11].

Due to surgical selection bias, it is not surprising that age, performance status, and sex did not significantly affect DFS in our population, while a higher Fuhrman grade and T/N pathological status were related to a shorter DFS. A previous study already suggested that gender might play a role in surgically treated RCC patients, but without statistical significance by the multivariate analysis [18]. Despite the trend of a shorter DFS for others histologies (including sarcomatoid tumors and mixed forms), no significance was observed regarding the histological type. These results were probably flawed by the small sample size, because it is well known that the chromophobe subtype (and to a lesser extent the papillary subtype) is related to better outcomes regarding both OS and DFS, when compared to the clear cell one [19–23]. Also, in our series, as already reported [24], bilateral synchronous forms at the moment of the surgery had a shorter DFS.

As stated, we chose the UISS score as the comparator, because it was the only one among the prognostic models/nomograms, for which we had availability of all the necessary parameters. The feasibility in a "real-life setting" of the SSIGN and Leibovich scores is flawed by histological tumor necrosis, which is a parameter usually underreported within histological reports. Moreover, the SSIGN and Leibovich models were developed to predict cancer-specific survival only in patients with clear cell RCC, while our cohort presented mixed histological features.

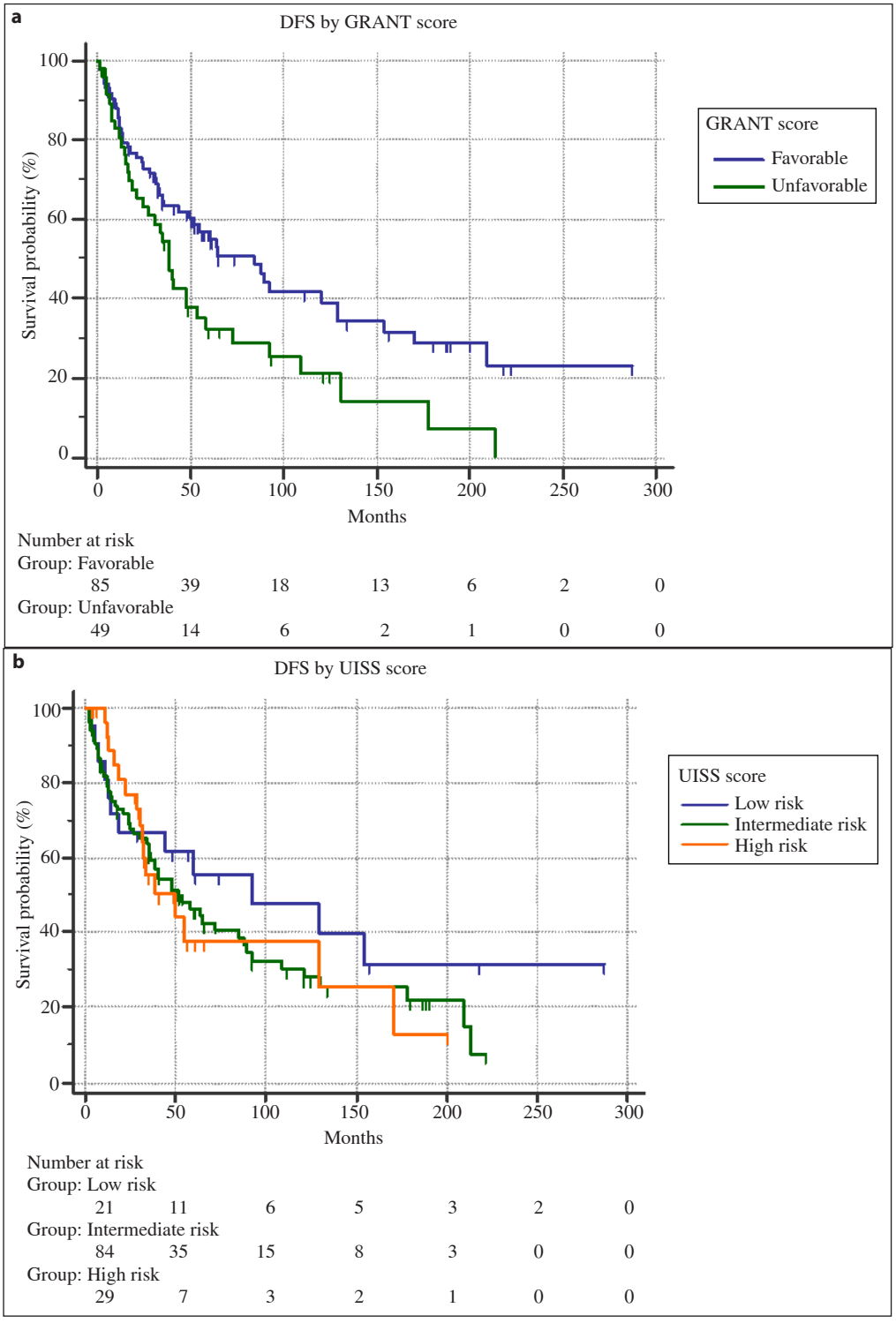

Fig. 1. Kaplan-Meier survival curves for DFS. **a** GRANT score (p = 0.0147); **b** UISS score (p = 0.4728).

The median DFS of patients with a favorable GRANT score was significantly longer when compared to patients with an unfavorable GRANT score, but the same cannot be said regarding UISS score risk groups. This evidence is concordant with the higher c-statistic of the GRANT score, compared to the UISS score, even though 0.59 does not seem to be an optimal value for a predictive model in absolute terms. Indeed, considering the c-statistic values, we found a low discriminatory potential of both GRANT and UISS scores.

The different predictive abilities could be related to the lack of concordance in patients' stratification with the UISS and GRANT scores. Among patients with a favorable GRANT risk there was a higher percentage of UISS high risk patients, when compared to the unfavorable subgroup, while among the unfavorable GRANT risk patients there was a prevalence of UISS intermediate risk patients. It is interesting to note that the Fuhrman grade and T/N pathological status, which were the only significant factors by the multivariate analysis (with the exception of bilateral disease), are included in both UISS and GRANT scores. At the same time the particular parameters of UISS and GRANT, ECOG-PS, and age, are not significantly related to DFS. So, the difference between the GRANT and UISS scores is probably related to the number of risk categories (2 vs. 3), because a 2-category score could have a stronger discriminatory capability. In this population, age did not affect DFS, but it seems that it is weakly related to the surgical outcome, so in our opinion it should be taken into consideration. Moreover, 60 years old is a weighed cut-off, between the aggressive phenotypes of the young patients [14, 15] and the prognostic impact that a more advanced cut-off might have. The other parameter to discuss is ECOG-PS, which has probably flawed the performance of the UISS score in our cohort. Indeed, only 2.2% of the study population had ECOG-PS ≥ 2, and ECOG-PS did not affect the DFS. Patients with poor clinical conditions do not usually undergo major surgery, mainly because the high risk of post-surgical complications, which may affect the outcome. Despite that, a percentage of patients with poor performance status still undergo surgery (e.g. for symptom management), so ECOG-PS should however be taken into account.

Before making conclusive considerations, we must consider the limitations of this study, particularly the small sample size and the retrospective design, which leads to several selection biases. The long study period also flawed the study. Over the last 2 decades the surgical management of RCC has significantly improved, leading to better outcomes [25, 26], such as the medical management of metastatic patients [27]. These factors negatively affected the outcomes of patients enrolled during the early years, compared to patients enrolled in recent years. The novelties of this analysis are the "real-life" population and the absence of adjuvant treatments, which gave us the opportunity to evaluate the performance of the GRANT score in a clinical practice setting. Indeed, the GRANT score was validated through a population prospectively collected for an adjuvant clinical trial, thus excluding patients with the lowest risks of recurrence [11].

Conclusion

To date, clinical practice still suffers a lack of simple and effective predictive models/nomograms for DFS of early RCC patients because of the inclusion of parameters not always available, such as tumor necrosis, which are not easy to use. In our opinion, the GRANT score might be a useful tool that is user-friendly and easy to perform in clinical practice. Looking to the ongoing immune checkpoint inhibitors trials [28–30], predictive models such as the GRANT score could become more and more useful in the future.

Acknowledgement

This work was supported by the Consorzio Interuniversitario Nazionale per la Bio-Oncologia (CINBO).

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