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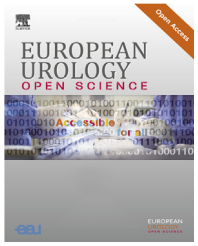

European Association of Urology

Brief Correspondence

Exploring the Diversity and Predictors of Histopathological Findings Across the European Association of Urology Guidelines Office Rapid Reaction Group Priority Groups for Patients with Renal Tumors: Implications for Individualized Prioritization of Renal Cancer Care

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Abstract

In response to the COVID-19 pandemic, the European Association of Urology (EAU) Guidelines Office Rapid Reaction Group (GORRG) defined priority groups to guide the prioritization of surgery for nonmetastatic renal cell carcinoma (RCC). In this study we explored the diversity and predictors of histopathological findings across the EAU GORRG priority groups using a large database of 1734 consecutive patients undergoing elective surgery for nonmetastatic renal masses between 2017 and 2020 at a referral institution. Overall, 940 (54.2%), 358 (20.6%), and 436 (25.2%) patients were classified as low-, intermediate-, and high-priority, respectively. The low-, intermediate-, and high-risk groups significantly differed regarding all primary histopathological outcomes: benign histology (21.6% vs 15.9% vs 6.4%; $p < 0.001$); non–organ-confined disease (5.0% vs 19.0% vs 45.4%; $p < 0.001$); and adverse pathological features according to validated prognostic models (including the median Leibovich score for clear-cell RCC: 0 vs 2 vs 4; $p < 0.001$). On multivariable analysis, beyond the EAU GORRG priority groups, specific patient and/or tumor-related characteristics were independent predictors of the aforementioned histopathological outcomes. To the best of our knowledge, our study shows for the first time the value of the EAU GORRG priority groups from a histopathological standpoint and supports implementation of such a prioritization scheme beyond the COVID-19 pandemic.

Patient summary: During the COVID-19 pandemic, the European Association of Urology designed a scheme to prioritize patients needing surgery for kidney cancer according to their tumor characteristics and symptoms. We used results from our hospital database to test the scheme and found that the priority classification can be used to predict cancer outcomes after surgery. This scheme may be useful in prioritizing kidney cancer surgeries after the COVID-19 pandemic.

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The COVID-19 pandemic forced disruptive changes in the prioritization of care in urology worldwide [1,2]. In response to the first peak of the outbreak, the European Association of Urology (EAU) Guidelines Office Rapid Reaction Group (GORRG) provided comprehensive recommendations to guide the prioritization of surgery for patients with genitourinary cancers [3].

For patients with locally confined or advanced nonmetastatic renal cell carcinoma (RCC), the EAU GORRG defined four priority categories for a risk-adapted tailored strategy for deferral of treatment according to the putative clinical harm caused by delayed care (from very unlikely to life-threatening). Specifically, patients are assigned to low-, intermediate-, and high-priority groups according to their clinical TNM stage (cT1aN0M0 vs cT1b–2aN0M0 vs cT2b–4N0/N1M0, respectively) and the presence of symptoms at diagnosis (all symptomatic patients were considered of high priority). Notably, these priority groups have not yet been validated from a histopathological perspective.

To fill this gap, we explored the diversity and predictors of histopathological findings across the EAU GORRG priority groups for renal tumors at an academic referral center.

We queried our prospectively collected institutional database to select consecutive patients undergoing elective surgery for cT1–4 N0–1 M0 renal masses between January 2017 and December 2020. A detailed overview of the study design is provided in the Supplementary material.

The primary outcome measures at histopathological analysis were: (1) benign histology; (2) non–organ-confined disease (pT3–4 and/or pN1); and (3) adverse pathological features for both clear-cell RCC (ccRCC) and papillary RCC according to validated prognostic models [4,5] as surrogate metrics for longer-term oncological outcomes.

The baseline patient, tumor, and surgery-related features, as well as the above-mentioned histopathological outcomes, were compared across the EAU GORRG priority groups (low vs intermediate vs high) using a Kruskal-Wallis or χ^2 test, as appropriate. An exploratory multivariable logistic regression analysis was performed to assess independent predictors of the primary histopathological outcomes.

Overall, 1734 patients were included in the analytical cohort. Of these, 940 (54.2%), 358 (20.6%), and 436 (25.2%) patients were classified as low, intermediate, and high EAU GORRG priority, respectively. The overall median waiting time for surgery was 35 d (interquartile range 22–41), with a significantly lower time for high- and intermediate-priority compared to low-priority patients (22 vs 30 vs 38 d; $p < 0.001$).

There were significant differences among the three groups for median tumor diameter, stage, and nephrometry score (all $p < 0.001$), as well as surgical treatment (proportion of patients undergoing partial nephrectomy) and approach (proportion of patients undergoing robotic surgery; Supplementary Table 1).

The main histopathological findings stratified by EAU GORRG priority group are shown in Table 1. We found significant differences in all primary outcomes across the low-, intermediate-, and high-priority groups, including (1) the proportion of patients with benign histology (21.6% vs 15.9% vs 6.4%; $p < 0.001$), (2) the proportion with non–organ-confined disease (5.0% vs 19.0% vs 45.4%; $p < 0.001$), and (3) the median Leibovich score for ccRCC (0 vs 2 vs 4; $p < 0.001$) as well as the proportion of patients with low-, intermediate-, and high-risk ccRCC (Table 1). Similarly, the median pathological tumor diameter and pTNM stage and grade significantly differed across the three priority groups.

The EAU GORRG priority groups were independent predictors of all outcomes of interest on multivariable analysis (Supplementary Table 2). In particular, EAU GORRG priority group (high vs low: odds ratio [OR] 0.28; $p < 0.001$), female gender (OR 1.83; $p < 0.001$), and tumor complexity (high vs low: OR 0.68; $p = 0.039$; intermediate vs low: OR 0.70; $p = 0.02$) were significant predictors of benign histology. Moreover, the EAU GORRG priority group (high vs low: OR 6.82; $p < 0.001$; intermediate vs low: OR 2.50; $p < 0.001$), patient age (OR per 10-yr increment 1.35; $p < 0.001$), and tumor complexity (high vs low: OR 5.16; $p < 0.001$; intermediate vs low: OR 1.87; $p = 0.004$) were significant predictors of non–organ-confined disease. The same factors were also independent predictors of Leibovich intermediate-/high-risk ccRCC (Fig. 1). Results for sensitivity analyses confirmed these findings (Supplementary Table 2).

Renal tumors are highly heterogeneous, ranging from indolent (not infrequently benign) small renal masses to aggressive, life-threatening, locally advanced cancers; this makes the contemporary decision-making process highly complex and nuanced [6]. In addition, the impact of a delay in surgical treatment for suspected RCC on oncological outcomes is still controversial [7]. Notably, the COVID-19 pandemic has unveiled and reinforced these concepts, making effective evidence-based prioritization of RCC care an urgent unmet need for both clinicians and policy-makers.

To the best of our knowledge, this is the first study providing real-life data on the diversity and predictors of histopathological findings across the EAU GORRG priority groups, which were developed to assist clinicians in identifying patients requiring timely interventions and patients whose treatment can be safely postponed.

A key finding of our study is that these priority groups accurately mirror histopathological outcomes after surgery (Fig. 1). In fact, more than one in five of the low-priority patients harbored a benign renal tumor; conversely, more than two in three of the high-priority patients had intermediate- to high-risk ccRCC, associated with worse prognosis and a higher risk of relapse [4,5]. A previous study assessing the extent to which EAU GORRG priority groups matched postoperative pathological risk (determined a priori according to the 2003 Leibovich score [8]) found the least concordance in the intermediate-priority group [9]. While the results of our study are not entirely comparable to those of Satish et al [9] (owing to a different concept and design), further research is needed to shed light on the association between prioritization schemes based on clinical variables and actual histopathological outcomes in efforts to refine decision-making and patient counseling for surgical candidates.

Our multivariable analysis results offer additional insights for refining shared decision-making and individualized management of nonmetastatic renal masses that might be valuable for different stakeholders, including patients. In

Table 1 – Histopathological characteristics of the renal masses in patients undergoing elective surgery for nonmetastatic renal masses between 2017 and 2020 at our institution, stratified by EAU GORRG priority group

	Overall	EAU GORRG priority group			
	(*n* = 1734)	Low (*n* = 940)	Intermediate (*n* = 358)	High (*n* = 436)	*p* value
Benign histology, *n* (%)	288 (16.6)	203 (21.6)	57 (15.9)	28 (6.4)	<0.001
Overall histological subtype, *n* (%)					<0.001
ccRCC	941 (54.3)	445 (47.3)	218 (60.9)	278 (63.8)	
pRCC	240 (13.8)	154 (16.4)	38 (10.6)	48 (11.0)	
chRCC	137 (7.9)	79 (8.4)	28 (7.8)	30 (6.9)	
Other malignant tumor	128 (7.4)	59 (6.3)	17 (4.7)	52 (11.9)	
Benign tumor	288 (16.6)	203 (21.6)	57 (15.9)	28 (6.4)	
ISUP grade ≥ 3, *n* (%)	487 (39.7)	172 (28.0)	112 (42.4)	203 (58.2)	<0.001
(where applicable; *N* = 1228)					
pT stage, *n* (%) (where applicable; *N* = 1435)					<0.001
T1a	807 (56.2)	655 (89.6)	82 (27.3)	70 (17.3)	
T1b	260 (18.1)	28 (3.8)	130 (43.3)	102 (25.2)	
T2a	48 (3.3)	0 (0)	21 (7.0)	27 (6.7)	
T2b	15 (1.0)	1 (0.1)	1 (0.3)	13 (3.2)	
T3a	268 (18.7)	45 (6.2)	64 (21.3)	159 (39.4)	
T3b	18 (1.3)	1 (0.1)	0 (0)	17 (4.2)	
T3c	8 (0.6)	0 (0)	0 (0)	8 (2.0)	
T4	11 (0.8)	1 (0.1)	2 (0.7)	8 (2.0)	
pN1 stage, *n* (%)					<0.001
N0	86 (5.0)	8 (0.9)	9 (2.5)	69 (15.8)	
N1	38 (2.2)	0 (0)	4 (1.1)	34 (7.8)	
Median tumor diameter, cm (IQR)	3.5 (2.3–5.5)	2.5 (2.0–3.0)	5 (3.9–6.5)	6 (4.1–9)	<0.001
Leibovich score [8] for ccRCC (*N* = 941)					
Median overall score (IQR)	1 (0–4)	0 (0–1)	2 (1–4)	4 (2–6)	<0.001
Risk group, *n* (%)					<0.001
Low (score 0–2)	612 (65.0)	410 (92.1)	114 (52.3)	88 (31.7)	
Intermediate (score 3–5)	219 (23.3)	34 (7.7)	92 (42.2)	93 (33.5)	
High (score ≥ 6)	110 (11.7)	1 (0.2)	12 (5.5)	97 (34.9)	
VENUSS score [13] for pRCC (*N* = 240)					
Median overall score (IQR)	2(0–4)	1 (0–2)	4 (2–4)	5 (3–7)	<0.001
Risk group, *n* (%)					<0.001
Low (score 0–2)	159 (66.3)	133 (86.4)	15 (39.5)	11 (22.9)	
Intermediate (score 3–5)	49 (20.4)	19 (12.3)	16 (42.1)	14 (29.2)	
High (score ≥ 6)	32 (13.3)	2 (1.3)	7 (18.4)	23 (47.9)	
Leibovich score [5] for pRCC, *n* (%) (*N* = 240)					<0.001
Low risk (group 1)	116 (48.3)	89 (57.8)	10 (26.3)	17 (35.4)	
Intermediate risk (group 2)	79 (32.9)	54 (35.1)	19 (50.0)	6 (12.5)	
High-risk (group 3)	45 (18.8)	11 (7.1)	9 (23.7)	25 (52.1)	
Leibovich score [5] for chRCC, *n* (%) (*N* = 137)					0.03
Low risk (group 1)	119 (86.9)	73 (92.4)	23 (82.1)	23 (76.7)	
Intermediate risk (group 2)	16 (11.7)	6 (7.6)	5 (17.9)	5 (16.7)	
High-risk (group 3)	2 (1.5)	0 (0)	0 (0)	2 (6.7)	
Non–organ-confined tumor, *n* (%)	313 (21.8)	47 (5.0)	68 (19.0)	198 (45.4)	<0.001

ccRCC = clear-cell renal cell carcinoma; chRCC = chromophobe RCC; EAU = European Association of Urology; GORRG = Guidelines Office Rapid Reaction Group; IQR = interquartile range; pRCC = papillary RCC.

addition to the EAU GORRG priority groups, specific patient and/or tumor-related characteristics were independent predictors of the aforementioned histopathological outcomes (Supplementary Table 2). At one extreme of the spectrum, our findings suggest that EAU GORRG low-priority female patients with low-complexity tumors might be able to safely postpone treatment or undergo preoperative tumor biopsy/additional imaging [10] or even be considered for active surveillance [11]. At the other extreme, older EAU GORRG intermediate-/high-priority patients with higher-complexity tumors may benefit the most from prompt surgical treatment given the highest risk of non–organ-confined disease and more aggressive ccRCC. These data may allow transparent, risk-adapted patient counseling in which the patient's perspectives and expectations are tailored according to the actual prioritization needs, especially during the COVID-19 pandemic [12].

Our findings should be interpreted in light of the study limitations, which are detailed in the Supplementary material. First, we could not assess the prognostic validity of the EAU GORRG priority groups. Yet, we relied on robust histopathological surrogates of longer-term oncological outcomes [4–6]. Second, our study did not assess the cost-effectiveness of the EAU GORRG priority groups or their impact on decision-making. Lastly, while we relied on a large data set that includes a contemporary and comprehensive case mix, the patients referred to our tertiary care center might not be entirely representative of the population of patients with nonmetastatic renal masses treated in other health care contexts, potentially limiting the reproducibility of our findings. The exclusion of patients with hereditary and/or bilateral tumors might have also contributed to this potential selection bias.

In conclusion, our study showed the value of the EAU GORRG priority groups from a histopathological standpoint, providing support for implementation of such a prioritization scheme beyond the COVID-19 pandemic. In this regard, use of the EAU GOORG priority groups might provide an

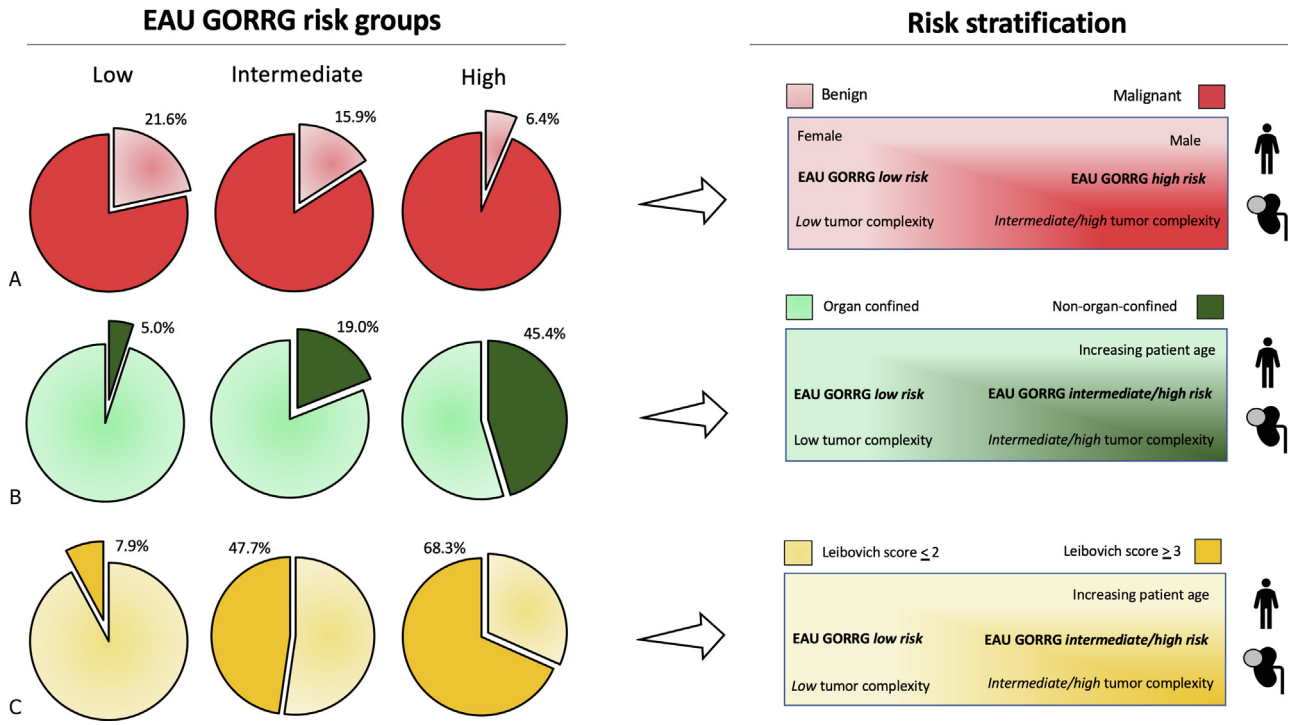

Fig. 1 – Graphical overview of the main study findings. Left: Proportion of patients with (A) benign histology, (B) non–organ-confined (pT3–4 or pN1) renal cell carcinoma, and (C) intermediate-/high-risk clear-cell renal cell carcinoma (Leibovich score ≥3), stratified by the European Association of Urology (EAU) Guidelines Office Rapid Reaction Group (GORRG) priority groups. Right: Pictorial representation of the multivariable analysis results for assessment of potential predictors of adverse pathology after partial or radical nephrectomy in the overall cohort. A detailed overview of the multivariable analysis is provided in Supplementary Table 3.

opportunity to improve the decision-making process for patients with renal tumors toward individualized, cost-effective, and value-based care.

Further research is needed to validate the prognostic value of the EAU GORRG priority groups for rational risk-adapted management of nonmetastatic renal tumors that balances available resources and the inherent tumor nature.

Author contributions: Riccardo Campi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Campi.
Acquisition of data: Pecoraro, Grosso, Tellini, Mari, Raspollini.
Analysis and interpretation of data: Campi, Tellini, Grosso, Pecoraro.
Drafting of the manuscript: Campi, Tellini, Grosso.
Critical revision of the manuscript for important intellectual content: Minervini, Serni, Carini, Gacci, Mari, Raspollini.
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Appendix A. Supplementary data

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