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ORIGINAL RESEARCH ARTICLE

Multiple factors influence decision making for the surgical treatment in patients with renal cell carcinoma

Britt-Inger Kröger Dahlin, Jan Hlodan, Ramin Ghaffarpour and Börje Ljungberg

Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden

ABSTRACT

Background: Surgical strategy in renal cell carcinoma (RCC) is considered based on the renal function. Partial nephrectomy (PN) preserves kidney function better than radical nephrectomy (RN), lowering risk of chronic kidney disease (CKD). The aim was to evaluate whether renal function and other clinical variables were important for surgical treatment selection.

Methods: Patients with RCC, surgically treated between 1994 and 2018 were included. There were 663 patients in all stages, 265 women and 398 men, mean age 66 years. Clinical data: estimated glomerular filtration rate (eGFR), WHO performance status (WHO-PS), Charlson comorbidity index (CCI), surgery, T-stage, M-stage, RCC type, tumor size, age, and gender were extracted from the medical records. Statistical analysis included Mann-Whitney U, X2-test, and logistic regression analysis.

Results: Of 663 patients, 455 were treated with RN and 208 with PN. In all patients, preoperative eGFR was significantly higher in PN (80.8) than in RN (77.1, $p = 0.015$). Using logistic regression tumor size (odds ratio [OR]: 0.96; 95% confidence interval [CI]: 0.95–0.98, T-stage (OR: 0.46; 95% CI: 0.33–0.65), WHO-PS (OR: 0.39; 95% CI: 0.04–0.57), and CCI (OR: 1.23; 95% CI: 1.05–1.44), associated to treatment selection, while eGFR, M-stage, age, and gender did not.

In cTa subgroup, eGFR was also higher in PN (84.6) than in RN (75.0, $p = 0.007$). Using logistic regression, tumor size (OR: 0.93; 95% CI: 0.83–0.98) and WHO-PS (OR: 0.36; 95% CI: 0.20–0.66) associated to treatment selection, while eGFR, CCI, age, and gender did not.

Conclusion: Tumor size, CCI scores, T-stage, and WHO-PS, all had an impact on the surgical strategy for all RCC patients. In patients with T1a RCC, tumor size and WHO-PS associated independently with treatment decision. After adjusted analysis, renal function lost its independent association with the treatment strategy in RCC patients.

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Introduction

The surgical treatment decision for patients with renal cell carcinoma (RCC) is multifactorial including tumor characteristics, co-morbidities, and performance status. Tumor characteristics include tumor size, tumor position, local tumor invasion including tumor thrombus, and distant tumor spread. Other important demanding factors include presence of a solitary kidney, bilateral and multiple renal masses. Furthermore, total and separate renal function of the kidneys will ultimately influence the treatment strategy [1].

It is well accepted that partial nephrectomy (PN) saves kidney nephrons and thus preserve kidney function better than radical nephrectomy (RN). It has been found in several retrospective analyses that a nephron sparing strategy, by saving renal function, lower the risk to develop cardiovascular disorders and improve overall survival (OS) [2, 3]. In some series, this held true only for younger patients and/or patients without significant comorbidity at the time of the surgical intervention [4]. Although a prematurely closed randomized study comparing PN with RN found no survival benefit with nephron sparing treatment, real-world register data suggest that nephron sparing is of advantage for patients OS [5]. This finding might also be true for patients with T2 RCCs [6]. However, in the absence of randomized clinical trials, the level of the evidence is generally low, because of imbalance between the PN and RN groups regarding patient's age, comorbidities, performance status, tumor size, stage, and tumor position.

The aim of this study was to evaluate whether renal function and other clinical variables including Charlson Comorbidity Index (CCI) scores, WHO performance status (WHO-PS), tumor size, 2017 TNM stage, age, and gender were important as preoperative guidance for treatment selection.

Materials and methods

Patients

Patients surgically treated for RCC between 1994 and 2018, at the Department of Urology at Norrland University Hospital, Umeå, were retrieved from the medical records. All patients with

CONTACT Börje Ljungberg borje.ljungberg@umu.se Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, SE-901 85 Umeå, Sweden

benign histology or other concurrent malignancies than RCC were excluded. Five patients with bilateral surgery were furthermore excluded. There remained 663 patients with histologically confirmed RCC, 398 males and 265 females. Data on renal function including estimated glomerular filtration rate, WHO-PS, comorbidity, tumor size, TNM stage, tumor grade, RCC type, and other patient characteristics were extracted from their medical records. All patients were subject to yearly follow-up, screened in the medical records and for being alive in the Swedish National Population Register. The last follow-up was done in December 2022. Cancer-specific survival time as well as OS time was defined as the time from diagnosis to the date of death of any cause or alive at the end of December 2022.

The 2017 TNM classification was used for tumor staging [7]. In the stage grouping, patients with NX were joined with N0. Tumor size, defined as the largest tumor diameter, was measured primarily on the computed tomography (CT) or magnetic resonance imaging (MRI) scans. Histopathologic RCC-type classification was performed according to the Heidelberg classification [8].

Comorbidity was evaluated and extracted from medical records, including the patients' medicine lists and any comorbidity was transferred to the CCI scores [9]. Renal cancer was not included in calculating CCI score, neither as renal disease nor as malignancy.

WHO PS was estimated according to the medical records [10]. Estimated glomerular filtrating rate (eGFR) was extracted from the original laboratory analysis. When eGFR data were missing, it was calculated according to Levey et al. [11]. All patients were followed-up until 5 years according to the EAU guidelines and clinically followed yearly.

Ethics

All patients had an informed consent, orally before 2000, and informed and written consent from 2000. The study was reviewed and approved by the Ethical Review Board (Dnr: 2015-146-31M and Dnr: 2018-296-32M) and the Ethical board of Sweden (Dnr: 2019-02579). The data used were anonymized before statistical processing. Throughout the project all data were treated under the regulations of the General Data Protection Regulation Act.

Statistical methods

Statistical analysis used non-parametric tests for continuous variables and $\chi 2$ test to evaluate differences in groups. Logistic regression analysis was used to evaluate possible association to treatment decision selection. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Of 663 patients, 455 were treated with RN and 208 with PN. Among 663 patients, 543 (74%) had clear cell, 88 (15%) papillary, 24 [85] chromophobe RCC, while eight (3%) had other RCC types. Clinical and patient's characteristics are shown in Table 1. In all patients treated with PN, preoperative eGFR was 80.8 significantly higher than eGFR in patients treated with RN (77.1, $p = 0.015$). Patients treated with PN had significantly more frequently low-stage tumors than patients treated with RN ($p < 0.001$). Tumor size, furthermore, was significantly smaller as well as better WHO PS in PN patients.

As shown in Table 2, univariate analysis revealed that gender, eGFR, tumor size, T-stage, M-stage, WHO-PS, and CCI, all associated with the surgical treatment performed. However, using an adjusted logistic regression model, tumor size (odds ratio [OR]: 0.96; 95% confidence interval [CI]: 0.95–0.98), T-stage (OR: 0.46; 95% CI: 0.33–0.65), WHO-PS (OR: 0.39; 95% CI: 0.04–0.57), and CCI (OR: 1.23; 95% CI: 1.05–1.44) remained as significantly associated with treatment decision while eGFR, M-stage, age, and gender did not.

In the subgroup of patients with T1a (≤4 cm) RCC, eGFR was also significantly higher in patients treated with PN (84.6) than in those treated with RN (75.0, $p = 0.007$). In univariate analysis, age, eGFR, tumor size, and WHO-PS associate with treatment selection, while gender and CCI did not (Table 3). Using a logistic regression model in patients with pT1ac, only tumor size (OR: 0.93; 95% CI: 0.83–0.98) and WHO-PS (OR: 0.36; 95% CI: 0.20–0.66) remained associated with treatment selection after adjusted analysis, while eGFR, CCI, age, and gender did not (Table 3).

Discussion

The decision of the surgical treatment in the present study was based on multiple clinical causes but renal function lost its independent importance after adjusted analysis. The surgical treatment of patients with RCC mainly consists of partial and RN strategies, using different surgical techniques. Historically, RN was the benchmark for the surgical treatment. During the last decades, it has been a fundamental change with a more frequent use of imaging techniques that also greatly have improved in its resolution quality. These changes have caused increased incidental and earliar tumor detection, which has led to a stage shift with smaller tumors and less advanced local tumor growth [12]. These modifications have endorsed the updated recommendation of nephronsparing treatment for T1 RCCs during the study period [1]. When locally advanced tumors or when localised renal masses are not treatable with PN, RN remains an treatment option [1]. The development of new surgical techniques, such as robot assisted and ablative therapies, have further shifted the surgery to more frequent nephron sparing treatments [13].

So far, the optimal surgical strategy is still equivocal based on mostly low-evidence data. For patients with T1 RCC, most guidelines recommend nephron sparing strategies [1]. The surgical treatment recommendation for T2 RCCs is miscellaneous. Some retrospective comparative studies of PN versus RN for T2 RCC have been published [6]. A multicentre study compared the survival outcomes in ccRCC patients with T2 tumors treated with PN versus RN with long-term follow-up. Compared to the RN

Table 1. Characteristics of the 663 patients with renal cell carcinoma according to performed surgical treatment.

Variable	All	Radical nephrectomy	Partial nephrectomy	*p*-value
	n = 663, (%)	*n*= 455, (%)	*n* = 208, (%)	
Male, *n* (%)	398 (60.0)	261 (57.4)	137 (65.9)	$p = 0.038$
Female, *n* (%)	265 (40.0)	194 (42.6)	71 (34.1)	
Age at surgery (years), mean (SD)	66.2 (11.1)	66.6 (10.8)	65.5 (11.6)	$p = 0.494$
Estimated GFR mean (SD)	78.3 (22.1)	77.1 (22.3)	80.8 (21.4)	$p = 0.015$
T-Stage, *n* (%)				$P < 0.001$
– T1a	169 (25.5)	37 (8.1)	132 (63.5)	
– T1b	146 (22.0)	81 (17.8)	65 (31.2)	
– T2	134 (20.2)	127 (27.9)	7 (3.4)	
– T3	193 (29.1)	189 (24.1)	4 (2.0)	
– T4	21 (3.2)	21 (4.6)	0 (-)	
M-stage, *n* (M1 %)	126 (19.0)	124 (27.3)	2 (1.0)	
Tumour size (mm), mean (SD)	72.4 (40.1)	88.2 (37.4)	37.8 (18.1)	$p < 0.001$
RCC type, *n* (%)				
– Clear cell	543 (74.3)	382 (71.8)	161 (70.8)	$p = 0.174$
– Papillary	88 (14.7)	53 (16.7)	35 (15.3)	
– Chromophobe	24 (7.7)	14 (8.0)	10 (10.7)	
– Other	8 (3.3)	6 (3.5)	2 (3.2)	
WHO-PS, *n* (%)				$p < 0.001$
– 0	418 (66.0)	251 (55.2)	167 (80.3)	
– 1	154 (23.2)	118 (25.9)	36 (17.3)	
– 2–4	91 (13.9)	86 (18.8)	5 (2.5)	
CCI, *n* (%)				NA
– 0–1	108 (15.6)	75 (16.4)	33 (4.8)	
– 2–3	238 (15.7)	1 (37.8)	21 (31,7)	
– 3–4	237 (35.4)	163 (35.9)	74 (355)	
– 5–6	157 (23.7)	99 (21.7)	58 (27.9)	
– 7–10	55 (10.2)	33 (7.4)	22 (10.5)	

Note: RCC, renal cell carcinoma; eGFR, estimated Glomerular Filtration Rate: CCI, Charlson Comorbidity Index; WHO, WHO-performance status; SD, standard deviation; NA, not analyzed. There were 2 (0.3%) missing values for CCI, and 1 (0.2%) missing value for eGFR.

group, the PN group had a significantly longer median OS and CSS [14]. Retrospective studies of cT1 and cT2 patients upstaged to pT3a RCC show contradictory results, one study reports similar oncologic outcomes between PN and RN [15], while another suggests that PN of clinical T1 when pathologically upstaged to pT3a was associated with a significantly shorter recurrence-free survival than RN [5, 16]. For patients with clinical T3-T4 RCC, RN remains the backbone of surgery [1]. In the present study, T-stage was independently significantly associated with the surgical treatment decision while M-stage lost its independent association after adjusted analysis.

However, most reported results on outcome parameters associated with different surgical techniques will not be relevant, when including different clinical patients characteristicss requiring different approaches [17]. The selection of the patients, their preferences, and the surgeons skill might be most important to achieve good and desirable results. The underlying general performance and clinical condition of the patients

Table 2. Results for logistic regression analyses from age, gender, estimated Glomerular Filtration Rate, tumor size, WHO performance status, and Charlson Comorbidity Index as predictors of surgical strategy of 663 patients with renal cell carcinoma of all stages. Odds ratio indicates higher probability of partial nephrectomy for values above 1.

Predictor	Unadjusted			Adjusteda		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	0.991	0.977–1.006	0.250	0.981	0.951–1.013	0.242
Gender	0.697	0.495–0.981	**0.039**	0.902	0.530–1.535	0.703
eGFR	1.008	1.000–1.015	**0.048**	1.001	0.988–1.014	0.867
Tumor size	0.930	0.919–0.941	**<0.001**	0.960	0.945–0.975	**<0.001**
T-stage	0.183	0.139–0.242	**<0.001**	0.463	0.331–0.646	**<0.001**
M-stage	0.026	0.008–0.106	**<0.001**	0.221	0.041–1.184	0.078
WHO-PS	0.387	0.288–0.520	**<0.001**	0.385	0.258–0.573	**<0.001**
CCI	1.093	1.011–1.183	**0.026**	1.229	1.050–1.438	**0.010**

Note: CI, confidence interval; OR, odds ratio; eGFR, estimated Glomerular Filtration Rate; WHO-PS, WHO performance status; CCI, Charlson Comorbidity Index. Significant *P*-values are given in **bold**. [a] Adjusted for: age at surgery (years), male versus female, eGFR, tumor size (mm), T-stage, M-stage, WHO-PS and CCI.

Table 3. Results for logistic regression analyses from age, gender, estimated Glomerular Filtration Rate, tumor size, WHO performance status, and Charlson Comorbidity Index as predictors of surgical strategy of 169 patients with stage T1a renal cell carcinoma. Odds ratio indicates higher probability of partial nephrectomy for values above 1.

Predictor	Unadjusted			Adjusted[a]		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	0.955	0.921–0.990	**0.013**	0.964	0.914–1.018	0.185
Gender	0.767	0.359–1.637	0.492	0.986	0.399–2.439	0.975
eGFR	1.021	1.004–1.038	**0.017**	1.018	0.997–1.039	0.100
Tumor size	0.915	0.867–0.965	**<0.001**	0.926	0.873–0.981	**0.009**
WHO-PS	0.392	0.234–0.656	**<0.001**	0.362	0.200–0.655	**<0.001**
CCI	0.914	0.767–1.088	0.312	1.252	0.941–1.665	0.123

Note: CI, confidence interval; OR, odds ratio; eGFR, estimated Glomerular Filtration Rate; Size, tumor size; WHO-PS, WHO performance status; CCI, Charlson Comorbidity Index. Significant *P*-values are given in **bold**. [a] Adjusted for: age at surgery (years), male sex (yes/no), eGFR, tumor size (mm), WHO-PS and CCI.

planned for surgery comprise a number of important co-factors such as concomitant diseases, age, renal function, tumor size, TNM-stage, PS, and previous surgery. Thus, most RCC studies have a high risk for selection bias due to imbalance between the PN and RN groups. These imbalances in covariates may have a greater impact on patient outcome than the choice of surgery.

Patients with higher age mostly have been offered surgeries, having less risk of complications [1]. Furthermore, an analysis of the U.S. Medicare database showed no OS benefit for patients ≥75 years of age when RN or PN were compared with non-surgical management [4]. In a retrospective analysis of the British Association of Urological Surgeons database, it was found a significant association between PS and age. The authors also concluded that age was an independent risk factor for postoperative complications after RN and should be considered when counseling elderly patients before treatment [18]. It has also been claimed that females generally have been offered RN before PN. Unadjusted results in the present study, indicated such biases between age and genders, but these imbalances disappeared and lost its significance after adjusted analysis when involving other clinical co-variates.

Renal function was claimed to be one important predictors of surgical decisions as loss of nephrons is important for the postoperative baseline renal function [19]. However, it is still unclear whether PN provides an OS benefit in patients with a normal contralateral kidney, but PN is currently recommended as the reference standard for most localized renal masses [1]. In a real-world register study, the advantage of PN over RN for OS was verified [5]. In the present study, we also found that renal function had a univariate association to surgical treatment decision, but surprisingly, renal function lost its significant association after adjusted analysis.

In a multicenter analysis comparing partial versus RN for complex renal masses, tumor size was significantly associated to survival and complications, while type of surgery was not [20]. Tumor size further associated with disease recurrence and OS in a real-world register-based analysis of patients with T1 RCC [5]. Our results confirm an independent importance of tumor size in the surgical treatment decision for all patients as well as for patients in the T1a subgroup.

Also, WHO-PS remained independently important for the treatment decision in all patients as well as in the T1a subgroup after adjusted analysis. WHO PS has mostly been studied in the treatment of metastatic RCC. The significant association between PS and age found in a retrospective analysis of the BAUS database was not confirmed in the present study [18]. In a large national database, performance status lost its significance after multivariate analysis in contrast to our results [21].

The impact of comorbidity is only limited evaluated in RCC. It has been found an association between high CCI scores and more complications, as well as increased mortality [13, 22]. In the RECORD study the patients selected based on CCI, the authors showed that efficiency and safety for PN were better for patients with lower CCI scores [23]. Our results showed that CCI was an important predictor for treatment decisions for all RCC patients but not remain important in the subgroup of patients with T1a.

Thus, the decision of the surgical treatment is based on several factors. In the present study, the surgeon's experience and patient's perspectives was unknown and could not be evaluated. The ultimate guidance for the optimal surgical treatment decision is therefore difficult to establish. However, our study points at the need to include robust variables to reduce biases in studies comparing outcomes of different treatments to define the optimal treatment for patients with RCC.

Conclusion

Tumor size, CCI scores, T-stage and WHO-PS had an impact on the choice of surgical strategy for all RCC patients. In patients with T1a RCC tumor size and WHO-PS associated independently to treatment decision. Renal function lost its independent importance on the treatment strategy in patients with RCC.

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ORCID

Börje Ljungberg https://orcid.org/0000-0002-4121-3753
Jan Hlodan, https://orcid.org/0009-0006-7393-5829

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