Elective Nephron Sparing Surgery Decreases Other Cause Mortality Relative to Radical Nephrectomy Only in Specific Subgroups of Patients with Renal Cell Carcinoma

Alessandro Larcher, Umberto Capitanio,* Carlo Terrone, Alessandro Volpe, Paolo De Angelis, Federico Dehó, Nicola Fossati, Paolo Dell'Oglio, Alessandro Antonelli, Maria Furlan, Claudio Simeone, Sergio Serni, Marco Carini, Andrea Minervini, Cristian Fiori, Francesco Porpiglia, Alberto Briganti, Francesco Montorsi and Roberto Bertini

From the Urological Research Institute, Division of Experimental Oncology, Istituto di Ricovero e Cura a Carattere Scientifico and Unit of Urology, Vita-Salute San Raffaele University, San Raffaele Scientific Institute (AL, UC, FD, NF, PD, AB, FM, RB), Milan, Departments of Urology, University of Piemonte Orientale (CT, AV, PDA), Novara, Università degli studi e Spedali Civili di Brescia (AA, MF, CS), Brescia, Clinica Urologica I, Azienda Ospedaliera Universitaria Careggi, Università degli studi di Firenze (SS, MC, AM), Firenze and Azienda Ospedaliero-Universitaria San Luigi Gonzaga, Università degli studi di Torino (CF, FP), Orbassano, Italy

Abbreviations and Acronyms

ACM = all cause mortality
BMI = body mass index
CCI = Charlson comorbidity index
EORTC = European Organisation for Research and Treatment of Cancer
NSS = nephron sparing surgery
OCM = other cause mortality
RN = radical nephrectomy

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* Correspondence: Unit of Urology, Via Olgettina 60, 20132 Milan, Italy (telephone: +39 02 26437286; e-mail: umbertocapitanio@gmail.com).

Purpose: There is no consensus regarding a protective effect on mortality due to a cause other than cancer in patients treated with elective nephron sparing surgery relative to their radical nephrectomy counterparts. We test whether the protective effect of nephron sparing surgery relative to radical nephrectomy is universal or present in specific subgroups of patients.

Materials and Methods: A collaborative database of 5 institutions was queried to evaluate 1,783 patients without chronic kidney disease diagnosed with a clinical T1 renal mass that was treated with nephron sparing surgery or radical nephrectomy. Multivariable Cox regression analysis was done to assess the impact of surgery type (nephron sparing surgery vs radical nephrectomy) on other cause mortality after adjustment for patient and cancer characteristics. Interaction terms were used to test the hypothesis that the impact of surgery type varies according to specific subcohorts of patients.

Results: Ten-year other cause mortality-free survival rates were 90% and 88% after nephron sparing surgery and radical nephrectomy, respectively. In the overall population radical nephrectomy was not associated with an increased risk of other cause mortality on multivariable analysis compared to nephron sparing surgery (HR 0.91, 95% CI 0.6–1.38, p = 0.6). However, radical nephrectomy increased the risk of other cause mortality according to the increasing baseline Charlson comorbidity index (interaction test p = 0.0008). For example, in a patient with a Charlson comorbidity index of 4 the probability of 10-year other cause mortality-free survival was 86% after nephron sparing surgery and 60% after radical nephrectomy.

Conclusions: Elective nephron sparing surgery does not improve other cause survival relative to radical nephrectomy consistently in all patients with kidney cancer. Patients who are more ill with relevant comorbidities are those who benefit the most from nephron sparing surgery in terms of other cause mortality.

Key Words: kidney; carcinoma, renal cell; nephrectomy; cause of death; comorbidity

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NEPHRON sparing surgery represents the standard of care for patients diagnosed with a cT1a renal mass.[1–4] Similarly, NSS should be preferred over RN when technically feasible in patients diagnosed with a cT1b renal mass.[1,2,4] The rationale of these recommendations in favor of NSS is to decrease the risk of chronic kidney disease[5–7] as well as the risk of cardiovascular events[8,9] while maintaining similar cancer control.

However, the controlled comparison of NSS vs RN presented in the EORTC 30904 trial showed no difference with respect to cancer specific mortality but lower ACM after RN,[10] implying a paradox advantage with respect to OCM after RN. Methodological limitations of this trial have been used to justify such a counterintuitive result and prompted further observational investigations that revealed the opposite finding, namely lower OCM after NSS relative to RN.[9,11–15] Recently, the inherent risk of bias in such observational studies[9,11–15] has been highlighted.[16,17] It was postulated that if present, a beneficial effect of NSS on OCM has yet to be proved.[18]

In this light the aim of the study was to examine the impact of surgery type, namely NSS vs RN, on the risk of OCM in a large multi-institutional study that allowed for adjustment for a detailed panel of intrinsic confounders such as BMI, CCI, and the presence and type of hypertension or diabetes. Our hypothesis stated that NSS might be associated with a lower risk of OCM and such a benefit might be more evident in specific subgroups of patients.

MATERIALS AND METHODS

Study Population

The current study relied on a collaborative database collected from 5 European tertiary care centers. Patients with a primary diagnosis of nonmetastatic clinical T1 unilateral kidney cancer without a baseline condition of chronic kidney disease treated with NSS or RN between 1984 and 2010 were included in analysis.

Outcome

The outcome of the study was OCM, defined as mortality due to a cause other than kidney cancer. Cause of death was defined according to death certificates.

Covariates

Covariates consisted of age at diagnosis, BMI, gender (male vs female), CCI,[19] hypertension (no hypertension vs hypertension controlled by therapy vs hypertension uncontrolled by therapy), diabetes (present vs absent), clinical tumor size (based on preoperative imaging and defined as the greatest tumor diameter in mm) and year of surgery.

Statistical Analyses

Statistical analyses, and reporting and interpreting the results were done according to established guidelines[20] and consisted of 4 steps. 1) The median and IQR or frequency and proportion are reported for continuous or categorical variables, respectively. The Mann-Whitney and chi-square tests were applied to compare the statistical significance of differences in the distribution of continuous or categorical variables, respectively. The Kaplan-Meier method was used to describe 10-year OCM-free survival rates.

2) Multivariable Cox regression analysis was done to assess the impact of surgery type on OCM after adjustment for all available covariates. The nonlinear nature of the relationship between each continuous predictor and the outcome was assessed by modeling each individual variable as a restricted cubic spline. However, no evidence of nonlinearity was recorded for each continuous term (each $p > 0.05$).

3) The hypothesis that the impact of surgery type was different by select patient subgroups was tested using an interaction term between treatment type (NSS vs RN) and each individual covariate.

4) Cox regression derived coefficients were used to estimate the 10-year OCM-free survival probability. The locally weighted scatterplot smoothing method[21] was used to graphically explore the probability of 10-year OCM-free survival after NSS or RN according to patient baseline characteristics (eg CCI) in compliance with established methodology.[22,23]

All statistical tests were performed using RStudio®, version 0.98 for R, version 3.0.2 (https://www.r-project.org/foundation/) with the packages Hmisc, stats, rms and graphics. All tests were 2-sided with significance considered at $p < 0.05$.

RESULTS

Patient Characteristics

Overall, 1,783 patients were included in study (table 1). Patients were treated with NSS (56% or 993) or RN (44% or 790). Patients treated with NSS were more frequently diagnosed with CCI 0 or greater (48% vs 39%, $p < 0.0001$), any kind of hypertension (37% vs 29%, $p = 0.0007$), diabetes (10% vs 6%, $p = 0.02$) and smaller tumors (median clinical size 30 vs 47 mm, $p < 0.0001$).

Survival

Median followup among survivors was 70 months and 430 patients (27%) had more than 10 years of followup. Overall, 214 deaths were recorded during the study period, including 66 due to kidney cancer and 148 due to another cause. Ten-year OCM-free survival rates were 90% after NSS and 88% after RN.

Surgery Type Impact

Overall Population. On multivariable Cox regression analysis RN was not associated with an increased risk of OCM when compared to NSS (HR 0.91, 95% CI 0.6–1.38, $p = 0.6$, table 2). Of note, age (HR 1.09, 95% CI 1.07–1.11, $p < 0.0001$) and CCI (HR 1.42,