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

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## 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

## 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

Nephron sparing surgery represents the standard of care for patients diagnosed with a cT1a renal mass.<sup>1, 2, 3 and 4</sup> Similarly, NSS should be preferred over RN when technically feasible in patients diagnosed with a cT1b renal mass.<sup>1, 2 and 4</sup> The rationale of these recommendations in favor of NSS is to decrease the risk of chronic kidney disease<sup>5, 6 and 7</sup> as well as the risk of cardiovascular events<sup>8 and 9</sup> 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,<sup>10</sup> 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.<sup>9, 11, 12, 13, 14 and 15</sup> Recently, the inherent risk of bias in such observational studies<sup>9, 11, 12, 13, 14 and 15</sup> has been highlighted.<sup>16 and 17</sup> It was postulated that if present, a beneficial effect of NSS on OCM has yet to be proved.<sup>18</sup>

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,<sup>19</sup> 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<sup>20</sup> 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<sup>21</sup> 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.<sup>22 and 23</sup>

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,  $p < 0.0001$ ).

Table 1.

Descriptive characteristics of patients treated with NSS or RN for cT1 kidney cancer

	NSS	RN	p Value
No. pts (%)	993 (56)	790 (44)	–
Median age (IQR)	61 (51–68)	61 (53–68)	0.2
<b>No. gender (%):</b>			0.3

	NSS	RN	p Value
M	331 (33)	281 (36)	
F	662 (67)	509 (64)	
Median kg/m <sup>2</sup> BMI (IQR)	26 (24–28)	26 (24–28)	0.3
<b>No. CCI (%):</b>			<0.0001
0	516 (52)	484 (61)	
1	165 (17)	144 (18)	
2	197 (20)	99 (13)	
3	63 (6)	35 (4)	
4 or Greater	52 (5)	28 (4)	
<b>No. hypertension (%):</b>			0.0007
No	623 (63)	563 (71)	
Controlled by therapy	210 (21)	132 (17)	
Uncontrolled by therapy	160 (16)	95 (12)	
<b>No. diabetes (%):</b>			0.02
No	897 (90)	739 (94)	
Yes	96 (10)	51 (6)	
Median mm clinical size (IQR)	30 (20–38)	47 (35–58)	<0.0001
<b>No. clinical stage (%):</b>			<0.0001
cT1a	828 (83)	312 (39)	
cT1b	165 (17)	478 (61)	
<b>No. diagnosis yr (%):</b>			<0.0001
1984–1999	190 (19)	429 (54)	
2000–2004	255 (26)	164 (21)	
2005–2010	548 (55)	197 (25)	

Table options

## 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, 95% CI 1.26–1.6,  $p = 0.0001$ ) were associated with an increased risk of OCM. Conversely, female gender (HR 0.62, 95% CI 0.43–0.9) and year of diagnosis (HR 0.92, 95% CI 0.88–0.95, each  $p = 0.0001$ ) were associated with a decreased risk of OCM.

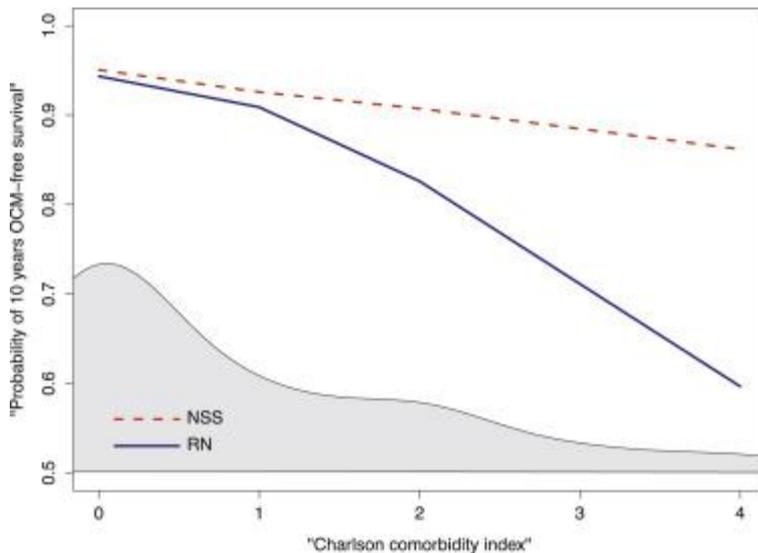
Table 2.

Multivariable Cox regression analysis predicting OCM in patients treated with NSS or RN for cT1 kidney cancer

Predictors	HR (95% CI)	p Value
<b>Surgery:</b>		
NSS	1.00 (referent)	–
RN	0.91 (0.6–1.38)	0.6
Age	1.09 (1.07–1.11)	<0.0001
BMI	0.99 (0.94–1.04)	0.6
<b>Gender:</b>		
M	1.00 (referent)	–
F	0.62 (0.43–0.9)	0.01
CCI	1.42 (1.26–1.6)	<0.0001
<b>Hypertension:</b>		
No	1.00 (referent)	–
Controlled by therapy	1.06 (0.65–1.71)	0.8
Uncontrolled by therapy	0.69 (0.4–1.2)	0.2
<b>Diabetes:</b>		
No	1.00 (referent)	–
Yes	0.61 (0.32–1.17)	0.1
Tumor size	1.04 (0.91–1.18)	0.5
Diagnosis yr	0.92 (0.88–0.95)	<0.0001
Table options		

### Patient Subgroups

The interaction tests for the hypothesis that the impact of surgery type on OCM varies according to age, BMI, gender, presence and type of hypertension, presence of diabetes, tumor size and year of diagnosis were not all statistically significant ( $p > 0.05$ ). Conversely, the interaction test for the hypothesis that the impact of surgery type on OCM varies according to patient baseline CCI was statistically significant ( $p = 0.0008$ ). Specifically, when compared to NSS, RN increased the risk of OCM according to increasing baseline CCI. The adjusted probability of 10-year OCM-free survival after NSS or RN was plotted according to patient baseline CCI (see figure). For example, in patients with CCI 0 the probability of 10-year OCM-free survival was 95% after NSS and 94% after RN. In patients with CCI 2 the probability of 10-year OCM-free survival was 91% after NSS and 83% after RN. Finally, in patients with CCI 4 the probability of 10-year OCM-free survival was 86% after NSS and 60% after RN.



Probability of 10-year OCM-free survival after NSS or RN for cT1 kidney cancer according to baseline CCI (gray area) in 1,783 patients, including 993 treated with NSS and 790 treated with RN for cT1 kidney cancer at total of 5 European tertiary care institutions from 1984 to 2010. For example, in patients with CCI 0 probability of 10-year OCM-free survival was 95% after NSS and 94% after RN while in patients with CCI 4 probability was 86% and 60%, respectively.

Figure options

## Discussion

Our hypothesis stated that NSS might be associated with a lower risk of OCM relative to RN and such a benefit might be more evident in specific subgroups of patients. To test this hypothesis we relied on a large, multi-institutional kidney cancer collaborative database collected at 5 European tertiary care institutions.

Our results rejected the first statement of our hypothesis, namely that NSS might be associated with a lower risk of OCM in the overall population. It showed no difference between NSS and RN with respect to OCM after adjustment for all available potential confounders (HR 0.91, 95% CI 0.6–1.38,  $p = 0.6$ ). Conversely, our results confirmed the second statement of our hypothesis, namely that NSS might be associated with a lower risk of OCM in a select subgroup of patients. The interaction test for the hypothesis that the impact of surgery type on OCM varies according to patient baseline CCI showed that relative to NSS RN increased the risk of OCM according to increasing baseline CCI ( $p = 0.0008$ ). This indicates that individuals who are more ill are those who maximally benefit from the choice of NSS (see figure). Specifically, a patient with several comorbidities (CCI 4) harbors a 10-year OCM-free survival probability of 86% after NSS and 60% after RN. Therefore, NSS should be strongly considered in patients who are more ill. On the other hand, a patient without comorbidities (CCI 0) harbors a 10-year OCM-free survival probability of 95% after NSS and 94% after RN. Such a marginal risk reduction provides weaker arguments for selecting NSS over RN.

These findings are not negligible with respect to clinical decision making since contemporary indications<sup>1, 2 and 3</sup> supporting NSS over RN suffer from a lack of consensus about the potential OCM benefit of NSS over RN.<sup>4, 13 and 18</sup> Moreover, our results represent another essential piece of

the puzzle regarding the impact of NSS on noncancer specific survival among individuals diagnosed with a cT1 renal mass.

When compared to NSS in a randomized, controlled study,<sup>10</sup> RN resulted in similar cancer specific mortality and similar if not lower ACM rates. However, the unmet accrual end point and the important contamination rates between the trial arms bounded the clinical applicability of this finding. When compared to NSS in retrospective, observational, population based studies,<sup>9, 11, 12 and 13</sup> RN resulted in higher ACM and OCM rates. However, more recent analyses of the same SEER (Surveillance, Epidemiology and End Results)-Medicare database showed that patients treated with RN achieved ACM-free survival comparable to that of their noncancer controls.<sup>16</sup> Surprisingly, patients treated with NSS achieved superior ACM-free survival than noncancer controls, highlighting the risk of a biased conclusion when these surgery types are compared in a population based setting.

Notably, the current study partially reconciles such contradictory findings. Our results showed that NSS does not confer an OCM benefit in the overall population diagnosed with a cT1 renal mass but NSS translates into an OCM benefit in a select subgroup of individuals, specifically patients who are more fragile due to relevant comorbidities. This observation might explain the opposite results in the EORTC 30904 trial<sup>10</sup> and the Medicare based studies<sup>9, 11, 12 and 13</sup> since the latter invariably relied on patients 65 years old or older and who were in consequence more ill by definition.

Moreover, the current analysis also corroborates many other findings reported in other studies with different designs. 1) The survival benefit associated with NSS was greatest in patients with a CCI of 1 or higher as also noted on subgroup analyses in a previous population based study.<sup>11</sup>

2) Prospective<sup>5</sup> and retrospective<sup>6 and 13</sup> studies showed superior renal function outcomes after NSS relative to RN and specifically a differential effect of NSS with respect to protection from postoperative CKD according to baseline renal function.<sup>24</sup> Likewise, patients without comorbidities might better tolerate the renal function detriment due to RN. In consequence, in healthier individuals the survival benefit of nephron sparing is masked. On the contrary, patients with relevant comorbidities might experience a greater renal function detriment due to RN. In consequence, in individuals who are more ill the survival benefit of nephron sparing is highlighted. Similarly, NSS has been associated with lower rates of cardiovascular events than RN.<sup>8</sup> Accordingly, it is possible that the burden of postoperative cardiovascular events is heavy enough to translate into OCM sequelae in more ill and more fragile patients, and it is lighter in healthier and more robust patients.

3) Finally, lower OCM-free survival in cases of chronic kidney disease due to medical etiology relative to surgically induced chronic kidney disease has been observed in other studies.<sup>25, 26 and 27</sup> Those findings validate the existence of a link between the general and the renal health status of the patient at baseline and the relative impact of nephron loss on the risk of OCM recorded in the current report.

It is important to remember that due to technical differences NSS is intrinsically associated with a higher risk of perioperative complication when compared to RN.<sup>28 and 29</sup> Also, the presence of comorbidities represents an established risk factor for surgical and medical complications following NSS.<sup>23</sup> Accordingly, when NSS is contemplated in patients with comorbidities, the OCM benefit demonstrated in the current study should be balanced with a potentially higher morbidity profile. Nonetheless, in the current series the overall 90-day mortality rate was extremely low at 0.3% (data not shown) and no difference was recorded after either treatment modality (unadjusted HR 6.22,  $p = 0.1$ , data not shown). This observation corroborates previous investigations,<sup>28 and 29</sup> suggesting that

the reported difference with respect to perioperative morbidity does not translate into a similar difference with respect to perioperative mortality. In consequence, a higher risk of perioperative complications might be worth exchanging for a potential long-term survival benefit.

The current study has several strengths, including multi-institutional design, detailed information on the baseline cardiovascular and comorbidity profile of the patients, and inclusion of patients without baseline chronic kidney disease. However, despite its appeal and uniqueness the current study is not devoid of limitations. First and foremost, a significant limitation is related to the retrospective design of the study, which could not exclude residual confounders even after adjustment for patient and cancer characteristics.<sup>30</sup> Recently, the risk of selection bias favoring NSS in population based studies<sup>16</sup> was highlighted by the presence of an ACM advantage after NSS relative to RN.<sup>13</sup> It is possible that, given the institutional nature of our report and the availability of a detailed panel of preoperative information, such biases are less relevant if not nonoperational in the current study. Accordingly, no difference was recorded after RN relative to NSS with respect to ACM (adjusted HR 1.12,  $p = 0.5$ , data not shown).

Finally, although our results demonstrated that CCI significantly affects the OCM survival benefit following NSS, our analysis did not identify which specific comorbidities should be evaluated for clinical decision making. The potential risk of a subjective CCI calculation represents an additional limitation of our comorbidities definition. In this light identifying the particular baseline health conditions that could specify the indications for NSS are yet to be investigated.

Nevertheless, despite these limitations the findings of the current study require special consideration. For the first time to our knowledge a specific group of patients who benefited from the choice of NSS over RN in terms of noncancer related survival was identified. Moreover, the information that individuals with normal preoperative renal function but who are more ill due to other comorbidities are those who maximally benefit from NSS is of the utmost importance for clinical decision making and trial planning.

## Conclusions

The impact of NSS on the risk of noncancer specific mortality is not equal in all patients with normal preoperative renal function who are diagnosed with a cT1 renal mass. Specifically, in healthier patients without comorbidities NSS does not decrease the risk of OCM relative to RN. Conversely, in patients who are more ill with relevant comorbidities NSS significantly decreases the risk of OCM relative to RN.

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