End-Stage Renal Disease After Renal Surgery in Patients with Normal Preoperative Kidney Function: Balancing Surgical Strategy and Individual Disorders at Baseline

End Stage Renal Disease after renal surgery in patients with a normal preoperative kidney function: the importance of the baseline individual disorders

Umberto Capitanio[1,2], Alessandro Larcher[1,2], Carlo Terrone[3], Alessandro Antonelli[4], Alessandro Volpe[3], Cristian Fiori[6], Maria Furlan[4], Federico Deho'[1,2], Andrea Minervini[5], Sergio Serni[5], Francesco Porpiglia[6], Francesco Trevisani[2,7], Andrea Salonia[1,2], Marco Carini[5], Claudio Simeone[4], Francesco Montorsi[1,2], Roberto Bertini[1,2]

[1]Unit of Urology, University Vita-Salute, San Raffaele Scientific Institute, Milan
[2]Division of Oncology/Unit of Urology; URI; IRCCS Ospedale San Raffaele, Milan, Italy
[3]Dept. of Urology, University of Piemonte Orientale, Novara
[4]Dept. of Urology, Universita' degli studi e Spedali Civili di Brescia
[5]Dept. of Urology, Clinica Urologica I, Azienda Ospedaliera Universitaria Careggi, Università degli studi di Firenze
[6]Dept. of Urology, AOU San Luigi Gonzaga, Università degli studi di Torino, Orbassano
[7]Unit of Nephrology, San Raffaele Scientific Institute, Milan

Corresponding Author:
Umberto Capitanio, MD
Unit of Urology, Division of Oncology/Unit of Urology, URI
IRCCS San Raffaele Scientific Institute, Milan, Italy
Via Olgettina 60, 20132 Milan, Italy.
Tel. +39 02 26437286
E-mail: umbertocapitanio@gmail.com

Word count (text): 1,019 (max 1000)
Word count (unstructured abstract): 193 (max 200)
References: 9 (max 10)
Tables and Figures: 2 (max 2)

Keywords: kidney cancer; partial nephrectomy; radical nephrectomy; nephron sparing surgery; end stage renal disease, dialysis.

Although a demonstrated benefit in terms of renal function preservation, it is still unclear whether nephron sparing surgery (NSS) might decrease also the risk of End Stage Renal Disease (ESRD), relative to radical nephrectomy (RN). In the current paper, we aimed to report the rate and the predictors of ESRD after surgery, accounting for detailed individual baseline characteristics and comorbidities.

A multi-institutional collaboration among five European Tertiary Care Centers allowed collecting 2,027 patients with normal preoperative renal function and a clinically localized T1abN0M0 renal mass. Descriptive and Cox regression analyses were used to predict the risk of ESRD (defined as the onset of a post-operative eGFR<15ml/min/1.73m^2) after adjusting for the individual baseline risk of developing chronic kidney disease.

Univariable ESRD rates at 5 and 10 years of follow-up were virtually equivalent between patients who underwent NSS (1.5 and 2.5%) vs. RN (1.9% and 2.7%) [HR 0.8 (95%CI 0.4-1.6)]. However, diabetes, smoke, uncontrolled hypertension and other comorbidities were consistently more frequent in the NSS group relative to their RN counterparts. After adjusting for detailed baseline individual characteristics, NSS showed an independent protective effect relative to RN [HR 0.4 (95%CI 0.2-0.8), p=0.02] at multivariable analyses.

Patient Summary

Also after considering individual baseline characteristics, such as age, diabetes, uncontrolled hypertension or other comorbidities, partial nephrectomy independently protects from dialysis relative to radical nephrectomy.

Unstructured text

When technically feasible, nephron sparing surgery (NSS) represents the standard of care for patients diagnosed with a clinically localized renal mass[1], mainly due to a demonstrated benefit in terms of renal function preservation[2]. In a recent subanalysis of 514 patients included in the European Organization for Research and Treatment of Cancer (EORTC) randomized trial 30904, the incidence of End Stage Renal Disease (ESRD) was nearly identical between patients treated with nephron sparing surgery (NSS) or radical nephrectomy (RN)[2]. In the current paper, we aimed to report the rate and the predictors of ESRD after renal surgery. To limit the inherent risk of bias, we create a large multiinstitutional cohort of patients that allowed adjustment for a detailed panel of intrinsic confounders such as uncontrolled hypertension, diabetes, body mass index (BMI) and other comorbidities.

The current study relied on a collaborative database collected among five European Tertiary Care Centres. Patients with a primary diagnosis of non-metastatic clinical T1, unilateral kidney cancer without a baseline condition of chronic kidney disease treated with NSS or RN between 1984 and 2010 were included. The outcome of the study was ESRD, defined as the onset of a post-operative eGFR<15ml/min/1.73m^2. Glomerular Filtration Rate was calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula in younger patients (age<70) and by the Berlin Initiative Study (BIS1) formula in the elderlies[3]. We included as covariates: age, year of surgery, pre-operative GFR, tumor size, hypertension (none vs. yes vs. controlled by medical therapy), diabetes, baseline Charlson comorbidity index (CCI), body mass index and smoker status (no vs. yes vs. former). First, descriptive statistics were reported. Second, multivariable Cox regression analyses were used to assess the impact of surgery type (NSS vs. RN) on ESRD after adjustment for all the available covariates. Finally, multivariable Cox

regression coefficients were used to plot the covariate-adjusted ESRD rates according to different patients' subgroups.

Overall, 2,027 patients were included in the study (Table 1). Patients were treated with NSS (65.8%; n=1,334) or RN (34.2%; n=693). No differences were recorded between NSS and RN patients in terms of age, gender and body mass index(Table 1). Patients treated with NSS were more frequently diagnosed with concomitant comorbidities (CCI≥0 (55 vs. 40%%; p<0.001), uncontrolled hypertension (21 vs. 13%; p<0.001), diabetes (12 vs. 7%; p<0.001) and smaller tumour (median clinical size 32 vs. 50 mm, p<0.001). Mean follow-up was 72 months. ESRD rates at 5 and 10 years of follow-up were virtually equivalent between patients who underwent NSS (1.5 and 2.5%) vs. RN (1.9% and 2.7%) [p=0.5; HR 0.8 (95%CI 0.4-1.6)]. Also clinical tumor size, preoperative eGFR, body mass index and smoke status were not statistically associated with the outcome. Conversely, patients' age [p<0.001, HR 1.1 (95%CI 1.1-1.1)], presence of diabetes [p=0.002, HR 3.4 (95%CI 1.5-7.4)], uncontrolled hypertension [p<0.001, HR 4.1 (95%CI 2.1-8.2)] and Charlson Comorbidity Index [CCI>1 vs.0, p=0.004, HR 3.4 (95%CI 1.5-7.8)] resulted strongly associated with ESRD risk (Supplementary Table). At multivariable analyses, after adjusting for all the detailed baseline individual characteristics, NSS showed an independent protective effect on ESRD relative to RN [HR 0.4 (95%CI 0.2-0.8), p=0.02] (Supplementary Table). Figure 1 shows the multivariate-derived ESRD cumulative rates according to treatment type, patients' age, diabetes and hypertension, which resulted, alongside the year of surgery, the most informative predictors of ESRD (Supplementary Table).

ESRD is a life-threatening condition[4]. In healthy young subjects, estimated risk of ESRD at 15 years is 0.04% (95%CI 0.008-0.09) reaching a peak of 0.3% (95%CI 0.2-0.4) in healthy kidney donors[5]. Due to older age and high prevalence of associated

comorbidities, ESRD risk after surgery for renal cancer is significantly more common. In such setting, ESRD has been already prospectively reported in the EORTC trial 30904, showing rates very similar to the current report (1.5-1.6% at a median follow-up of 6.7 months), with again no difference in terms of ESRD crude rates between patients treated with NSS and RN [–0.1% (95% CI, –2.2 to 2.1)] [2]. Although many limitations affected the original trial (e.g. limited recruitment, crossover treatment and lack of detailed comorbidity data of the patients, etc.), the EORTC trial suggested that ESRD might be related to intrinsic factors (e.g. medical conditions, such as diabetes) non amendable by the type of surgical technique delivered. Also Lin WY reported similar findings in a recent nationwide population-based study, although they could not adjust their findings for important determinants of CKD, such as the presence of uncontrolled hypertension, body mass index and smoke status[6]. Finally, Yap et al. have recently anticipated a beneficial effect of NSS in decreasing the risk of ESRD (HR 0.44, 95%CI 0.25–0.75), although they could not adjust the results for tumor characteristics (e.g. tumor size, TNM) which are main determinants of surgical indication (NSS vs. RN) and survival outcomes[7].

The current report introduces key findings: once considering important causes of ESRD, such as diabetes, uncontrolled hypertension and age, NSS appears to decrease, or at least to delay, the onset of ESRD after surgery. As already verified by others[8], baseline medical conditions which may produce renal function impairment remain the key and the most informative causes of renal failure regardless all the surgical efforts in preserving nephrons[9]. However, our findings add other supportive data on the role of nephron sparing tactic in the mitigation of the consequences of the baseline medical aetiology of chronic kidney disease[9].

The current study has several strengths, which include the multi-institutional design, the relatively long follow-up and the inclusion of patients without a condition of baseline

chronic kidney disease. However, despite its appeal and uniqueness, the current study is not devoid of limitations, mainly due to the retrospective design of the study that cannot exclude the presence of residual confounders.

In conclusion, roughly 2% of the patients with normal eGFR before kidney surgery will develop ESRD in the first 10 years of follow-up. Besides the already known protective benefits in terms of cardiovascular events and renal function preservation, NSS seems to be associated with a lower risk of ESRD relative to RN. Nonetheless, individual inherent baseline risk factors (especially age, diabetes and uncontrolled hypertension) appear to be crucial predictors of ESRD regardless the treatment delivered.

Table 1: Clinical characteristics of n=2,027 patients with cT1N0M0 renal tumor with normal renal function before surgery and treated with either NSS or RN. Data are further stratified according to treatment delivery.

Variable	NSS (n=1,334, 65.8%)	RN (n=693, 34.2%)	p-value
Age (years)	61 (51-69)	61 (52-69)	0.4
Gender Male Female	 66.0% 34.0%	 66.2% 33.8%	0.9
eGFR pre-surgery (ml/min/1.73m^2)	86 (82-98)	85 (85-93)	0.002
Body Mass Index	25.7 (23.8-27.9)	25.8 (23.8-27.9)	0.7
Smoke status No Smoker Former	 59.2% 27.3% 13.6%	 53.1% 22.6% 19.8%	<0.001
Diabetes	12.5%	7.4%	<0.001
Hypertension No Hypertension (uncontrolled) Hypertension controlled by therapy	 56.5% 21.1% 22.4%	 67.2% 13.3% 19.5%	<0.001
Charlson Comorbidity Index 0 1 >1	 45.3% 16.2% 38.6%	 60.0% 18.2% 21.7%	<0.001
Clinical tumor size	3.2 (2.5-4.0)	5.0 (3.7-6.0)	<0.001

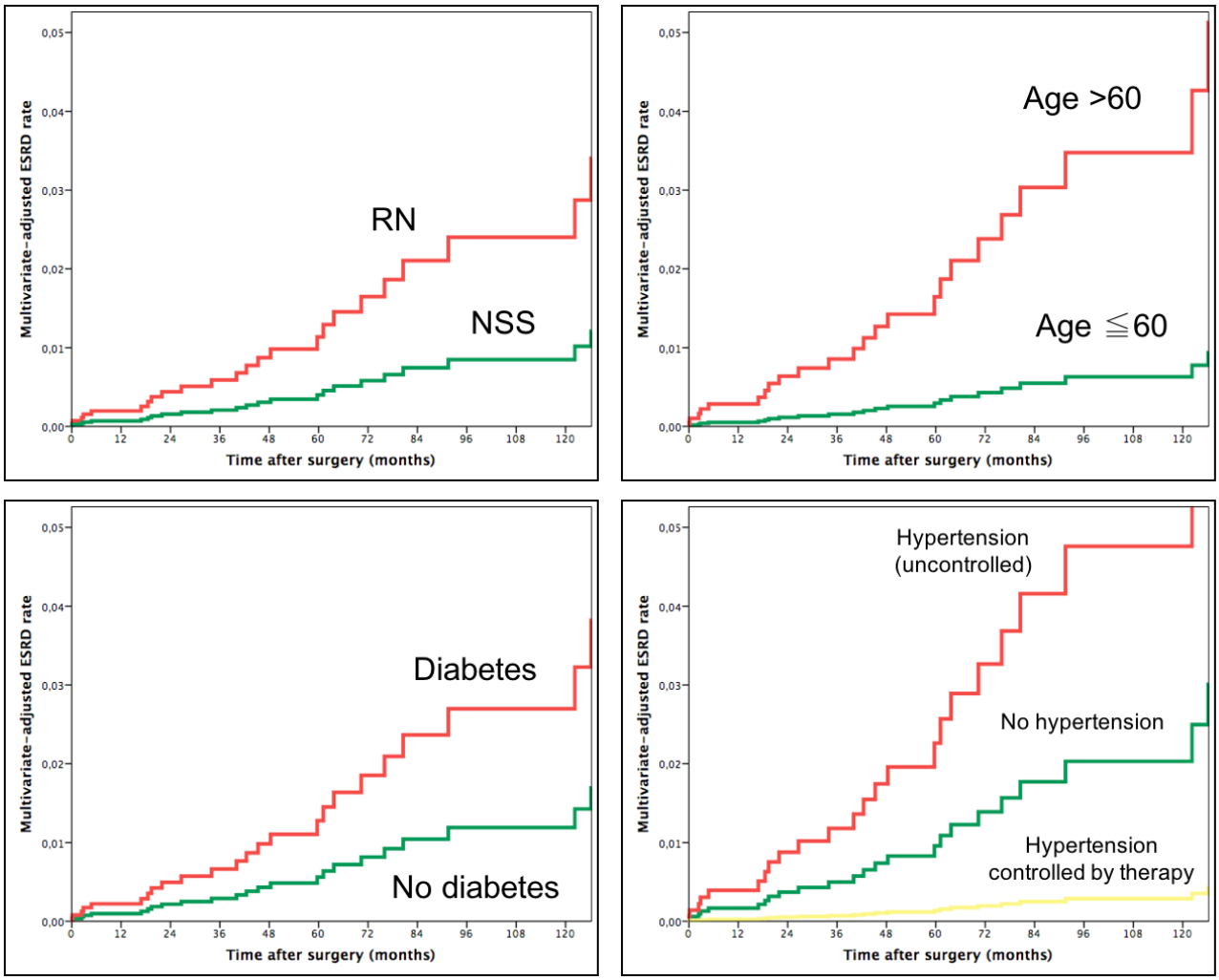
Mann-Whitney and Chi-square tests were used to compare the statistical significance of differences in the distribution of continuous or categorical variables, respectively.
Legend: NSS, Nephron Sparing Surgery; RN, Radical Nephrectomy; eGFR, estimated Glomerular Filtration Rate. Results are reported as median (IQR, InterQuartile Range) for continuous variables, percentages for categorized variables

Table 2 (Supplementary Table): Univariable and multivariable analyses predicting ESRD in patients treated with NSS vs. RN.

	Univariable analyses		Multivariable analyses (reduced model after backward stepwise)	
Variable	**p**	**HR (95%CI)**	**p**	**HR (95%CI)**
Treatment type NSS vs. RN	0.5	0.8 (0.4-1.6)	0.02	0.4 (0.2-0.8)
Year of surgery	<0.001	1.2 (1.1-1.3)	0.002	1.2 (1.1-1.3)
Clinical tumor size	0.2	1.2 (0.9-1.5)	-	-
Age (years)	<0.001	1.1 (1.1-1.1)	<0.001	1.1 (1.1-1.2)
eGFR pre-surgery	0.8	1.0 (1.0-1.0)	-	-
Body Mass Index	0.3	1.0 (0.9-1.1)	-	-
Smoke status	0.4	1.2 (0.8-1.8)	-	-
Diabetes	0.002	3.4 (1.5-7.4)	0.06	2.3 (1.0-5.6)
Hypertension Hypertension (uncontrolled) vs. no Hypertension controlled by therapy vs. no	<0.001 <0.001 0.2	 4.1 (2.1-8.2) 0.4 (0.1-1.8)	0.07 0.2 0.09	 1.6 (0.7-3.7) 0.2 (0.1-1.3)
Charlson Comorbidity Index 1 vs. 0 >1 vs. 0	0.01 0.06 0.004	 2.4 (0.9-6.2) 3.4 (1.5-7.8)	-	-

Legend: HR: Hazard Ratio; 95%CI: 95% Confidence Interval; NSS: Nephron Sparing Surgery; RN: Radical Nephrectomy; eGFR: estimated Glomerular Filtration Rate

Figure 1: Multivariate-derived ESRD cumulative rates stratified according 1A) treatment delivery (NSS vs. RN), 1B) patients' age, 1C) presence of diabetes and 1D) hypertension (none vs. controlled by medical therapy vs. uncontrolled). Data are adjusted for age, year of surgery, Body Mass Index, clinical tumor size, hypertension (no vs. controlled vs. uncontrolled), preoperative eGFR, Charlson Comorbidity Index, diabetes and smoker status.



References

[1] capitanio U, Montorsi F. Renal cancer. Lancet 2015. doi:10.1016/S0140-6736(15)00046-X.

[2] Scosyrev E, Messing EM, Sylvester R, Campbell S, Van Poppel H. Renal Function After Nephron-sparing Surgery Versus Radical Nephrectomy: Results from EORTC Randomized Trial 30904. Eur Urol 2013:1–6. doi:10.1016/j.eururo.2013.06.044.

[3] capitanio U, Terrone C, Antonelli A, Minervini A, Volpe A, Furlan M, et al. Nephron-sparing Techniques Independently Decrease the Risk of Cardiovascular Events Relative to Radical Nephrectomy in Patients with a T1a-T1b Renal Mass and Normal Preoperative Renal Function. Eur Urol 2014. doi:10.1016/j.eururo.2014.09.027.

[4] Fox CS, Matsushita K, Woodward M, Bilo HJG, Chalmers J, Heerspink HJL, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012;380:1662–73. doi:10.1016/S0140-6736(12)61350-6.

[5] Muzaale AD, Massie AB, Wang M-C, Montgomery RA, McBride MA, Wainright JL, et al. Risk of End-Stage Renal Disease Following Live Kidney Donation. Jama 2014;311:579–15. doi:10.1001/jama.2013.285141.

[6] Lin W-Y, Liang F-W, Lu T-H. Risk of End-Stage Renal Disease after Cancer Nephrectomy in Taiwan: A Nationwide Population-Based Study. PloS One 2015;10:e0126965–8. doi:10.1371/journal.pone.0126965.

[7] Yap SA, Finelli A, Urbach DR, Tomlinson GA, Alibhai SMH. Partial nephrectomy for the treatment of renal cell carcinoma (RCC) and the risk of end-stage renal disease (ESRD). BJU Int 2015;115:897–906. doi:10.1111/bju.12883.

[8] Lane BR, Demirjian S, Derweesh IH, Riedinger CB, Fergany AF, Campbell SC. Is all chronic kidney disease created equal? Current Opinion in Urology 2014;24:127–34. doi:10.1097/MOU.0000000000000029.

[9] Lane BR, Demirjian S, Derweesh IH, Takagi T, Zhang Z, Velet L, et al. Survival and Functional Stability in Chronic Kidney Disease Due to Surgical Removal of Nephrons: Importance of the New Baseline Glomerular Filtration Rate. Eur Urol 2015;68:996–1003. doi:10.1016/j.eururo.2015.04.043.