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A Prospective, Randomised EORTC Intergroup Phase 3 Study Comparing the Oncologic Outcome of Elective Nephron-Sparing Surgery and Radical Nephrectomy for Low-Stage Renal Cell Carcinoma

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Abstract

Background: Nephron-sparing surgery (NSS) can safely be performed with slightly higher complication rates than radical nephrectomy (RN), but proof of oncologic effectiveness is lacking.
Objective: To compare overall survival (OS) and time to progression.
Design, setting, and participants: From March 1992 to January 2003, when the study was prematurely closed because of poor accrual, 541 patients with small ($\leq$5 cm), solitary, T1–T2 N0 M0 (Union Internationale Contre le Cancer [UICC] 1978) tumours suspicious for renal cell carcinoma (RCC) and a normal contralateral kidney were randomised to NSS or RN in European Organisation for Research and Treatment of Cancer Genito-Urinary Group (EORTC-GU) noninferiority phase 3 trial 30904.
Intervention: Patients were randomised to NSS (n = 268) or RN (n = 273) together with limited lymph node dissection (LND).
Measurements: Time to event end points was compared with log-rank test results.
Results and limitations: Median follow-up was 9.3 yr. The intention-to-treat (ITT) analysis showed 10-yr OS rates of 81.1% for RN and 75.7% for NSS. With a hazard ratio

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(HR) of 1.50 (95% confidence interval [CI], 1.03–2.16), the test for noninferiority is not significant ($p = 0.77$), and test for superiority is significant ($p = 0.03$). In RCC patients and clinically and pathologically eligible patients, the difference is less pronounced (HR = 1.43 and HR = 1.34, respectively), and the superiority test is no longer significant ($p = 0.07$ and $p = 0.17$, respectively). Only 12 of 117 deaths were the result of renal cancer (four RN and eight NSS). Twenty-one patients progressed (9 after RN and 12 after NSS). Quality of life and renal function outcomes have not been addressed.

Conclusions: Both methods provide excellent oncologic results. In the ITT population, NSS seems to be significantly less effective than RN in terms of OS. However, in the targeted population of RCC patients, the trend in favour of RN is no longer significant. The small number of progressions and deaths from renal cancer cannot explain any possible OS differences between treatment types.

1. Introduction

Historically, Robson et al introduced radical nephrectomy (RN) as the standard treatment for localised renal cell carcinoma (RCC) [1]. During the past decade, the status of RN has been called into question because of a higher risk of chronic kidney disease (CKD) and possible overtreatment of small renal masses (SRM), with a significant proportion of benign tumours (≤20%). In recent years, partial nephrectomy (PN) has become the standard surgical treatment for T1a renal tumours (<4 cm) [2–4] and select T1b tumours (4–7 cm) [4–13]. The rationale for wider use of nephron-sparing surgery (NSS) is based on data that suggest equal cancer control with RN while preserving renal function. However, none of the studies comparing NSS and RN were randomised [14]. To establish the role of NSS in relation to RN, a prospective, randomised study has been conducted to compare RN and NSS for small, low-stage RCC. A first report on surgical morbidity was published in 2007 and revealed that NSS is safe, with a slightly higher complication rate than RN [15]. This paper is the first report of oncologic results from a randomised study comparing NSS and RN for small, low-stage RCC.

2. Patients and methods

2.1. Study design

The study was designed to assess both morbidity and cancer control in the two treatment arms—RN and conservative surgery (NSS)—both with limited lymphadenectomy (LND). The primary end point was overall survival (OS). Secondary end points were disease-specific survival (DSS), progression, and surgical side-effects.

The study was originally designed as a randomised, noninferiority, multicentre, phase 3 study requiring 310 patients, trying to rule out a difference of 10% in 5-yr survival from 90% on RN to 80% on PN. Accrual began in April 1992, and 300 patients were entered in 5.5 yr. In early 1998, the European Organisation for Research and Treatment of Cancer Genito-Urinary Group (EORTC-GU) decided to open the trial to other groups (Southwest Oncology Group [SWOG], Eastern Cooperative Oncology Group [ECOG], American College of Surgeons Oncology Group, National Cancer Institute of Canada [NCIC]) to redesign the study based on a more realistic difference of 3% in 5-yr survival from 90% on RN to 87% on PN (hazard ratio [HR]: 1.3). For this difference, a minimum of 1300 patients and 368 deaths were now required based on a one-sided log-rank test for noninferiority at error rates of $\alpha = 0.05$ and $\beta = 0.20$. In January 2003, the study was prematurely closed because of poor accrual. In total, 541 patients were randomised (EORTC: 527 patients; NCIC: 11 patients; USA (ECOG/SWOG): 3 patients).

Eligibility criteria for entry in the study consisted patients with a solitary, T1–T2 N0 M0 (Union Internationale Contre le Cancer [UICC] 1978), renal tumour ≤5 cm suspicious for RCC, a normal contralateral kidney, and a World Health Organisation (WHO) performance status (PS) of 0–2. After verification of the eligibility criteria, patients were centrally randomised at the EORTC Data Centre to undergo NSS or RN. Prior to surgery, eligible patients had to provide written informed consent according to European Union International Conference on Harmonisation Good Clinical Practice and national/local regulations. Details concerning the surgical procedure were previously published [15].

2.2. Statistical analysis

The primary analysis included all randomised patients based on the intention-to-treat (ITT) principle; sensitivity analyses were performed in clinically and pathologically eligible patients and in patients with RCC. Survival curves were estimated using the Kaplan-Meier method, and differences were compared with the log-rank test ($p < 0.05$ was considered statistically significant). Tests for both noninferiority and superiority were carried out. The prognostic role of several variables was tested in univariate fashion with the log-rank test.

3. Results

From March 1992 to January 2003, 541 patients from 45 institutions (17 countries) were randomised to undergo NSS ($n = 268$) or RN ($n = 273$). Four patients were clinically ineligible (because of multifocality or other cancers), and 136 additional patients were pathologically ineligible (no renal adenocarcinoma ($n = 70$), tumour pT3 or higher ($n = 29$), tumour >5 cm ($n = 19$), multifocality ($n = 15$), positive surgical margins ($n = 3$; Fig. 1).

Patient characteristics (Table 1) were well balanced between the treatment arms at entry, with a median age of 62 yr (range: 23–84), 65.8% males, 84.3% with WHO PS 0, 35.9% with associated chronic disease, and 91.9% having a normal serum creatinine. Table 2 summarises the clinical and pathologic disease characteristics. Clinical disease characteristics were well balanced, with 98.3% of patients having a solitary tumour, 50% having T1N0M0 tumours, and

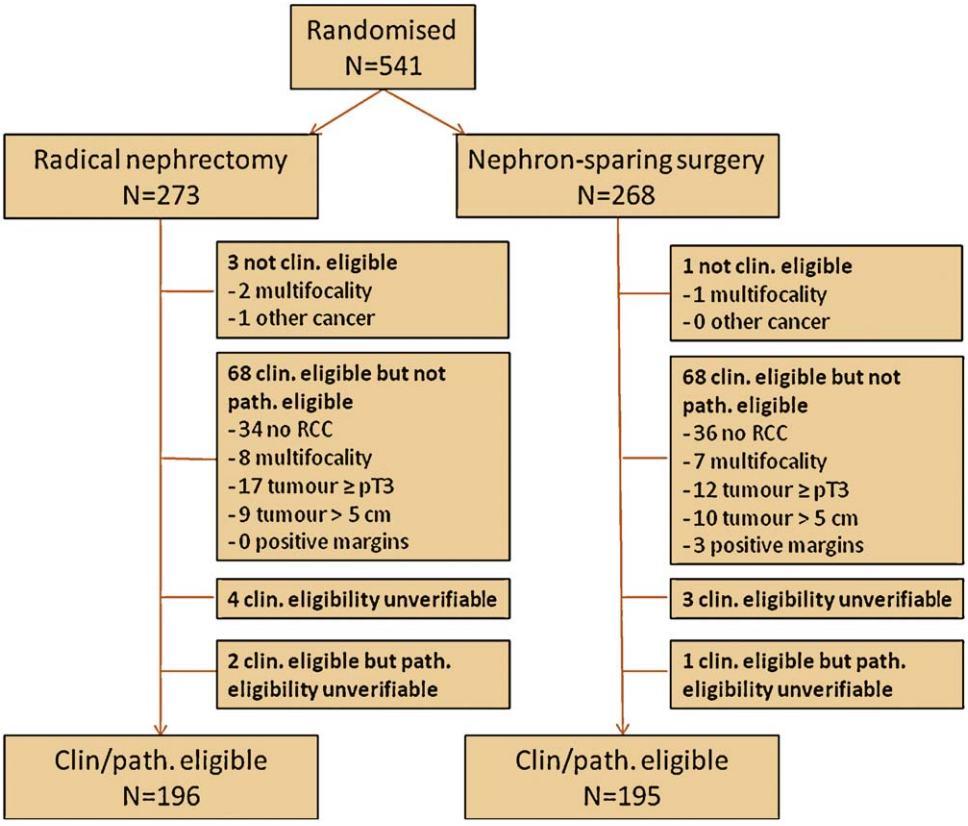

Fig. 1 – Consolidated Standards of Reporting Trials diagram.
RCC = renal cell carcinoma.

50% having T2N0M0 tumours. The majority of patients had grade 1 (18.2%) and grade 2 (54.2%) tumours. Central pathology review was available in 266 (49%) of 541 patients. Final histopathologic analysis revealed RCC in 84.8% of patients, of which 62.8% were clear-cell RCC, 81.7% had a solitary renal tumour, 40.9% had a pT1 tumour, and 38.4% had a pT2 renal tumour.

Table 3 shows the surgical characteristics according to randomised treatment and treatment actually received. Nine patients who were not operated on or who had no surgical information were excluded. Of the 273 patients randomised to RN, 16 (5.9%) underwent NSS (in general as a result of the patient's decision). Of the 268 patients randomised to NSS, 39 (14.6%) underwent RN (in general as a result of pathologic disease characteristics). LND was performed in 56% of patients and most often in those who underwent RN; 57% of patients who underwent NSS had hilar clamping, with a median duration of 20 min.

Table 4 summarises the incidence of acute side-effects. Both surgical treatments are safe: There was little acute

Table 1 – Patient characteristics

		RN (n = 273)	NSS (n = 268)	Total (n = 541)
Age, yr	Median (range)	62.0 (23.0–84.0)	62.0 (29.0–82.0)	62.0 (23.0–84.0)
Sex, no. (%)	Male	178 (65.2)	178 (66.4)	356 (65.8)
	Female	91 (33.3)	87 (32.5)	178 (32.9)
	Missing	4 (1.5)	3 (1.1)	7 (1.3)
WHO PS, no. (%)	0	227 (83.2)	229 (85.4)	456 (84.3)
	1	37 (13.6)	35 (13.1)	72 (13.3)
	2	6 (2.2)	1 (0.4)	7 (1.3)
	Missing	3 (1.1)	3 (1.1)	6 (1.1)
Chronic disease, no. (%)	No	174 (63.7)	166 (61.9)	340 (62.8)
	Cardiovascular	61 (22.3)	57 (21.3)	118 (21.8)
	Pulmonary	13 (4.8)	8 (3.0)	21 (3.9)
	Other	21 (7.7)	34 (12.7)	55 (10.2)
	Missing	4 (1.5)	3 (1.1)	7 (1.3)

RN = radical nephrectomy; NSS = nephron-sparing surgery; WHO = World Health Organization; PS = performance status.

Table 2 – Disease characteristics

	Clinical		Pathologic	
	RN (*n* = 273)	NSS (*n* = 268)	RN (*n* = 273)	NSS (*n* = 268)
Cell type, no. (%):				
Clear cell	–	–	163 (59.7)	177 (66.0)
Other malignant tumours (RCC)	–	–	69 (25.3)	50 (18.7)
Other cell type	–	–	34 (12.5)	37 (13.8)
Missing	–	–	7 (2.6)	4 (1.5)
No. of tumours (%)				
1	268 (98.2)	264 (98.5)	222 (81.3)	220 (82.1)
>1	2 (0.8)	1 (0.4)	10 (3.7)	7 (2.6)
Missing	3 (1.1)	3 (1.1)	6 (2.2)	3 (1.1)
No RCC	–	–	35 (12.8)	38 (14.2)
Largest diameter, cm				
Median	3.0	3.0	3.0	3.0
Range	0.3–5.0	0.3–5.0	0.8–7.5	1.0–9.0
No. observed	270	265	232*	227*
T category, no. (%)				
T1	139 (50.9)	127 (47.4)	116 (42.5)	105 (39.2)
T2	130 (47.6)	137 (51.1)	98 (35.9)	110 (41.0)
T3	1 (0.4)	0 (0.0)	18 (6.6)	12 (4.5)
Missing	3 (1.1)	4 (1.5)	6 (2.2)	3 (1.1)
No RCC	–	–	35 (12.8)	38 (14.2)
Grade, no. (%)				
G0	–	–	1 (0.4)	3 (1.1)
G1	–	–	49 (17.9)	49 (18.3)
G2	–	–	145 (53.1)	148 (55.2)
G3	–	–	28 (10.3)	18 (6.7)
G4	–	–	2 (0.7)	1 (0.4)
Missing	–	–	13 (4.8)	11 (4.1)
No RCC	–	–	35 (12.8)	38 (14.2)

RN = radical nephrectomy; NSS = nephron-sparing surgery; RCC = renal cell carcinoma.
* Largest diameter of the tumour only on patients with RCC.

Table 3 – Surgical characteristics

	Randomised to RN		Randomised to NSS	
	RN (*n* = 251)	NSS (*n* = 16)	RN (*n* = 39)	NSS (*n* = 226)
Surgical approach, no. (%)				
Lumbotomy				
Laparotomy	100 (39.8)	9 (56.3)	15 (38.5)	158 (69.9)
Thoracolaparotomy	133 (53.0)	7 (43.8)	18 (46.2)	58 (25.7)
Other	12 (4.8)	–	4 (10.3)	7 (3.1)
	6 (2.4)	–	2 (5.1)	3 (1.3)
Lymphadenectomy, no. (%)				
No	82 (32.7)	11 (68.8)	14 (35.9)	126 (55.8)
Yes, limited	136 (54.2)	4 (25.0)	20 (51.3)	99 (43.8)
Yes, radical	33 (13.1)	–	5 (12.8)	1 (0.4)
Unknown	–	1 (6.3)	–	–
Satellite or secondary lesions, no. (%)				
No	243 (96.8)	14 (87.5)	220 (97.3)	36 (92.3)
Yes	8 (3.2)	1 (6.3)	6 (2.7)	3 (7.7)
Unknown	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)
Hilar clamping, no. (%)	–		–	
No		7 (43.8)		97 (42.9)
Yes		9 (56.3)		129 (57.1)
Unknown		–		–

RN = radical nephrectomy; NSS = nephron-sparing surgery.

Table 4 – Acute side-effects

	Randomised to RN		Randomised to NSS	
	RN (n = 251)	NSS (n = 16)	RN (n = 39)	NSS (n = 226)
Spleen damage, no. (%)				
No	250 (99.6)	16 (100.0)	38 (97.4)	225 (99.6)
Yes	1 (0.4)	–	1 (2.6)	1 (0.4)
Pleural damage, no. (%)				
No	227 (90.4)	15 (93.8)	37 (94.9)	200 (88.5)
Yes	23 (9.2)	1 (6.3)	2 (5.1)	26 (11.5)
Unknown	1 (0.4)	–	–	–
Perioperative bleeding, no. (%)				
No	211 (84.1)	15 (93.8)	29 (74.4)	158 (69.9)
Yes	39 (15.6)	1 (6.3)	10 (25.7)	68 (30.1)
Unknown	1 (0.4)	–	–	–
Urinary fistula, no. (%)				
No	251 (100.0)	16 (100.0)	39 (100.0)	217 (96.0)
Yes	–	–	–	9 (4.0)

RN = radical nephrectomy; NSS = nephron-sparing surgery.

toxicity, and pleural damage occurred in only 9.8% of patients, perioperative bleeding in 22.2% of patients, and urinary fistula in 1.7% of patients (and only in those patients undergoing NSS). There was a slightly higher complication rate after NSS [15].

RN patients had a median follow-up serum creatinine of 1.5 mg/dl (minimum: 0.9; maximum: 4.7). In NSS patients, the median follow-up serum creatinine was 1.3 mg/dl (minimum: 0.78, maximum: 9.6) [15]. Based on a median follow-up of 9.3 yr, 117 patients had died, with 67 of 268 deaths (25%) in the NSS group and 50 of 273 deaths (18.3%) in the RN group. Only 12 of 541 patients (2.2%) died of renal cancer, including 8 renal deaths in the NSS group and 4 in the RN group. Three deaths were related to surgery, one in the RN group and two in the NSS group. Cardiovascular (CV) disease was the leading cause of death (38.4% of deaths), with 25 CV deaths (9.3%) in the NSS group and 20 (7.3%) in the RN group (Table 5).

The ITT analysis showed 10-yr OS rates of 75.7% (95% confidence interval [CI], 69.4–81.0) for NSS and 81.1% (95% CI, 75.0–85.9) for RN. With an estimated HR of 1.50 (95% CI, 1.03–2.16), the statistical test for noninferiority of OS is not significant (p = 0.77), while the test for superiority is significant (p = 0.03; Fig. 2).

When considering the targeted population of RCC patients only (Fig. 3) and clinically and pathologically eligible patients (Fig. 4), the differences in terms of OS between the treatment groups is less pronounced (HR: 1.43 and 1.34, respectively), and the test for superiority is no longer statistically significant (p = 0.07 and p = 0.17, respectively). The 10-yr OS rates after NSS and RN were 75.2% and 79.4%, respectively, for RCC patients and 78.0% and 79.6%, respectively, for clinically and pathologically eligible patients.

In a sensitivity analysis of the primary end point, we assumed that the 53 patients lost to follow-up patients had died at their date of last follow-up. With this assumption, 170 patients have died, 95 (35.4%) in the NSS group and 75 (27.5%) in the RN group. Data are not shown, because this analysis does not show any major differences compared to the results cited earlier.

There were 12 renal cancer–related deaths: 4 in the RN group and 8 in the NSS group. The estimated risk of death from renal cancer was not significantly higher in the NSS arm (HR: 2.06), with a very wide CI (95% CI, 0.62–6.81; Gray's test p = 0.23) resulting from the small number of renal cancer–related deaths.

Regarding the secondary end point, progression was detected in 12 patients in the NSS group and in 9 patients in the RN group (HR: 1.37; 95% CI, 0.58–3.24; Table 6; Fig. 5). The 10-yr progression rates were 4.1% (95% CI, 1.7–6.5) after NSS and 3.3% (95% CI, 1.2–5.4) after RN (Gray's test p = 0.48; Fig. 5). Among the 21 patients with progression, 1 died of renal cancer with no information about recurrence, lymph node metastases, or distant metastases.

Table 5 – Survival status and cause of death

	RN (n = 273)	NSS (n = 268)	Total (n = 541)
Survival status no. (%)			
Alive	198 (72.5)	173 (64.6)	371 (68.6)
Dead	50 (18.3)	67 (25.0)	117 (21.6)
Lost to follow-up	25 (9.2)	28 (10.4)	53 (9.8)
Alive/lost to follow-up, no. (%)	223 (81.7)	201 (75.0)	424 (78.4)
Cause of death, no. (%)			
Liver related	0 (0.0)	4 (1.5)	4 (0.7)
Renal related	4 (1.5)	8 (3.0)	12 (2.2)
Surgery related	1 (0.4)	2 (0.7)	3 (0.6)
Infection	3 (1.1)	2 (0.7)	5 (0.9)
Cardiovascular death	20 (7.3)	25 (9.3)	45 (8.3)
Chronic pulmonary disease	2 (0.7)	3 (1.1)	5 (0.9)
Second primary	7 (2.6)	11 (4.1)	18 (3.3)
Natural	5 (1.8)	2 (0.7)	7 (1.3)
Other (not chronic renal disease)	3 (1.1)	7 (2.6)	10 (1.8)
Unknown	5 (1.8)	3 (1.1)	8 (1.5)

RN = radical nephrectomy; NSS = nephron-sparing surgery.

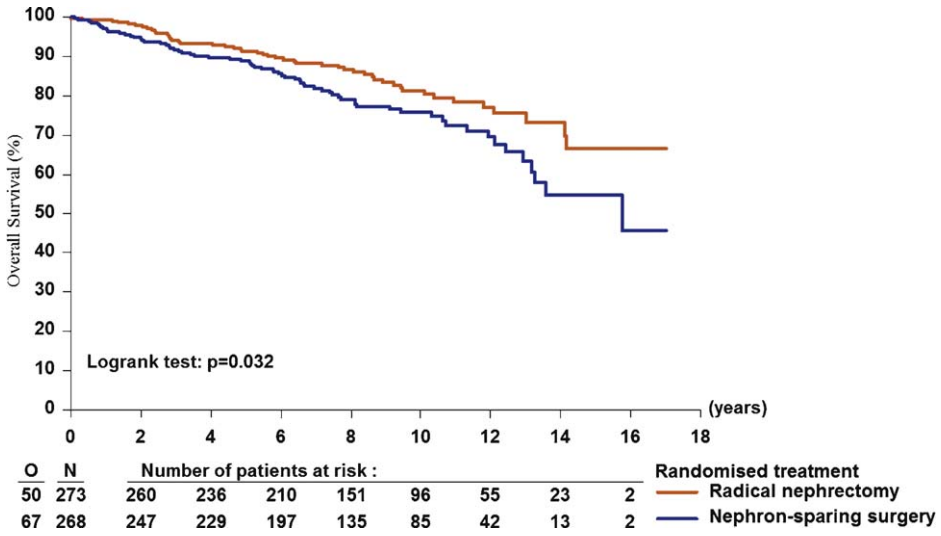

Fig. 2 – Kaplan-Meier estimates with log-rank test for overall survival in all randomised patients (intent to treat) after nephron-sparing surgery and radical nephrectomy.

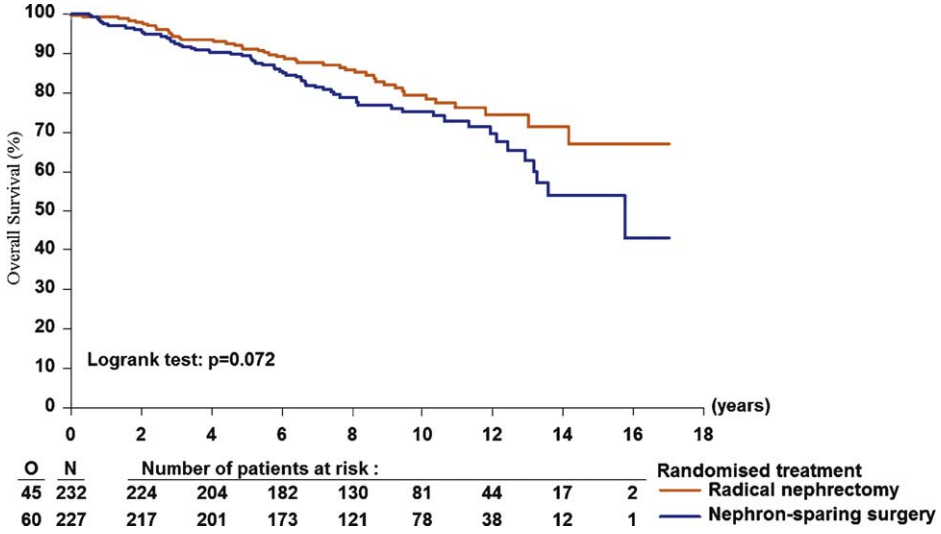

Fig. 3 – Kaplan-Meier estimates with log-rank test for overall survival in renal cell carcinoma patients after nephron-sparing surgery and radical nephrectomy.

Table 6 – Disease status

	RN (n = 273)	NSS (n = 268)	Total (n = 541)
Progression, no. (%)			
No	264 (96.7)	256 (93.9)	520 (96.1)
Yes, specify:	9 (3.3)	12 (4.5)	21 (3.9)
Local recurrence, no.	1	6*	7
Lymph node metastases, no.	3	1	4
Distant metastases, no.	7	6	13
Second primary, no. (%)			
No	252 (92.3)	246 (91.8)	498 (92.1)
Yes, contralateral kidney	5 (1.8)	3 (1.1)	3 (1.5)
Yes, other	16 (5.9)	19 (7.1)	35 (6.5)

RN = radical nephrectomy; NSS = nephron-sparing surgery.
* Four of six recurrences elsewhere in the kidney.

With the small number of recurrences and deaths from renal cancer, it is difficult to draw conclusions from prognostic and predictive factor analyses. Age, WHO PS, and associated chronic disease were prognostic factors of OS, but none were predictive factors.

4. Discussion

Several nonrandomised studies have compared survival in patients treated with NSS or RN for T1 renal tumours [5,7,11,13,16–19]. Although some have found PN to be associated with better OS than RN and have hypothesised that this is the result of better preservation of renal function, these comparisons have been difficult to interpret, because the individual studies were not randomised, had small

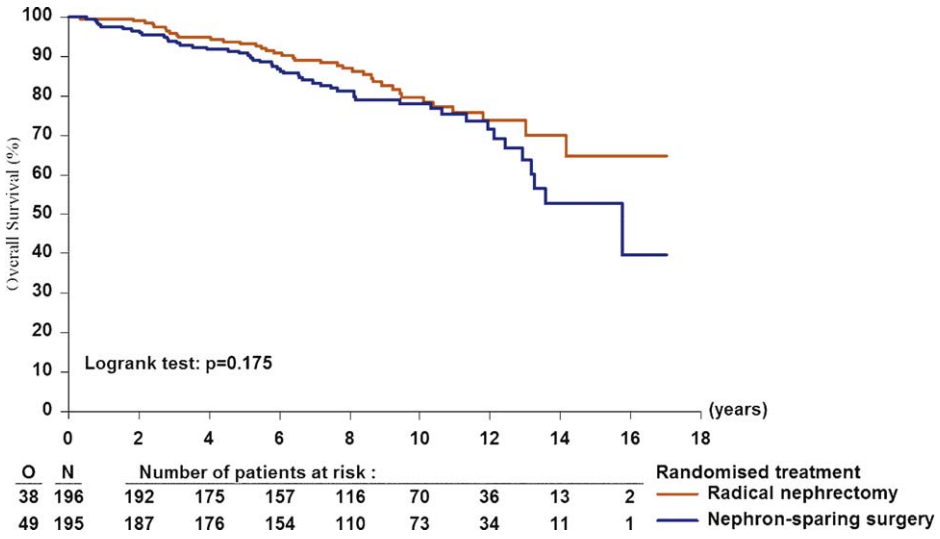

Fig. 4 – Kaplan-Meier estimates with log-rank test for overall survival in clinically and pathologically eligible patients after nephron-sparing surgery and radical nephrectomy.

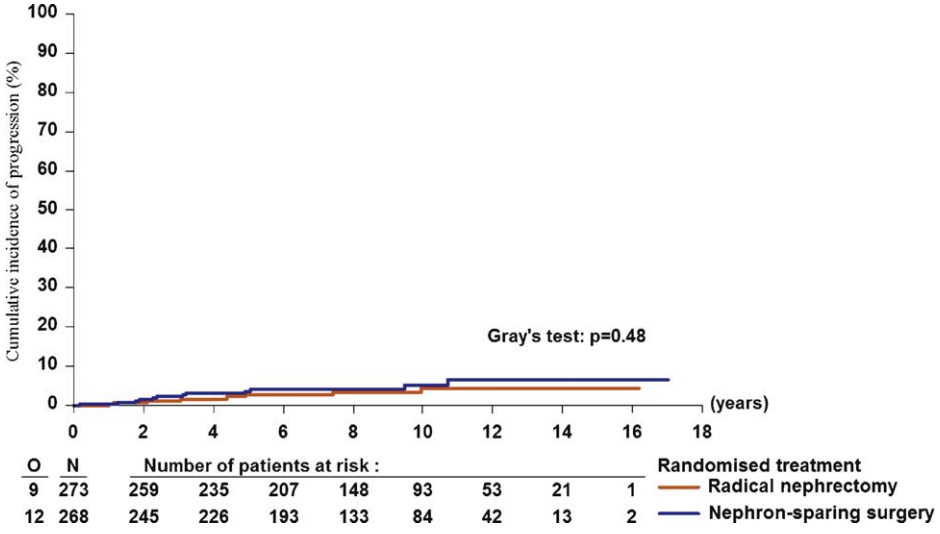

Fig. 5 – Cumulative incidence of the time to progression in all randomised patients (intent to treat).

patient numbers, and may have been subject to selection bias. Other limiting factors were the heterogeneous pathologic stage of tumours, with larger, more aggressive tumours and often less healthy and older patients in the RN cohort, and the lack of renal function outcomes. Previous studies have shown that PN leads to less renal function loss than RN and reduces the risk of CKD [18–22]. A recent retrospective study demonstrated that PN is associated with better OS compared to RN in patients with unanticipated benign tumours. This survival benefit appears partly to be the result of better preservation of the estimated glomerular filtration rate (eGFR), but other measures of kidney function or unmeasured selection factors may also play a role [23].

Unexpectedly, in our ITT analysis, the duration of survival demonstrated a better outcome for patients treated with RN compared to those treated with NSS ($p = 0.032$). However, our analyses of the targeted population of RCC patients and of the population of clinically pathologically eligible patients revealed that the trend for a better OS is not significantly different when NSS is compared to RN. Although patients with SRMs are being detected and treated at earlier stages, there is a continuing increase in mortality.

One of the possible mechanisms by which surgery may increase non–cancer-related deaths is the development of CKD. Previous studies suggest that RN increases the risk of CKD, which is a significant risk factor for CV events and death [21,22,24]. The recent findings of Zini et al revealed that RN predisposes patients to a rise in overall mortality and non–cancer-related mortality rate in patients with T1aN0M0 RCC [25]. In our study, slightly more CV deaths

occurred in the NSS group (25 of 268; 9.3%) than in the RN group (20 of 273; 7.3%). This result is in contrast with results seen in the literature, which suggest that NSS may be beneficial in preventing CV morbidity and mortality [17,20,23]. At this time, no explanation for this controversy can be provided. The present study was not designed to test the hypothesis of reduced CV events with NSS. Recent data suggest that NSS may improve survival only insofar as it prevents postoperative renal insufficiency. OS stratified according to postoperative eGFR demonstrated an increasing risk of death from any cause or CV death with decreasing renal function. Therefore, NSS should be completed within a reasonable ischemia time to prevent renal function loss and not compromise OS [19].

A limitation of our study is that the required sample size of 1300 patients was not reached and that quality of life (QoL) and renal function outcomes have not been addressed. In addition, 55 patients switched treatment: 16 patients (5.9%) randomised to RN received NSS, and 39 patients (14.6%) randomised to NSS received RN, generally because of tumour characteristics. To avoid bias, the efficacy analysis was carried out in the ITT population. Furthermore, in our study, the cut-off for tumour size was 5 cm, while currently the level is put at 4 cm. This cut-off of 5 cm was decided at the time the study was designed based on information available at that time.

Oncologic equivalence of NSS and RN could not be definitively shown in this randomised study but is nowadays generally accepted. The fact that the present study reveals that NSS can be safely performed and results in only a very low percentage of patients with progression (4.5%) and renal cancer–related death (3%) adds to the existing arguments favouring NSS in patients with T1 tumours. It supports the recommendation to use NSS in small tumours as a first-line procedure whenever technically feasible, even in the presence of a normal contralateral kidney [4]. RN remains a viable option when the tumour is not amenable to NSS. If RN is required, laparoscopic RN (LRN) should be considered, as it is now an established standard and allows more rapid recovery. To date, however, it is overutilised in SRMs; too many renal units are removed while NSS would be possible. Widespread training in open PN (OPN)/laparoscopic PN (LPN) and increased use whether by OPN or LPN approaches are needed. PN use should be encouraged, with conversion to OPN instead of LRN when LPN encounters difficulties.

5. Conclusions

Both RN and NSS provide excellent oncologic results. In the targeted population of RCC patients, the OS trend in favour of RN is not statistically significant. The numbers of progressions and deaths from renal cancer are very small and cannot explain any possible OS differences between the two treatment arms.

Author contributions: Hendrik Van Poppel 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: Van Poppel, Da Pozzo, Albrecht, Matveev, Bono, Borkowski, Colombel, Klotz, Skinner, Keane, Marreaud, Collette, Sylvester.
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