Original Study

Long-Term Oncological Efficacy of Retroperitoneoscopic Radical Nephrectomy of Localized Renal Cell Cancer pT1-3 (≤12 cm)

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Investigation of oncological efficacy in retroperitoneoscopic radical nephrectomy (RRN) of patients with localized renal cell carcinoma (RCC). Consecutive patients undergoing RRN for localized stage pT1-3 RCC in 2 tertiary care centers in Switzerland were evaluated. Excellent long-term oncological efficacy was found. Our long-term follow-up validates the survival outcome from comparable literature after conventional open or laparoscopic radical nephrectomy.

Clinical Genitourinary Cancer, Vol. 000, No.xxx, 1–8 © 2022 The Author(s). Published by Elsevier Inc.
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Introduction

The first laparoscopic nephrectomy by Clayman almost 30 years ago was a milestone in the treatment of kidney cancer.[1] Surgery for renal cell cancer (RCC) has significantly changed since then and the advantages of minimal-invasive techniques compared to open radical procedures are nowadays well known.[2] Over the past 2 decades, nephron-sparing surgery (NSS) became the new standard of care for patients with localized stage T1 RCC (up to stage T2 where technically feasible).[3] Robot-assisted laparoscopic partial nephrectomy is nowadays widely used as standard treatment modality. Rapid postoperative recovery and preservation of kidney function, combined with cancer-specific survival (CSS) comparable to survival rates after radical nephrectomies (RN), were important factors that led to the change in management of patients with localized RCC.[4-6]

Nonetheless, RN still plays a role in selected patients, especially in conditions where NSS is neither indicated, nor feasible.[7,8]

RN can be performed as an open or video-endoscopic procedure. Various studies show similar oncological outcomes for open radical nephrectomy (ORN) and transabdominal laparoscopic radical nephrectomy (LRN),[9-11] which offers several advantages over ORN (ie, reduced blood loss, postoperative pain, recovery time and length of hospital stay).[11,12] Retroperitoneoscopic radical nephrectomy (RRN) has been introduced as an alternative to transabdominal LRN.[13,14] The 2 most important advantages of the RRN are the faster control of the renal hilum and the fact that bowel mobilization is not necessary. This is particularly beneficial for patients with morbid obesity or previous abdominal surgery. Potential disadvantages are the limited retroperitoneal space, a more difficult identification of anatomical landmarks and, if indicated, the feasibility to perform lymphadenectomy. These advantages and disadvantages might impact the oncological safety of the procedure.

Short-term oncological outcome following RRN has been reported to be comparable to ORN and LRN.[13-15] However, long-term oncological outcome after RRN is still unknown. The aim of the present investigation was to determine long-term oncological efficacy of RRN.

Patients and Methods

Patient Cohort

We retrospectively evaluated all patients treated with straight RRN for suspected localized stage pT1 to pT3 RCCs in 2 tertiary care centers in Switzerland between 2001 and 2015. RRN was performed as described previously.[16-21] RRN was the preferred

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Submitted: Oct 21, 2021; Revised: Apr 19, 2022; Accepted: Apr 23, 2022; Epub: xxx

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https://doi.org/10.1016/j.clgc.2022.04.016

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minimal-invasive treatment option in the 2 institutions. Alternative surgical approaches (LRN or ORN) were chosen at the discretion of the surgeon and according to size (limited retroperitoneal space), location (ie, large lower pole) or adverse aspects (lymph node, renal vein or vena cava involvement) of the tumor. Patients with suspicion of nodal dissemination (cN+) or systemic metastasis (cM+) were excluded from the analysis. The study was approved by the local ethics committee (BASEC-Nr. 2016-01085).

Clinical Parameters

The following parameters were retrieved from the electronic medical charts. Baseline characteristics: treatment site, age, sex, body-mass index, American Society of Anesthesiologists risk classification, previous operations, and date of surgery. The following intraoperative characteristics were recorded: operation side, operative time, estimated blood loss, number of trocars used, surgeons, conversion (from laparoscopic to open), and intraoperative complications. Postoperative characteristics: duration of hospital stay, postoperative complications (according Clavien-Dindo classification), local failure, metastases, and number of deaths during follow-up. Pathological characteristics: tumor size, resection status, TNM-stage, Fuhrman nuclear grade, and histopathological classification.

The following data was further documented during follow-up: survival status, last visit, evidence of disease with the presence of local recurrence, lymph-node metastases and/or distant metastases (including location), time from surgery to recurrence, date of death and reason of death.

Survival Outcome Parameters

The disease status during follow-up was determined by means of standard imaging with computer tomography, alternatively with magnetic resonance imaging or ultrasound and chest x-ray in selected cases. Overall survival (OS) was defined as the time from the surgery to death. CSS was defined as the time from surgery to cancer-related death. Time to recurrence was defined as time from surgery to disease recurrence (determined by imaging).

Pathological Analysis

Histopathological classification was performed according to the 2004 WHO classification of renal cell tumors.[22,23] Grading was applied using the Fuhrman nuclear grade. Grading was not re-assessed using the updated ISUP/WHO2016 nuclear grading system because patients were treated according to the former grading system.[24] For staging the sixth and seventh edition of the TNM classification was used.[25,26]

Statistical Analysis

The statistical analysis was performed using the software *R* for statistical computing.[27] Descriptive statistics were presented as numbers and percentages or ranges. Survival analysis was computed using time-to-event data. Patients still at risk at the end of follow-up or patients lost to follow-up were censored. Kaplan-Meier survival estimates were plotted for OS and CSS, as well as for OS and CSS stratified by T-stage (T1/T2 vs. T3). Hazard ratios (HR) were calculated including 95% confidence interval (CI) according cox proportional hazards regression method. Hypothesis testing with a 2-sided alternative hypothesis was used to compare survival times of the stratified groups according to the log-rank method. A P-value $<.05$ was considered statistically significant.

Results

A total of 110 patients were identified. Eight patients were excluded due to lymph node metastases ($n = 2$) or organ metastases ($n = 6$) found on preoperative tumor staging. For the final analysis, 102 patients were available. Median age was 65 years with a range of 31 to 86 years. The distribution ratio between the 2 centers was 2:1. Baseline characteristics are displayed in Table 1A.

Intraoperative characteristics are shown in Table 1B. Patients underwent successful RRN in all except 1 case (1.0%), where conversion to open surgery was necessary due to adhesions and severe collateral circulation due to cirrhosis of the liver.

Postoperative characteristics are displayed in Table 1C. Median duration of hospitalization was 6 days (range 3-17). Seven patients (6.9%) had postoperative complications with Clavien-Dindo classification ≤ grade IIIb. Included were 3 hematomas of the abdominal wall (2.9%) of which 1 required surgical treatment. Other postoperative complications included retroperitoneal hematoma with need for operative revision ($n = 1$), gastric ulcer with gastroscopic intervention ($n = 1$), and cardiac decompensation with pulmonary edema ($n = 1$). Further, postoperative blood transfusion was necessary in 1 patient. All these complications were treated accordingly and resolved without sequelae.

Pathological findings are presented in Table 2. Median diameter of the resected tumor was 4.3 cm (range 0.8-12 cm). Eighty-two, 3, and 17 patients had pT1, pT2, and pT3 tumors (80.4%, 2.9%, and 16.7%), respectively. Histology revealed clear cell RCC in 62 patients (60.8 %), papillary RCC in 25 patients (24.5 %), chromophobe RCC in 5 patients (4.9 %), and other subtypes of RCCs in 10 patients (9.8%). Positive surgical margin were not found in any of the patients.

Median follow-up for OS was 74 months (range 0-190 m), in which seven patients (6.9%) presented with disease recurrence: All seven (6.9%) with organ metastasis and 4 (3.6 %) patients with additional local recurrence at the same time. Three out of 4 patients with local recurrence had clear cell and 1 had papillary type 2 histology. Five out of 7 patients (71.4%) with systemic recurrence were initial T3 tumors. Four out of 7 patients (57.1%) with systemic recurrence were clear cell RCC and the remaining either sarcomatoid, papillary type 2 or of unclassified histology. Only 2 patients (28.6%) with T1 disease were diagnosed with systemic dissemination (1 clear cell RCC and 1 papillary RCC type 2).

In total, 29 patients (28.4 %) died during the follow-up after a median of 41 months (1-143 m) after surgery. Death was cancer-specific in 6 cases (5.9 %) and occurred after a median of 27 months (2-51 m). Five- and 10-year OS rates were 76.6 % and 69.8 % (Figure 1A). Figure 1B illustrates the survival outcome of patients stratified according to their T-stage (pT1/2 vs. pT3). For pT2 disease OS survival rates were 84.0% at 5 years and 75.7% at 10 years, for pT3 41.2% at 5 years and 41.2% at 10 years. OS was significantly different in T3 tumors compared to T1/T2 tumors regarding overall death (HR = 4.17, 95% CI: 1.97 to 8.86, $P<$ .001). Five- and 10-year CSS rates for all patients were 93.3% and

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Figure 1 (A, B) Kaplan-Meier estimate for overall survival (A). Kaplan-Meier estimate for overall survival stratified by T-stage (B). Abbreviations: HR = hazard ratio; RRN = retroperitoneoscopic radical nephrectomy.

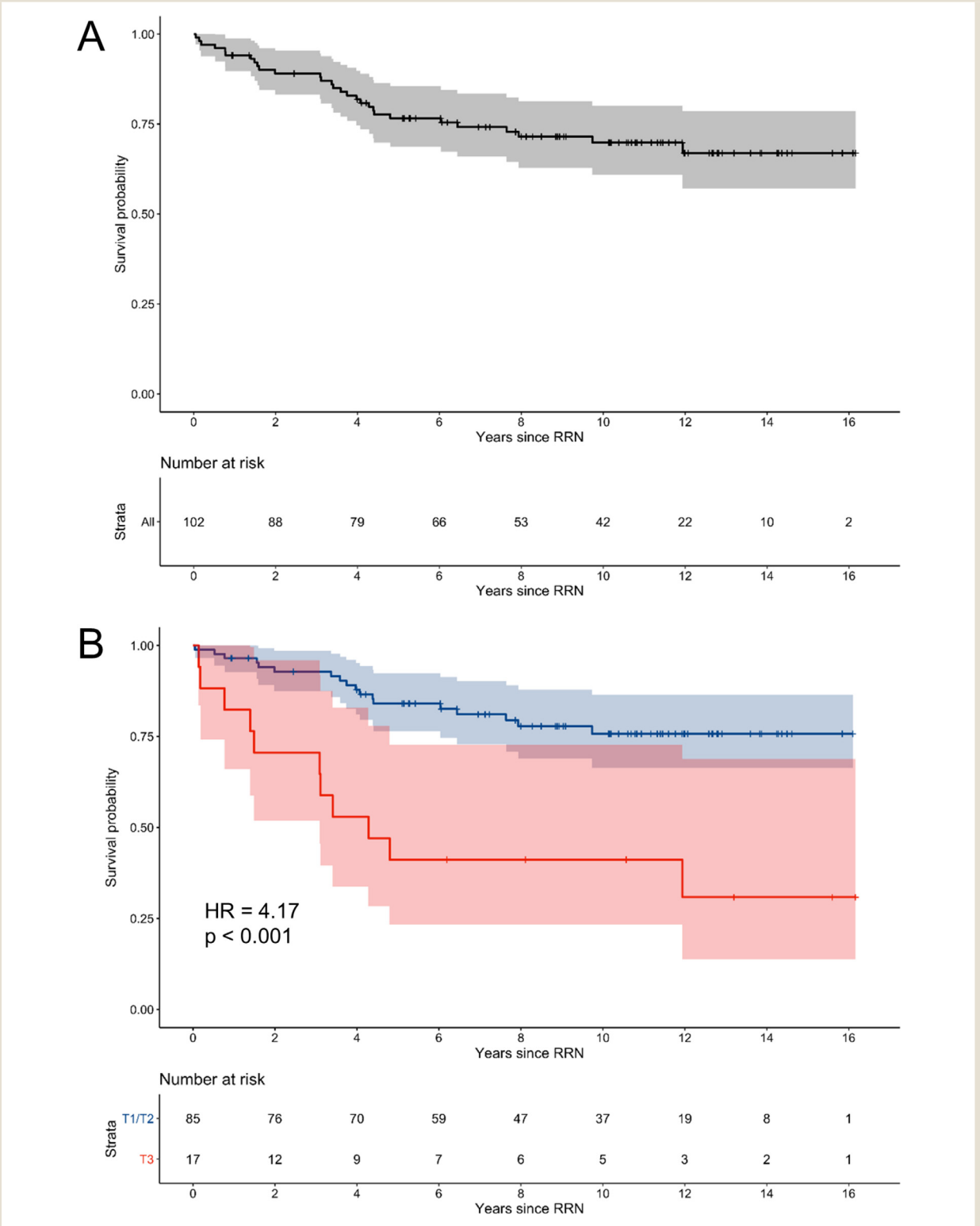

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Table 1 (A) Baseline Characteristics of Cohort (n = 102); (B) Intraoperative Characteristics; (C) Postoperative Characteristics During Follow-up

A)		
Number of patients (n)	Zurich	70 (68.6%)
	Basel	32 (31.4%)
Age (median)	Years (range)	65 (31-86)
Sex (n)	Female	36 (35.3%)
	Male	66 (64.7%)
BMI (median)	kg/m^2 (range)	25 (18-35)
ASA score (n)	1	18 (17.6%)
	2	47 (46.1%)
	3	32 (31.4%)
	4	3 (2.9%)
Previous operation (n)	No	57 (55.9%)
	Retroperitoneal	1 (1.0%)
	Abdominal	42 (41.1%)
	Retroperitoneal and abdominal	2 (2.0%)
B)		
Operation side (n)	Right	45 (44.1%)
	Left	57 (55.9%)
Operative time (median)	Minutes (range)	155 (50-360)
Estimated blood loss (median)	mL (range)	200 (40-1500)
Trocar sites used (n)	3	57 (55.9%)
	4	26 (25.5%)
	5	2 (2.0%)
	Unknown	17 (16.6%)
Surgeon (n)	Head of department	40 (39.2%)
	Senior attending	15 (14.7%)
	Junior attending	47 (46.1%)
Conversion (n)	No	101 (99.0%)
	Yes	1 (1.0%)
Intraoperative complication (n)	No	100 (98.0%)
	Yes	2 (2.0%)
C)		
Postoperative hospital stay (median)	Days (range)	6 (3-17)
Postoperative complications (n)	No	95 (93.1%)
	Yes	7 (6.9%)
Local failure (n)	No	98 (96.1%)
	Yes	4 (3.9%)
Metastasis (n)	No	95 (93.1%)
	Yes	7 (6.9%)
Death (n)	No	73 (71.6%)
	Yes	29 (28.4%)

93.3% (Figure 2A). Similar results were found regarding CSS rate after stratification of T-stage: the groups of pT1/2 with 98.7% CSS at 5 years and 98.7% CSS at 10 years vs. pT3 with 65.5% CSS at 5 years and 65.5% CSS at 10 years. CSS was significantly different in T3 tumors compared to T1/T2 tumors regarding cancer-specific death (HR = 31.4, 95% CI: 3.66 to 269.6, P= .0017) (Figure 2B).

Discussion

To the best of our knowledge, we present the longest oncological follow-up with up to 190 months (median 74 months) in a patient cohort undergoing RRN for localized T1-3 stage RCC. The demonstrated long-term oncological efficacy is excellent. RRN is a safe surgical procedure with a low intra- and postoperative complication rate. Overall disease recurrence (local failure or metastasis) was diagnosed in less than 7% of patients (predominantly T3 tumors

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Figure 2 (A, B) Kaplan-Meier estimate for cancer-specific survival (A). Kaplan-Meier estimate for cancer-specific survival stratified by T-stage (B). Abbreviations: HR = hazard ratio; RRN = retroperitoneoscopic radical nephrectomy.

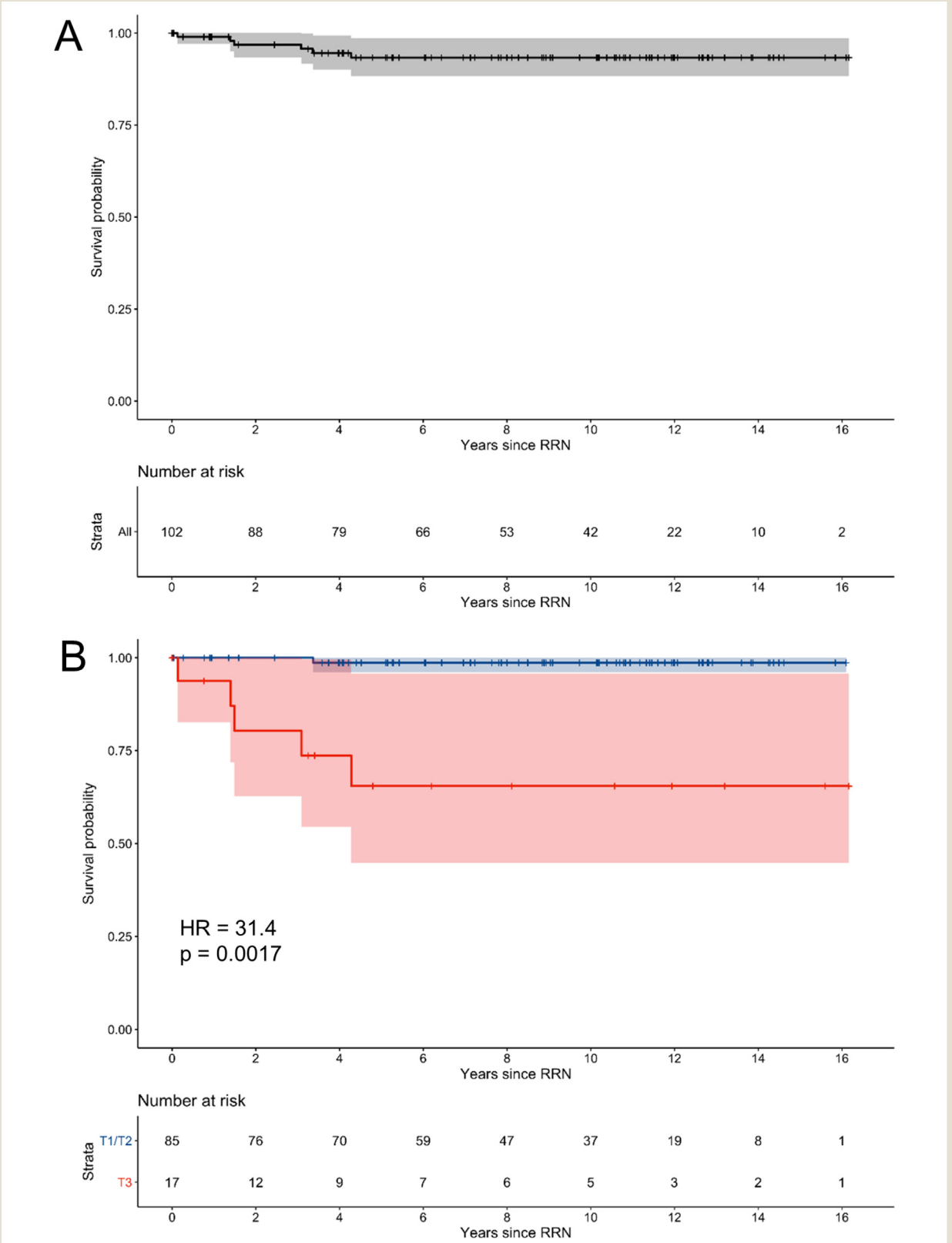

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Table 2 Pathological Findings

Tumor size (median)	cm (range)	4.3 (0.8-12)
Margin status (%)	R0	102 (100.0%)
	R1	0 (0.0%)
T-stage (%)	T1	7 (6.9%)
	T1a	34 (33.3%)
	T1b	41 (40.2%)
	T2	3 (2.9%)
	T3	1 (1.0%)
	T3a	14 (13.7%)
	T3b	2 (2.0%)
Nodal status (%)	N0	102 (100.0%)
cN and pN	N1-2	0 (0.0%)
Metastasis (%)	M0	102 (100.0%)
cM	M1	0 (0.0%)
Fuhrman grading (%)[a]	1	15 (15.8%)
	2	57 (60.0%)
	3	20 (21.1%)
	4	3 (3.1%)
Histopathology (%)	Clear cell	62 (60.8%)
	Papillary type 1	13 (12.7%)
	Papillary type 2	12 (11.8%)
	Chromophobe	5 (4.9%)
	Other	10 (9.8%)

Abbreviation: MTSC = mucinous tubular spindle-cell carcinoma.
[a] Only 95 cases included; excluded from Fuhrman grading are chromophobe and MTSC carcinoma.

[71%]). Cancer-specific death occurred in only 6% of all patients after a median follow-up of 27 months. CSS was excellent with 93% after 10 years of follow-up. As expected, cancer-specific death was significantly higher in patients with T3 tumors compared to T1/2 tumors.

The oncological long-term outcomes in our RRN cohort of 102 patients with an OS of 76.6 % after 5 years and 69.8 % after 10 years and CSS 93.3% after 5 years and 10 years are comparable to the results in the published literature of other surgical approaches, such as LRN or ORN.[28-30] The longest published follow-up (median 73 months) by Permpongkosol et al for LRN in 67 patients with T1-3 stage RCC showed a slightly higher OS with 85% after 5 years and 76% after 10 years, whereas CSS was 97% after 5 and 10 years.[28] ORN in 54 patients with T1-2 stage RCC revealed an OS of 72% after 5 years and 58% after 10 years, whereas CSS was 89% after 5 years and 86% after 10 years.[28] Portis et al presented similar numbers of only T1-2 stage RCC in 64 patients with LRN (OS 81%, CSS 98%) as well as 69 patients with ORN (OS 89%, CSS 92%) after 5 years follow-up (median follow-up of 54 and 69 months, respectively).[29] Colombo et al revealed, in comparison to our study, almost identical numbers after 5 and 7 years of follow-up in 63 patients with T1-4 stage RCC undergoing LRN (OS 78% and 72%, CSS 91% and 91%) and 53 patients with T1-3 stage RCC undergoing ORN (OS 84% and 84%, CSS 93% and 93%).[30] Median follow-up was 65 months for LRN and 76 months for ORN.[30]

The available data regarding oncological outcome following RRN is limited. Compared to our follow-up of up to 190 months, most other studies present a rather short oncological follow-up. One randomized controlled trial by Nambirajan et al presented short-term results of 40 patients with T1-3 stage RCC randomized to either RRN or LRN.[14] They reported no local recurrence or distant metastasis in the RRN group after a median follow-up of 15 months.[14] Makhoul et al investigated a cohort of 39 patients undergoing RRN for T1 stage RCC and reported no tumor recurrence (local and systemic) after short-term median follow-up of 20 months.[31] Intermediate oncological results were presented by Larré et al in a cohort of 146 patients with T1-T3 stage RCC undergoing RRN with a mean follow-up of 35 months: OS at 5 and 10 years was 91% and 63%, whereas CSS was 96% and 92%, respectively.[32] Ha et al published a multi-institutional study with also mid-term oncological follow-up results (median 36 months) of 106 patients with T1-2 stage RCC treated by RRN, where 5-year OS was 95 % (no CSS reported) with no local but two distant tumor recurrences.[33] Tobias-Machado and colleagues prospectively compared RRN to hand-assisted LRN in patients with renal tumors <12cm): RRN was performed in 25 patients with T1-3 stage RCC and mean follow-up of 48 months, where no deaths but one local recurrence was documented during the oncological follow-up period.[34] Hemal et al published similar results in a cohort of only T2 stage RCC of 41 patients with LRN (mixed group of 15 RRN and 26 transperitoneal approaches) after a follow up of 54 months: 5-year OS was 88% and CSS 95% in the whole group.[9] A retrospective study from China revealed the 5-year survival data of patients operated with RRN ($n = 84$) for T2-3 stage RCC after a mid-term median follow-up of 57 months: OS in the RRN group was 86% and CSS 95%.[35] The longest follow-up with median of 134 months was reported by Berger *et al.* in a combined cohort of either RRN or LRN, where 69 patients with T1-4 stage RCC showed an OS of 65% and 39% as well as CSS of 92% and 78% after 10 and 12 years, respectively.[36]

The postoperative complication rate in our cohort was low with only 7 patients (6.9%) having ≤ grade IIIb complications according to Clavien-Dindo classification. These results are well comparable to the published literature and the complications did not compromise oncological outcome. Perioperative outcome and complications are well investigated and do not relevantly differ between minimally invasive surgical techniques (RRN vs. LRN).[5,33] However, ORN is known to lead to higher blood loss, more pain, longer hospital stays and higher morbidity.[9] Nambirajan et al revealed no significant differences regarding intra- and postoperative complications between 2 groups of patients prospectively randomized to either RRN or LRN for T1-3 stage RCC.[14] Desai et al reported on 102 patients with RCC ≤15cm randomized to either RRN or LRN with equal intra- and postoperative complications, blood loss, hospital stay, and amount of pain.[13] Dillenburg and colleagues compared a matched cohort of 23 RRN vs. 25 ORN procedures with large renal tumors (>7 cm), where transfusion rate, complications and hospital stay were in favor of RRN.[37] Zhu et al reported almost identical results of 152 patients with T2-3 stage RCC undergoing either RRN or ORN: perioperative outcome parameters were all in favor of RRN.[35] Goel et al reported the short-term outcome of 27 RRN

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vs. 11 ORN patients and found lower postoperative morbidity and faster recovery in the RRN group.[38]

Our study has limitations. As in every retrospective analysis, selection bias is a well-known issue that may induce confounding factors and possibly affect the interpretation of the results. Further, no comparison group as standard treatment was used in the underlying study. Results can only be compared to what we know from the literature. Strict randomization to treatment groups (ORN, LRN, or RRN) would hardly be feasible and simple retrospective comparison of the different treatment approaches would harbor the risk of introducing a relevant selection bias.

Importantly, there is a potential that T3 tumors in RRN cohorts are less advanced compared to LRN or ORN procedures due to the limited retroperitoneal space. This could therefore beneficially influence the long-term OS and CSS of isolated T3 tumors in our cohort.

In addition, we lack information regarding the complexity of the cases and had a high proportion of T1 tumors in our cohort. Nowadays, the majority of the included T1 tumors would eventually be treated with NSS instead. Since the early 2000s, minimally invasive NSS evolved mainly in favor of robotic assisted procedures. This also applies for our center. However, in selected cases T1 tumors still require RN (eg, unfavorable tumor location) and particularly patients with previous abdominal operations benefit from the retroperitoneal minimal-invasive surgery. Therefore, our data adds important evidence to the existing literature.

Excluded from our interpretation are the aspects of renal insufficiency and cardiovascular events, which happen to become predictors of OS in patients with RN when compared to cohorts treated with NSS.[39,40] However, the difference between CSS and OS partly puts this into perspective.

Conclusion

Our analysis revealed that RRN in patients with clinically localized RCC $\leq$ 12 cm results in excellent oncological long-term outcome. Overall CSS and OS rates after RRN are comparable to survival rates regarding ORN or LRN known from the literature. Thus, particularly in patients who benefit from a retroperitoneal approach, RRN is an oncologically safe minimally invasive alternative.

Clinical Practice Points

• Although nephron-sparing surgery has been established as the standard of care for localized renal cell carcinoma, radical nephrectomy still plays a role in selected patients—especially in conditions where nephron-sparing surgery is neither indicated, nor feasible. • In specific cases, retroperitoneoscopic radical nephrectomy may offer several advantages over conventional open and transperitoneal laparoscopic procedures. However, there is limited evidence available regarding the long-term survival of patients undergoing radical nephrectomy with a retroperitoneoscopic approach. • To the best of our knowledge, we present the so far longest follow-up in a consecutive series of patients undergoing retroperitoneoscopic radical nephrectomy due to renal cell carcinoma. • Our study demonstrates an excellent long-term oncological efficacy and validates earlier results from comparable data with a shorter follow-up period. • Specific patients may particularly benefit from the retroperitoneal approach, for which retroperitoneoscopic radical nephrectomy is still an important and oncologically safe minimally invasive alternative in form of a definite treatment solution for localized renal cell carcinoma.

CRediT authorship contribution statement

Florian A Schmid: Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Kathrin Bausch:** Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing. **Marian S Wettstein:** Methodology, Validation, Formal analysis. **Antje Feicke:** Conceptualization, Methodology, Investigation. **Boris Weltzien:** Conceptualization, Methodology, Investigation. **Daniel M Schmid:** Investigation, Resources, Supervision. **Räto T Strebel:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Cedric Poyet:** Methodology, Validation, Formal analysis, Investigation, Writing – review & editing. **Niels J Rupp:** Validation, Investigation, Resources, Data curation. **Tullio Sulser:** Investigation, Resources, Supervision. **Hans Helge Seifert:** Conceptualization, Investigation, Resources, Data curation, Writing – review & editing, Project administration. **Thomas Hermanns:** Conceptualization, Methodology, Resources, Data curation, Writing – review & editing, Supervision, Project administration.

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Please cite this article as: Florian A Schmid et al, Long-Term Oncological Efficacy of Retroperitoneoscopic Radical Nephrectomy of Localized Renal Cell Cancer pT1-3 (≤12 cm), Clinical Genitourinary Cancer, https://doi.org/10.1016/j.clgc.2022.04.016