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Laparoscopic cytoreductive nephrectomy is associated with significantly improved survival compared with open cytoreductive nephrectomy or targeted therapy alone

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Abstract. The aim of the present study was to compare the survival outcomes for patients with metastatic renal cell carcinoma (mRCC) who underwent laparoscopic cytoreductive nephrectomy (CN) vs. open CN vs. targeted therapy (TT) alone at our institution. A retrospective chart review was performed at our institution for patients who underwent CN prior to TT (laparoscopic, n=48; open, n=48) or who were deemed unfit for surgery and received TT alone (n=36), between January 2007 and December 2012. Kaplan-Meier estimated survival and Cox proportional hazards analyses were performed. Laparoscopic CN was associated with significantly longer survival compared with open CN or TT alone (median survival 24 vs. <12 months, respectively; $P<0.01$). On multivariate analysis, laparoscopic CN was an independent predictor of survival [hazard ratio (HR)=0.48, $P<0.01$], controlling for preoperative risk factors, while survival was similar between open CN and TT alone (HR=0.85, $P=0.54$). In our experience, laparoscopic CN appears to be a significant predictor of survival in mRCC. Selection bias of the surgeon for patients with improved survival may account for clinical variables that were otherwise difficult to quantify. For patients who were not candidates for laparoscopic CN, open CN did not confer a survival benefit over TT alone, while it was associated with increased morbidity.

Introduction

The role of cytoreductive nephrectomy (CN) in patients with metastatic renal cell carcinoma (mRCC) was initially defined during the era of open surgery and first-generation immunotherapy (e.g., interleukin-2 and interferon α) (1-3). For some patients with mRCC a survival benefit from CN was not achieved, while there was increased morbidity as a result of surgery; therefore, risk factors for prognosis were defined in order to aid in surgical candidate selection (4,5). Since then, the landscape of systemic therapy for mRCC has changed drastically with targeted therapy, such as tyrosine kinase inhibitors and mammalian target of rapamycin (mTOR) inhibitors, as the mainstays of treatment (6,7). The benefit of CN in the era of targeted therapy (TT) was subsequently defined (8), and noted to be most pronounced for selected patients (9-11).

In parallel with the advances in systemic therapy for mRCC, the paradigm for CN has shifted from an open to a laparoscopic approach (12). The oncological safety of laparoscopic CN was established during the first-generation immunotherapy era, and has expanded into the TT era (13-15). The reduced convalescence associated with laparoscopic surgery is particularly important for patients with mRCC, as this may reduce their time to systemic therapy initiation. However, the interplay between laparoscopic CN and patient survival has not been studied in the TT era.

The aim of the present study was to compare the survival outcomes of laparoscopic CN, open CN and TT alone (for patients who were deemed unfit for surgery) at our institution during the TT era.

Patients and methods

Patient information. After obtaining Institutional Review Board approval, all mRCC patients who received systemic TT between January 2007 and December 2012 at our institution (n=132) were retrospectively reviewed. TT patients were defined as those who received tyrosine kinase inhibitors, mTOR inhibitors and vascular endothelial growth factor inhibitors. We identified a total of 96 patients who received

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Abbreviations: mRCC, metastatic renal cell carcinoma; CN, cytoreductive nephrectomy; TT, targeted therapy; ACE, adult comorbidity evaluation; OS, overall survival

Key words: metastatic renal cell carcinoma, laparoscopic cytoreductive nephrectomy, open cytoreductive nephrectomy, targeted therapy alone

CN prior to TT, and 36 patients who received TT alone, as they were deemed unfit for CN. Laparoscopic CN was performed in 50% (48/96) of the patients, with the remainder receiving open CN. The histological subtypes for the CN patients included 71% clear cell, 17% sarcomatoid, 7% papillary type II and 5% other types. Subtype classification for the patients receiving TT alone could not be determined, as the patients were diagnosed clinically or on biopsy of their metastatic site, which presented pathological limitations.

Patient clinical variables were collected, including age, adult comorbidity evaluation score (16) and Karnofsky performance status score. The preoperative risk stratification variables for CN described by Culp *et al* and validated by our institutional experience were also collected (10,11). These variables included: i) Serum albumin below laboratory normal, ii) clinical T3 or T4 disease, iii) presence of liver metastasis, iv) symptomatic metastasis, v) retroperitoneal lymphadenopathy and vi) supradiaphragmatic lymphadenopathy. Survival data were gathered using available medical records and the Social Security death index, with final query on August 31, 2017.

Statistical analysis. Kaplan-Meier-estimated overall survival (OS) was compared among laparoscopic CN, open CN and TT alone. The OS end-point was reached by 100% (36/36) of patients in the TT cohort, 98% (47/48) of patients in the open CN cohort, and 96% (46/48) of patients in the laparoscopic CN cohort. Multivariate Cox proportional hazards analysis was also performed adjusting for age, Karnofsky performance status score and preoperative risk stratification variables. To calculate statistical significance, the χ^2 test was used for categorical variables and the Student's t-test was used for continuous variables, with $P < 0.05$ considered to indicate statistically significant differences. All statistical analyses were completed using R software, version 3.2.2.

Results

Patient characteristics. Patient baseline clinical and tumor characteristics are provided in Table I. The open CN, laparoscopic CN and TT alone groups differed significantly in the proportion of patients with Karnofsky performance status score $\leq 60\%$, mean number of preoperative risk stratification variables, proportion of patients with serum albumin ≤ 3.5 g/dl, clinical stage $>T3$, symptomatic metastasis and supradiaphragmatic lymphadenopathy ($P < 0.01$ in all cases).

The survival of patients undergoing laparoscopic CN is superior to that of the other two cohorts. Kaplan-Meier-estimated survival curves are provided in Fig. 1. The median OS was 23.9 months in the laparoscopic CN group (2 patients censored), 10.8 months in the open CN group (1 patient censored), and 10.7 months in the TT alone group ($P < 0.01$). Multivariate Cox proportional hazards analysis identified laparoscopic CN as an independent predictor of survival (hazard ratio=0.48, 95% confidence interval: 0.31-0.74, $P < 0.01$), controlling for age, Karnofsky performance status score and the number of preoperative risk stratification variables.

Median survival was examined with subsets of the open CN and laparoscopic CN cohorts, which are provided in Table II.

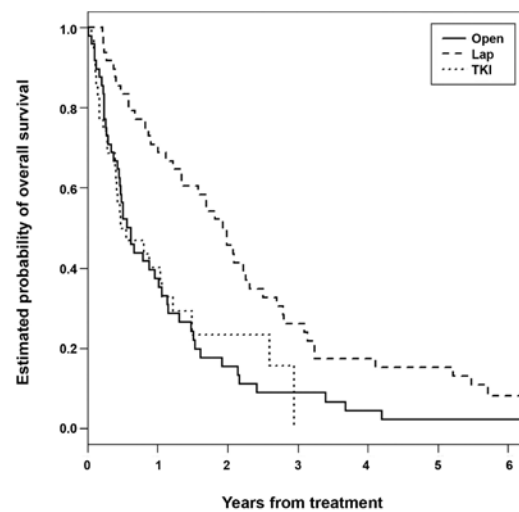


Figure 1. Kaplan-Meier estimated overall survival for open CN, laparoscopic CN, and targeted therapy alone. CN, cytoreductive nephrectomy; TKI, tyrosine kinase inhibitor.

When excluding patients with Karnofsky performance status score $\leq 60\%$, the median survival remained significantly greater for the laparoscopic CN group (27 vs. 11 months, respectively; $P < 0.01$). When additionally excluding patients with ≥ 3 preoperative risk stratification variables, the median survival remained significantly greater for the laparoscopic CN group (28 vs. 11 months, respectively; $P < 0.01$). When additionally excluding patients with clinical stage T3 or T4 disease, the median survival remained significantly greater for the laparoscopic CN group (29 vs. 12 months, respectively; $P < 0.01$).

Discussion

In the present study, laparoscopic CN was found to be associated with a significant increase in OS compared to open CN and TT alone, independent of patient and tumor characteristics. To the best of our knowledge, this is the first direct examination of the CN approach and its impact on survival. It was demonstrated that the difference in median survival between laparoscopic and open CN was ~ 12 months, while open CN and TT alone exhibited similar survival. Furthermore, this survival benefit in favor of laparoscopic over open CN persisted in multivariate and subset analyses.

The initial studies of laparoscopic CN focused on its non-inferiority compared with conventional open CN, with limited numbers of patients and limited oncological follow-up (13-15). The studies by Rabets *et al* and Eisenberg *et al* included substantially fewer patients compared with the present study ($n=64$, $n=27$ and $n=132$, respectively), and only included 1-year estimated survival (14,15). Furthermore, these studies were performed in the era of first-generation immunotherapy (e.g., interleukin-2 and interferon α), which makes their study findings difficult to compare to those of the present study and contemporary practice for mRCC. Additionally, the use of laparoscopic nephrectomy and, thus, laparoscopic CN, has markedly increased since then (12). Zlatev *et al* reported a decrease in open CN from 77 to 66% between 2003 and 2015, within the Premier Hospital Database. Associated with this increase in utilization, they also found that laparoscopic CN significantly reduced the

Table I. Patient baseline clinical and tumor characteristics.

Variables	Open CN, n=48	Laparoscopic CN, n=48	TT alone, n=36	P-value
Mean age (SD), years	56.4 (9.2)	58.8 (12.0)	57.8 (10.4)	0.54
Mean ACE score (SD)	1.2 (0.8)	1.0 (1.0)	1.3 (1.0)	0.32
Karnofsky performance status score <60, n (%)	3/48 (6.3)	7/48 (14.6)	12/36 (33)	<0.01
Mean preoperative risk stratification variables (SD)	2.6 (1.1)	2.0 (1.3)	3.1 (1.1)	<0.01
Albumin <3.5 g/dL, n (%)	17/48 (35)	10/48 (21)	20/36 (56)	<0.01
Clinical stage >T3, n (%)	32/48 (67)	17/48 (35)	14/36 (39)	<0.01
Liver metastasis, n (%)	10/48 (21)	9/48 (19)	11/36 (31)	0.41
Symptomatic metastasis, n (%)	20/48 (42)	29/48 (60)	27/36 (75)	<0.01
Retroperitoneal LN, n (%)	22/48 (46)	15/48 (31)	20/36 (56)	0.08
Supradiaphragmatic LN, n (%)	20/48 (42)	13/48 (27)	22/36 (61)	<0.01

CN, cytoreductive nephrectomy; TT, targeted therapy; SD, standard deviation; ACE, adult comorbidity evaluation; LN, lymphadenopathy.

Table II. Median survival for subsets of patients receiving open and laparoscopic CN.

Patient subsets	Median survival		P-value
	Open CN, n (months)	Laparoscopic CN, n (months)	
Entire cohort	48 (10.8)	48 (23.9)	<0.01
Karnofsky <60% excluded	45 (11.1)	41 (26.9)	<0.01
>3 risk factors excluded	22 (11.4)	29 (28.3)	<0.01
Clinical stage >T3 excluded	11 (12.1)	24 (28.9)	<0.01

CN, cytoreductive nephrectomy.

rate of blood transfusion [odds ratio (OR)=0.46] and length of hospital stay (OR=0.50) (17). Similarly, Gershman *et al* found that laparoscopic CN significantly reduced the length of hospital stay (OR=0.12) and, more importantly, significantly reduced the time to initiation of TT (OR=5.1), when compared to open CN in their institutional experience (n=294) (18).

Although a number of studies have focused on the perioperative outcomes following laparoscopic CN, comparatively few studies have been published on the OS of patients receiving laparoscopic CN in the TT era. Nunez Bragayrac *et al* reported the survival of a contemporary (2001-2013) pooled cohort of mRCC patients (n=120) receiving laparoscopic CN at three high-volume cancer centers. The median survival was reported as 25.7 months, with a 3-year survival rate of 35% (19). A similar survival rate was found our laparoscopic CN cohort, with a median survival of 23.9 months and a 3-year survival rate of 26%. However, with no comparator arm, the study by Nunez Bragayrac *et al* did not demonstrate the comparative survival benefit of laparoscopic CN over open CN or TT alone.

To the best of our knowledge, the present study is the first to directly compare OS following laparoscopic CN, open CN and TT alone in the TT era. Although previous studies have demonstrated the survival benefit of CN over TT alone (8-11,20,21), many have argued that the survival benefit is a result of surgeon selection bias (22,23). Given the retrospective nature of these

studies (including our own), surgeon selection bias cannot be eliminated, and likely contributes to the survival differences seen in patients who receive CN. An example of surgeon selection bias impacting retrospective studies of survival was published by Shuch *et al*, who demonstrated that the OS in patients receiving partial nephrectomy in the Medicare population was improved over non-cancer controls (24).

Although some patients may not tolerate the insufflation associated with laparoscopic surgery and some tumors (i.e., higher clinical T stage) were not amenable to a laparoscopic approach, we observed that laparoscopic CN was associated with improved survival independent of these factors from a statistical standpoint (multivariate model), as well as in a subset analysis. However, as a retrospective study, confounding variables associated with surgical selection bias could not be eliminated. Furthermore, the survival benefit observed with laparoscopic CN was likely a result of unaccounted for variables, or the value of surgeon cognitive bias in clinical decision-making. Despite our single-institution study being adequately powered to detect statistically significant differences between treatment groups, and being significantly larger than previously published studies on the same subject, the overall size of the study (n=132) remains limited. Of note, by including patients between 2007 and 2012, nearly all patients in the study (129/132=98%) had reached their survival end-points.

In conclusion, it was herein demonstrated that laparoscopic CN was an independent and significant predictor of survival in mRCC when compared to open CN or TT alone. In our experience, for patients who were not candidates for laparoscopic CN, open CN did not confer a survival benefit over TT alone.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

All authors made substantial contributions to this article. KZ, EHK, JJH, SBB, RSF contributed to the conception and design of the study. Data collection was performed by JMV and RV. Data analysis was performed by KZ and EHK. The manuscript was drafted by KZ and EHK. All authors have revised and corrected the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was performed with Institutional Review Board approval.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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