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Brief Correspondence

The Learning Curve for Radical Nephrectomy for Kidney Cancer: Implications for Surgical Training

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Abstract

Although radical nephrectomy (RN) is the most common treatment for kidney cancer, no data on the learning curve for RN are available. In this study we investigated the effect of surgical experience (EXP) on RN outcomes using data for 1184 patients treated with RN for a cT1–3a cN0 cM0 renal mass. EXP was defined as the total number of RNs performed by each surgeon before the patient's operation. The primary study outcomes were all-cause mortality, clinical progression, Clavien-Dindo grade $\geq$2 postoperative complications (CD $\geq$2), and the estimated glomerular filtration rate (eGFR). Secondary outcomes were operative time, estimated blood loss, and length of stay. Multivariable analyses adjusted for case mix revealed no evidence of association between EXP and all-cause mortality (p = 0.7), clinical progression (p = 0.2), CD $\geq$2 (p = 0.6), or 12-mo eGFR (p = 0.9). Conversely, EXP was associated with shorter operative time (estimate −0.9; p < 0.01). Mortality, cancer control, morbidity, and renal function might not be affected by EXP. The very large cohort examined and the extensive follow-up support the validity of these negative findings.

Patient summary: For patients with kidney cancer undergoing surgical removal of a kidney, those treated by novice surgeons have similar clinical outcomes to those treated by experienced surgeons. Thus, this procedure represents a convenient scenario for surgical training if longer operating theatre time can be planned.

Renal cell carcinoma (RCC) is one of the most common solid malignancies and more than 50% of RCC cases are diagnosed with localized disease [1]. In this context, surgery is the cornerstone of management [2].

Although the relationship between patient outcomes and surgical factors such as skill and experience (EXP) has been extensively investigated for nephron-sparing surgery [3,4], there is no description of the surgical learning curve for radical nephrectomy (RN); this gap is highly relevant, as RN is the most frequent treatment modality for clinically localised RCC [5].

It has been suggested that learning curve studies drive interventions to prevent suboptimal outcomes during a surgeon's learning phase, such as referral strategies and

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structured training programs [6–8]. Therefore, we hypothesised that increasing EXP is associated with better outcomes after RN.

To test this hypothesis, clinical data for 1184 patients diagnosed with a cT1–3a cN0 cM0 renal mass treated with RN between 1987 and 2018 at a single institution were collected (Supplementary Fig. 1) after institutional ethics board approval (protocol RENE 29/08/2007).

For each individual patient, the variable of interest, namely EXP, was defined as the total number of RNs performed by each surgeon before that patient's operation [4,9,10]. Owing to the importance of EXP in our analysis, we excluded cases treated by surgeons who performed fewer than 30 RNs during their entire careers. Given the hypothesis that EXP might impact mortality, cancer control, morbidity, and renal function after surgery, the primary outcomes of the study were all-cause mortality (ACM), defined as death from any cause during follow-up, clinical progression (CP), defined as either local recurrence or systemic progression during follow-up, any Clavien-Dindo (CD) grade ≥2 complication [11], and the 12-mo estimated glomerular filtration rate (eGFR). Secondary outcomes of the study were operative time (OT), estimated blood loss (EBL), and length of stay (LOS).

Statistical analyses and reporting and interpretation of the results were conducted according to established guidelines [12,13]. Multivariable regression models were used to evaluate the effect of EXP on ACM and CP (Cox), CD ≥2 (logistic), and eGFR, OT, EBL, and LOS (linear). CP was investigated in the subgroup of confirmed RCC cases only. Covariates consisted of age at diagnosis, Charlson comorbidity index, preoperative eGFR, pathological tumour size, tumour grade (grade 1–2 vs grade G–4 vs grade x), pathological T stage (pT1–2 vs pT3–4 vs pTx), pathological N stage (pN0 vs pN1 vs pNx), surgical approach (open vs minimally invasive surgery), and year of surgery. Since the relationship between EXP and each outcome of interest might be nonlinear as result of a learning process, EXP was modelled using restricted cubic splines. In cases of a significant relationship between EXP and an outcome, model-derived coefficients and the local polynomial smoothing method were used to depict actual curves. Sensitivity analyses according to age at surgery or clinical tumour stage were performed. Statistical analysis was performed using the RStudio graphical interface v.0.98 for R software environment v.3.0.2 (http://www.r-project.org) and tests were two-sided, with the significance level set at $p < 0.05$.

The median EXP was 60 procedures (Supplementary Table 1). After median follow-up of 81 mo, 5-yr rates of ACM and CP were 13% and 12%, respectively. The rate of CD≥2 was 14%. The median 12-mo eGFR was 56 ml/min/1.73 m^2. Multivariable analyses adjusted for case mix (Table 1 and Supplementary Table 2) revealed that the associations between EXP and ACM ($p = 0.7$), CP ($p = 0.2$), CD ≥2 complications ($p = 0.6$), 12-mo eGFR ($p = 0.9$), EBL ($p = 0.4$), and LOS ($p = 0.7$) were not statistically significant. Conversely, EXP was associated with shorter OT ($p < 0.01$; Fig. 1). Sensitivity analyses according to patient age, clinical stage, and year of surgery confirmed these findings (all $p > 0.05$ on interaction tests).

The study hypothesis was that patients diagnosed with kidney cancer who opt for RN have better clinical outcomes if treated by experienced surgeons, in line with the concept that surgical results are highly dependent on human factors such as individual skills and previous background. The analysis of a very large population of RCC patients treated with RN did not provide any evidence of a relationship between

Table 1 – Multivariable models predicting all-cause mortality, clinical progression, Clavien-Dindo grade ≥2 complications, and 12-mo eGFR after radical nephrectomy among 1184 patients diagnosed with a cT1–3a cN0 cM0 renal mass

Predictor	Cox regression analysis				Logistic regression analysis			
	All-cause mortality		Clinical progression [a]		CD grade≥ complications		12-mo eGFR	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	OR (95% CI)	*p* value	EST (95% CI)	*p* value
Surgical experience	1.00 (0.99–1.00)	0.3	0.99 (0.99–1.00)	0.3	0.99 (0.99–1.00)	0.1	0.002 (−0.01 to 0.01)	0.9
Age at diagnosis	1.05 (1.04–1.07)	**<0.001**	1.02 (1.00–1.03)	**0.01**	1.01 (1.00–1.03)	0.2	−0.5 (−0.7 to −0.3)	**<0.001**
CCI	1.3 (1.2–1.4)	**<0.001**	1.03 (0.9–1.2)	0.5	1.2 (1.1–1.4)	**<0.001**	1.6 (−0.2 to 3.4)	0.08
Preoperative eGFR	0.99 (0.99–1.00)	0.5	1.0 (0.99–1.01)	0.9	0.99 (0.98–1.00)	0.7	0.3 (0.2 to 0.4)	**<0.001**
Pathologic size	1.1(1.05–1.13)	**<0.001**	1.1 (1.1–1.2)	**<0.001**	0.9 (0.9–1.02)	0.2	−0.7 (−1.5 to −0.08)	0.08
Tumour stage								
pT1–2	Reference	–	Reference	–	Reference	–	Reference	–
pT3–T4	1.4 (1.01–1.8)	**0.04**	2.5 (1.8–3.5)	**<0.001**	1.2 (0.8–1.8)	0.3	1.6 (−3.1 to 6.4)	0.5
pTx	0.4 (0.1–1.7)	0.2	–	–	2.3 (0.2–55)	0.5	6.9 (−23 to 37)	0.6
Tumour grade								
Grade 1–2	Reference	–	Reference	–	Reference	–	Reference	–
Grade 3–4	1.7 (1.3–2.3)	**<0.001**	2.4 (1.7–3.3)	**<0.001**	1.3 (0.9–1.9)	0.2	−1.6 (−6.6 to 3.4)	0.5
Grade x	1.9 (0.5–8.0)	0.3	0.6 (0.1–2.3)	0.5	0.5 (0.02–4.6)	0.8	0.4(−27 to 28)	0.9
Nodal stage								
pN0	Reference	–	Reference	–	Reference	–	Reference	–
pN1	1.9 (1.01–3.5)	**0.04**	2.4 (1.3–4.6)	**<0.01**	1.5 (0.5–4.1)	0.4	−2.2 (−6.8 to 2.4)	0.3
pNx	1.1 (0.8–1.4)	0.5	0.8 (0.5–1.1)	0.2	1.2 (0.8–1.7)	0.4	−0.5(−20 to 19)	0.9
Surgical approach								
Open surgery	Reference	–	Reference	–	Reference	–	Reference	–
MIS	0.8 (0.4–1.6)	0.6	0.8 (0.4–1.6)	0.6	0.4 (0.2–0.7)	**<0.001**	3.4 (−2.1 to 8.8)	0.2
Year of surgery	0.95 (0.93–0.97)	**<0.001**	0.98 (0.96–1.01)	0.3	1.05 (1.02–1.07)	**<0.001**	−0.2 (−0.6 to 0.2)	0.2

CCI = Charlson comorbidity index, eGFR = estimated glomerular filtration rate; CD = Clavien-Dindo; HR = hazard ratio; OR = odds ratio; EST = estimate; CI = confidence interval; MIS = minimally invasive surgery.
[a] Clinical progression was investigated in a subcohort of 1097 patients with confirmed renal cell carcinoma at final pathology.

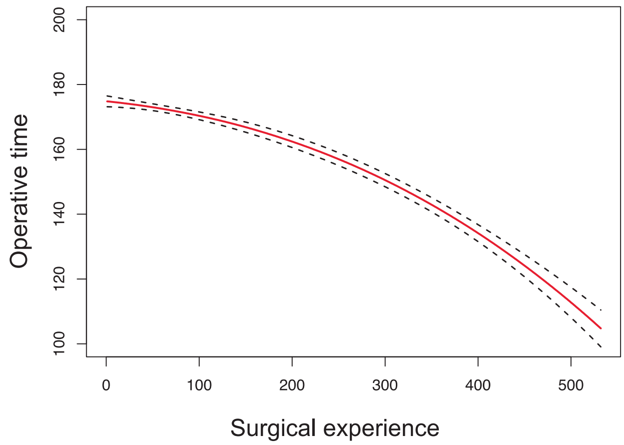

Fig. 1 – Surgical learning curve for radical nephrectomy: effect of increasing experience on operative time. The estimate is adjusted for age at surgery, gender, Charlson comorbidity index, pathological tumour size, pathological T stage, tumour grade, pathological N stage, surgical approach, and year of surgery. The red line denotes the probability and black dotted lines indicate the 95% confidence intervals.

EXP and clinical outcomes. Specifically, the risks of long-term mortality, cancer progression, perioperative morbidity, and renal function impairment are virtually the same for expert surgeons and novice surgeons. Hence, our observations reject this hypothesis and are in contrast to other studies demonstrating better outcomes after increased EXP in urology. For example, a patient diagnosed with prostate cancer treated by an experienced surgeon has a lower risk of positive surgical margins [14], biochemical recurrence [9,10], and poor functional outcomes [15,16] after radical prostatectomy. Similarly, in the case of urethroplasty, the higher the EXP of the treating physician, the lower the risk of repeat surgery [17]. In the context of renal surgery, perioperative complications and ischaemia time in patients undergoing nephron-sparing surgery fluctuate significantly according to the background and ability of the surgeon [3,4].

However, a similar learning effect does not apply to RN, for which the impact of EXP on patient outcomes was irrelevant. This discrepancy might be explained by the technical differences that distinguish nephron-sparing surgery from RN: the latter does not involve parenchymal resection, opening of the collecting system, reconstructive suturing, or time-sensitive parameters such as warm ischaemia time. As a consequence, RN can be regarded as a less challenging surgical procedure than nephron-sparing surgery.

The clinical implications of these observations are clear: during surgical training it is mandatory to protect patients from suboptimal outcomes resulting from the learning process. In this light, RN should be regarded as an ideal scenario for clinical training in urological surgery. This important notion corroborates many other training strategies aimed at maximal reduction of any detrimental effects on patient outcome caused by the learning process, such as emphasis on preclinical training [18], modular configuration of the curriculum [6], and structured training programmes [7,8].

Despite no evidence of superior results after extensive EXP in terms of mortality, cancer control, morbidity, and renal function, increasing EXP was associated with shorter OT. In this regard, it is important to remember that although the relevance of this finding for RN candidates might be marginal, operating theatre occupation affects daily surgical planning and health care expenditure [8].

Our study is not devoid of limitations, such as the observational noncomparative design. The inclusion of cases treated over a wide time span is both a weakness, since indications for RN or nephron-sparing surgery were different and nephrometry scores were not available, and an important strength, since a key element in learning curve analysis is the inclusion of any single patient treated by the surgeons in the study cohort. Notably, the sensitivity analyses did not provide evidence of such a confounding effect. Notwithstanding these limitations, the study has multiple important strengths, including the large study population, the long follow-up, the consideration of hard clinical endpoints, and the inclusion of very experienced surgeons, all of which are noteworthy with respect to the negative findings recorded.

In conclusion, patients undergoing RN performed by novice surgeons have similar clinical outcomes to those for patients treated by experienced surgeons. This finding highlights the status of RN as a convenient setting for clinical training in urological surgery, provided that longer operating theatre time is planned.

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Study concept and design: Larcher, Capitanio.
Acquisition of data: Cei, Belladelli, Rosiello, Bravi, Fallara, Basile, Lucianò, Briganti, Salonia, Bertini, Montorsi.
Analysis and interpretation of data: Larcher, Rosiello, Capitanio.
Drafting of the manuscript: Larcher, Rosiello.
Critical revision of the manuscript for important intellectual content: Cei, Belladelli, Bravi, Fallara, Basile, Lucianò, Karakiewicz, Mottrie, Breda, Briganti, Salonia, Bertini, Montorsi, Capitanio.
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Appendix A. Supplementary data

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