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Impact of Hospital Nephrectomy Volume on Intermediate to Long-term Survival in Renal Cell Carcinoma

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ABSTRACT

OBJECTIVE

To evaluate the relationship between hospital volume and intermediate and long-term patient survival for patients undergoing nephrectomy for renal cell carcinoma (RCC).

PATIENTS & METHODS

Adult RCC patients treated with nephrectomy between 2000 and 2010 were identified from the English Hospital Episode Statistics and National Cancer Data Repository. Patients with nodal or metastatic disease were excluded. Hospitals were categorised into low (<20/yr), medium (20-39/yr) and high (≥40/yr) volume based on annual cases of RCC nephrectomy.

Multivariable Cox regressions were used to calculate hazard ratios for all-cause mortality by hospital volume, adjusting for patient, tumour and surgical characteristics. We assessed conditional survival over three follow-up periods: short (30d-1yr), intermediate (1-3yr) and long (3-5yr). We additionally explored whether associations between volume and outcomes varied by tumour stage.

RESULTS

12,912 patients were included. Patients in high volume hospitals had 34% reduction in mortality risks up to one year compared to those in low volume hospitals (HR 0.66, 95% CI 0.53-0.83, p<0.01). Assuming causality, treatment in high volume hospitals was associated with one fewer death in every 71 patients treated. Benefit of nephrectomy centralisation did not change with higher T stage (p=0.17). No significant association between hospital volume and survival was observed beyond the first year.

CONCLUSIONS

RCC nephrectomy in high volume hospitals was associated with improved survival for up to one year after treatment. Our results contribute new insights regarding the value of nephrectomy centralisation.

INTRODUCTION

A volume-outcome relationship in surgery was first proposed by Luft in 1979 with the hypothesis that higher surgical volumes and/or greater experience led to lower mortality [1]. Since then, numerous studies have reported on the inverse association between hospital volume and patient outcomes in a wide range of surgical and medical procedures. This evidence has compelled the implementation of volume-based referral strategies, most notably by the Leapfrog Group, a watchdog organisation consisted of large corporations and public agencies that purchase healthcare in the US [2]. Similar guidance for urological procedures has also been published in the UK in 2002 in the Improving Outcomes in Urological Cancer Guidance, where centralisation was recommended for radical prostatectomy, cystectomy and in parts for radical nephrectomy where patients have

bilateral renal cancer, tumour invading the renal vein or vena cava, or metastatic disease amenable to resection [3]. Trends of increasing hospital caseloads have been reported for urological cancer operations in different countries, suggesting the general acceptance of surgical centralisation within the urology community [4–6]. Evidence to support this change for RCC nephrectomy is however based on studies that analysed volume-outcome relationship primarily on short-term perioperative results including mortality within 30 days of surgery, complications, length of stay and readmission rates [7]. It is currently not well understood how hospital RCC nephrectomy volume is associated with patient survival beyond the immediate post-operatively period. Such information can be useful for policy makers and healthcare providers to drive care quality improvements, particularly as the worldwide incidence of RCC is predicted to rise [8]. In this study, we investigate the volume-outcome relationship in renal cancer nephrectomy focusing specifically on survival beyond 30 days.

PATIENTS & METHODS

Data

Full data were supplied by Public Health England and contains fields from both English Hospital Episode Statics (HES) and National Cancer Data Repository (NCDR). Characteristics of the datasets have previously been described, but in short, these are major administrative databases with full population coverage containing details of all National Health Service hospital admissions in England together with tumour level records and survival information [4]. Ethics approval was granted by the National Research Ethics Committee (reference 15/EM/0340) and Confidentiality Advisory Group (reference 15/CAG/0169).

Exposure Variables

Patients diagnosed with RCC and treated with either total or partial nephrectomy between 2000 and 2010 were identified using the International Statistical Classification of Diseases and Related Health Problems 10th revision code and Office of Population Censuses and Surveys Classification of Interventions and Procedures version code (Supplementary Table 1). We excluded patients aged 17 or under at the time of surgery as well as those treated with nephroureterectomy or nephrectomy of transplanted kidney. A total of 30,763 renal cancer nephrectomies were recorded in the database. We further excluded individuals recorded as having had multiple renal cancer operations or bilateral procedures. In order to control for differences in tumour stage, only patients with complete TNM data were included in our analyses. Patients with nodal or metastatic disease at diagnosis were excluded. We analysed only those surviving beyond the initial 30 days after nephrectomy. All patients were followed up for death until end of 2015.

Patient level variables included age, sex, ethnicity and socioeconomic deprivation. Comorbidities at the time of surgery were tabulated using the Royal College of Surgeons Charlson Score [9]. Type of nephrectomy (radical, partial) and surgical access (open, minimally-invasive) were derived from HES procedure codes.

Hospital annual operative caseloads were calculated based on the number of nephrectomies performed by the responsible hospitals. Our previous study found that the median annual hospital nephrectomy volume in England was 23 (IQR 12-39.5) in year 2010 [4]. We therefore categorised hospitals into low (LV), medium (MV) and high (HV) volume using practical annual thresholds of twenty and forty cases. All 30,763 RCC nephrectomy cases were used for this calculation.

Analysis

All statistical analyses were performed using Stata 14 [10]. P-values <0.05 were considered statistically significant. Differences in patient characteristics amongst the hospital volume categories were compared using chi-square tests or analysis of variance. We further explored missing TNM data across hospital volumes and other patient characteristics with chi-square tests.

Kaplan-Meier survival estimates of patients treated in different hospital volume categories were generated and compared using log-rank test.

Cox proportional hazard regression analyses were used to assess the association between hospital nephrectomy volume and survival. Survival time was calculated from date of surgery until date of death from any cause. Univariable and multivariable models with appropriate adjustment for potential confounders were created. These were identified a priori and included age group (≤64, 65-74, ≥75), sex, ethnicity (white, non-white), socioeconomic deprivation, number of comorbidities, year of nephrectomy (2000-2002, 2003-2005, 2006-2008, 2009-2010), type of nephrectomy, type of surgical access, tumour T stage, tumour grade and histological subtype (clear cell, others). Shared frailty Cox models were used to account for clustering of patients within given hospitals and year of nephrectomy. We analysed survival over three follow-up periods to determine the effects of hospital volume on survival at different post-surgical intervals. They were defined as short (30d to 1yr), intermediate (1 to 3yr) and long (3 to 5yr) term. Each period was evaluated conditional on patients surviving the previous follow-up interval. We calculated Harrell's C statistics for each model to assess goodness of fit. When significant improvement is demonstrated for HV hospitals, we quantified the clinical effectiveness by calculating the numbers needed to treat (NNT) associated with centralisation [11]. This number may represent the number of cases that need to be centralised

from LV hospitals to HV hospitals in order to prevent one death, assuming that the association is causal.

To examine whether missing TNM data could have affected the estimates of the hospital volume-outcome relationship, we further repeated our analyses only on patients operated between 2009 and 2010, where TNM coverage was more complete.

Differences in T stages can have significant impact on the nephrectomy complexity and may therefore benefit differently from surgical centralisation. We therefore performed subgroup analyses based on tumour T stage. To examine whether interaction between hospital volume and T stages contribute significantly to the volume-outcome relationship, we also used likelihood ratio test to compare multivariable Cox models with and without interaction terms between hospital volume and T stage categories. Due to the small number of patients with T4 disease, these were considered together with T3 patients.

RESULTS

A total of 12,912 patients were included in the final analyses with a median follow-up of 8.1 years (Supplementary Figure 1). 52.7% of eligible patients were excluded due to unrecorded TNM data. Coverage of TNM data varied across hospital volume groups and were less complete for those treated in HV hospitals than for patients treated in LV or MV hospitals, but were increasingly complete in later years of the study up to 69.0% (Supplementary Table 2).

Mean age of the analysis cohort was 63.4 years (range 19 to 95) with 62.6% being male. Characteristics of the patients treated in each hospital volume group are described in Table 1. There was no difference in the age and sex compositions amongst the hospital volume categories. Patients treated in HV hospitals were more likely to have higher numbers of comorbidities. HV hospitals also performed higher proportion of partial and minimally invasive surgeries. There were significant differences in the T stage distribution amongst hospital volume categories with higher proportion of patients in HV hospitals having T1 disease.

Patients in HV hospitals had significantly lower crude unadjusted mortality rates at one, three and five years. Kaplan-Meier analysis also demonstrated improved survival between thirty days and five years post nephrectomy for patients treated in higher volume hospitals ($p<0.01$) (Figure 1).

Short-term Survival (30d-1yr)

In the univariable model, treatment in HV centres resulted in significantly better outcomes compared to treatment in LV centres (HR 0.57, CI 0.46-0.70, $p<0.01$) (Table 2). After adjusting for covariates, patients treated in HV centres continued to have better outcomes, with a 34% reduction in mortality hazard (HR 0.66, CI 0.53-0.83, $p<0.01$) (Table 2). A typical patient in HV hospitals had a predicted survival probability of 97.4% at one year, compared to 96.0% for a patient in LV hospitals, corresponding to NNT of 71 (Figure 2).

As expected, being older, having higher number of comorbidities, higher tumour T stage and grade were associated with poorer outcomes. Treatment with partial nephrectomy or minimally invasive surgery and treatment in later periods were predictors of improved survival.

Intermediate (1-3yr) and Long-term (3-5yr) Survival

Beyond the first post-operative year, there was no evidence that surviving patients treated in MV or HV hospitals had different outcomes compared to LV hospitals (Table 2). Higher age, number of comorbidities, tumour T stage and grade remained significant predictors of lower survival, while operations in more recent years and with nephron-sparing surgery and minimally invasive access continue to be predictors of the reverse. Social deprivation did not consistently affect patient survivals.

Restricted Cohort

To examine whether missing TNM data affected our results, we repeated our analyses on patients treated between 2009 and 2010. In this restricted cohort, TNM data was available for 69.0% of the eligible patients, compared to 47.3% in the entire cohort.

Results remained consistent with patients treated in HV hospitals having a 36% reduction in mortality hazard in the first year compared to those treated in LV hospitals (HR 0.64, CI 0.43-0.94, p=0.02) (Table 2). No association between hospital volume and survival was observed after one year.

T Stage Subgroup Analyses

During the short-term follow-up period between 30d to 1yr, treatment in HV hospitals were seen to improve survival for patients with T1 (HR 0.57, CI 0.33-0.97, p=0.04) and T2 (HR 0.41, CI 0.20-0.83, p=0.01) disease (Table 3). These corresponded to NNT of 143 and 37 respectively, assuming

causality. No significant association was observed between hospital volume and survival for patients with T3 or T4 disease or beyond the first year of follow-up. However, difference between "significant" and "not significant" is not itself statistically significant and when examined using likelihood ratio test, there was no statistical evidence of interaction between hospital volume and T stage categories (p=0.17).

DISCUSSION

In this study, we found that a survival benefit exists for RCC patients treated in HV hospitals up to one year after nephrectomy. Benefit beyond the first year of follow-up was not observed. Patient age, number of comorbidities, tumour T stage and grade at time of surgery remained significant predictors of long-term survival, although there was no evidence that particular T stage benefited preferentially to surgical centralisation.

The effect of hospital volume on RCC patient outcomes has been a subject of interest and well characterised in widespread publications in recent years [12–15]. Most of these studies have concluded that higher hospital volume correlates to better outcomes particularly during the perioperative period. Our previous meta-analysis on the effect of radical nephrectomy centralisation showed that HV hospitals reduced surgical mortality risks by 26% and complications by 18% compared to LV hospitals [7]. Due to the relatively low mortality rates associated with RCC nephrectomy, we suggested that the perceived clinical benefit of centralisation was however marginal. Longer-term survival in this instance may therefore represent more appropriate outcome measure, particularly as one and five-year survival are more often used as benchmarks for assessing the efficacy of oncological treatment.

Similar findings of improved long-term oncological outcomes in HV centres have been reported in other cancer resections including those for breast and oesophageal cancer and pancreatic ductal adenocarcinoma [16–18]. Hospital volume should however be viewed as a proxy measure for healthcare quality encompassing the quality of surgical treatment and pre and post-operative care, but does not in itself identify the exact aspects and practices of HV hospitals that drive the observed association to survival. There are several mechanisms that could explain our findings. First, surgeons in HV hospitals have greater experience and skills in RCC nephrectomy resulting in lower perioperative morbidity and therefore reduced one-year mortality. Second, HV hospitals may also have more streamlined perioperative pathways that contribute to the improved short-term outcomes. Third, greater patient exposure by the complementary multidisciplinary team including radiologists and oncologists may also lead to improvements in detecting disease relapse facilitating more timely interventions. Fourth, larger centres also often have the required infrastructure to enable quicker adoption of new clinical guidelines and greater access to novel treatments including clinical trials, although this may not be as relevant in our cohort which focused only on patients with localised disease at time of nephrectomy. The association between hospital volume and survival attenuated after adjustments for patient-level characteristics suggesting a role of case-mix in explaining the crude variation, but also indicating that case-mix alone is unlikely to explain the whole difference.

Our findings are suggestive of the presence of a volume-outcome relationship for RCC nephrectomy across volume categories, with patients treated by hospitals with higher activity having lower risks of mortality, consistent with previous studies examining volume-outcome relationships in patients with lung, bladder and stomach cancer [19,20]. The body of prior evidence and our own findings support that centralising nephrectomy activity for RCC is associated with improved survival beyond the immediate post-operative period.

To further contextualise the effect of surgical centralisation on RCC nephrectomy, we calculated NNT. Assuming causality and that patients treated in LV centres had the same outcomes as those treated in HV centres, prevention of one death in the first year could be realised after centralising 71 patients. This is substantially lower than the 234 patients estimated in our previous review that is required to be centralised to prevent one perioperative death, and may therefore represent stronger evidence to support RCC nephrectomy centralisation [7].

Positive volume-outcome relationship is more likely to be observed in technically challenging procedures that carry higher morbidities and mortalities. It is therefore surprising that T stage did not affect the benefit of nephrectomy centralisation in our analyses, particularly as T3 and T4 represent advanced disease with perinephric invasion. It is plausible that T3 and T4 patients have generally poorer prognosis diminishing the effect of hospital volumes, as evident in the higher point estimate for hazard ratio. Our stage-specific sample size may also not be sufficient to detect statistical significance in individual subgroups.

To the best of our knowledge, this is currently the only study to describe the association between hospital volume and RCC nephrectomy survival beyond the immediate postoperative period. Other strengths of our study include the use of data with whole population coverage with all patients followed up for a minimum of five years. Patient reporting in HES and NCDR are mandatory leading to case ascertainment of >98% [21]. Linkage of the two databases also allowed patient, hospital and tumour level variables to be included in our statistics model resulting in improved model fits. Using patient data from England where the healthcare system relies more on regional network referral and where patients have less choice on their treatment doctors, selective referral where high performing hospitals are more likely to receive further cases, is less likely to be a confounding factor.

There are several limitations to our study. There is potential selection bias in our study as a significant proportion of our cohort had incomplete TNM records. However, we observed consistent results when analyses were repeated on a restricted cohort with significantly more complete TNM data coverage. Use of adjuvant or neoadjuvant systemic therapy were not recorded in NCDR and were therefore not adjusted in our analyses. While systemic therapy can have significant impact on long-term survival, these have not traditionally been advocated for patients with localised disease for which our study focused exclusively on. We measured the effect of hospital volume on overall survival, but did not control for the differences in background mortality. It is possible that patients treated by different volume hospitals had different non-renal cancer mortality risks, although adjustment for comorbidities mitigated these concerns.

Future research should focus on identifying the exact quality and process of care in HV centres that drive outcome improvements, allowing lower performing hospitals to adopt these practices. In the era of centralisation, guidelines have been published on the volume threshold that hospitals should achieve annually. Yet these have been based on very limited evidence and there is currently no consensus on the definition of HV hospital. More study should therefore focus on ascertaining the minimum number of nephrectomy that providers should carry out to attain acceptable outcomes.

In this analysis of volume-outcome relationship, we further characterised the survival benefit of RCC nephrectomy centralisation and found that improvement exists beyond the immediate perioperative period and extends to one year after surgery. Our results contribute to the growing evidence in support of nephrectomy centralisation for RCC patients.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCE

1. Luft HS, Bunker JP, Enthoven AC. Should Operations Be Regionalized? N Engl J Med. 1979;301(25):1364–9.

2. Finks J, Osborne N, Birkmeyer JD. Trends in hospital volume and operative. N Engl J Med. 2011;364:2128–37.

3. National Institute for Clinical Excellence. Guidance on cancer services: Improving outcomes in urological cancers. London; 2002.

4. Hsu RCJ, Barclay M, Loughran MA, Lyratzopoulos G, Gnanapragasam VJ, Armitage JN. Time Trends in Service Provision and Survival Outcomes for Renal Cancer Patients Treated by Nephrectomy in England 2000-2010. BJU Int. 2018;

5. Hounsome LS, Verne J, McGrath JS, Gillatt DA. Trends in operative caseload and mortality rates after radical cystectomy for bladder cancer in England for 1998–2010. Eur Urol. 2015;67(6):1056–62.

6. Cooperberg MR, Modak S, Konety BR. Trends in regionalization of inpatient care for urological malignancies, 1988 to 2002. J Urol. 2007 Nov;178(5):2103–8.

7. Hsu RCJ, Salika T, Maw J, Lyratzopoulos G, Gnanapragasam VJ, Armitage JN. Influence of hospital volume on nephrectomy mortality and complications: a systematic review and meta-analysis stratified by surgical type. BMJ Open. 2017;7(9):e016833.

8. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [cited 2018 Jun 3]. Available from: http://globocan.iarc.fr

9. Armitage JN, van der Meulen JH. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. Br J Surg. 2010;97:772–81.

10. StataCorp. Stata Statistical Software: Release 14. College Stata, Texas: StataCorp LP; 2015.

11. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ. 1999;319(7223):1492–5.

12. Hjelle KM, Johannesen TB, Beisland C. Postoperative 30-day Mortality Rates for Kidney Cancer Are Dependent on Hospital Surgical Volume: Results from a Norwegian Population-based Study. Eur Urol Focus. 2016;1–8.

13. Becker A, Bianchi M, Hansen J, Tian Z, Shariat SF, Popa I, et al. Benefit in regionalization of care for patients treated with nephrectomy: a Nationwide Inpatient Sample. World J Urol. 2014;32:1511–21.

14. Sun M, Bianchi M, Trinh Q-D, Abdollah F, Schmitges J, Jeldres C, et al. Hospital volume is a determinant of postoperative complications, blood transfusion and length of stay after

radical or partial nephrectomy. J Urol. 2012;187(2):405–10.

15. Xia L, Strother MC, Taylor BL, Chelluri RR, Pulido JE, Guzzo TJ. Hospital volume and short-term outcomes after cytoreductive nephrectomy. J Surg Oncol. 2018 Jun;117(7):1589–96.

16. Vrijens F, Stordeur S, Beirens K, Devriese S, Van Eycken E, Vlayen J. Effect of hospital volume on processes of care and 5-year survival after breast cancer: a population-based study on 25000 women. Breast. 2012;21(3):261–6.

17. Brusselaers N, Mattsson F, Lagergren J. Hospital and surgeon volume in relation to long-term survival after oesophagectomy: systematic review and meta-analysis. Gut. 2014;63:1393–400.

18. Ahola R, Siiki A, Vasama K, Vornanen M, Sand J, Laukkarinen J. Effect of centralization on long-term survival after resection of pancreatic ductal adenocarcinoma. Br J Surg. 2017;104(11):1532–8.

19. Lüchtenborg M, Riaz SP, Coupland VH, Lim E, Jakobsen E, Krasnik M, et al. High Procedure Volume Is Strongly Associated With Improved Survival After Lung Cancer Surgery. J Clin Oncol. 2013;31(25):3141–6.

20. Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. Ann Surg. 2007;245(5):777–83.

21. Møller H, Richards S, Hanchett N, Riaz SP, Lüchtenborg M, Holmberg L, et al. Completeness of case ascertainment and survival time error in English cancer registries: impact on 1-year survival estimates. Br J Cancer. 2011;105(1):170–6.

Table 1: Patient characteristics stratified by hospital volume categories. CCI Charlson Comorbidities, IMD Index of Multiple Deprivation.

	LV Hospital (<20)	MV Hospital (20-39)	HV Hospital (≥40)	P Value
n	4,468	5,309	3,135	
Number of hospitals	146	96	42	
Mean age (yr) (range)	63.6 (19-93)	63.4 (19-95)	63.2 (20-92)	0.33
Male (%)	63.2	62.5	61.9	0.51
White (%)	84.9	88.5	91.7	<0.01
CCI				
0 (%)	64.8	61	58.9	<0.01
1 (%)	25.8	27.8	28.1	
≥2 (%)	9.4	11.3	13	
IMD				
1 – Least Deprived (%)	20.3	17.6	20.4	<0.01
2 (%)	23.3	22.8	21.9	
3 (%)	21.8	23.3	23	
4 (%)	20.4	20	18.5	
5 – Most Deprived (%)	14.3	16.3	16.1	
Nephrectomy Type				
Radical nephrectomy (%)	95.8	90.1	83.4	<0.01
Partial nephrectomy (%)	4.2	9.9	16.6	
Minimally-invasive access (%)	19.4	33.6	44.8	<0.01
T Stage				
T1 (%)	42.4	47.6	50.9	<0.01
T2 (%)	23.6	18.7	15.4	<0.01
T3/T4 (%)	34.1	33.8	33.7	0.91
Grade				
1 (%)	11.3	8.6	5.8	<0.01
2 (%)	48.6	47	45.1	
3 (%)	32	34.7	36.4	
4 (%)	8.2	9.6	12.7	
Morphology				
Clear cell (%)	92.7	91	90.8	0.15
Others (%)	7.3	9	9.2	
Mortality				
1-year (%)	8.8	7.1	5.4	<0.01
3-year (%)	20.3	18.3	14.6	<0.01
5-year (%)	28.6	25.8	22.6	<0.01

Table 2: Univariable and multivariable Cox proportional hazard regression models with shared frailty examining conditional survival over three follow-up periods for patients treated in three hospital nephrectomy volume categories. Restricted cohort consisted of patients treated in 2009 and 2010 analysed separately showing consistent results. CCI Charlson Comorbidities. IMD Index of Multiple Deprivation.

	Short (30d-1yr)			Intermediate (1-3yr)			Long (3-5yr)		
Variables	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Univariable Model									
Hospital Volumes									
<20	Ref			Ref			Ref		
20-39	0.77	0.66-0.90	<0.01	0.96	0.84-1.09	0.5	0.88	0.76-1.02	0.09
≥40	0.57	0.46-0.70	<0.01	0.75	0.64-0.88	<0.01	0.89	0.75-1.06	0.2
C-Index	0.56 (0.53-0.58) p<0.01			0.53 (0.51-0.54) p<0.01			0.51 (0.50-0.53) p<0.01		
Multivariable Model									
Hospital Volumes									
<20	Ref			Ref			Ref		
20-39	0.87	0.74-1.03	0.11	1.05	0.93-1.20	0.42	0.95	0.81-1.11	0.5
≥40	0.66	0.53-0.83	<0.01	0.86	0.73-1.01	0.07	1.01	0.83-1.22	0.93
Age									
≤64	Ref			Ref			Ref		
65-74	1.19	1.00-1.41	0.04	1.31	1.16-1.49	<0.01	1.41	1.21-1.64	<0.01
≥75	1.51	1.25-1.81	<0.01	1.76	1.54-2.01	<0.01	2.43	2.08-2.84	<0.01
Sex									
Male	Ref			Ref			Ref		
Female	1.09	0.93-1.27	0.28	0.93	0.83-1.04	0.22	0.84	0.73-0.96	0.01
Ethnicity									
White	Ref			Ref			Ref		
Non-white	0.8	0.54-1.16	0.24	0.85	0.65-1.11	0.24	0.74	0.54-1.02	0.07
CCI									
0	Ref			Ref			Ref		
1	2	1.69-2.37	<0.01	1.75	1.55-1.97	<0.01	1.39	1.20-1.60	<0.01
≥2	3.39	2.79-4.13	<0.01	2.35	2.02-2.73	<0.01	2.13	1.78-2.55	<0.01
IMD									
1	Ref			Ref			Ref		
2	1.06	0.84-1.33	0.63	0.94	0.80-1.11	0.48	1.02	0.84-1.25	0.81
3	1.11	0.88-1.39	0.37	1.03	0.87-1.21	0.72	1.03	0.84-1.25	0.8
4	1.28	1.02-1.60	0.04	1.05	0.89-1.24	0.57	1.18	0.96-1.45	0.11
5	1.06	0.81-1.37	0.67	1.04	0.87-1.25	0.64	1.26	1.02-1.56	0.03
Year									
2000-2002	Ref			Ref			Ref		
2003-2005	0.82	0.65-1.04	0.11	0.88	0.73-1.105	0.16	0.78	0.62-0.99	0.04
2006-2008	0.79	0.62-1.00	0.05	0.74	0.61-0.89	<0.01	0.78	0.62-0.98	0.03
2009-2010	0.67	0.52-0.88	<0.01	0.65	0.53-0.79	<0.01	0.7	0.55-0.89	<0.01
T stage									
1	Ref			Ref			Ref		
2	1.54	1.19-2.00	<0.01	1.62	1.37-1.91	<0.01	1.34	1.12-1.61	<0.01
3	3.13	2.54-3.85	<0.01	2.61	2.27-3.00	<0.01	1.92	1.65-2.23	<0.01
4	11.65	8.30-16.37	<0.01	4	2.64-6.06	<0.01	3.56	2.06-6.15	<0.01
Grade									
1	Ref			Ref			Ref		
2	0.66	0.45-0.95	0.03	1.2	0.91-1.58	0.21	0.94	0.72-1.22	0.62
3	1.45	1.01-2.08	0.04	1.74	1.32-2.31	<0.01	1.34	1.03-1.75	0.03
4	2.5	1.71-3.65	<0.01	3.45	2.56-4.64	<0.01	1.49	1.08-2.05	0.02
Morphology									
Clear Cell	Ref			Ref			Ref		
Others	1	0.59-1.71	0.99	1.19	0.86-1.65	0.29	1.1	0.75-1.61	0.62
Nephrectomy Type									
Radical	Ref			Ref			Ref		
Partial	0.33	0.18-0.59	<0.01	0.58	0.43-0.77	<0.01	0.52	0.38-0.71	<0.01
Surgical access									
Open	Ref			Ref			Ref		
Minimally Invasive	0.69	0.56-0.85	<0.01	0.71	0.61-0.81	<0.01	0.77	0.66-0.90	<0.01
C-Index	0.79 (0.78-0.80) p<0.01			0.73 (0.72-0.75) p<0.01			0.70 (0.69-0.72) p<0.01		
Multivariable Model (2009-2010 Cohort)									
Hospital Volumes									
<20	Ref			Ref			Ref		
20-39	0.72	0.50-1.03	0.07	1.13	0.84-1.53	0.42	1.18	0.84-1.66	0.33
≥40	0.64	0.43-0.94	0.02	0.95	0.69-1.31	0.75	1.22	0.86-1.75	0.27

Table 3: Multivariable Cox proportional hazard regression models with shared frailty examining conditional survival over three follow up periods for patients with localised RCC stratified by T stages.

		Short (30d-1yr)			Intermediate (1-3yr)			Long (3-5yr)		
	Hospital Volume	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
T1	<20	Ref			Ref			Ref		
	20-39	0.69	0.45-1.04	0.07	1.03	0.79-1.36	0.82	1.04	0.81-1.35	0.76
	≥40	0.57	0.33-0.97	0.04	0.88	0.62-1.26	0.49	0.98	0.70-1.37	0.89
T2	<20	Ref			Ref			Ref		
	20-39	0.55	0.36-0.84	0.01	0.96	0.73-1.26	0.76	0.84	0.60-1.17	0.3
	≥40	0.41	0.20-0.83	0.01	0.65	0.44-0.95	0.03	0.93	0.60-1.46	0.76
T3/T4	<20	Ref			Ref			Ref		
	20-39	0.98	0.79-1.21	0.87	1.09	0.92-1.29	0.31	0.91	0.71-1.15	0.42
	≥40	0.77	0.58-1.02	0.07	0.9	0.73-1.11	0.31	1.05	0.79-1.39	0.75