Guideline adherence for the surgical treatment of T1 renal tumours correlates with hospital volume: an analysis from the British Association of Urological Surgeons Nephrectomy Audit.

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Conflicts of Interests: MT, MS, GS, BC, AM, PP, FM, RB and AB practice clinically in institutions that provide specialist kidney cancer services and are considered high volume centres.

Introduction

Since 2010, the European Association of Urology (EAU) Renal Cancer Guidelines have recommended partial nephrectomy (PN) for patients with T1 tumours, and radical nephrectomy (RN) for tumours not amenable to PN or other local treatment options [1, 2]. Oncological outcome of PN in terms of cancer specific and overall survival is proven to be comparable to RN, but whether decreased mortality from any cause can be attributed to PN is still unresolved [2-4]. Nonetheless, PN is the preferred surgical treatment option when feasible, to minimize deterioration in renal function [4]. Thus, the proportion of T1 tumours treated with PN compared to RN in a given hospital can be considered a surrogate indicator of recommendation adherence.

Technical feasibility for PN entails a complex decision process and is dependent on patient and tumour related factors such as anaesthetic risk and renal tumour complexity scoring. Most national and international high volume registries lack details that allow for case adjustment at this level. The British Association of Urological Surgeons (BAUS) Nephrectomy Audit is the largest UK kidney cancer registry with surgeon inputted data and is enriched for patient and tumour specific data items.

Our objective was to determine the relationship of adherence to EAU guidelines with hospital volume (HV); and whether centralization of care has any impact on the type of surgery, approach and complication risk that a patient with a T1 tumor is likely to receive.

Patients and methods

The British Association of Urological Surgeons (BAUS) Nephrectomy Audit is a surgeon reported registry that has ethical approval under section 251 of the NHS Act 2006. Urological surgeons practicing in England are mandated to report nephrectomies to this registry since 2012. For surgeons in Scotland, Wales and Ireland, data imputation is not compulsory. From 2015 to 2017, the database captured between 89 and 93% of all nephrectomies recorded in the UK Hospital Episode Statistics registry, indicating good completeness of procedures recorded. The BAUS Nephrectomy Audit Data is directly recorded by surgeons and is the most comprehensive surgical kidney cancer registry in the UK in terms of clinical data items. It includes multiple patient and tumour-specific data items, as well as perioperative outcomes. Of particular importance and relevance to any study comparing surgical outcomes, it also includes tumour complexity data using the PADUA score (but not other scores) since 2015. However, one of the registry's limitations is the lack of long term follow-up data entries.

We compared surgical management of T1 tumours (defined as tumours of 7cm or under, confined to the renal parenchyma) in different hospitals across the UK and investigated the association between hospital surgical volume (HV), surgical complications, as well as completeness of BAUS data registered. All cT1a (tumours of 4cm or under) and cT1b (tumours between 4 and 7cm) tumours (malignant and benign) that underwent total nephrectomy (recorded as radical or simple) or PN in the BAUS Nephrectomy Audit during the period 2012-2016 were retrieved with the following specification: type of approach (laparoscopic, robotic assisted, open); PN or nephrectomy; renal complexity by PADUA score; pathology report; surgical complications graded according to CD classification [9]. Oncological outcomes were not assessed because this data is not available in the BAUS registry.

HV was defined as the total number of PN and nephrectomy (recorded as simple or radical) done for cT1 tumours per year in each centre. In the absence of a universally accepted classification system for HV, for the purpose of this study, increments of surgical cT1 volume per hospital were defined as lowest volume being approximately 1-2 procedures per month (n=25), low volume being up to 1 procedures a week (25-49/year), medium volume being more than 1-2 procedures per week (50-99) and high volume being more than 2 procedures a week (>100). These thresholds were defined arbitrarily.

cT1 tumours were grouped in low (6-7), intermediate (8-9) and high-complexity (10-13) as per PADUA score. For those cT1 tumours with missing data on complexity; the percentage of missing data were analyzed for lowest, low, medium and high volume hospitals. All other missing data were evaluated in the same manner. Those patients with full data available for cT1 were further investigated to determine whether there was an association between HV and PN rate or type of approach (open or minimally invasive laparoscopic or robotic) within cT1 tumours of matched complexity groups (low, intermediate and high complexity). Sub-analyses were performed for cT1a and cT1b subgroups.

Statistical analysis

Descriptive analyses were performed, providing percentages and means where appropriate. A funnel plot including 95% and 99.7% confidence intervals was used to illustrate the variability of the proportion of PN by HV. χ^2 and Cochran-Armitage trend tests were performed to evaluate differences and trends. Univariable and multivariable logistic regression analyses were performed to evaluate the association between HV and probability of PN, adjusted for case-mix (age, gender, PADUA score group, presence of a genetic syndrome, laterality (left, right, bilateral), and WHO performance status (0 or 1 versus ≥1). Only patients treated in 2015 and 2016, with known PADUA scores were included in the regression analyses. Analyses were performed for all T1 patients and stratified by year of surgery, HV, and PADUA complexity score. Logistic regression was used to model the probability of complications

of CD≥3 as a function of the annual number of PN per hospital. Without prior hypothesis tests of non-linearity, we used a restricted cubic spline with three knots to allow for non-linearity of the association. The results from the model were transformed to the probability scale in order to make them easier to interpret. All analyses were conducted using SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA) and R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 13045 surgically treated cT1 tumours were included in the analyses (Figure 1). Patient and tumor data are provided in **Table 1**. Over time, there was an increase in PNs among surgically treated cT1 tumours from 39.7% in 2012 to 44.9% in 2016, which was 63.4% to 69.9% and 18.5% to 19.0% for cT1a and cT1b tumours respectively (supplementary Figure 1a and b). PADUA complexity score was registered in 39% of cases (30 % in lowest and 43% in highest volume hospitals) (Table 1; supplementary Figure 2). Incomplete or missing information on post-operative complications appeared constant over the years analysed (8.5-9%).

Association between type of surgery and complication rate with hospital surgical volume

There was a trend over time towards more patients being treated in hospitals undertaking 100 or more surgical procedures for cT1 tumours over time (highest volume centres). In 2012, there were no hospitals performing in excess of 100 procedures. In 2013, 166 (7%) patients with cT1 tumours were treated in high volume hospitals, and this rose to 983 (32%) in 2016. In the same period, the number of high volume hospitals increased while the number of lowest volume hospitals decreased (supplementary Figure 3). An association was found between HV and the proportion of T1 tumours treated with PN rather than RN (see Figure 2 and 3; for subgrouping into cT1a and b see supplementary Figure 4). In the subset of patients with available PADUA score (Figure 1, table 1) this association persisted after adjustment for PADUA complexity. (Figure 4a-c; supplementary Table 1). The complication rates decreased with increasing hospital volume, for all patients as well as patients undergoing PN (Figure 5). A similar association was found in the sub-analysis for cT1a and cT1b tumours (data not shown).

Restricted cubic spline regression was used to model the probability of CD ≥ 3 complications with annual utilization of PN (Figure 6). The association was statistically significant (p=0.0124), although the test for non-linearity (at the log-odds scale) was not (p=0.24). We also found that the probability of major complications with PN decreased with increasing HV.

Association between PN surgical approach and hospital volume

There was a higher rate of robotic-assisted PN in high and highest volume hospitals compared to low- and lower volume hospitals (supplementary Figure 5a). The proportion of PN performed using an open surgical approach was low in the highest volume centers and reduced further during the period studied (Supplementary Figure 5b). Robot assisted PN, on the other hand, increased to almost completely replacing laparoscopic PN. In fact, the use of the robot-assisted approach was so prominent in the highest volume hospitals, that complication rate in association with HV could not be

corrected for type of approach. Only in low and medium volume hospitals are the majority of patients still offered an open PN, with an exception for the year 2016 in medium volume hospitals.

Discussion

Centralisation of specialist care, including complex functional and cancer surgery, is evident on a global basis and has been lauded to reduce variation in quality of care and improve clinical outcomes [10-12]. In the UK, there has been increased interest in cancer care provision in 'integrated cancer systems' with specialist surgical pathway initiatives in prostate, bladder, kidney and esophageal cancer [13, 14] in London and Greater Manchester. Advocates of centralisation of care argue that increased patient volume allows greater concentration of specialised services, expertise and staff to enable improved outcomes. Critics on the other hand, could cite inconvenience to patients with increased travel time, limiting access to care and de-skilling of health professionals in local hospitals. A recently reported discrete-choice experiment involving patients, clinicians and members of the public showed that these concerns appear to be unfounded and patient preferences were particularly influenced by risk of complications, death and access to specialist multidisciplinary teams (tumor boards) [14].

Evaluating the association between improved oncological outcomes and centralisation, HV or individual surgeon volume has been difficult in kidney cancer. This is possibly because surgical mortality in renal cancer surgery is relatively low and cancer-specific survival at 5 and 10 years is high for localized disease. Thus, other quality indicators are needed which require knowledge of patient and tumor related factors to adjustment in the comparison of performance across health care providers.

Although mortality is low, PN is recognised to be a complex procedure with higher complication rates than RN [15]. Yet, it is recommended by the major international kidney cancer guidelines, including the EAU guideline panel since 2010, for the treatment of T1 renal masses [2]. Analysis of the BAUS nephrectomy audit for the year 2012 showed a PN rate among 1768 surgeries of 38.8 % and a higher risk of severe surgical complications (CD ≥3) compared to RN [6].

The rate of PN performed and associated surgical complication rates are therefore appropriate quality indicators to assess in association with HV. Recently, several studies using large databases have evaluated the relationship between HV and outcome after PN. Xia *et al.* identified 18724 cases between 2010 and 2013 in the National Cancer Database [16]. Using multivariate analyses, the authors concluded that undergoing RAPN at higher-volume hospitals may have better peri-operative outcomes in terms of lower conversion to RN and positive margin rates. However, while their study included information on Charlson comorbidity and tumor size, it was limited by the absence of

information on tumor complexity scores. A previous Dutch analysis was confounded by a similar absence of comparative data[17].

Arora *et al*. attempted to define a threshold annual HV to achieve optimal inpatient complication rates[18]. They reported that the odds of complications had an inverse nonlinear relationship with increasing annual HV. Lower complication levels were seen at 35-40 annual cases for any inpatient complications, including major inpatient complications[18]. We also found a statistically significant association (p=0.0124), with a plateau for hospitals with extremely low volumes, after which the probability of complications decreases gradually.

The impact of individual surgeon volume (SV) on PN outcomes has also been investigated. A nationwide population-based analysis from 2003 to 2015 investigated the incidence of unsuccessful PN, defined as conversion to radical nephrectomy, within the United States [19]. Overall rates of unsuccessful PN declined from 33.5% to 14.5% over the period studied and was significantly different between very high and very low volume surgeons (open: 39.4% vs. 13.3%, laparoscopic: 51.2% vs. 32.2%, and robot assisted: 27.1% vs. 9.4%, all P<0.001).

A recent French study involving 1222 RAPN from 11 institutions evaluated the impact of HV and SV on Trifecta achievement rates [21]. Trifecta was defined as absence of complications, warm ischemia time <25 min, and negative surgical margins. In multivariate analysis, only HV remained the main predictive factor of Trifecta achievement (odds ratio [OR] 3.70 for very high vs low HV; P < 0.001) compared to SV (OR 1.58 for very high vs low SV; P = 0.34). The authors attributed this finding to the standardized management of small renal masses pre- and post-operatively in these tertiary centres where the entire chain of primary and secondary care relies on the institutions' protocol for perioperative care. We agree that high-quality patient care is delivered by a combination of individual surgical skills and volume (which is often high in high-volume centers) and a standardised care pathway involving a trained team and allied specialties such as interventional radiology [22]. Therefore we opted to focus our analyses on HV rather than SV.

Our study shows a yearly increase in utilisation of PN in the UK since the issuance of the EAU recommendation in 2010 [2] and closer adherence to guideline recommendations for PN in higher volume hospitals (>100 cases). The general PN rate appears low but reflects only the rate among surgically treated T1 tumours and is not representative for the overall rate of nephron sparing approaches which includes ablation and surveillance.

An increase in PN has been shown in other European databases, and is probably attributable to the introduction of robotic surgery [17, 23, 24]. In addition, a recent systematic review of more than 20,000 patients shows that robot-assisted PN was significantly superior for blood loss, transfusions, complications, hospital stay, readmissions and even overall mortality (OR 4.45, p <0.0001) compared

to open PN [25]. The association of HV with postoperative complications in our analysis may therefore be a reflection of the increased use of robot assisted surgery in higher volume centres (supplementary Figure 5a and b) rather than a direct consequence of lower versus higher volume. It is likely that higher volume centres are more frequently equipped with surgical robotic platforms than lower volume centres, which can also explain some of the discrepancies found. Due to inequality in the use of robotic versus laparoscopic or open PN between lower and higher volume hospitals we were unable to correct the analysis of postoperative complications in association with HV (Figure 5) for type of approach.

Finally, we considered whether completeness of data collection could be a reflection of the quality of self-auditing. However, we found no association between completeness of data and HV.

This study has several limitations. It is retrospective analysis and data collection is based on self-auditing, surgeon reported data, which could lead to underreporting of complications, for example. In addition, no long-term follow up data is collected, and complete data on complexity and comorbidities were not available in all cases. It is also important to note that the nephrectomy audit does not include patients who underwent ablation or active surveillance; and patient characteristics may be skewed towards a more surgically selected population. Further, it cannot be excluded that the predominant use of robotic PN in high-volume centers may be the driver of an increased use of PN and lower postoperative complications. We did not statistically prove that the association between volume and complication rate is non-linear (on the log odds scale), but as the volume can never be lower than zero we used a flexible model with a spline curve. Consequently, the association could not be summarized by a single odds ratio, and a graph was presented instead. Finally, referral patterns involving more cT1a tumours or complex cases from low volume hospitals to be treated in high volume hospitals cannot be ruled out. The availability of the robotic platform could also lead to referral of PN suitable cases from low to higher volume centres, as a means to provide minimally invasive nephron-sparing surgery to patients that could not access it if they remained in their local hospitals. The higher rate of cT1b tumours in lowest volume hospitals seems to suggest this in part.

None-the-less, our study is one of the largest studies with information on complexity of the renal tumours to allow detailed comparisons of PN rate and surgical complications in relation to hospital volume.

In conclusion, our study of the BAUS nephrectomy audit found that the probability of treatment of cT1 tumours with PN increased with increasing HV (from 18.1 % in centres performing <25 cases/year [Lowest volume] to 61.8% in centres performing >100 cases/year [high volume]), whereas an inverse association of HV with overall and major (Clavien Dindo ≥) complication rate is found (from 12.2% and 2.9% in low volume centres to 10.7% and 2.2% in high volume centres, respectively), for all patients including those treated with PN. These results show closer adherence to international guidelines in

higher volume centers in the UK, and support the centralization of specialist cancer surgical services to improve patient outcomes.

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Table and figure legends

Table 1 Patient characteristics categorised by hospital volume from 2012-2016

Figure 1Consort flow chart of study design

Figure 2 Proportion and absolute number of partial nephrectomies for clinical T1 renal lesions by annual nephrectomy hospital volume categories from 2012 to 2016

Figure 3 Funnel plot illustrating the association between annual nephrectomy hospital volume and the proportion of partial nephrectomies for clinical T1 renal lesions in 2016

Figure 4A) Predicted probability of partial nephrectomy by annual nephrectomy hospital volume categories in cases with a low complex renal tumor score (Padua scores 6 and 7) adjusted for age; B) Predicted probability of partial nephrectomy by annual nephrectomy hospital volume categories in cases with a intermediate complex renal tumor score (Padua scores 8 and 9) adjusted for age; C) Predicted probability of partial nephrectomy by annual nephrectomy hospital volume categories in cases with a high complex renal tumor score (Padua scores 10 to 13) adjusted for age.

Figure 5Post operative complications graded by the Clavien Dindo classification by tumour complexity score (low - Padua scores 6 and 7 -, intermediate - Padua scores 8 and 9 -, high - Padua scores 10 to 13) and annual nephrectomy hospital volume categories.

Figure 6Restricted cubic spline curve of the association between major postoperative complications (Clavien Dindo grade 3 and above) and annual hospital partial nephrectomy volume. The dotted lines indicate the 95% confidence interval.

Supplementary Figure 1 – A) Distribution of surgically treated clinical T1a lesions by procedure from 2012 to 2016; B) Distribution of surgically treated clinical T1b lesions by procedure from 2012 to 2016.

Supplementary Figure 2 – Proportion of cases with recorded tumour complexity score (using the Padua classification) in surgically treated clinical T1 lesions by procedure from 2012 to 2016

Supplementary Figure 3 – Absolute number of hospitals with clinical T1 lesions surgically treated from 2012 to 2016 categorised by annual nephrectomy hospital volume.

Supplementary Figure 4 – A) Proportion of procedure type for clinical T1a lesions by annual nephrectomy hospital volume categories from 2012 to 2016; B) Proportion of procedure type for clinical T1b lesions by annual nephrectomy hospital volume categories from 2012 to 2016.

Supplementary Figure 5 – A) Distribution of partial nephrectomy surgical approach (open, laparoscopic, robotic or unknown) by annual nephrectomy hospital volume categories from 2012 to 2016; B) Distribution of partial nephrectomy surgical approach (open, laparoscopic, robotic or unknown) per year according to annual nephrectomy hospital volume categories.