Contemporary Surgical Management of Renal Oncocytoma: A nation's outcome

Keywords

renal oncocytoma, oxyphilic adenoma, nephrectomy, intraoperative complications, postoperative complications

Abbreviations

ASA – American Society of Anaesthesiologists

BAUS – The British Association of Urological Surgeons

CT – x ray based computed tomography

eGFR – estimated glomerular filtration rate

IQR – Interquartile range

MDRD – Modification of diet in renal disease

MRI – Magnetic resonance imaging

NHS – National health service

SPECT – Single-photon emission computed tomography

TNM – Tumour Node Metastasis

UK – United Kingdom

WHO – World Health Organization

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Abstract

Objectives: To report on the contemporary UK experience of surgical management of renal oncocytomas.

Subjects and methods: Descriptive analysis of practice and postoperative outcomes of cases with a final histological diagnosis of oncocytoma included in The British Association of Urological Surgeons (BAUS) nephrectomy registry from 01/01/2013 to 31/12/2016. Short term outcomes were assessed over a follow-up of 30 days.

Results: Over 4 years, 32130 renal surgical cases were recorded in the UK, of which 1202 were oncocytomas (3.7%). Most patients were male (n=756; 63.3%), the median age was 66.8 years (interquartile range (IQR) 13). Median lesion size was 4.1cm (IQR 3; range 1-25cm), 43.5% were ≤4cm and 34.2% were 4 to 7cm lesions. Thirty-five patients (2.9%) had preoperative renal tumour biopsy. The majority of patients had minimally invasive surgery, either radical (n=683; 56.8%), partial nephrectomy (n=483; 40.2%) or other procedures (n=36; 3%). One in five (n=253; 20.2%) patients had in-hospital complications: 48 were Clavien-Dindo classification grade III or above (4% of total cohort), including 3 deaths. Two additional deaths occurred within 60 days of surgery. The analysis is limited by the study's observational nature, not capturing lesions on surveillance or ablated after biopsy, possible underreporting, short follow-up, and lack of central histology review.

Conclusion: We report on the largest surgical series of renal oncocytomas. In the UK, the complication rate associated with surgical removal of a renal oncocytoma was not negligible. Centralisation of specialist services and increased utilisation of biopsy may inform management, reduce overtreatment, and change patient outcomes for this benign tumour.

Introduction

Increasing use of imaging has led to a rise in the diagnosis of renal lesions in general, and of small renal masses (<4cm of greater axis) in particular[1]. The classic diagnostic and treatment pathway of renal masses typically involves contrast-enhanced imaging followed by surgery, usually either in the form of partial or radical nephrectomy[2]. While imaging can be helpful to recognise some benign lesions, such as classic fat-containing angiomyolipomas, the diagnostic accuracy between oncocytomas and renal cell carcinoma is generally poor[3].

Oncocytomas arise from the distal tubular epithelium of the kidney. Even when associated with typical features of aggressiveness, such as large size, perinephric fat and vascular invasion, they display non-malignant behaviour and have an excellent prognosis[4, 5]. Renal tumour biopsy can be used to ascertain the histological nature of small renal masses and guide management but has yet to be adopted into standard clinical practice. Reflecting this, oncocytoma is a postoperative diagnosis in 3 to 4% of partial and radical nephrectomies[5]. A previous analysis of the BAUS nephrectomy registry has demonstrated that, in the UK, 3.9% of surgeries for both benign and malignant renal tumours are associated with major complications[6]. However, given its benign nature, surgery may represent overtreatment in small asymptomatic renal oncocytomas.

In this study, using data from a nationwide surgical registry, we aim to assess the contemporary UK surgical experience with renal oncocytomas, and evaluate the postoperative short-term outcomes associated with this benign tumour.

Subjects and methods

In England, urological surgeons are mandated to report on all nephrectomy cases to The British Association of Urological Surgeons (BAUS) registry (www.baus.org.uk/patients/surgical_outcomes) since December 2012. Surgeons from Scotland, Wales, and Ireland can also input data but this was not mandated in the time period studied. The BAUS surgical registry has ethical approval under section 251 of the NHS Act 2006.

We audited this registry for all cases with a final diagnosis of renal oncocytoma from 01/01/2013 to 31/12/2016 and sought to assess clinical practice and outcomes over a follow-up period of 60 days. Long term outcomes were not analysed due to the high rate of underreporting (not reported for 83.4% of cases).

Data items included demographic characteristics, comorbidity index (using Charlson index, age-related Charlson index, and ASA grading systems), performance status (using the WHO performance status classification), pathologic tumour staging (according to the 2010 TNM staging classification), use of pre-operative biopsy, type of surgery, surgical approach, and operative complications.

All complications were categorised and predefined in the registry, and surgeons reporting to the database chose the most appropriate options. More than one complication could be reported for each patient. In addition to formal report of intra-operative bleeding, the event was also considered present if both of the following conditions were met: there was blood loss in excess of 1 litre during surgery; and the transfusion of packed red blood cells was required intra-operatively. Postoperative bleeding was defined solely by the surgeon's report of occurrence of a postoperative bleeding event. Baseline renal function was considered normal if the estimated glomerular filtration rate (eGFR; calculated using the MDRD study

equation) was equal or above 60 ml/min/1.73m^2 or, when eGFR was missing, if serum creatinine levels were below 110 μmol/L. Post-operative eGFR was recorded as a categorical variable in the registry (normal as above 60 ml/min/1.73m^2 or abnormal as below 60 ml/min/1.73m^2). In addition to formal report by the surgeon of postoperative renal impairment as a complication, the event was also considered if an eGFR below 60 ml/min/1.73m^2 was recorded post-operatively on a patient who had normal baseline renal function preoperatively.

Patients who had in-hospital operative complications were attributed a Clavien-Dindo classification grade by the data reporting surgeon (the highest graded complication was considered for analysis). Events graded III or above were considered major complications. Where an unplanned intensive care unit admission had taken place, cases were re-graded as a major complication (grade IV) if the Clavien-Dindo classification grade was missing (4 cases) or a grade of I or II had been attributed (4 cases). Finally, 60-day mortality was also recorded and incorporated any deaths occurring during or after admission within the first 30 days after surgery.

Descriptive analysis of all data was performed using Microsoft Excel. Continuous variables are presented as median, range, and interquartile range. Categorical variables are presented as absolute number, and relative proportion of cases (%). When relevant, missing data was presented as absolute number, and relative proportion of cases (%).

BAUS funds data management of the BAUS registry database. No specific funding was allocated to conduct the present study.

Results

During the four-year period analysed, out of 32130 renal surgeries performed, 1202 cases (3.7%) had a final histological diagnosis of oncocytoma. Overall, 210 procedures with a final diagnosis of renal oncocytoma were recorded in the year of 2013 (2.8% of all 2013 cases), 322 in 2014 (4% of all 2014 cases), 348 in 2015 (4.2% of all 2015 cases), and 322 in 2016 (4% of all 2016 cases). The total number of surgical procedures reported on the registry were 7625 in 2013, 8129 in 2014, 8324 in 2015, and 8052 in 2016.

The 1202 cases of oncocytoma were operated in 136 centres: the median number of cases per centre was five (interquartile range (IQR) 9.25; range from 1 to 49). Most patients were male (n=756; 63.3%), with a median age of 68 years (IQR 13; range from 25 to 100 years; Table 1). Only two patients (0.2%) had confirmed hereditary syndromes (one case of tuberous sclerosis, and one of Birt-Hogg-Dubé syndrome) and 16 (1.3%) patients had bilateral renal lesions. The majority were asymptomatic (n=860; 74.1%) and had normal baseline renal function (n=797; 78.6%). The median tumour size was 4.1 cm (IQR 3; range from 1 to 25), and the majority of lesions were at or under 7cm (n=887; 83.4%).

Of 1202 oncocytoma cases, 35 patients had pre-operative renal tumour biopsy (3.2%): eight biopsies occurred in 2013, seven in 2014, seven in 2015, and 13 in 2016. Of biopsied patients, the median renal mass size was 3.8cm (IQR 2.3; range from 1.5 to 8.5). Over half had benign histology on biopsy (n=18; 54.6%) but seven (21.2%) were reported malignant on histology, eight (24.2%) biopsies were non-diagnostic, and in two cases biopsy histology was missing (Table 2). This means that only 18 in 1202 patients (1.5%) had knowingly benign histology pre-operatively and all other patients were diagnosed post-operatively.

Just over half of all patients had radical nephrectomy (n=683; 56.8%), primarily via the laparoscopic approach (n=560; 82% of all radical nephrectomies; Table 3). Partial nephrectomy was the second most frequent management option (n=483; 40.2% of all patients), preferentially done using robotic assistance (n=186; 38.5% of all partial nephrectomies) or via open approach (n=163; 33.8% of all partial nephrectomies). A small number of patients were diagnosed with oncocytoma after simple nephrectomy, nephroureterectomy, or other surgical procedure (n=36). Looking solely at tumours up to 4cm, 343 out of 523 cases were diagnosed after partial nephrectomy (65.6%), 163 after radical nephrectomy (31.2%), and 17 after other non-nephron sparing approaches (3.2%).

The conversion rate from all minimally invasive techniques to open surgery was 3.4% (n=32). After surgery, the median length of hospital stay was four days (IQR 3; range from 0 to 99).

Overall, one in five patients suffered from in-hospital complications (n=243; 20.2%). These included 31 (12.8%) patients with intra-operative complications, 195 (80.2%) with postoperative complications, and 17 (7%) patients with both intra- and postoperative complications. The most frequent intra-operative complication was bleeding (n=35), followed by pneumothorax (n=3), splenectomy (n=2), bowel injury (n=1), liver injury (n=1); 7 intra-operative complications were classified as “other” (of note, one patient developed more than one intra-operative complication). The most frequent postoperative complication was renal impairment (n=57, representing 6.4% of all patients with reported normal baseline renal function), followed by chest infection (n=37), bleeding (n=27), ileus (n=20), wound infection (n=23), problematic pain control (n=2), and deep vein thrombosis/pulmonary embolus (n=1); in 60 cases post-operative complications were classified as “other”, and in 3 they were not

classified (of note, 15 patients developed more than one postoperative complication). In total, 123 patients (10.2%) were admitted to intensive care unit after surgery: 104 (84.6%) admissions were planned but 17 (13.8%) were unplanned (data was missing for two patients).

Clavien-Dindo classification grades were attributed to 168 cases (69.1% of all cases with complications), 48 of which were considered major complications (representing 4% of the whole cohort). Of all cases with complications, 46 were classified as Clavien-Dindo grade I, 74 as grade II, 16 as grade IIIa, 17 as grade IIIb, 12 as grade IVa/b, and three as grade V.

Apart from the three in-hospital deaths, one additional death occurred within 30 days of surgery and another within 60 days of surgery, totalising a 30-day mortality rate of 0.3% and a 60-day mortality rate of 0.4%. All five deaths occurred in male patients that had over 65 years old. One patient had a lesion under 4cm (38mm) and two had lesions between 4 and 7cm (44mm and 61mm). Two patients had an ASA grade of 3. The cause of death (acute pancreatitis after surgery for a left sided renal tumour and bowel ischaemia that required resection after an open radical nephrectomy) was only detailed for two patients that died during hospital admission.

Discussion

We report on the largest published surgical series of renal oncocytomas. Our analysis shows that, in the UK, a significant number of patients with this benign kidney tumour are currently diagnosed after surgery. Nearly half (49.2%) of cases operated on were small renal masses and 83.4% were tumours under 7cm. Moreover, one in five patients suffered in-hospital operative complications, most commonly bleeding and renal impairment. Importantly, 4% of the cohort experienced major complications and five deaths occurred within 60 days following surgery.

This study has a number of limitations: it's observational nature, possible under or misreporting, lack of central pathology review, and short-follow up. Likewise, the registry does not capture lesions on surveillance or ablated after biopsy, so the true incidence of oncocytomas and outcomes of other management options cannot be extrapolated. Still, we believe that the study results warrant some reflection on current practices.

Renal oncocytomas are typically non-aggressive tumours, and the risk of treatment complications which are justifiable in the context of malignancy or symptom control may be less acceptable with a benign indolent tumour. The frequency of oncocytomas in the overall registry (3.7%) and the short-term complication rate of this surgical cohort was similar to previous publications encompassing both benign and malignant surgical cases[5, 6]. In the UK, previous analysis of the BAUS registry has shown that 3.9% of patients who had surgery for benign or malignant kidney tumours suffered major operative complications[6]. A risk of this magnitude may be acceptable considering the potential mortality of localised kidney cancer (five-year relative survival rate of around 80% for stage I and II disease[7]), but may be questionable in the context of benign disease. To our

knowledge, not a single disease-specific death has been reported in the literature for patients with renal oncocytomas. In the present cohort, surgery led to the death of five patients. Moreover, in the current analysis possible underreporting and the lack of long term follow up may have contributed towards underestimation of the total complication burden. We observed that over 70% of patients in this cohort were asymptomatic and nearly half presented with small renal masses. At least 21.4% had preoperative renal dysfunction and almost half were aged 70 years or above. Thus, surgery likely represented overtreatment for a significant proportion of the cohort and a preoperative diagnosis of a benign tumour might have led to a more informed consultation and consent process.

The BAUS registry reports only surgical cases so the number of patients undergoing preoperative biopsy must not be interpreted as an estimate of total UK utilisation of renal tumour biopsy. However, considering the high number of small renal tumours in the present series, we suspect tumour biopsy is still underutilised in the UK. Likewise, the fact that only half of cases with a preoperative biopsy were correctly categorised should not be interpreted as the nationwide biopsy diagnostic accuracy. This data is skewed by the fact that it was captured on a surgical registry. If patients who had a biopsy diagnosis of an oncocytoma were offered other management options instead of surgery, we would expect that the pre-operative biopsies captured in any surgical registry to be almost all malignant, non-diagnostic or inconclusive. A systematic review of large volume centre series has reported a median diagnostic accuracy rate of 90.3%[8]. Thus, in centralised care a high diagnostic rate can be achieved and using this strategy could help prevent overtreatment associated morbidity.

European guidelines advise that renal oncocytomas can be managed with active surveillance if histological diagnosis has been attained[2]. Studies performed in high volume tertiary referral centres have shown that renal tumour biopsy is an accurate and safe procedure[8, 9]: bleeding that requires transfusion or intervention is rare (<1%) and the fear of tumour seeding is unfounded with the use of coaxial needles. However, due to shared morphologic features between oncocytoma and chromophobe renal cell carcinoma, the distinction between both on biopsy can be challenging. In a recent systematic review including ten renal tumour biopsy series, a quarter of 46 cases initially diagnosed as oncocytic tumours on biopsy turned out to be renal cell carcinoma after surgery[10]. Nonetheless, in this analysis equivocal biopsies were not distinguished from cases with more definitely benign features. Moreover, from the aggregated analysis of 205 biopsy cases, only 46 proceeded to surgery: selection bias of dubious cases towards surgery rather than other management strategies could have influenced results. A large single centre series (144 biopsied oncocytic tumours) not included in the above cited systematic review suggests and uses morphologic features and expression markers that can aid in the distinction between oncocytoma and malignancy on biopsy[11]. Using these tools, out of 28 cases that underwent resection, concordance between biopsy and final histology was 94%, with only one oncocytoma in six on biopsy being reclassified as possible low grade renal cell carcinoma after surgery[11]. Studies that have reported on the diagnostic rate and accuracy of renal tumour biopsy stem from large expert centres. Additionally, in the present cohort a considerable number of patients were deemed to have a malignant mass at biopsy that later was confirmed to be an oncocytoma. Thus, the widespread adoption of renal tumour biopsy for the pre-operative diagnosis of oncocytoma may only be applicable if accompanied by

centralisation of services and histology review by specialist uro-pathologists. Finally, once validated, alternative diagnostic modalities with high specificity such as multi-parametric MRI and/or ^{99m}Tc-sestamibi SPECT/CT could potentially be used to further elucidate any diagnostic uncertainties[12, 13].

Currently in the UK, there is only a surgical mandatory registry. Thus, the proportion of oncocytoma cases on active surveillance or subject to other management modalities remains unknown. Active surveillance is a safe management option for T1 oncocytomas and chromophobe renal cell carcinomas[14, 15]. Moreover, tumour ablation has been shown to be more cost effective and safer than surgery for small renal masses[16] and could be an attractive alternative treatment option for histologically proven symptomatic oncocytomas or for oncocytic tumours with hybrid features.

Similarly to other health systems, the direction of policy change in the UK is towards far greater centralisation for the evaluation and management of renal masses. With such centralisation, it may be feasible to set critical mass among interventional radiology and pathology, enabling an increased and accurate use of tumour biopsy for small renal masses. This will also aid the development of translational and clinical research to predict more accurately the subtype in equivocal cases, the natural course of disease, and the establishment of active surveillance and ablation registries. Increased utilisation of renal tumour biopsy in the kidney mass diagnostic pathway will allow a more informed consultation and empower patients and clinicians. This will enable reduction in the overtreatment of benign lesions, thus improving clinical outcomes, and redirect efforts and costs towards potentially life-threatening malignancies.

To conclude, the complication burden associated with surgical removal of renal oncocytoma in the UK is not negligible. Treatment morbidity is significant in the context of a benign indolent tumour. Histology disclosure by increased use of renal tumour biopsy at diagnosis can redirect patients with renal oncocytomas and other benign tumours to other less morbid and less costly management options, including active surveillance or ablation.

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Tables