Incidental small renal tumours: are we performing unnecessary surgery?

Written for Trends in Urology and Men's Health

Hannah Warren[1,2], Maxine Tran[1,2]

1. Division of Surgery and Interventional Sciences , University College London, UK
2. Specialist Centre for Kidney Cancer, Royal Free Hospital, London, UK

Introduction

Kidney cancer is currently the 7th most common cancer in the developed world(1). It is more common in men than women (5 men: 3 women). The expanding use of cross-sectional imaging across medical practice has resulted in a rise in incidentally detected renal tumours. UK national cancer statistics demonstrate an 88% increase in incidence of kidney cancer since 1990s (2), in keeping with international data (1). While incidence has risen, there has been a stage migration in diagnosis, as incidental tumours are more likely to be detected at an earlier stage than those presenting with symptoms. However, despite increased detection at earlier stages, and earlier treatment, there has been no impact on mortality from Kidney Cancer (3).

Early detection of organ confined cancer allows the opportunity for treatment with curative intent. The UK National Health Service (NHS) has published in its Long Term Plan the ambition of further increasing the proportion of cancer detected at stages 1 and 2 from 50% to 75% of all cases by 2028 (4). In kidney cancer, introduction of screening through imaging (5), or emerging serum biomarkers (6) may allow this ambition to be realised.

Small renal tumours (SRTs), defined as a tumour <4cm in maximum diameter represent a spectrum of disease, from benign, through indolent malignant tumours to high-grade aggressive disease. Up to 30% of SRTs in surgical series are found to be benign on histopathology (7), with a higher proportion of benign histology in tumours of smaller size (8). National audit data from the British Association of Urological Surgeons (BAUS) reported that in 2012, 18% of all nephron sparing surgery had resulting benign histology. Of the malignant tumours, the majority were low grade, with high grade disease representing only 18-22% of cases (8), which is in keeping with national data from the USA(9).

Does early detection and treatment really improve outcomes?

One might assume that diagnosing and treating tumours at an earlier stage would lead to improved outcomes. Cancer Research UK reports that kidney cancer survival is improving with 32% of adults diagnosed with kidney cancer surviving to 10 years in 1990, rising to 50% in 2010. However, increased survival can mean a number of things. Bringing forward the time point of diagnosis automatically increases survival by virtue of patients living longer with disease, even if they die at exactly the same age. This survival bias in cases of earlier detection is known by epidemiologists as lead-time bias.

Another bias to consider when reporting survival trends is overdiagnosis bias. Screening for cancer can lead to detection of tumours that if left untreated would have remained stable, regressed or progressed slowly enough that the patient died of an unrelated cause before symptoms of the cancer ever appeared. This is known as overdiagnosis. Historically patients with kidney cancer presented with symptoms as a sign of late-stage disease e.g. haematuria due to the tumour invading the urinary collecting system. These patients experience poor survival. Unintentional screening for kidney cancer through imaging has introduced diagnosis of clinically indolent disease, and shifted

the kidney cancer population to include those who will experience very long survival regardless of how they are managed. This is overdiagnosis bias.

In order to truly understand if earlier detection of kidney cancer improves patient outcomes, we need to look at cancer-specific mortality. If treatment of incidentally detected disease prevented kidney-cancer related deaths, we would expect to see a reduction in kidney cancer-specific mortality at the population level. Figure 1 demonstrates this is not the case, with national data from Cancer Research UK showing rising incidence but no reduction in mortality, the hallmark of over-detection and in turn overtreatment. The same pattern has been demonstrated in the United States with data from the Surveillance, Epidemiology, and End Results registry (3).

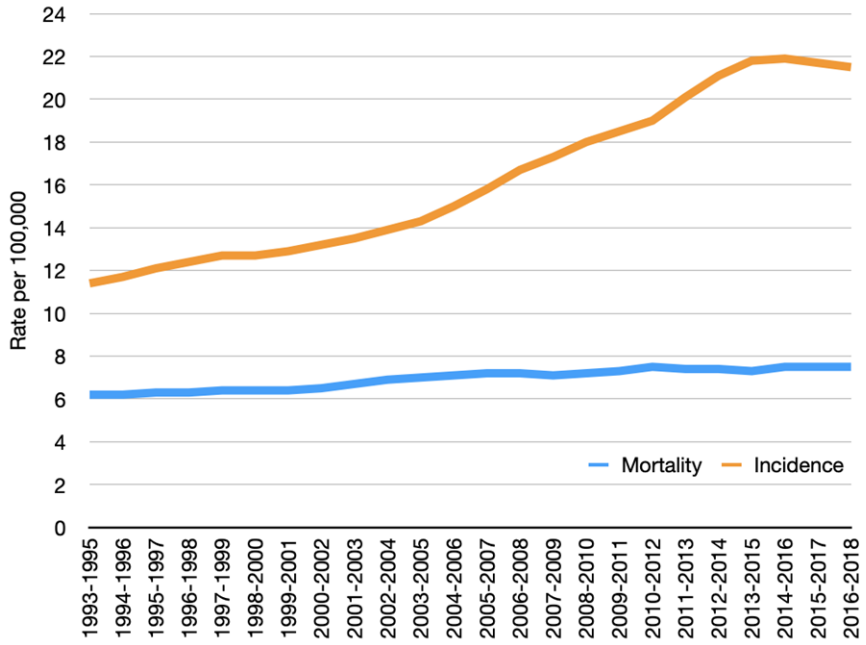

Figure 1: Temporal trend in age-standardised incidence and mortality for renal cancer per 100,000 persons population, UK.
Data from Cancer Research UK (1)

Natural history of small renal tumours

Our understanding of natural history of SRTs in the short and medium term has been largely based on observational cohort studies in patient populations unfit or unwilling to undergo active treatment. In the USA, a prospective registry of 271 patients who opted for initial management with active surveillance reported that over a median follow up of 1.83 years, mean growth rate was 0.9 mm/year with no patients developing metastases or dying from kidney cancer (10). At 5 years, the same registry reported cancer-specific survival of 100% (11). While 22% of study participants experienced tumour progression, defined as rapid tumour growth >5 mm/year or crossing the 4 cm threshold, none developed metastases(11). In a similar Canadian study of 127 patients with SRTs followed up for a median 2.3 years, 79% of patients' tumours remained stable or regressed with an overall mean growth rate of 1.3 mm/year (12). Of remaining cases, 20% demonstrated local progression still amenable to curative treatment, and 1% developed metastatic disease (12).

Initial active surveillance of SRTs appears to be safe, while retaining the opportunity for curative treatment in the minority of patients who develop progressive disease. The majority of the literature reporting active surveillance outcomes is from observational studies in elderly or co-morbid

populations and thus applicability to younger, fitter populations is limited. While there is some emerging data supporting the use of surveillance in younger patients (13), most are managed surgically and thus we lack data on the natural history of tumours in younger patients. As these existing registries mature, they will provide longer term follow-up data, which will be useful for clinicians to counsel patients regarding the risks and benefits of active surveillance in the management of small renal tumours.

Surgery for small renal tumours

International urology guidelines recommend offering surgery to achieve cure in suspected localised renal cancer (14,15). Partial nephrectomy should be performed when technically feasible, offering preservation of renal function and good oncological control. However, partial nephrectomy is a complex operation with a 20% overall risk of complications from surgery, and 5% risk of major complications (8). Partial nephrectomy is usually performed with the use of a surgical robot, with consumables costing approximately £1600/case, on top of the robot purchase and maintenance costs.

Thermal ablation

Thermal ablation therapy offers an alternative active treatment option for SRTs with a favourable complication profile and comparable oncological outcomes to partial nephrectomy, according to propensity score matched observational data (9). Thermal energy (either cryo, microwave or radiofrequency) is delivered through a probe or needle to ablate the SRT. The procedure is typically performed percutaneously under image guidance, and offers shorter hospital stay and faster recovery.

Currently there are no head-to-head RCTs comparing ablation to surgery for small renal masses, but results of the feasibility RCT NEphron Sparing Treatment (NEST) comparing cryoablation to partial nephrectomy are anticipated soon (ISRCTN18156881).

Risk stratification

Clearly a subset of kidney cancer patients will benefit from early detection and treatment to prevent progression to metastatic disease and kidney cancer-related death. However, this has to be balanced against the significant proportion of patients with benign or indolent small renal tumours whom would do well to avoid treatment and the associated morbidity.

Contemporary imaging with CT, MRI or ultrasound cannot reliably distinguish benign tumours from malignant, nor high from low grade malignant disease. Pre-operative renal tumour biopsy is under-utilised and often not routinely offered by clinicians due to concerns regarding bleeding, tumour seeding, misdiagnosis, and non-diagnostic rates(16,17) and its routine use is not currently recommended by clinical guidelines in the work up of SRTs(14,15).

At our own institution we routinely offer biopsy. Our local audit data has shown 78/266 (30%) patients biopsied between 2014-2016 had benign diagnoses with 75/78 (96%) choosing management with surveillance, and the remaining 3 (4%) ablation(18). No patient with benign histology chose surgical excision. We would therefore advocate routinely offering renal tumour biopsy where technically feasible to facilitate patient-centred decision making.

Emerging evidence

Investigation of new imaging approaches to improve characterisation of incidentally detected small renal masses has been identified as a priority research need by the Renal Cancer Gap Analysis Collaborative, composed of clinicians, researchers, patients and carers(19).

^{99m}Tc-sestamibi SPECT/CT is an emerging tool for the non-invasive identification of benign renal oncocytomas and other oncocytic neoplasms of low malignant potential. ^{99m}Tc-sestamibi is a lipophilic cationic radiopharmaceutical that readily accumulates in oncocytic cells that are packed with high concentrations of mitochondria with negative membrane potential. Other renal cell carcinomas have relatively few mitochondria, and additionally multi-drug resistance proteins on the cell surface pumping the radiotracer out of cells (20). These biological differences in 99mTc-sestamibi processing result in benign and indolent tumours appearing avid, and other renal cell carcinomas photopenic, as shown in figure 2. The ability to predict oncocytic histology would allow patients with these groups of benign and indolent tumours to be spared unnecessary surgery.

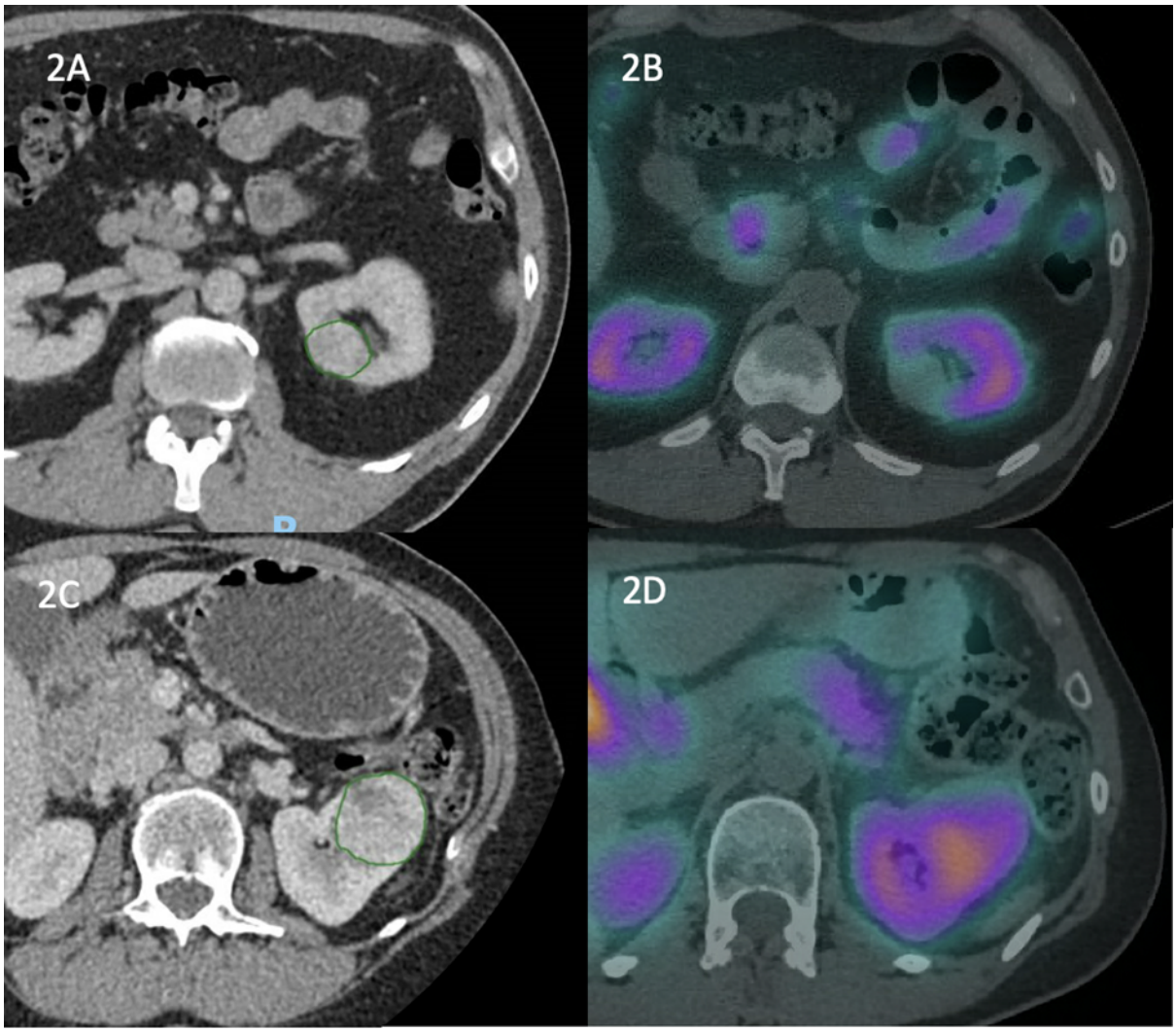

Figure 2: Indeterminate contrast-enhancing renal masses on cross sectional imaging later proven on histology to be clear cell renal cell carcinoma (RCC) (2A) and renal oncocytoma (2C). On 99mTc-sestamibi SPECT/CT the clear cell RCC is devoid of radiotracer (2B) while the oncocytoma shows uptake (2D).

Imaging-based diagnostic tools are also being investigated for their ability to prospectively predict clear cell histology, typically a more aggressive histological subtype of renal cell carcinoma. An MRI-based 5-point 'clear cell likelihood score' (ccLS) for has demonstrated high sensitivity and specificity in a prospective study (21). Additionally, the ZIRCON study (NCT03849118) is an open-label phase 3 trial investigating 89Zr radiolabelled girentuximab for the detection of clear cell renal cell carcinoma. Clear cell renal cell carcinomas uniquely express the enzyme carbonic anhydrase IX and girentuximab is an anti-CAIX antibody. The limitation of both tests is that they do not differentiate high grade from low grade clear cell tumours, nor further differentiate the non-clear cell tumours into benign and malignant. They may however have a role to play in future diagnostic algorithms.

Conclusions

Surgery for incidentally detected SRTs represents the mainstay of current management, but can represent overtreatment in a significant proportion of patients. There is an unmet clinical need for better diagnostic tools to risk stratify tumours and inform management decisions. Consultations with patients with SRTs should include discussions of biopsy, surveillance, ablation and surgery as potential initial strategies. It is hoped that emerging imaging-based diagnostics for better risk stratification of renal tumours will help facilitate these conversations and allow better informed, patient-centred management.

Key Messages:

- Inadvertent screening for small renal tumours through imaging for other indications has led to tumour detection at an earlier stage
- Kidney cancer specific mortality has not improved, suggesting overdiagnosis and overtreatment of indolent disease
- Risk stratification with renal tumour biopsy allows can allow those with benign or indolent tumours to avoid invasive treatment
- Novel imaging techniques such as 99mTc-sestamibi SPECT/CT may allow non-invasive risk stratification of small renal tumours

1. Ervik M, Lam F, Laversanne M, Ferlay J, Bray F. Global Cancer Observatory: Cancer Over Time. [Internet]. International Agency for Research on Cancer. 2021 [cited 2022 Jul 15]. Available from: https://gco.iarc.fr/overtime
2. Cancer Research UK. Kidney Cancer Incidence Statistics [Internet]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer/incidence?_ga=2.25678974.257405545.1609191159-651160254.1609191159
3. Welch HG, Skinner JS, Schroeck FR, Zhou W, Black WC. Regional Variation of Computed Tomographic Imaging in the United States and the Risk of Nephrectomy. JAMA Intern Med. 2017;178(2):221–7.
4. The NHS Long Term Plan [Internet]. 2019. Available from: www.longtermplan.nhs.uk

5. Usher-Smith JA, Godoy A, Burge SW, Burbidge S, Cartledge J, Crosbie PAJ, et al. The Yorkshire Kidney Screening Trial (YKST): protocol for a feasibility study of adding non-contrast abdominal CT scanning to screen for kidney cancer and other abdominal pathology within a trial of community-based CT screening for lung cancer. BMJ Open [Internet]. 2022 Sep 20;12(9):e063018. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2022-063018
6. Beer TM, McDonnell CH, Nadauld L, Liu MC, Klein EA, Reid RL, et al. Interim results of PATHFINDER, a clinical use study using a methylation-based multi-cancer early detection test. Journal of Clinical Oncology. 2021 May 20;39(15_suppl):3010–3010.
7. Kim JH, Li S, Khandwala Y, Chung KJ, Park HK, Chung BI. Association of Prevalence of Benign Pathologic Findings after Partial Nephrectomy with Preoperative Imaging Patterns in the United States from 2007 to 2014. JAMA Surg. 2019;154(3):225–31.
8. Fernando A, Fowler S, Brien TO. Nephron-sparing surgery across a nation – outcomes from the British Association of Urological Surgeons 2012 national partial nephrectomy audit. BJU Int. 2016;117:874–82.
9. Xing M, Kokabi N, Zhang D, Ludwig JM, Kim HS. Comparative effectiveness of thermal ablation, surgical resection, and active surveillance for T1a renal cell carcinoma: A surveillance, epidemiology, and end results (SEER)–Medicare-linked population study. Radiology. 2018;288(1):81–90.
10. Uzosike AC, Patel HD, Alam R, Schwen ZR, Gupta M, Gorin MA, et al. Growth Kinetics of Small Renal Masses on Active Surveillance: Variability and Results from the DISSRM Registry. Journal of Urology. 2018 Mar 1;199(3):641–8.
11. Pierorazio PM, Johnson MH, Ball MW, Gorin MA, Trock BJ, Chang P, et al. Five-year Analysis of a Multi-institutional Prospective Clinical Trial of Delayed Intervention and Surveillance for Small Renal Masses: The DISSRM Registry. Eur Urol. 2015 Sep 1;68(3):408–15.
12. Jewett MAS, Mattar K, Basiuk J, Morash CG, Pautler SE, Siemens DR, et al. Active Surveillance of Small Renal Masses : Progression Patterns of Early Stage Kidney Cancer. Eur Urol. 2011;60(1):39–44.
13. Metcalf MR, Cheaib JG, Biles MJ, Patel HD, Pe VN, Chang P, et al. Adult Urology Oncology : Adrenal / Renal / Upper Tract / Bladder Outcomes of Active Surveillance for Young Patients with Small Renal Masses : Prospective Data from the DISSRM Registry. Journal of Ur. 2021;205(May):1286–93.
14. Ljungberg B, Albiges L, Bensalah K, Bex A, Giles R, Hora M, et al. EAU Guidelines on Renal Cell Carcinoma. 2020.
15. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal Mass and Localized Renal Cancer: AUA Guideline. Journal of Urology [Internet]. 2017;198(3):520–9. Available from: http://dx.doi.org/10.1016/j.juro.2017.04.100
16. Warren H, Neves JB, Tran MGB. Renal oncocytoma : landscape of diagnosis and management. BJU Int. 2021;128(6):685–7.
17. Richard PO, Martin L, Lavallée LT, Violette PD, Evans AJ, Jain K, et al. Identifying the use and barriers to the adoption of renal tumour biopsy in the management of small renal masses Patrick. Canadian Urological Association Journal. 2018;12(8):260–6.
18. Tanabalan C, Tadtayev S, Raman A AA, Webster G, Patki P, Mumtaz F, et al. Routine use of biopsy in the management of the small renal mass. J Clin Urol. 2017 Jun;10(2_suppl):7–83.

19. Rossi SH, Blick C, Handforth C, Brown JE, Stewart GD. Essential Research Priorities in Renal Cancer: A Modified Delphi Consensus Statement. Eur Urol Focus [Internet]. 2019;6(5):991–8. Available from: https://doi.org/10.1016/j.euf.2019.01.014
20. Rowe SP, Gorin MA, Solnes LB, Ball MW, Choudhary A, Pierorazio PM, et al. Correlation of 99m Tc-sestamibi uptake in renal masses with mitochondrial content and multi-drug resistance pump expression. EJNMMI Res. 2017;7(1):80.
21. Johnson BA, Kim S, Steinberg RL, de Leon AD, Pedrosa I, Cadeddu JA. Diagnostic performance of prospectively assigned clear cell Likelihood scores (ccLS) in small renal masses at multiparametric magnetic resonance imaging. Urol Oncol [Internet]. 2019;37(12 PG-941–946):941–6. Available from: NS -