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**Change in nephrometry scoring in small renal masses (<4cm) on active surveillance:
Preliminary observations from Tayside Active Surveillance Cohort (TASC) study**

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Key words: Kidney, partial nephrectomy, nephrometry score, complications

Abstract

Background: Prediction of growth, in particular knowing possibility of aggressive cancer in small renal masses on active surveillance remains poorly understood.

Objective: The study was designed to determine whether serial nephrometry score measurements could predict possibility of aggressive malignancy (grade of cancer) in patients with small renal masses (SRMs) opting for active surveillance initially.

Patients and methods: One hundred sixteen patients between January 2000 and December 2016 undergoing partial nephrectomy. Out of these, ninety seven were analyzed using different nephrometry scoring systems. Measurement of nephrometry scores (RENAL, PADUA, C-Index) was performed by two researchers. Amongst the patients opting for partial nephrectomy, 40 were on active surveillance for at least 12 months (mean 32; 12-60 months) prior to partial nephrectomy. CT scan images of these patients were retrieved and analysed including comparison with histopathology.

Results: Nephrometry scores measured on serial CT scan images showed a significant correlation between change in score and grade of cancer on multivariate analysis (p-value 0.001). Addition of multivariate analysis to nomogram based on change in size alone did not improve predictive value of AUC significantly.

Conclusions: Change in nephrometry scoring measurements correlates with grade of cancer in small renal masses but falls short of significantly predicting presence of malignancy or grade of cancer on nomogram in patients opting for active surveillance for small renal masses. At present, this approach may be inadequate for decision-making.

INTRODUCTION

The size of small renal masses (SRMs) correlates with the rate of malignancy on histology following excision { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. Whether changes in nephrometry scoring, a system which measures a range of parameters including the position of tumours in relation to hilar structures, can predict the rate of malignancy or aggressiveness of cancer is not known. The information related to growth patterns in relation to hilar structures, may inform physicians to adopt the best possible management plans, including the prediction of postoperative complications { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}.

There are three main nephrometry scoring systems described for kidney tumours according to pre-intervention computed tomography images and these are: RENAL (Radius of tumours, Exo/Endophytic; Nearness of tumours to the collecting system or sinus; Anterior/posterior; Location in relation to polar lines) nephrometry score { ADDIN EN.CITE { ADDIN EN.CITE.DATA }} , PADUA (Preoperative Aspects and Dimensions Used for Anatomical) nephrometry score { ADDIN EN.CITE { ADDIN EN.CITE.DATA } } , and Centrality index (C-index) { ADDIN EN.CITE <EndNote><Cite><Author>Simmons</Author><Year>2010</Year><RecNum>476</RecNum><DisplayText>[8]</DisplayText><record><rec-number>476</rec-number><foreign-keys><key app="EN" db-id="dr95wrtar2dsxmesffnpxe2qzserx02d0dxt" timestamp="1499595601">476</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Simmons, M. N.</author><author>Ching, C. B.</author><author>Samplaski, M. K.</author><author>Park, C. H.</author><author>Gill, I. S.</author></authors></contributors><auth-address>Department of Urological Oncology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio 44195, USA. simmonm2@ccf.org</auth-address><titles><title>Kidney tumor location measurement using the C index method</title><secondary-title>J Urol</secondary-title><alt-title>The Journal of urology</alt-title></titles><periodical><full-title>J

Urol</full-title></periodical><pages>1708-13</pages><volume>183</volume><number>5</number><edition>2010/03/20</edition><keywords><keyword>Adult</keyword><keyword>Aged</keyword><keyword>Aged, 80 and over</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Intraoperative Complications</keyword><keyword>Kidney Neoplasms/*diagnostic imaging/*surgery</keyword><keyword>Laparoscopy/methods</keyword><keyword>Male</keyword><keyword>Middle Aged</keyword><keyword>Nephrectomy/methods</keyword><keyword>Postoperative Complications</keyword><keyword>*Preoperative Care</keyword><keyword>Regression Analysis</keyword><keyword>Statistics, Nonparametric</keyword><keyword>Tomography, X-Ray Computed/*methods</keyword><keyword>Warm Ischemia</keyword></keywords><dates><year>2010</year><pub-dates><date>May</date></pub-dates></dates><isbn>0022-5347</isbn><accession-num>20299047</accession-num><urls></urls><electronic-resource-num>10.1016/j.juro.2010.01.005</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote> } . Detailed

description of these methods are described in their original reports{ ADDIN EN.CITE { ADDIN EN.CITE.DATA }}; however these measurement methods are designed to separate complex renal masses from non-complex ones by measuring their anatomical location within renal parenchyma and their relationship to hilar vessels and renal pelvis. Published literature mainly focuses on using these scoring systems to assess the possibility of complications or technical difficulties that surgeons may encounter in the surgical resection of SRMs. Reports in literature suggest a good inter-observer agreement in experienced hands { ADDIN EN.CITE { ADDIN EN.CITE.DATA }} and a predictability value of these scoring systems for postoperative complications following surgical excision { ADDIN EN.CITE { ADDIN EN.CITE.DATA }} and cryotherapy { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}.

There is little known about the predictive ability of these measurements to distinguish between benign and malignant histology and the grade of cancers. Few studies exploring the relations between nephrometry scores and histology concentrate on the single measurement of nephrometry scores { ADDIN EN.CITE { ADDIN EN.CITE.DATA } }, and a detailed correlation between changes in nephrometry scores and histology has not been reported.

A Tayside Active Surveillance Cohort (TASC), study prospectively acquired a group of patients with SRMs in a well-defined geographical area with robust follow-up using electronic systems. The cohort has been reported recently { ADDIN EN.CITE { ADDIN EN.CITE.DATA } } including an emphasis that measurements based on unidimensional, linear measurements of the tumour diameter remain inaccurate in predicting the rate of malignancy in SRMs. The traditional methods of measurement are based on the Response Evaluation Criteria in Solid Tumours (RECIST) criteria which assume that tumours are growing as spheres, an assumption held for a long time. There is a subgroup in the TASC cohort of patients who underwent surgical excision after showing progression on serial follow-up imaging in the active surveillance cohort. The group was compared with those with no progression in size during the same study period.

In this study, we measured three different nephrometry scores on a cohort of patients undergoing a partial nephrectomy and particularly assessed the predictive ability of changes in scores in distinguishing benign from malignant histology, including the grade of tumours. The patients with change in nephrometry scores were compared to those who remained static. Multivariate regression (including other possible factors) was carried out to assess the predictive ability of changes in nephrometry scoring.

PATIENTS AND METHODS

Study cohort

The TUCAN (Tayside Urological Cancers Network) hosts a database for TASC study with institutional Caldicott approval to publish data. A further description of the cohort including regulatory approvals (Caldicott/CSAppGN021211; Caldicott/IGTCAL2973) has been described previously { ADDIN EN.CITE <EndNote><Cite><Author>Paterson</Author><Year>2017</Year><RecNum>451</RecNum><DisplayText>[14]</DisplayText><record><rec-number>451</rec-number><foreign-keys><key app="EN" db-id="dr95wrtar2dsxmesffnpxe2qzserx02d0dxt" timestamp="1499343956">451</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Paterson, C.</author><author>Yew-Fung, C.</author><author>Sweeney, C.</author><author>Szewczyk-Bieda, M.</author><author>Lang, S.</author><author>Nabi, G.</author></authors></contributors><auth-address>Academic Section of Urology, Division of Cancer Research, School of Medicine, Ninewells Hospital, Dundee, UK.Academic Section of Urology, Division of Cancer Research, School of Medicine, Ninewells Hospital, Dundee, UK. Electronic address: g.nabi@dundee.ac.uk.</auth-address><titles><title>Predictors of growth kinetics and outcomes in small renal masses (SRM </=4 cm in size): Tayside Active Surveillance Cohort (TASC) Study</title><secondary-title>Eur J Surg Oncol</secondary-title><alt-title>European journal of surgical oncology : the journal

of the European Society of Surgical Oncology and the British Association of Surgical Oncology</alt-title></titles><periodical><full-title>Eur J Surg Oncol</full-title></periodical><edition>2017/04/04</edition><keywords><keyword>Active surveillance</keyword><keyword>Co-morbidities</keyword><keyword>Growth patterns</keyword><keyword>Outcomes</keyword><keyword>Small renal masses</keyword></keywords><dates><year>2017</year><pub-dates><date>Mar 16</date></pub-dates></dates><isbn>0748-7983</isbn><accession-num>28365130</accession-num><urls></urls><electronic-resource-num>10.1016/j.ejso.2017.03.006</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>}. A group of patients undergoing an open partial nephrectomy for SRMs between 2000 and 2016 were reviewed as part of this study using a unique 10-digit identifier- Community Health Index (CHI) number.

Inclusion criteria were as follows:

- 1) Patients who underwent a partial nephrectomy for renal masses of less than 4cm.
- 2) Availability of pre-operative imaging and information of on episodes of care on electronic databases (Clinical Portal, Integrated Clinical Environment etc.) from the initiation of a GP or other sources of referral to the latest follow-up. The Tayside Health Board caters to a population of more than 400,000 with all of the GP surgeries electronically connected for referrals and receiving discharge.

Exclusion criteria were as follows:

- 1) A partial nephrectomy for masses larger than 4cm.
- 2) No pre-operative imaging available through the archived system of the PACS (Picture Archiving and Communications System)

Indications for a partial nephrectomy for masses of less than 4cm; were patients' choice or renal masses increasing in size during active surveillance. Most patients opted for active surveillance with masses of less than 3cm according to a protocol published recently { ADDIN EN.CITE

<EndNote><Cite><Author>Paterson</Author><Year>2017</Year><RecNum>83</RecNum><DisplayText>[14]</DisplayText><record><rec-number>83</rec-number><foreign-keys><key app="EN" db-id="dr95wrtar2dsxmesffnpxe2qzserx02d0dxt" timestamp="1499337718">83</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Paterson, C.</author><author>Yew-Fung, C.</author><author>Sweeney, C.</author><author>Szewczyk-Bieda, M.</author><author>Lang, S.</author><author>Nabi, G.</author></authors></contributors><auth-address>Academic Section of Urology, Division of Cancer Research, School of Medicine, Ninewells Hospital, Dundee, UK.Academic Section of Urology, Division of Cancer Research, School of Medicine, Ninewells Hospital, Dundee, UK. Electronic address: g.nabi@dundee.ac.uk.</auth-address><titles><title>Predictors of growth kinetics and outcomes in small renal masses (SRM </=4 cm in size): Tayside Active Surveillance Cohort (TASC) Study</title><secondary-title>Eur J Surg Oncol</secondary-title></titles><periodical><full-title>Eur J Surg Oncol</full-title></periodical><keywords><keyword>Active surveillance</keyword><keyword>Co-morbidities</keyword><keyword>Growth patterns</keyword><keyword>Outcomes</keyword><keyword>Small renal masses</keyword></keywords><dates><year>2017</year><pub-dates><date>Mar 16</date></pub-dates></dates><isbn>1532-2157 (Electronic)0748-7983 (Linking)</isbn><accession-num>28365130</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/28365130</url></related-urls></urls><electronic-resource-num>10.1016/j.ejso.2017.03.006</electronic-resource-num></record></Cite></EndNote>}. Briefly, patients were scanned using CT scan every 6-12 months using a departmental agreed protocol described before { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. An increase in the size of the tumour was re-discussed in multidisciplinary meetings and management options were revisited and re-discussed with patients. If renal masses increased to more than 4cm, surgical excision was

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offered during the study. The baseline of the cohort is shown in **Table 1**. CT scan images of patients who had at least 12 months of active surveillance prior to choosing surgery were retrieved through the CARESTREAM Vue PACS (Picture Archiving and Communications System). The system provides one single source that captures, stores, distributes and then displays medical images, essentially acting as a central imaging data-rich repository.

Image Retrieval and Measurements

Serial computer tomography (CT) images were reviewed by two researchers (WZ,MHK) and tumour characteristics (size, exophytic/endophytic properties, anterior/posterior, distance of tumour to the collection system/ sinus, location to polar lines/sinus lines) were recorded, as were the data of three nephrometry scoring systems (RENAL, PADUA, C-index). In cases, where there was a lack of clarity senior authors (GN, MB) were consulted. The mean value of two score points from two researchers for each nephrometry score was used for analysis and inter-observer agreement between two assessors was calculated.

Pathological and Follow-Up Data.

The pathology of each patient included the size, whether cancerous or benign, and the grade of the cancer as reported by an experienced uropathologist (SL) and discussed in multidisciplinary meetings. Complications were recorded from follow-up data using cross-linked methodology of the electronic systems as described previously { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. Malignant tumours were categorized into clear cell renal carcinoma, papillary renal cell carcinoma and chromophobe renal cell carcinoma while benign tumours included benign renal cysts, papillary adenomas and oncocytomas. Complications during or within 60 days were recorded and were as follows: need for transfusion, retroperitoneal haematoma, urinary leak, pseudoaneurysm, pyelonephritis,

perinephric abscess, pneumothorax, re-exploration, and conversion to an open procedure.

Statistical Analysis

Data were analyzed by SPSS version 21.0 (Armonk, NY: IBM Corp) for windows. A p value and ROC curve were obtained. A p-value of <0.05 was considered significant. Statistical calculations (paired McNemar's test, testing null hypothesis and calculations of probabilities) were carried out to show the association between nephrometry scoring and surgical complications, grade, histology, and tumour characteristics. Serial scores using three different systems were compared with type of pathology (cancerous vs. benign) and the grade of cancer (low grade vs. high grade). Regression analysis and predictive modelling were conducted to see the impact of change in nephrometry scores on predicting the grade of tumours.

RESULTS

One hundred and sixteen patients underwent nephron sparing surgery between January 2000 and December 2016. Imaging data could not be retrieved for 10, as these cases were not registered on the PACS. 9 cases were excluded, as they were operated for tumours of more than 4cm. Complete imaging data were available on 97 for further analysis. Twenty-four cases (24/97; 24.8%) had perioperative complications. The most common surgery-related complication was pseudoaneurysm (n= 7) leading to haematuria and requiring angioembolisation. Histology of the resected specimen ranged from benign (cyst, oncocytoma, angiomyolipoma) to histologically different cancers (clear cell carcinoma, papillary renal cell carcinoma, chromophobe and tubulocystic). There were 67 clear cell renal carcinoma patients, 14 papillary cell carcinoma, 4 chromophobe and one tubulocystic tumour. Eleven cases were benign on histology (Oncocytoma-5; angiomyolipoma-3, benign cysts-2; haematoma/infarct-1). **Table 2** shows the different complications for each histological category of the lesions. There were no statistical differences between complications and histology.

There were 40 cases with a history of active surveillance for at least 12 months prior to opting for surgical treatment. Nineteen of these cases had shown progression in nephrometry scores. Two researchers independently assessed nephrometry scores and had a good inter-observer agreement for RENAL (kappa coefficient 0.70); PADUA (kappa coefficient 0.69) and C-Index (kappa coefficient 0.74) scores respectively.

Figure 1 shows the prevalence of the histological grade of excised small renal masses between those with progression on their nephrometry score and those with no progression (static). As seen, those with progression in scores showed a high prevalence of high-grade disease. **Figure 2** illustrates changes in nephrometry

scores over time along with an increasing size in two patients over the period of the follow-up. The tumour on the partial nephrectomy showed a T3 lesion (renal sinus involvement) and a high Fuhrman grade in the progressing patient. There were 12 (12/19; 63%) patients upstaged (pathologic stage was higher than the stage predicted on radiology) to pathological T3 stage in the progressing group in contrast to 6 (6/21; 28.5%) in the non-progressing group (**Figure 3**). This was statistically significant (p-value 0.003). The type of malignancy did not correlate with the complexity of small renal masses or changes in nephrometry scores. **Table 3** shows the correlation between mean scores using three systems and the histology of the excised masses.

In respect of the regression analysis using factors which could predict the grade of cancer such as age, gender, obesity, co-morbid condition, change in size and change in nephrometry score, both univariate and multivariate analyses showed that changes in size and changes in nephrometry scores during active surveillance were significantly associated with higher-grade tumours of the excised specimen after a partial nephrectomy (**Table 4**).

Driving information from the regression model, we calculated the area under curves (AUC) for predicting high-grade pathology in patients on active surveillance. Both the change in size and the nephrometry score showed an AUC of modest significance. The sensitivity and specificity of model for change in nephrometry score was 0.56 and 0.70 respectively. The AUC for the change in size was 0.58 which increased to 0.65 with the addition of a change in the nephrometry score and this was not statistically significant (p-value 0.19).

Discussion

The study assessed the predictive accuracy of comprehensive nephrometry scoring metrics in predicting the grade of excised cancer tissues in patients with small renal masses on active surveillance. The results suggest that this approach significantly but modestly is associated with the presence of high grade cancers. Previous literature reporting on this topic has mainly included a heterogeneous population with a mixture of small and large renal cancers { ADDIN EN.CITE { ADDIN EN.CITE.DATA }} and shown conflicting results { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. Most of these studies used a single measurement of nephrometry scores often using one measurement system alone. Not surprisingly, a recent systematic review and literature synthesis have shown challenges in the reported studies in predictive modelling using scoring systems, particularly implications for clinical practice and research { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. We have comprehensively used all three systems on serial CT scan imaging in patients undergoing partial excision of kidneys for cancers. The mean number of scans was 3 (ranging from 2 to 5). Each scan was assessed using three scoring systems with good inter-observer agreement. The study also showed a high rate of upstaging of small renal masses on histopathology in those patients with increased complexity on serial CT scan imaging prior to surgery. With regard to predictive modelling, changes in nephrometry scores on serial scans in small renal masses on active surveillance did improve the ability of changes in size in predicting the presence of high grade disease alone albeit in a modest way.

A number of factors have been considered and their ability to predict histology (benign vs. malignant) analyzed in different models. Broadly, these factors can be classified into patient and tumour characteristic groups. Age, sex, comorbidity and obesity have been used as predictors of histology in different studies { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. The size of the tumour- measured as the maximum tumour diameter- remained the most commonly reported tumour characteristic, with a higher size indicating the presence of malignant histology.

Murphy et al { ADDIN EN.CITE

<EndNote><Cite><Author>Murphy</Author><Year>2009</Year><RecNum>462</RecNum><DisplayText>[28]</DisplayText><record><rec-number>462</rec-number><foreign-keys><key app="EN" db-id="dr95wrtar2dsxmesffnpxe2qzserx02d0dxt" timestamp="1499550707">462</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Murphy, A.

M.</author><author>Buck, A. M.</author><author>Benson, M.

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amm251@columbia.edu</auth-address><titles><title>Increasing detection rate of benign renal tumors: evaluation of factors predicting for benign tumor histologic features during past two

decades</title><secondary-title>Urology</secondary-title><alt-title>Urology</alt-title></titles><periodical><full-title>Urology</full-title></periodical><alt-periodical><full-title>Urology</full-title></alt-periodical><pages>1293-7</pages><volume>73</volume><number>6</number><edition>2009/04/18</edition><keywords><keyword>Aged</keyword><keyword>Diagnostic Techniques, Urological/statistics &

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 rovider><language>eng</language></record></Cite></EndNote>} showed a
 significantly higher rate of malignant histology following surgical excision in tumours
 larger than 3.5cm than in those of less than 3cm. Pahernik et al { ADDIN EN.CITE
 <EndNote><Cite><Author>Pahernik</Author><Year>2007</Year><RecNum>463</R
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 S.</author><author>Ziegler, S.</author><author>Roos,
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 W.</author></authors></contributors><auth-address>Department of Urology,
 Johannes Gutenberg University, Mainz, Germany.
 Pahernik@urolgie.klinik.uni-mainz.de</auth-address><titles><title>Small renal
 tumors: correlation of clinical and pathological features with tumor
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Neoplasms/diagnosis/*pathology/surgery</keyword><keyword>Male</keyword><keyword>Middle Aged</keyword><keyword>Neoplasm

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Topic</keyword></keywords><dates><year>2007</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0022-5347

(Print)0022-5347</isbn><accession-num>17561161</accession-num><urls></urls><electronic-resource-num>10.1016/j.juro.2007.03.129</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>} reported a higher grade, stage and

metastasis in malignant tumours with an increasing size of small renal masses.

Various studies have reported a good correlation between malignant histology and tumour location, especially when near to hilar structures { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. Mullins et al { ADDIN EN.CITE

<EndNote><Cite><Author>Mullins</Author><Year>2012</Year><RecNum>266</RecNum><DisplayText>[20]</DisplayText><record><rec-number>266</rec-number><fo

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S.</author><author>Rogers, C. G.</author><author>Stifelman, M.

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Urological Institute, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA.

jmulli12@Jhmi.edu</auth-address><titles><title>Tumor complexity predicts

malignant disease for small renal masses</title><secondary-title>J

Urol</secondary-title></titles><periodical><full-title>J

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Urol</full-title></periodical><pages>2072-6</pages><volume>188</volume><number>6</number><keywords><keyword>Carcinoma, Renal Cell/*pathology/surgery</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Kidney/*pathology/surgery</keyword><keyword>Kidney Neoplasms/*pathology/surgery</keyword><keyword>Logistic Models</keyword><keyword>Male</keyword><keyword>Nephrectomy</keyword><keyword>Prognosis</keyword><keyword>Risk Factors</keyword><keyword>Sex Factors</keyword></keywords><dates><year>2012</year><pub-dates><date>Dec</date></pub-dates></dates><isbn>1527-3792 (Electronic)0022-5347 (Linking)</isbn><accession-num>23083863</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/23083863</url></related-urls></urls><electronic-resource-num>10.1016/j.juro.2012.08.027</electronic-resource-num></record></Cite></EndNote>} showed a higher rate of malignant tumours in patients with a more complex anatomy of small renal masses on nephrometry scores; however, this did not predict the grade of tumours. Gorin et al { ADDIN EN.CITE { ADDIN EN.CITE.DATA }} have shown a tendency of a higher grade and stage of disease in small renal masses close to the hilum of the kidney similar to the findings of the present study. The complex anatomy of tumours especially those growing on serial imaging is significantly predictive of high-grade disease as seen in multivariate analysis in the present study. We have shown that both changes in size and nephrometry scores in small renal masses on active surveillance significantly predict higher grade disease (**Table 4**). On multivariate analysis, these two are complementary to each other and in fact changes in nephrometry scores improve the AUC of changes in size in predictive models.

Variability in measuring a tumour size remains a major issue in clinical oncology especially in patients opting for active surveillance or active chemotherapeutic treatment. Besides inter-observer variation, CT scan protocols such as contrast dose, slice thickness and reconstruction parameters also affect measurements. Zhao et al

{ ADDIN EN.CITE { ADDIN EN.CITE.DATA }} suggested that measurements made either manually or using computer models have similar inter-reader variability. The study supported having the same reader review all of a single patient's scans or even all patients' scans. In the present study, all of the scans were reviewed and reported for diagnosis by the same experienced reader (MB) and acquired previously agreed protocols published elsewhere { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}.

In the context of small renal masses, Punnen et al { ADDIN EN.CITE

<EndNote><Cite><Author>Punnen</Author><Year>2006</Year><RecNum>467</RecNum><DisplayText>[32]</DisplayText><record><rec-number>467</rec-number><foreign-keys><key app="EN" db-id="dr95wrtar2dsxmesffnpxe2qzserx02d0dxt" timestamp="1499587359">467</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Punnen,

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G.</author><author>Moulding, F.</author><author>O'Malley, M.

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masses smaller than 4 cm on computerized tomography</title><secondary-title>J Urol</secondary-title><alt-title>The Journal of

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Urol</full-title></periodical><pages>2386-90; discussion

2390</pages><volume>176</volume><number>6 Pt

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Computed</keyword></keywords><dates><year>2006</year><pub-dates><date>Dec</date></pub-dates></dates><isbn>0022-5347
(Print)0022-5347</isbn><accession-num>17085106</accession-num><urls></urls><electronic-resource-num>10.1016/j.juro.2006.07.142</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>} in a small series have highlighted the challenges of inter and intra-observer variations in the size measurement of CT scan images.

Similar to our study, colleagues from the USA { ADDIN EN.CITE { ADDIN EN.CITE.DATA }} have shown adverse pathological outcomes following delayed resection of growing small renal masses on active surveillance. Although most of us have pointed out in the past that growth may be an indicator of high-grade disease on active surveillance, the definition of growth remains debatable. Three studies { ADDIN EN.CITE { ADDIN EN.CITE.DATA }} using three different sources of cohorts have described growth using different parameters. With growth in data and its interpretation in this area, there is an urgent need to reach a consensus thereon as pointed out by Nayyar et al in a recent publication { ADDIN EN.CITE
<EndNote><Cite><Author>Nayyar</Author><Year>2016</Year><RecNum>472</RecNum><DisplayText>[36]</DisplayText><record><rec-number>472</rec-number><foreign-keys><key app="EN" db-id="dr95wrtar2dsxmesffnpxe2qzserx02d0dxt" timestamp="1499589987">472</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nayyar, M.</author><author>Cheng, P.</author><author>Desai, B.</author><author>Cen, S.</author><author>Desai, M.</author><author>Gill, I.</author><author>Duddalwar, V.</author></authors></contributors><auth-address>From the *Keck School of Medicine, daggerDepartment of Radiology, and double daggerInstitute of Urology, University of Southern California, Los Angeles,

CA.</auth-address><titles><title>Active Surveillance of Small Renal Masses: A
Review on the Role of Imaging With a Focus on Growth
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Tomogr</secondary-title><alt-title>Journal of computer assisted
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0000000000000407</electronic-resource-num><remote-database-provider>NLM</r
emote-database-provider><language>eng</language></record></Cite></EndNote>}.
A nephrometry score, as suggested in the present study may help in selecting out
more complex lesions and in measuring changes in complexity of renal masses on
active surveillance besides indicating a possibility of aggressive disease. Whether
delayed interventions in these masses would lead to a higher rate of morbidity
needs further study. Rate of peri-operative complications (24.8%) in the present
series is comparable to those described in the contemporary literature { ADDIN
EN.CITE { ADDIN EN.CITE.DATA }} including those where minimally access surgery
was contemplated.

There are some limitations of the present study; small number of patients introduces a bias. However, the participants were drawn from a stable population in a defined geographical area with a large single centre providing care for the targeted condition. Each participant was imaged on more than one occasion and data were analysed using three different scoring systems with good inter-observer agreement between the assessors similar to previous study { ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. All of the imaging was carried out using standardized protocols to avoid any detection or measurement bias, however in a moving organ with breathing such as kidney, there is still a small but immeasurable risk of bias. Recently MRI scans can be offered as an alternate imaging method, especially for better characterization of cystic masses with its extremely good T2-weighted contrast resolution { ADDIN EN.CITE

<EndNote><Cite><Author>Helenon</Author><Year>2012</Year><RecNum>925</RecNum><DisplayText>[39]</DisplayText><record><rec-number>925</rec-number><foreign-keys><key app="EN" db-id="dr95wrtar2dsxmesffnpxe2qzserx02d0dxt" timestamp="1516530858">925</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Helenon, O.</author><author>Eiss, D.</author><author>Debritto, P.</author><author>Merran, S.</author><author>Correas, J. M.</author></authors></contributors><auth-address>Universite Paris-Descartes, 15, rue de l'Ecole-de-Medecine, 75270 Paris cedex 06, France. olivier.helenon@nck.aphp.fr</auth-address><titles><title>How to characterise a solid renal mass: a new classification proposal for a simplified approach</title><secondary-title>Diagn Interv Imaging</secondary-title></titles><periodical><full-title>Diagn Interv Imaging</full-title></periodical><pages>232-45</pages><volume>93</volume><number>4</number><keywords><keyword>Humans</keyword><keyword>Kidney Neoplasms/*classification/*diagnosis</keyword><keyword>*Magnetic Resonance

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Imaging</keyword><keyword>*Tomography, X-Ray
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 (Linking)</isbn><accession-num>22476035</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/22476035</url></related-urls></urls><electronic-resource-num>10.1016/j.diii.2012.01.016</electronic-resource-num></record></Cite></EndNote>}. Alternatively, image guided biopsies are now frequently pursued as a method of knowing histological diagnosis of renal masses. The masses detected on image guided biopsies have similar outcomes as those without biopsies { ADDIN EN.CITE
 <EndNote><Cite><Author>Somani</Author><Year>2007</Year><RecNum>927</RecNum><DisplayText>[40]</DisplayText><record><rec-number>927</rec-number><foreign-keys><key app="EN" db-id="dr95wrtar2dsxmesffnpxe2qzserx02d0dxt" timestamp="1516531073">927</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Somani, B.
 K.</author><author>Nabi, G.</author><author>Thorpe,
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 1296-7</pages><volume>51</volume><number>5</number><keywords><keyword>Adolescent</keyword><keyword>Adult</keyword><keyword>Aged</keyword><keyword>Aged, 80 and

over</keyword><keyword>Biopsy</keyword><keyword>*Biopsy, Needle/adverse effects/methods</keyword><keyword>Carcinoma, Renal Cell/*diagnosis/surgery</keyword><keyword>Female</keyword><keyword>Human s</keyword><keyword>Kidney/pathology</keyword><keyword>Kidney Neoplasms/*diagnosis/surgery</keyword><keyword>Male</keyword><keyword>Middle Aged</keyword><keyword>Nephrectomy</keyword><keyword>*Radiography, Interventional</keyword><keyword>*Ultrasonography, Interventional</keyword></keywords><dates><year>2007</year><pub-dates><date>May</date></pub-dates></dates><isbn>0302-2838 (Print)0302-2838 (Linking)</isbn><accession-num>17081679</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/17081679</url></related-urls></urls><electronic-resource-num>10.1016/j.eururo.2006.10.022</electronic-resource-num></record></Cite></EndNote>}. Non-invasive imaging modalities and image guided minimally interventions to predict behavior of small renal masses remains hotly debated topic and underpins future research. Further large multicentre studies are needed in order to address some of these methodological challenges, nevertheless, ours and reported literature provide enough pointers with regard to the possibility of a tumour complexity measurement and its correlation with aggressive disease.

Conclusions

In summary, our preliminary results suggest that a change in nephrometry scoring measurements correlates with grade of cancer in small renal masses but falls short of significantly predicting presence of malignancy or grade of cancer on nomogram in patients opting for active surveillance for small renal masses. At present, this approach may be inadequate for decision-making. Our findings suggest further large multicentre studies to confirm or refute this observation.

Declarations

1. Ethics approval and consent to participate

Institutional permission obtained through NHS Tayside Research and Development with Caldicott number Caldicott/CSAppGN021211; Caldicott/IGTCAL2973

2. Consent to publication- NA
3. Availability of data and material: For transparency and and sharing, data is available on (<http://www.nisg.scot.nhs.uk/currently-supporting/pacs-and-ris>).
4. Competing Interests: The authors declare that they have no competing interests.
5. Funding: No specific funding for this project
6. Authors' contributions

M.H.K has been responsible for collecting and analyzing data. Also, he prepared first draft of the manuscript. W.Z. has collected, analyzed data and contributed to the first draft. M. B. been responsible for radiological data supervision and critical scientific input, C.P. has contributed to intellectual input, drafting and revision of the manuscript. S.L. has been responsible for intellectual

input and pathological input of the manuscript. G.N. is overall responsible for the study including its concept, supervision, preparation of manuscript and critical intellectual input of the final version.

7. Acknowledgment: NA

Reference

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Legends for Figures

Figure 1: Grade of tumours following partial nephrectomy for small renal masses (N=40)

Figure2: Images showing progression and changes in nephrometry scores in a patient in comparison to another case with no progression.

Figure 3: Correlation between changes in nephrometry scores and final histopathological staging after partial nephrectomy.

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Characteristics	N (SD/%)
Numbers	97
Age(years)	59.7(±12.4)
Sex	
Male	61
Female	36
Operative characteristics	
Kidney	
Right	43
left	54
Tumor characteristics	
Tumor location	
anterior	9
posterior	88
Tumor diameter Mean (range)	3.8 (range 2 to 4)
Tumor pathology	
malignant	86
Clear cell carcinoma	67
Papillary cell carcinoma	14
Chromophobe	4
Tubulocystic	1
benign	11
Grade of cancer	
Low (Furhman 1& 2)	46
High (Furhman 3&4)	51
RENAL nephrometry (mean)	6.8 (± 4.2)
PADUA score (mean)	8.3 (±4.8)
C-index (mean)	2.1(±1.9)

Table 1: Shows basic demographics of the cohort

Grade of tumours following partial nephrectomy in small renal masses (N=40)

