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Predictors of growth kinetics and outcomes in small renal masses (SRM ≤4cm in size): Tayside Active Surveillance Cohort (TASC) Study

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Keywords: Small Renal Masses; Active Surveillance; Co-morbidities; Outcomes; Growth Patterns

Abstract

Objective: To determine outcomes of small renal masses (≤4cm) on active surveillance and explore factors which can influence their growth

Patients and Methods: 226 patients between January 2007 and December 2014 were analyzed using cross-linked methodology of healthcare data and independent review. Cancer specific and non-specific survival were the primary outcomes. Growth kinetics, factors influencing growth and need for interventions were secondary outcomes.

Results: 101 (64.4%) solid and 4 (5.9%) cystic SRMs showed growth. 43 (19.02%) of SRMs required treatment interventions. Seven patients (7/158; 4.4%) died due to renal cancer at a median follow-up of 21.7 (SD 10.6, min 6-42) months, all in solid category. Independent review of serial radiological imaging of these 7 cases showed two patients had subtle metastatic disease at the initial presentation, and 5 of the 7 did not adhere to recommended imaging regime. 33 (33/158; 20.8%) died due to other causes including non-renal cancers (14/158; 8.8%). Multivariate analyses showed that lower eGFR at baseline, co-morbidities and tumour location were independently associated with growth in size.

Conclusions: A higher cancer-specific mortality was seen in the present study compared to the reported literature, including finding of subtle non-reported metastatic lesions at the time of diagnosis on independent review. Critical review of imaging and adherence to imaging protocols through a chosen imaging modality (CT or MRI) are crucially important to the outcomes of active surveillance in the management of SRMs. Comorbid conditions had a significant impact on growth and overall survival of patients with SRMs.

Introduction

Predictors of growth and progression in SRMs on active surveillance remain poorly defined mainly due to a dearth of good quality longitudinal observational data (1-4). The universal healthcare model in the National Health Services (NHS) of the United Kingdom has the advantage of studying longitudinal observational data, especially through linkage methodology using a common identifier such as unique Community Health Care Index (CHI) number. The universal healthcare cover to a population in a well-defined geographical area provides an ideal environment to study natural history of diseases such as early renal cancer (SRMs), in particular outcomes of continued surveillance. Electronic patient records including demographic, clinical episodes, imaging and histopathology data can easily be linked to answer research question. Third party certification and review by independent body of the data where researchers have little influence remains a significant advantage. One of the key questions in SRMs remains cancer-specific and non-cancer specific mortality in patients opting for active surveillance. What influences growth of these masses is also not known, in particularly influence of co-morbid conditions has not been reported (5, 6). Multiple chronic medical ailments are associated with poorer outcomes, morbidities of treatment, complications following surgery, poorer quality of life, psychological distress, and higher mortality. This knowledge base should inform the appropriate follow-up for patients diagnosed with SRMs. In a large population based cohort in a well-defined geographical area we aimed to address the following objectives:

1. Assess progression and outcomes (cancer specific and overall survival) in both cystic and small renal masses.
2. Explore factors which can influence progression of these masses including impact of co-morbid conditions.

Patients and Materials

Study cohort

The TUCAN (Tayside Urological Cancers Network Database) collects routine data from the patient population affected by urological cancers in Tayside, Scotland. NHS Tayside serves a population of more than 405,721 based on mid-year 2011 population estimates published by the General Register Office for Scotland. Each inhabitant of this area has a 10 digit CHI number and health records can be accessed using this common identifier. Patients were identified from TUCAN Database using validated record linkage methodology as described previously (7). All patients with SRM in this defined population were recorded in a database after discussion in multidisciplinary tumours board meetings using an agreed data sheet (Supplementary material). The study had an initial and updated Institutional approval (Caldicott/CSAppGN021211; Caldicott/IGTCAL2973). 226 patients who opted for active surveillance for SRMs after review at multidisciplinary meetings and face-to-face meetings with an urologist between January 2007 and December 2014 were identified and recruited into the study. 158 patients were diagnosed with solid SRMs. 68 were identified as cystic masses.

Outcome data

Patients opting for active surveillance for SRMs were imaged at regular interval (6-12months) using CT/MR scans and reviewed in multidisciplinary meetings if reported any change in size. All imaging data and reports were available on CARESTREAM Vue Picture Archiving and Communication System (PACS) (http://www.carestream.com/specials/campaign/search-pacs) for review and follow-up. Similarly clinic letters and other communications including re-admissions, blood investigations were available on Clinical Portal System of the organization. There were only a few patients where ultrasound was used for follow-up with immediate conversion to CT scan in case of any suspicious of growth or poor visualization. The information was retrieved for a number of demographic variables: age, gender, and Scottish Index of Multiple Deprivation (SIMD). The SIMD is a scoring system utilized by Scottish Government to identify areas of deprivation (www.scotland.gov.uk/topics/statistics/SIMD). The system uses a quintile scoring system, which classifies geographical areas as most deprived (1) to least deprived (5). Clinical factors included growth in size, initial presentation (symptomatic versus asymptomatic), multiplicity, Charlson index, location of tumour, and baseline eGFR (at least 3 months prior to the diagnosis) and most recent eGFR (within last 3 months of most recent scan).

Primary outcomes and Interventions

Primary outcome of the study was cancer-specific and non-cancer specific survival of patients on active surveillance. Secondary outcomes were growth of SRMs. Cystic SRM growth was defined as an increase in cyst complexity and migration of a class to a higher level and was determined by the uro-radiologist mainly based on changes in the wall or septal enhancement, increased nodularity, or calcifications over a time period on follow-up scans. Tumour growth of solid SRM was defined as any increase in the maximum axial dimensional size (two axial measurements perpendicular to each other) found on scans over a time period. All SRMs were reviewed in multidisciplinary tumour meetings at the time of initial diagnosis and on follow-up, if there was increase in growth.

Surgical excision/interventions were offered for solid SRMs more than 4 cm in size, those opting for change in surveillance protocol following increase in size on imaging (but still less than 4cm) and in younger patients with reluctance to follow-up. Similarly, surgical intervention was offered in cystic masses classified following MDT review for bosniak III or IV and follow-up for Bosniak IIF (see **Figure 1** for TASC management algorithm, supplementary files). The type of surgical procedure, pathological outcome including benign or malignant, presence of metastases and progression, and cause of death was recorded as an indicator of outcome.

Independent review of records and imaging data

Patients developing metastases were reviewed in multidisciplinary meetings (radiologist, urologists, pathologist and renal oncologist) and their record linkage was reviewed by at least two experienced researchers to ascertain the clinical events. Cancer-specific deaths were reviewed by an independent radiologist not involved in the initial meetings using serial images. Any subtle metastatic lesion on initial or follow-up scans were recorded. Radiological evidence of these events is available on patient Picture Archiving and Communication System (PACS) maintained by NHS Scotland as part of commitment to data transparency and sharing (http://www.nisg.scot.nhs.uk/currently-supporting/pacs-and-ris). Death certificates review and cause of death was provided by an independent third party (CS, contribution acknowledged).

Statistical Analysis

Data were double-entered in to SPSS version 21.0. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. Cox proportional hazard model was used to assess the relationship between prognostic variables and tumour growth. Finally, cancer specific and overall survival were estimated using Kaplan-Meier analysis in particular exploring the impact of comorbidities.

Results

The clinical and demographic characteristics are detailed in **Table 1**. Statistically significant differences were observed in gender, progression of mass size and multiplicity between the cystic and the solid SRM groups. Interestingly, cystic masses were less common in women, showed less progression and tended to be multiple when compared to solid masses. The initial presentation for the majority of patients was incidental 46 (74.2%) in the cystic and 113 (78.4%) in the solid SRM groups. One-hundred-and-one (64.4%) solid SRM and four (5.9%) cystic SRM showed growth, and 7 (7/158; 4.4%) metastasized during the follow-up. The mean growth rate from initial scan to final scan was 0.57cm (SD 0.97cm, range 0.2 to 7.0 cm) with a median of 0.2 cm. The average growth rate per annum was mean .29 cm/year (SD .48 cm, min 0 cm and max 3.5 cm) with a median of .1 cm. A retrospective independent clinical and radiological review showed that two patients had subtle undiagnosed metastases at presentation which were not identified even at MDT board meetings (**Figure 2** for illustrative examples, in supplementary files). The follow-up of the 7 (4.4%) patients (all solid masses) who developed metastases during follow-up is detailed in **Table 2.** In three patients, we observed undiagnosed progression of disease on renal ultrasound imaging alone (see **Figure 3,** in supplementary files). Two patients developed metastasis within 3 months of diagnosis and a case could be argued that they had metastatic disease at the time of detection, however radiology review did not confirm this. Moreover, only 5 of the 7 patients who developed metastatic disease did not adhered to our recommended follow-up imaging regime.

The number of patients with observed growth in the cystic SRM group were too small and insufficient to analyze further, therefore growth of solid SRM was alone identified as the dependent variable for further analysis. The results from the cox proportional hazard analyses $\chi^2(1) = 847.9$, $p < .000$ identified that estimated glomerular filtration rate (eGFR) of less than 60/min/1.73m2 at baseline (2.152, p<0.048), central tumour location (.559, p=0.024), and presence of con-current co-morbidity (1.142, p=0.016) was statistically associated with growth, (**Table 3**). The eGFR was considered as dichotomous variables as less than or more than 60 and co-morbidities were considered as continuous variable. Location of masses was estimated from imaging and in relation to normal parenchyma. In terms of treatment, (16, 10.0%) patients received RFA, (17, 10.6%) partial nephrectomy, (10, 6.3%) radical nephrectomy. Twenty five (25, 15.6%) patients were offered renal tumour biopsy in our cohort. Based upon the available pathology (12 identified benign pathology and excluded from analysis), no clear trend or pattern of growth was observed between pathology and baseline eGFR, (**Table 4** in supplementary

files). Changes in the maximum axial diameter (cm) based upon baseline scan and follow-up scan for each renal lesion for 226 patients is detailed in (**Figure 4** in supplementary files). There does not appear to be any significant differences in growth rate between histologically confirmed benign and malignant masses. In total, 42 patients died in this series, 9 deceased (7 developing metastatic disease on follow-up for active surveillance, 2 who were followed up for clinically localized disease but actually had spread at the time of initial diagnosis) due to renal cancer. Thirty-three patients died from other causes that included (9 from cardiovascular disease, 3 respiratory disease, 1 CKD, 1 meningitis, 1 rheumatoid disease, 1 blood disorder, 1 vascular dementia, 1 Parkinson disease, 1 diabetes mellitus, and 14 from other cancers), see (**Figure 5**) for disease specific survival and overall survival. **Figure 6** shows the impact of co-morbid conditions on survival during the follow-up of SRMs and as can be seen, most of deaths happen with first three years of follow-up.

Discussion

Tayside Active Surveillance Cohort (TASC) is a longitudinally established group of patients with SRMs drawn from a large stable population of more than 400,000. We have published initial reports (7) and this is a further update. SRMs growth was associated with baseline eGFR, tumour location and co-morbidity. It is well-established that chronic renal failure is associated with four to five times increased risk of development of cancers in native kidneys (8, 9). Moreover, lower eGFR is associated with high mortality from cancers (10). Renal function in the elderly may change over time in particular due to many factors such as drug use, and other co-morbid conditions and certainly could have implications for patients on active surveillance for SRMs. The vast majority of the SRMs in this series were identified incidentally, occasionally at a time when patients may have been hospitalized due to an acute condition or other co-morbidity that may have caused reduced renal function at that time during baseline follow-up. However, we observed that the distribution of eGFR remained fairly stable over follow-up. Co-morbid conditions could also influence growth as observed in the present study. Hofman and colleagues have identified that patients with hypertension and diabetes tended to have a worse renal cell carcinoma prognosis due to progression, and this relationship was more prominent in the African black ethnic group (11). Finally, we observed that central tumour location significantly predicted tumour growth and this has been identified elsewhere. Specifically, reports have suggested that the risk of malignancy is 3.5 times higher for centrally located tumours (12). Progression to metastatic disease in much higher in our series, 7 patients (4.4%), higher than what has been reported in the literature to date (1, 13-16).

Findings of the present study add to the reported literature, in particular to the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) study as they documented a decline in renal function for patients on active surveillance (1, 16). The decline could be attributed to tumour itself and potentially affect growth of these masses. Pending further research in this area, we cannot rule out the possibility that even benign tumour growth is being influenced by low baseline eGFR in our data as majority of masses did not have histological confirmation - a situation similar to the DISSRM study. This hypothesis generating observation would certainly benefit from further research.

Previous studies (17-19) showed a higher mortality in elderly patients' with SRMs not necessarily due to renal cancer. In the present study, most of patients with more than one co-morbid conditions on active surveillance died within or around the first three years of follow-up and this may guide future research

and decision making. Although, cancer specific mortality was higher in our cohort, non-cancer mortality still remained a predominant factor in the present study. There was a strong correlation between number of co-morbid conditions and overall survival as seen in Figure 5. In most decision making policies, performance status of patients is taken into consideration (20) however, our data suggests that a measure of morbidity should also be recorded and taken into consideration.

There are a number of differences between our findings and data reported from the United States and Canada. Our growth rate is higher and this could be attributed to the differences in the way growth has been defined between the studies. We considered any increase in size (confirmed in multidisciplinary team meetings and reviewed by experienced uro-radiologists) as growth whereas increase above a certain limit or doubling time was reported as growth in the previous studies (1, 16). Most common criteria used for growth of SRMs is increase in anatomic tumour size on radiological imaging and this has own its limitations, clearly influenced by quality of imaging, imaging protocols, objectivity of observer including errors in measurement (21). There is urgent need for consensus on agreed protocols on baseline and follow-up imaging protocols in SRMs on active surveillance.

The main trigger for intervention is believed to be growth rate, but to date there is a lack of robust evidence to clearly define what are the growth rate parameters to trigger intervention, as benign tumors can display similar growth rates to malignant masses, which inevitably can result in over and unnecessary treatment. Studies have confirmed that biopsy proven RCC and benign tumors displayed similar growth rates (22), hence size alone as a marker of aggressiveness and growth becomes questionable. Secondly, in the present study, a higher percentage (>35%) of solid renal masses showed zero growth which is more than reported (10% in Johns Hopkins report), and we also observed some masses decreased in size.

Ours is the first study to conduct an independent retrospective clinical and radiological review of all the patients who showed progression and developed metastatic disease (15, 23, 24). Two patients in our series and one in Canadian series progressed at 3 and 5 months of diagnosis respectively suggesting many possibilities including missing of subtle metastatic disease at the time of detection. This prompted our review and in fact two of our cases were clearly seen to have subtle (one in lung and other in liver) lesions which progressed on follow-up radiological imaging. It is important to carefully scrutinize SRM patients opting for active surveillance for subtle metastatic lesions (see Figure 1) at the time of

diagnosis. None of the studies on this subject has used an independent review of imaging and our observation and experience clearly makes a case for it. In contrast to DISSRM data (16) and Canadian report (25) where the rate of metastatic progression was thought to be low <2%, rate of progression to metastatic disease in the present study is 4.4%. One explanation to account for the higher rate of patients who developed metastasis in our series, is that 5 of the 7 patients did not adhered to recommended follow-up imaging regime. This observation might well explain the increased rates of metastasis. Adherence to imaging protocols through CT or MRI imaging modality is important as this may affect patient outcomes.

It is our experience that the use of ultrasound imaging is sub-optimal to safely assess tumor growth on surveillance. The cost and burden of serial imaging is significant, and there is conflicting reports regarding the risk of secondary malignancy (26-28). No recommendations or guidelines exist for imaging modality and timing of surveillance but it is evident from our observation that US imaging is not safe to detect renal cancer progression. This may be due to operator dependence in nature using this imaging modality.

Despite its merits, the current study is not devoid of limitations. Firstly, some data has been collected retrospectively and this is a single institutional series, therefore, the results should be replicated with a multi-institutional larger sample. As is true for cohort studies in general, data collection in population-based studies relies on robust linkage with available databases (e.g., hospital records, death certificates, etc) and we have demonstrated a methodology in ascertaining validity of this approach in the past (Ganeswaren prostate biopsy and a recent biopsy study). Moreover, using a unique identifier for a stable population in a well-defined geographical area provided us a good opportunity to assess various factors which can potentially contribute to the growth of small renal masses. Secondly, there may be debate on the manner of determining presumed tumor growth rates. The calculated presumed growth rates may represent an underestimation of tumor growth as the exact time and growth pattern is unknown. Additionally, observed growth rates are likely biased by only including tumors undergoing 12 months of observation, as tumors demonstrating rapid growth would be more likely to undergo definitive treatment. There is also the possibility that subtle growth changes might have been missed when combining the utility of CT and ultrasonography over time. Thirdly, not all the patients had histological characterization right at the beginning of recruitment into this study. There is a possibility of

some benign masses growing during the observation period or some malignant lesions with low growth potential showing no growth.

Conclusions

In the present study, a higher rate of metastatic progression and disease specific mortality was seen in the present study. Baseline eGFR <60/min/1.73m2, central tumour location and concurrent co-morbidities are significant predictors of growth in small renal masses. Critical review of imaging and adherence to imaging protocols through a chosen imaging modality (CT or MRI) are crucially important to the outcomes of active surveillance in the management of SRMs. Co-morbid conditions should be taken into account while decision making as a significant number of patients still die due to non-renal cancer causes.

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The authors have no conflicts of interests to declare.

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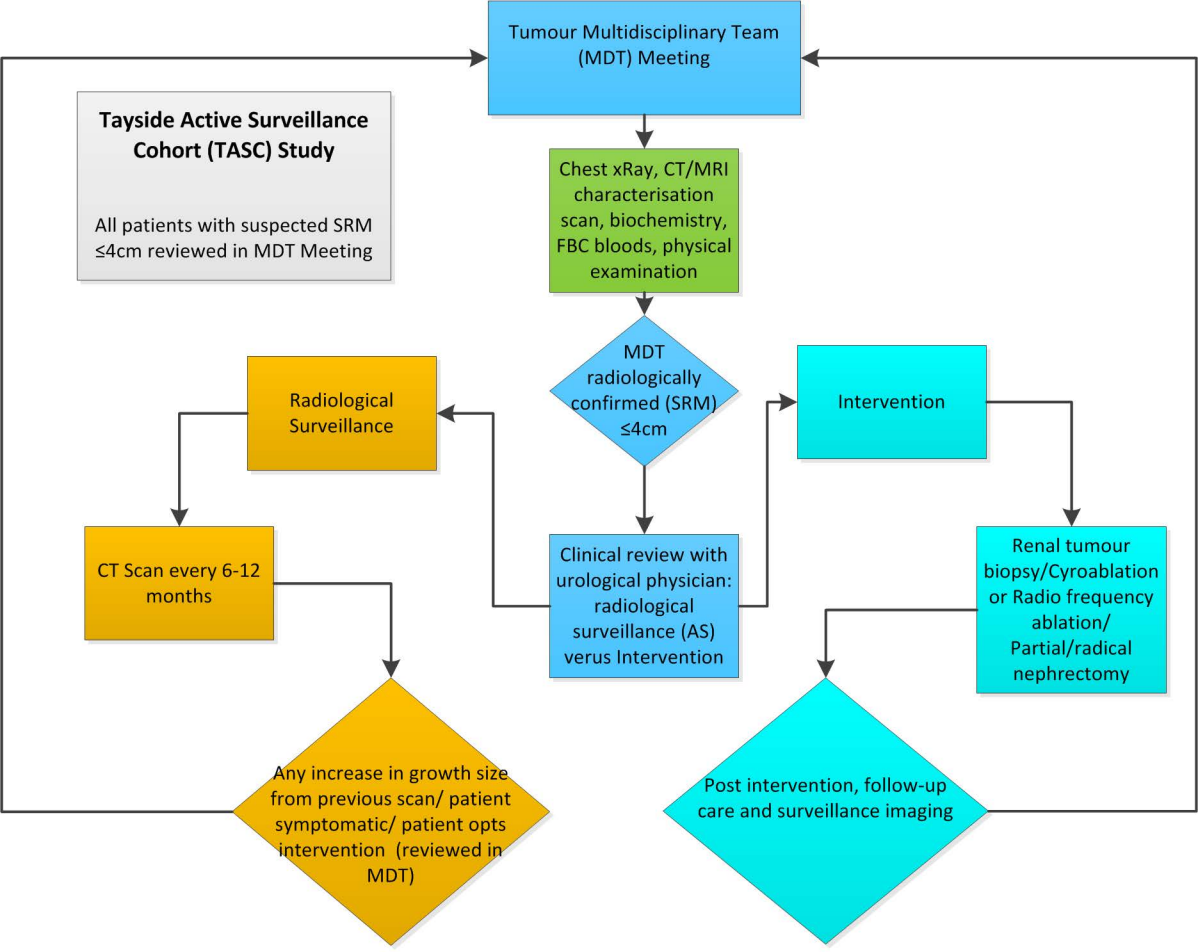
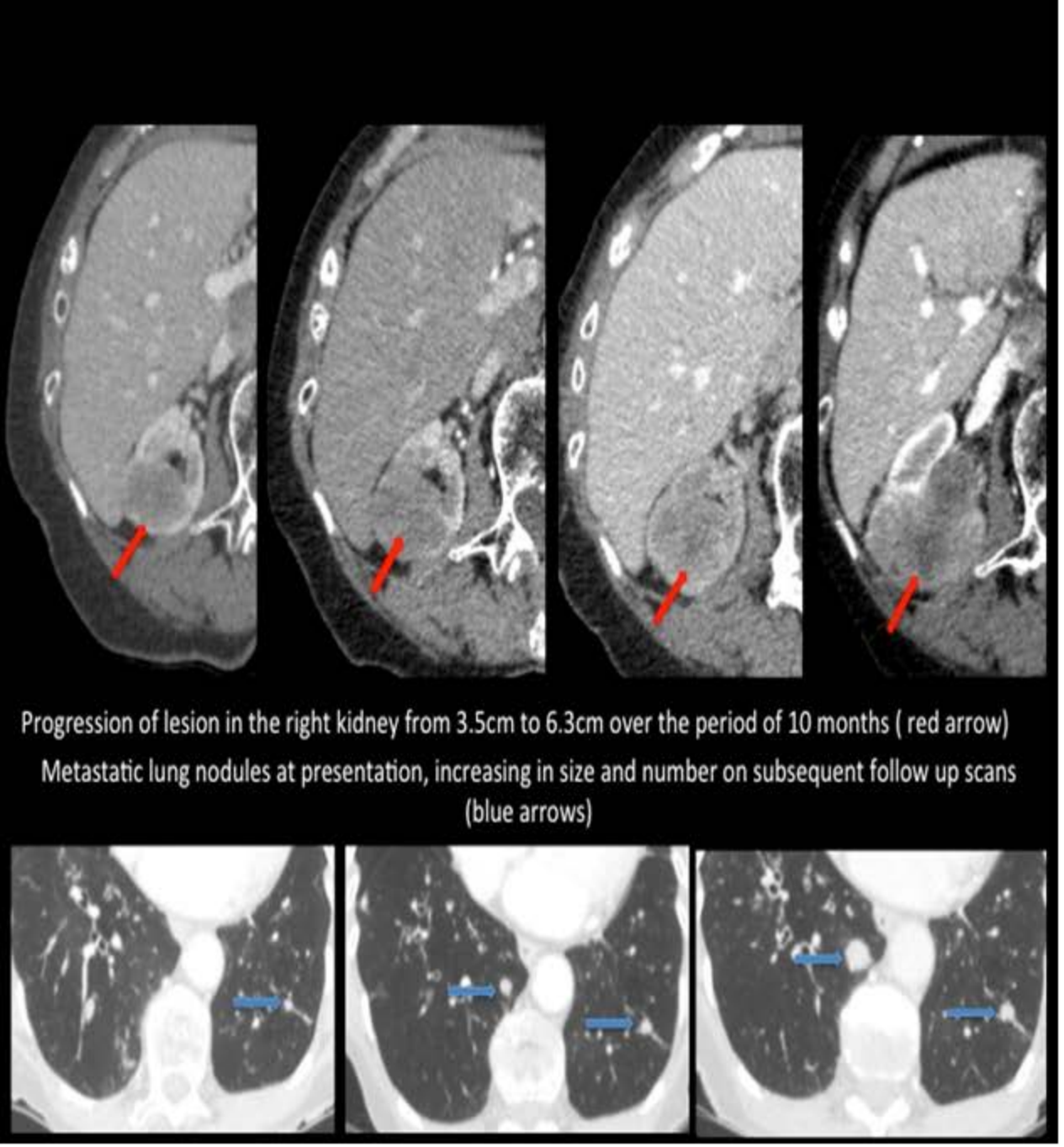


Figure 1. TASC clinical management algorithm for participants with SRM (≤4cm)



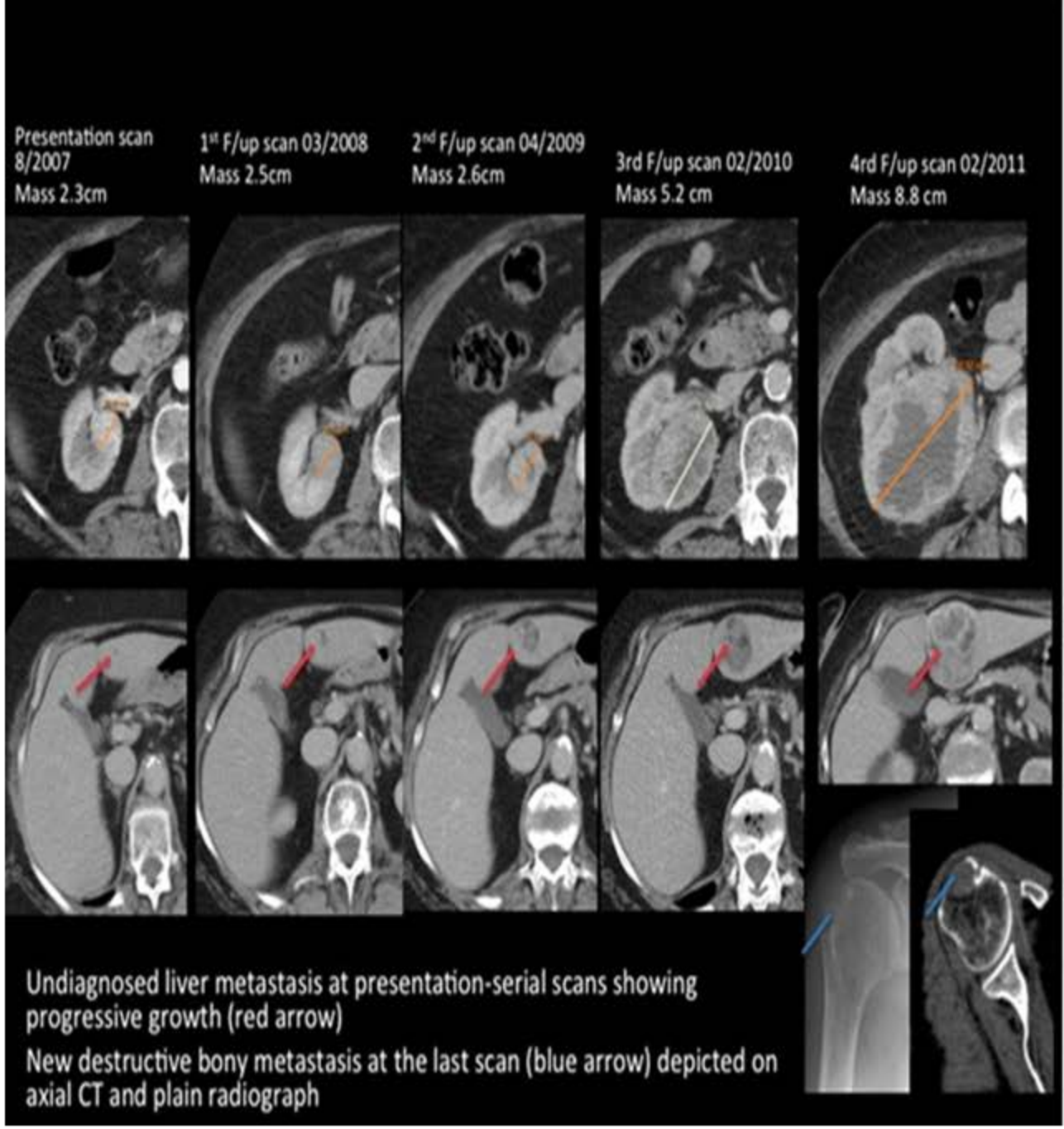
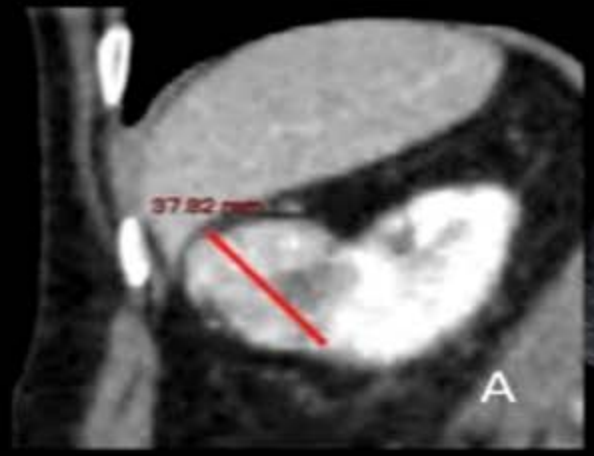
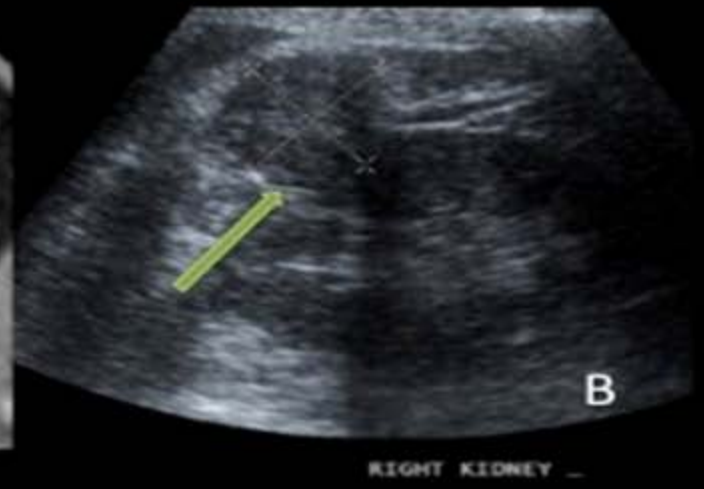
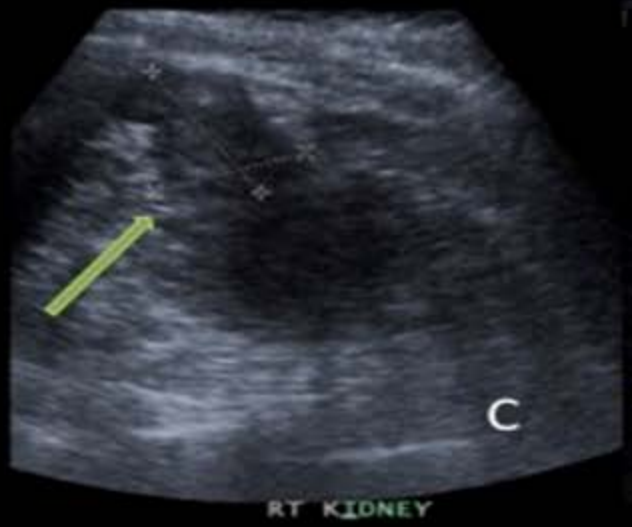
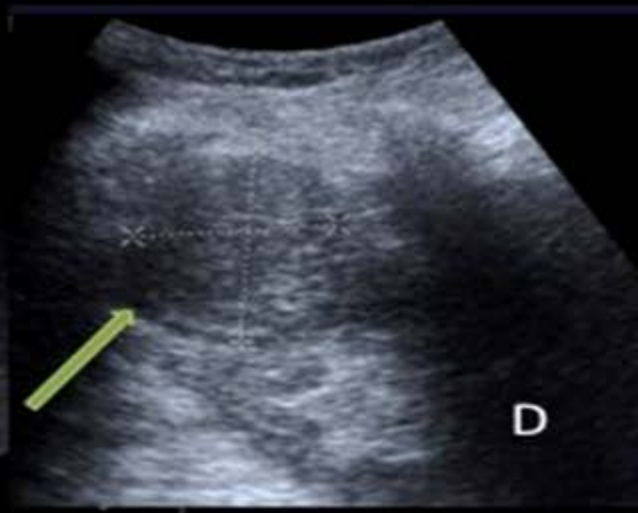


Figure 2. Undiagnosed metastatic disease at presentation







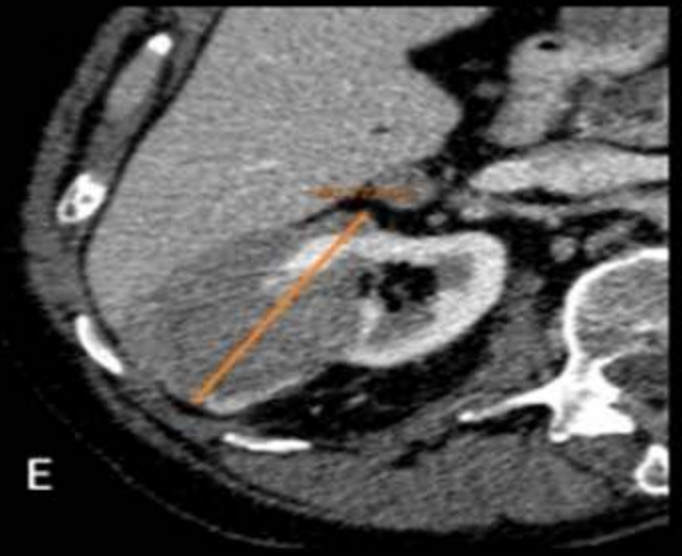


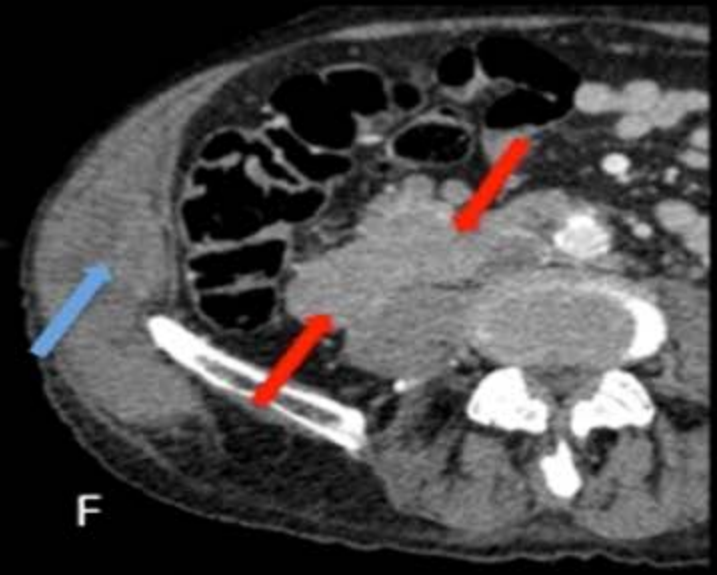
Right renal mass measured at 3.7cm at presentation CT scan (coronal plane) (A).

It was followed up by 3 subsequent US scans (B,C,D) over a period of 2 years and appeared stable in size under 4cm (green arrows).

CT scan performed 4 months after last US showed that the mass has in fact increased in size to 8.1cm (axial plane) (E).

Metastatic disease to abdominal wall muscles(blue arrow), lymphadenopathy and local recurrence following nephrectomy (red arrows) (F)





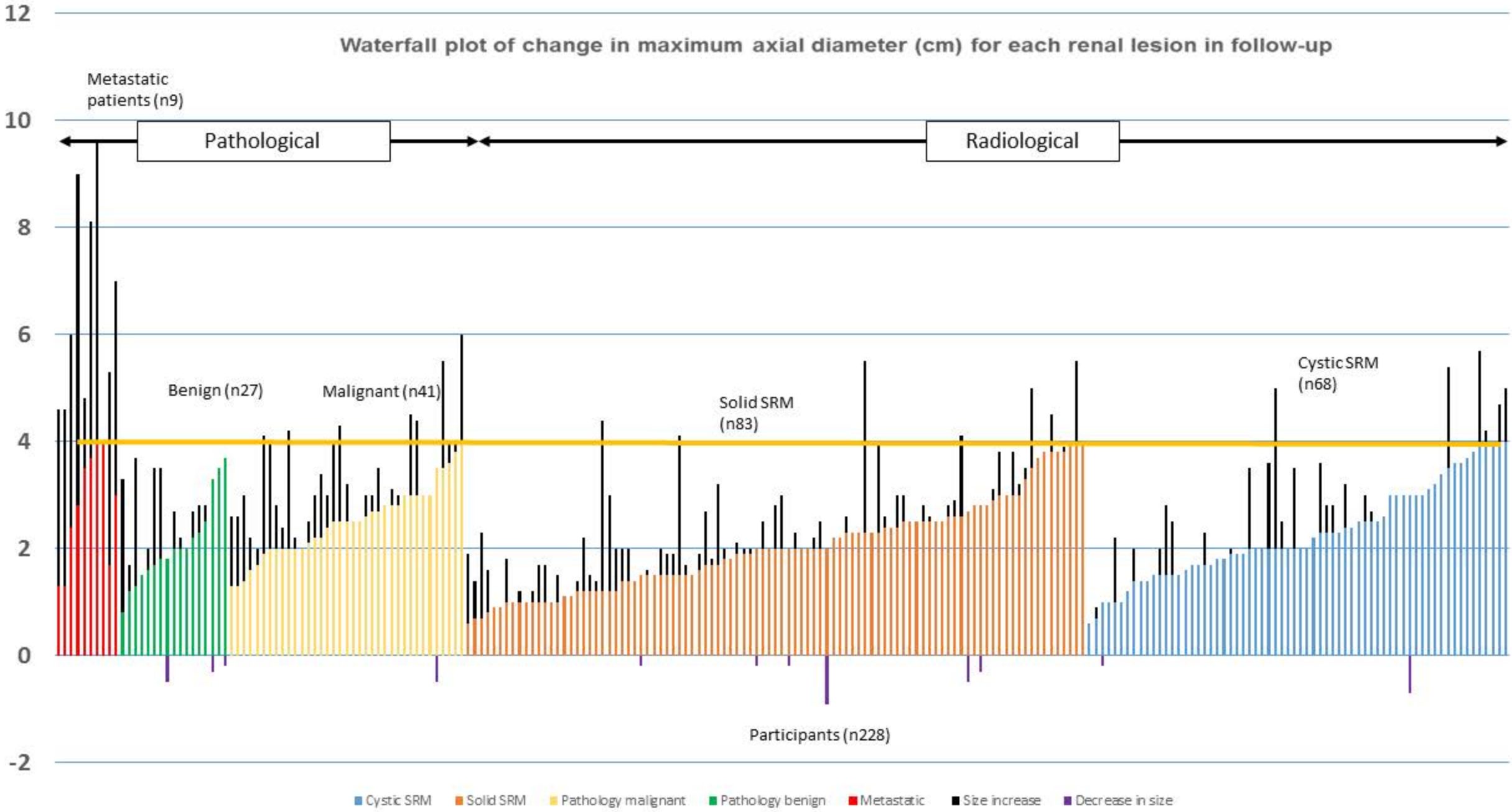
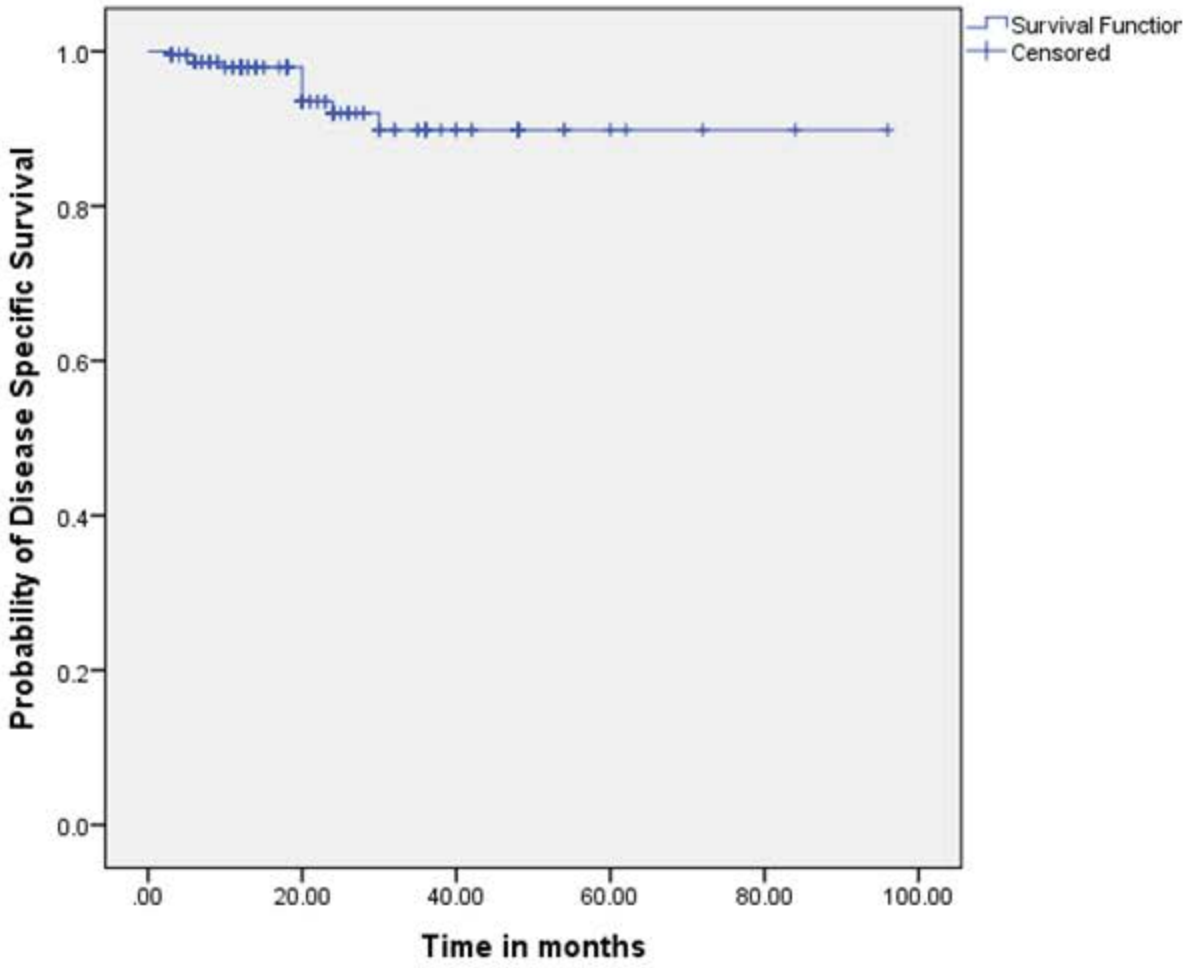


Figure 4. Waterfall plot of change in maximum axial diameter (cm) for each renal lesion



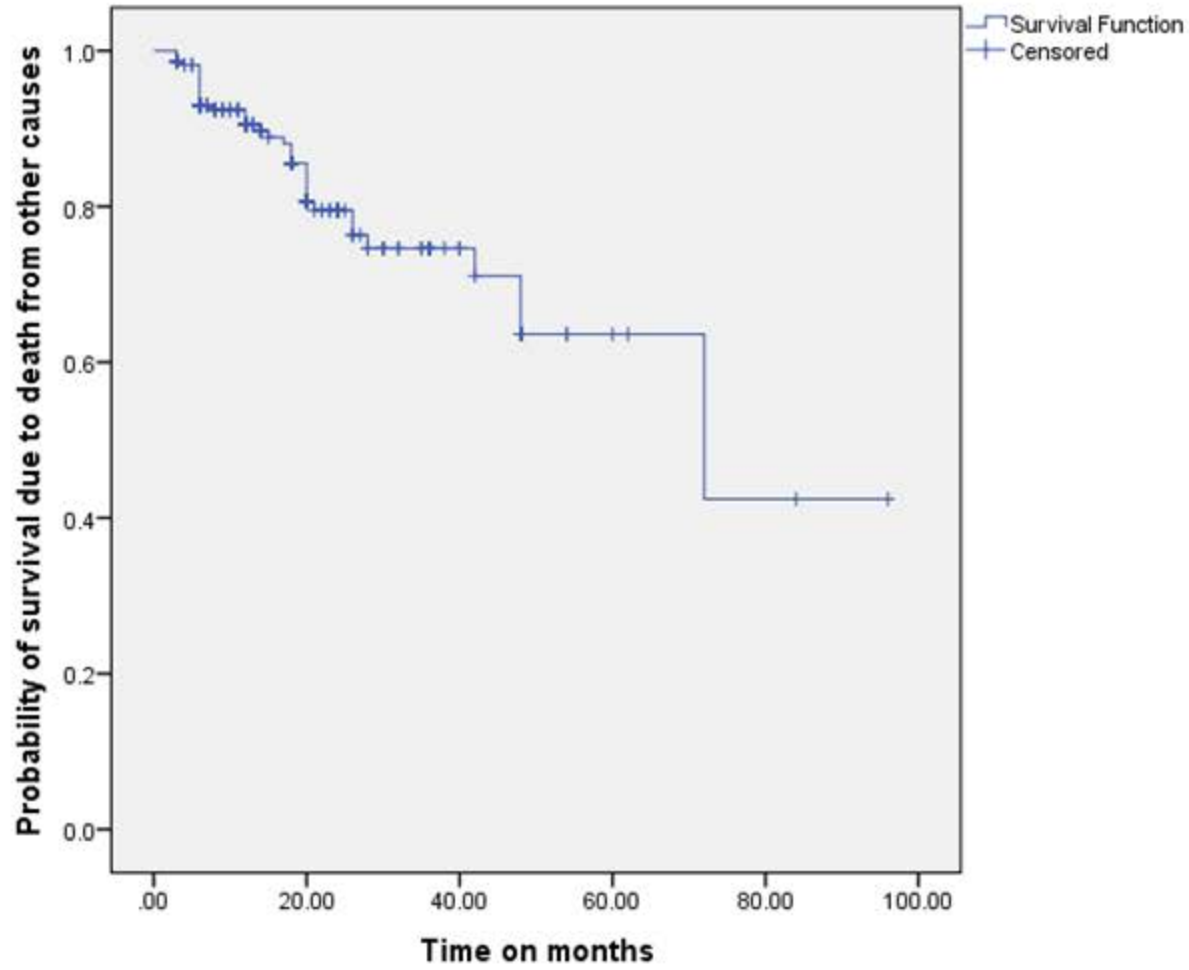


Figure 5. Disease specific and overall survival due to other causes.

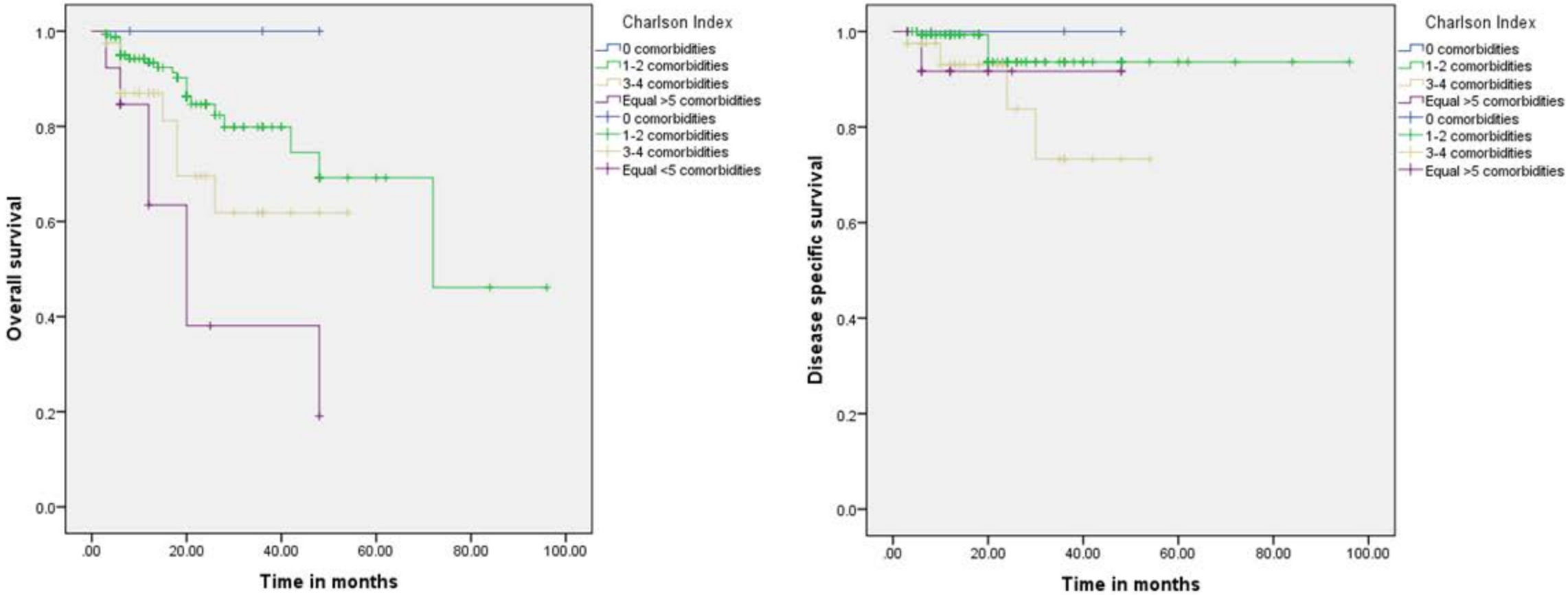


Figure 6. Impact of co-morbidities on cancer specific and overall survival estimated using Kaplan-Meier analysis.

Table 1. Clinical and Demographic Characteristics of the Participants.

Clinical demographic Variable	Cystic SRM (68, 29.8%)	Solid SRM (158, 70.2%)	p Value
Age (in years)	68.2 (± 13.0)	71.5 (± 12.3)	p=0.061
Follow-up (in months)	18.9 (± 15.4, min 3 and max 72)	19.5 (± 15.9 min 3 and max 96)	p=.317
Maximum axial diameter dimension baseline scan (cm) (median, min and max)[b]	2.2 (.9, min .6 and max - 4.0cm)	2.2 (.9, min .6 and max 4.0cm)	p=0.886
Maximum axial diameter dimension last scan (cm) (median, min and max) [b]	2.6 (1.1, min .6 and max 5.7cm)	2.9 (1.5, min .7 and max 11.2cm)	p=.344
Number of co-morbidities (median, min and max) [b]	2.0 (0-9.0)	2.0 (0-9.0)	p=.361
eGFR baseline			
≥60 mls/min/1.73m2	44 (64.7%)	103 (65.6%)	p=.841
<60 mls/min/1.73m2	24 (35.3%)	55 (34.4%)	
eGFR most recent			
≥60 mls/min/1.73m2	43 (63.2%)	103 (65.6%)	p=.740
<60 mls/min/1.73m2	25 (36.8%)	55 (34.4%)	
Location of lesion:			p=.714
Lower pole	32 (47.1%)	79 (50.6%)	
Central	25 (36.8%)	49 (30.6%)	
Upper pole	11 (16.2%)	30 (18.8%)	
Multiplicity:			
No	32 (47.1%)	126 (80.0%)	p=.000**
Yes	36 (52.9%)	32 (20.0%)	
SIMD: [a] 1	10 (14.7%)	22 (15.0%)	p=.809
2	12 (17.6%)	22 (13.8%)	
3	12 (17.6%)	24 (15.0%)	
4	19 (27.9%)	55 (34.4%)	
5	15 (22.1%)	35 (21.9%)	
Gender:			
Male	50 (73.5%)	82 (51.9%)	p=.002*
Female	18 (26.5%)	76 (48.1%)	
Initial Presentation:			
Incidental	46 (74.2%)	113 (78.4%)	p=.521
Microscopic haematuria	3 (4.8%)	7 (4.7%)	
Frank haematuria	7 (11.3%)	17 (11.5%)	
Pain	6 (9.7%)	8 (5.4%)	
Increase in tumour size			
Yes	4 (5.9%)	101 (64.4%)	p=.000**
No	64 (94.1%)	57 (35.6%)	

[a] Scottish Index of Multiple Deprivation 1 (most deprived) and 5 (least deprived)
[b] Median value presented for data not normally distributed.
*Significant level $p < 0.05$, **significant level $p < 0.01$, ***significant level $p < 0.001$.

Table 2. Patients Developing Metastases in SRMS on follow-up

Patient	Date of Diagnosis	Date of Progression	Imaging and date		Findings	Date and cause of death
1	03.08.2007	06.10.2009	Renal USS	(03.08.2007)	3.7 cm upper pole right kidney	02.03.2011
			CT Abdo and Pelvis	(23.08.2007)	3.7 cm upper pole right kidney, no metastasis	Renal cancer
			CT Abdo and Pelvis	(22.01.2008)	3.8 cm upper pole right kidney, no metastasis	
			Renal USS	(06.03.2009)	3.5 cm upper pole right kidney, no further abnormality	
			Renal USS	(09.06.2009)	3.8 upper pole right kidney, no further abnormality	
			Chest X-ray	(24.06.2009)	Clear, no metastasis	
			CT Abdo and Pelvis	(06.10.2009)	Progression 8.1 cm, lung and liver metastasis	
2	03.08.2007	07.09.2009	MRI Renal	(03.08.2007)	2.8 cm central left kidney	01.07.2011
			CT Renal	(20.08.2007)	2.0 cm central left kidney, no metastasis	Renal cancer
			CT Renal	(03.03.2008)	2.5 cm central left kidney, no metastasis, hypodense cyst liver	
			CT Liver	(01.09.2008)	2.5 cm central left kidney, no metastasis, 1.9cm hypodense cyst	
			CT Liver	(20.04.2009)	2.7 cm central left kidney, no metastasis, 1.9cm haemangioma	
			CT Renal	(07.09.2009)	3.5 cm central left kidney, liver lesion 3.1 cm may represent met	
			CT Abdo and pelvis	(12.11.2009)	Both lesion progressed 4.6cm renal and 3.4cm liver	
			CT Renal	(01.02.2010)	Both lesion progressed 5.3cm renal and 3.6cm liver	
			CT Renal	(01.02.2011)	Both lesion progressed 8.9cm renal and 5.7cm liver, new pulmonary metastasis	
3	05.07.2010	30.09.2014	CT Abdo and Pelvis	(05.07.2010)	4cm right kidney, no mets	04.01.2015
			CT Abdo and Pelvis	(14.05.2010)	4cm right kidney, no mets	Renal cancer
			X-ray chest	(22.01.2014)	No mets	
			Bone scan	(30.09.2014)	Metastasis right acetabulum	
4	02.02.2009	07.12.2010	Abdomen USS	(13.07.2005)	1.3cm right kidney “cyst”	23/04/2015
			MRI Renal	(06.04.2007)	2.0cm right cortical lesion	Renal cancer
			CT Renal	(02.05.2007)	1.9cm right heterogeneously enhancing mass	
			USS Kidneys	(03.12.2007)	2.5cm right solid mass	
			USS Kidneys	(30.06.2008)	2.5cm right solid mass	
			Chest Xray	(28.12.2008)	Clear, no metastasis	
			USS Kidneys	(02.02.2009)	2.8cm right solid mass	
			USS Kidneys	(14.08.2009)	3.3cm right solid mass	
			CT Renal	(11.09.2009)	2.5cm right solid mass, no metastasis	
			CT Abdo and Pelvis	(03.06.2010)	3.0cm right solid mass, 2 indeterminate left pulmonary nodules	
			CT Abdo and Pelvis	(07.12.2010)	4.6cm solid renal mass, intrapulmonary nodules	
5	28.02.2002	06.08.2003	CT Abdo and Pelvis	(28.02.2002)	4cm midpolar exophtic right kidney	02.06.2009
			Renal USS	(24.01.2003)	No change	Renal cancer
			Renal USS	(08.08.2003)	No change	
			Renal USS	(06.02.2004)	4.8cm increased in size, offered surgery but declined due to co-morbidities	
			Renal USS	(20.08.2004)	4.6cm and became symptomatic, haematuria	
			Renal USS	(18.05.2007)	6.7cm, no metastasis	
			CT Abdo and Pelvis	(19.06.2007)	10cm, ? nodal disease. Decided to go for cytoreductive nephrectomy	
			CT Abdo and Pelvis	(12.10.2007)	Multiple lung and large petroperitoneal mass	
			CT Abdo and Pelvis	(29.04.2008)	Stable disease	
			CT Abdo and Pelvis	(03.10.2008)	Progression of disease	

6	05.06.2009	10.06.2009	Renal USS (02.02.2004) Renal USS (03.08.2006) Renal USS (11.05.2009) Chest X-ray (03.06.2009) CT Abdo and Pelvis (10.06.2009)	1.7cm complex cyst lower pole right kidney 2cm complex cyst lower pole right kidney Cortical complex cysts left kidney No mets 3.6cm SRM lower pole left kidney, complex cysts right kidney, bilateral pleural effusion, free fluid in the liver	24.06.2009 Renal cancer
7	01.07.2012	15.10.2013	CT Renal (01.07.2012) CT Renal (15.10.2013) CT Thorax, Abdo and Pelvis (15.01.2014)	3cm SRM upper pole left kidney (not reported at that time) 3.8cm SRM upper pole left kidney 4cm SRM upper pole left kidney, mass left ischium, right humerus, multiple pulmonary nodules	20.08.2014 Renal cancer

Table 3 Cox proportional hazard analysis of increase in size of renal lesion

Variables	Categories	P Value	Hazard Ratio	(95 % confidence interval)
Tumour location	Peripheral vs Central	p=.024*	.559*	.350-.895*
SIMD	Categorical scale	p=994	.999	.870-1.148
eGFR	eGFR <60 vs ≥ eGFR 60	p=. 048*	2.152*	1.006-4.605*
Co-morbidity	Number (continuous)	p=.016*	1.142*	1.025-1.272*
Multiplicity	Categorical scale	p=.180	1.330	.877-2.015
Age	Continuous	p=.734	1.003	.986-1.020
Gender	Male vs Female	p=.789	.949	.648-1.020
Initial presentation	Symptomatic vs incidental	p=.765	.969	.790-3.567

****Significant at the 0.01 level, *significant at the 0.05 level**

Table 4. Interventions, pathology and distribution of baseline eGFR. (supplementary)

Intervention/Treatment in SRM cohort (n, %)	Pathology (n, %)	eGFR <60 (n)	eGFR>60 (n)
RFA (n16, 10.0%)	Clear cell 5 (31.3%)	3	2
	Papillary (chromophil) 2 (12.5%)	2	0
	Non-malignancy 3 (18.8%)	2	1
	Oncocytoma 1 (6.1%)	1	0
	Biopsy Missed lesion 5 (31.3%)	2	3
Partial nephrectomy (n17, 10.6%)	Clear cell 13 (76.5%)	1	12
	Papillary (chromophil) 2 (11.8%)	1	1
	Angiomyolipoma 1 (5.9%)	0	1
	Oncocytoma 1 (5.9%)	0	1
Renal Tumour Biopsy (n25, 15.6%)	Clear Cell 10 (40.0%)	8	2
	Papillary (chromophil) 4 (16.0%)	2	2
	Non-malignancy 3 (8.0%)	2	1
	Oncocytoma 1 (4.0%)	1	0
	Missed renal lesion 7 (28.0%)	4	3
Radical Nephrectomy (n10, 6.3%)	Clear Cell 5 (50.0%)	3	2
	Papillary (chromophi) 1 (10.0%)	1	0
	Non-maligancy 2 (20.0%)	2	0
	Mucinous Tubular and spidle cell 2 (10.0%)	1	1