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TITLE PAGE

Clinical Influences in the Multidisciplinary Management of Small Renal Masses in a Tertiary Referral Center

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ABSTRACT

INTRODUCTION

We designed a multidisciplinary Small Renal Mass Center (SRMC) to help patients decide between treatment options and to individualize therapy for the management of small renal masses. In this model, physicians and support staff from multiple specialties work as a team to evaluate and devise a treatment plan for patients within the same organized visit.

METHODS

A retrospective review was performed on a total of 263 patients seen from 2009-2014. Patient characteristics monitored included age, Charlson comorbidity index, body mass index, nephrometry score, tumor size and estimated glomerular filtration rate. Univariate and multivariate analyses were performed to identify patient characteristics associated with each treatment choice.

RESULTS

Among the patient cohort, 88 elected active surveillance (AS), 64 underwent ablation and 111 had surgery (74 partial and 37 radical nephrectomy). There were significant associations between treatment modality and age, CCI, tumor size and eGFR. The mean patient age on presentation was 61.1 years. Patients with high CCI scores (>5) or decreased eGFRs (<60) were more likely to undergo AS (41.6%; 35%) and ablative therapy (29.6%; 34%) versus partial nephrectomy (10.6%, $p < 0.001$; 9%, $p < 0.001$). In multivariable analysis, age ($p < 0.001$), tumor size ($p < 0.001$) and eGFR ($p < 0.001$) remained significantly associated with modality after adjustment for all other factors.

CONCLUSIONS

The SRMC enables patients to assess the various treatment modalities for their small renal mass in a single setting. By providing simultaneous access to the various specialists, it provides an invaluable opportunity for informed patient decision making.

INTRODUCTION

Renal cancer is the third most common urologic cancer. Small renal masses (SRMs), defined as those less than four cm in diameter, are an increasing subset¹. The continued rise in use of imaging has led to the increase in incidentally detected SRMs². However, while the resolution of cross-sectional imaging has steadily improved, it is still challenging to confidently differentiate benign versus malignant masses of this size³. **Percutaneous renal mass biopsy has long been put forward as one means of obtaining diagnostic data for these masses⁴. However, there has been a history of indeterminate results with these so the practice has not been generally utilized.** Hence, for many patients with SRMs, treatment decisions are still being made without a clear diagnosis of malignancy.

The overarching goal of treatment for SRMs is the preservation of functional outcomes while addressing the tumor. Chronic kidney disease (CKD) is an indicator of morbidity, end stage renal disease and even mortality⁵. A high prevalence of CKD has been documented in patients with localized SRMs, with some series suggesting a rate of 25% of patients having CKD III or greater⁶. Hence, the nephron-sparing partial nephrectomy procedure has been recommended and is now considered the gold standard for management of these masses⁷, particularly since the publication of several series suggesting worsening CKD and, in some cases, the new development of CKD after radical nephrectomy as compared to partial nephrectomy⁵. While emerging data question whether extirpative management causes persistent subsequent CKD^{8,9}, there is nonetheless a concern that more aggressive management may have undesirable sequelae in certain patients.

Other treatment modalities have also been proven successful in some patients ¹⁰. Thermal ablation has been particularly useful in older or infirm patients ¹¹. Cryoablation, a form of thermal ablation in which the target tumor and surrounding parenchymal margins are frozen to critically low temperatures, likely has lower major complication rates as compared to surgery ¹⁰. However, the short term rates of treatment failure may be greater than those of surgical management ¹⁰. A third treatment option is active surveillance (AS). This was initially described as a means of management of patients with SRMs who were not surgical candidates due to comorbidities or age ¹². AS is increasingly becoming adopted by physicians as a treatment plan for more patients.

In recent years, all therapeutic options are increasingly being offered to patients by their physicians. Choosing can be an overwhelming experience for some individuals. The multidisciplinary Small Renal Mass Center (SRMC) of the Sidney Kimmel Cancer Center at Thomas Jefferson University Hospital was developed based on a previous model for prostate cancer first developed at this institution ^{13 14}. The goal of this clinic is to provide patients with all appropriate options such that patients are able to decide on an appropriate plan for management.

METHODS

CLINIC FORMAT

This concept was a spin off from our successful Multidisciplinary GU Oncology clinic established at Thomas Jefferson University Hospital in 1996 to provide a more focused attention on this group of patients¹³. The SRMC comprises physicians and support staff

from the Departments of Urology (Urologic Oncology) and Department of Radiology, Division of Interventional Radiology in close collaboration with additional physicians from the Departments of Radiology and Pathology. Patients are referred by their local providers or from the Department of Urology at Jefferson. A navigator evaluates each patient to obtain the basic history and ensure that imaging is available the day of the visit. The SRMC team meets prior to each clinic session to review the cases of the patients presenting for evaluation later that day. Radiology films are assessed along with available patient history and tentative treatment plans are discussed. Patients are subsequently evaluated. History intake and physical examinations are performed separately by members of the urologic and interventional radiology teams. Patients are then presented to the entire team and the final joint consultation is undertaken by the attending physicians of both teams together with the patient.

PATIENT MANAGEMENT

Pathology data was obtained for all patients who underwent partial or radical nephrectomies. Renal mass biopsies were performed at the beginning of all cryoablation procedures starting in the year 2011. A total of 48 needle biopsies have been performed during the study period. Patient education includes discussion of likely outcomes, metastasis and growth rate of SRMs using data from the literature. Patients who have undergone surgery or thermal ablation are subsequently followed every 4 months for the first year, every 6 months for year 2, then every 12 months. Patients following the active surveillance protocol are seen on a 6 month basis for 3 years then annually if there is minimal increase in size of the mass. Most patients present initially with an abdominal and pelvis CT scan. MRI scans with and without contrast are the imaging modality requested for surveillance. These studies are performed on a biannual or annual basis dependent on several factors including stability of growth rate of the mass, patient age or comorbidities.

ASSESSMENT OF PATIENT OUTCOMES

A retrospective review of patients seen at Jefferson SRMC between January 2009 and June 2014 was undertaken. The review was submitted to and approved by our institutional IRB. A total of 327 patients were seen by a single urologist along with urology support staff and residents as well as the interventional radiology team. Patients were divided by treatment modality chosen for management of their SRM. Univariable and multivariable multinomial logistic regression models were then used to assess the association between treatment modality and six clinical factors: age of diagnosis, nephrometry score, Charlson comorbidity index (CCI), tumor size, estimated glomerular filtration rate (eGFR) and body mass index (BMI). The reference response category for the generalized logits was active surveillance. All analyses were performed using SAS v9.4.

RESULTS

Between January 2009 and June 2014, 327 patients with SRMs were seen in consultation by a single urologist along with urology support staff and members of the interventional radiology team. Complete records were available for 263 patients, and long term follow-up was retrospectively evaluated. Treatment modalities were summarized by clinical factors and associations were then determined from univariable analyses (Table 1).. There were significant associations between treatment modality and age, CCI, eGFR and tumor size. Older patients tended to choose cryoablation with average age at diagnosis 69.3 years versus 51.6 years for patients who underwent partial nephrectomy and 64.9 years for those who underwent active surveillance ($p < 0.001$, Table 1). Patients with a higher CCI chose active surveillance as seen in 59 patients with $CCI > 5$, as compared to 42 who underwent cryoablation and 15 who chose partial nephrectomy ($p < 0.001$). Similarly, patients with a low eGFR less frequently chose partial nephrectomy (15 patients with $eGFR < 60$) versus cryoablation (34 patients) and active surveillance (35 patients). **Tumor size was also associated with treatment**

decision, with patients with tumors 2cm or less in diameter more likely to select AS (51 patients) versus 27 who chose cryoablation, 24 who chose partial and 8 who underwent radical nephrectomy (Table 1).

In multivariable analysis (Table 2), age ($p<0.001$), eGFR ($p<0.001$) **and tumor size ($p<0.001$)** remained significantly associated with modality after adjustment for all other factors. When compared with AS, older individuals were more likely to undergo cryoablation (OR=1.05, $p=0.018$) versus partial (OR=0.89, $p<0.001$) or radical nephrectomy (OR=0.96, $p=0.048$). Patients with a higher eGFR were less likely to have cryoablation (OR=0.48; $p=0.054$) and radical (OR=0.34, $p=0.026$), versus partial nephrectomy (OR=3.98, $p=0.012$). **Patients with tumors greater than 2cm were less likely to choose cryoablation (OR= 2.25, $p=0.007$), versus radical (OR=4.90, $p=0.001$) or partial nephrectomy (OR= 2.46, $p=0.003$).**

We investigated nephrometry score¹⁵ and BMI which showed no statistically significant differences as compared by treatment modality choice. However, for those patients with available data, there was a slight trend towards increased partial nephrectomy versus cryoablation in patients with low nephrometry scores (Table 1).

Pathology reports were obtained for patients who underwent partial or radical nephrectomies as well as a subset of patients who underwent cryoablation. Specimens were obtained after surgical resection or as needle biopsies performed during the cryoablation procedure. Similar to previous reports¹⁶, the majority of these SRMs were renal cell carcinomas (55.6%) with 12.3% oncocytomas, 18.0% angiomyolipomas and 13.9% otherwise benign or insufficient for diagnosis.

DISCUSSION

The assumption that providers are more likely to recommend the treatment modality they perform to patients presenting for consultation has been shown in the arena of low risk prostate cancer¹⁷. Surgeon characteristics have similarly been shown to influence treatment modality in patients with SRMs¹⁸. Evaluation of multidisciplinary clinics for prostate cancer have shown that patients seen in these settings, after presumably being introduced to all appropriate treatment options, may be more likely to undergo active surveillance for low risk prostate cancer¹⁹. The multidisciplinary clinic setting provides an opportunity for patients to fully evaluate possible treatment modalities. This arrangement often allows for a more extensive consultation than is normally available at the typical urologist's office. That, in addition to the opportunity to ask questions of the various physicians in the same setting may aid patients in choosing the treatment plan best suited to them and their families.

The treatment decision should take into consideration all viable options for a given patient, using all tools available to make that decision. One promising preoperative aid is the RENAL nephrometry score¹⁵. This is a quantitative method for characterizing the potential degree of difficulty involved in definitive management of a SRM. Our data do not indicate a statistically significant association between the assignment of nephrometry scores and treatment choice. However, there is a slight trend towards the performance of partial nephrectomies in patients with low nephrometry scores.

In addition to consideration of the health, age or renal function of the patient, the decision making process should include a discussion of factors associated with benign masses or masses with decreased risk of metastasis such as tumor size. It has been shown in a number of retrospective studies that tumors less than 3cm have a decreased risk of metastasis²⁰. We have demonstrated that patients with tumors 2 cm or less in diameter are more likely to choose AS, which is consistent with the natural history of masses of this size.

We now make a point of performing a renal mass biopsy on all patients undergoing percutaneous ablation of a SRM when possible, and also employ it in cases where it will affect management. Current standard of care for SRM does not require a precise tissue

diagnosis prior to definitive treatment. However, given that approximately one quarter of renal masses have been reported to be benign at surgery²¹, the ability to obtain evidence of malignancy will likely become an absolute imperative with time. The regular use of percutaneous biopsy as a diagnostic tool may decrease the number of procedures undertaken for benign masses. This has long been avoided in the field due to concerns over possible complications such as biopsy tract seeding with cancer cells and post-biopsy bleeding. Early attempts resulted in low diagnostic yield, leading to the widespread practice by physicians of foregoing biopsies prior to treatment²². There is now a growing body of evidence suggesting better yields and allaying the concerns for seeding²². A recent study demonstrated a correlation of 92% of biopsy with final pathology²³. Moreover, biopsy can be used to give an indication of the aggressiveness of a given tumor since grade can be determined²⁴. Although there continues to be some level of false negatives and indeterminate findings²⁵, the concurrent performance of needle core biopsies and fine needle aspirates may increase diagnostic precision²⁴. Increased success may come with immunostaining, thus diminishing the level of uncertainty involved.

The goal of management is to avoid compromising cancer specific survival. The SRMC presents a unique opportunity for patients to undergo consultation in a setting that allows for the appropriate presentation of treatment outcomes. Patients evaluate each treatment modality with the urologic oncology and interventional radiology teams simultaneously. This format encourages more thorough discussion of all options, thus enabling a more informed patient choice. **We have recently incorporated the use of nomograms in our discussions on possible patient outcomes. Although not demonstrated to be statistically significant in this work, it is possible that specific patient characteristics including comorbidities and anatomic restrictions may influence decision making with regard to treatment options by the patient as well as the SRMC team.** An additional consideration is the finding in several series that most SRMs grow quite slowly²⁶ with mean growth rates less than 0.4 cm each year. Hence, AS can be adopted as an initial management plan which does not preclude later definitive treatment. Indeed, an emerging body of retrospective studies is showing similar patient outcomes with active surveillance versus more definitive treatment¹². One recent multi-institutional study has also

demonstrated equivalent short term overall and cancer specific survival in patients assigned to an active surveillance arm as compared to those who underwent nephrectomy or thermal ablation²⁷. **While this study was not randomized, our data have encouraged us to consider evaluating a more robust role for AS in the management of patients with SRMs.** Through the SRMC, patients can be easily followed for several years such that new treatment decisions can be made as information or patient circumstances change. **However, there must be unwavering dedication by both the patient and the treatment team to ensure that the patient returns in a timely fashion for periodic evaluation. Our review revealed that twenty-four (17.8%) of the patients who initially chose active surveillance were lost to follow up. This underscores the need for the multidisciplinary team to put safeguards in place to ensure that patients continue to be evaluated as necessary.**

It is intriguing to surmise that the SRMC will influence treatment patterns at this institution. More extensive experience with this clinical model will allow for an evaluation of whether the SRMC influences treatment modality choice by patients. Future work will focus on determining the effect this multidisciplinary model has on improving long-term overall outcomes as well. This initial study of the SRMC is limited by its retrospective design as well as the relatively small patient numbers. Almost 20% of patients (64) were lost to follow up. Many had decided on a program of active surveillance. Since this is a tertiary referral center, patient loss was often due to patients' return to their home urologists for routine follow up. Additionally, there were losses due to patient death from other comorbidities.

CONCLUSION

The SRMC provides a novel opportunity for patients to evaluate all treatment modalities in an attempt to encourage more informed patient decision making with regard to care. **Our current data suggest that older patients underwent the less invasive treatment modalities of active surveillance and cryoablation while those with higher estimated glomerular filtration rate were less likely to choose cryoablation as compared to partial nephrectomy.** A longer term investigation will be performed to evaluate patient satisfaction levels and clinical outcomes as compared to other published series.

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