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## Treatment of Exophytic Renal Cancer Smaller than 3 cm: Surgery versus Active Surveillance

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### Active Surveillance

The incidence of renal cell carcinoma (RCC) is rising due in large part to increased use and better resolution of 3-D imaging. Combined with only a modest decrease in RCC mortality rates, there is concern of overtreatment. As a result, the acceptance of active surveillance (AS) for RCC becomes a clear reality.

An exophytic lesion smaller than 3 cm is typically amenable to minimally invasive nephron sparing surgery or ablative therapy, prompting clinicians and patients to commonly opt for treatment but is treatment truly necessary? A 3 cm threshold has significance for RCC in the von Hippel-Lindau literature, being the size at which metastatic potential increases and surgical intervention is indicated. Given the inherent problem of comparing the natural history of hereditary and sporadic RCC, this criterion does not seamlessly transfer over to the typical incidental small renal mass. Although in a population based study approximately 16% of 20,000 patients with RCC smaller than 3 cm demonstrated a nuclear grade of 3 or greater, this number was only 3% higher for tumors smaller than 2 cm and increased by just 2% for tumors smaller than 4 cm and 4% for those smaller than 5 cm.<sup>1</sup> Another population based study examining RCC tumor size and mortality demonstrated an extremely low (3.8%) 5-year cancer specific mortality for tumors 2 to 3 cm, with modestly increased rates (4.1%) for tumors 3 to 4 cm.<sup>2</sup> Although it is cautionary to interpret a uniform natural history of small RCC by these observational studies, it is nonetheless suggestive that the 3 cm size threshold for RCC may not be absolute and aggressive treatment of these tumors may not be necessary.

Based on several published reviews and meta-analyses, it is now generally accepted that active surveillance of small renal masses (SRMs) is safe and potentially preferable in certain clinical situations. However, the limitations of these studies are they are retrospective, followup is short and histopathological confirmation is lacking. A prospective phase 2 multi-institutional trial of 178 patients with 209 SRMs (mean maximum dimension 2.1 cm) was reported in 2011 with a mean follow-up of 28 months.<sup>3</sup> Biopsy was performed in 72 of 151 (48%) cases followed for longer than 12 months, of which 33% were nondiagnostic. Metastatic progression was observed in just 2 patients (1.1%). Interestingly, a third of the SRMs observed had either a negative or no growth rate, and biopsy proven RCC lesions grew at a rate equivalent to that of benign tumors. Although not definitive and also lacking in uniform biopsy evidence and longer followup, this Level 1 evidence again supports that growth and metastases of small RCC are uncommon, and points to the safety of AS for RCC in a select population.

It is hard to argue that if a patient were young with a perfect functional status that prompt extirpative nephron sparing surgery, the standard of care, would be discouraged. Conversely, few would hesitate to place an elderly, infirm patient with a short life expectancy and an incidental SRM on an AS protocol, feeling confident that RCC would not be the ultimate cause of death. However, these disparate clinical situations do not represent reality for the majority of patients faced with this scenario. For a variety of medical and psychosocial reasons, a healthy individual may want to delay definitive treatment, just as a less healthy patient on AS may risk progression. Delayed intervention of SRM for patients on an AS protocol has been shown to be an effective treatment plan by Crispen et al.<sup>4</sup> They followed 82 patients with 87 SRMs 4 cm or smaller for a median of 14 months. Treatment was delayed 12 months or longer in 60 (69%) and 24 months or longer in 29 (33%) patients. Of the 87 SRMs treated 73 (84%) were RCC and 76% were managed by nephron sparing surgery. Only 2 RCCs were up staged to pT1b and there was no metastatic progression or cancer related deaths.

There is an implication in this case scenario of a renal cancer smaller than 3 cm that a renal mass biopsy (RMB) has been performed. Accordingly, the role of biopsy in patients with a SRM being considered for active surveillance should be defined. Immediate treatment would be recommended for patients with aggressive histopathological features (histology and grade), whereas those with features of low malignant potential would be comfortably placed on AS. Indeed, for renal masses smaller than 2 cm that are pathologically confirmed to be RCC, 90% or more are Fuhrman 1-2.<sup>5</sup> Despite the known limitations of biopsy sensitivity, the use of RMB for small renal masses is increasing. A recent international consortium recommended RMB in patients being considered for AS in whom histopathological data would change the treatment plan.<sup>5</sup>

In conclusion, in the patient presenting with an exophytic RCC smaller than 3 cm, given the associated unknown clinical, anatomical and psychosocial issues, an AS protocol with potential delayed therapy, incorporating RMB to help drive the decision making process, is a reasonable therapeutic alternative.

## Surgery

The increased diagnosis of small renal masses following the increased use of cross-sectional imaging has resulted in a stage migration in renal cell carcinoma without a corresponding decline in RCC mortality. Due to the often indolent nature of SRMs, various active surveillance paradigms have been proposed. The concept of active surveillance for RCC has been supported by several retrospective studies showing a low rate of progression to metastatic disease in patients with SRMs.<sup>3</sup> Certainly this approach is appropriate for patients who are elderly or infirm, that is those whose competing risks for mortality likely outweigh their risk of RCC related mortality. However, the majority of patients diagnosed with SRMs are healthy enough to bear significant oncologic risk over time and, therefore, may benefit from surgery.

The risk of synchronous metastasis in patients with SRMs is thought to be less than 5%, which serves to highlight the variable and unpredictable biology of RCC.<sup>6</sup> In a multi-institutional phase 2 trial from Canada 178 patients who were not deemed candidates for surgery due to comorbidities, age or patient refusal were placed on active surveillance until progression.<sup>3</sup> Overall, in 25 patients (14%) tumor size progressed to larger than 4 cm or tumor volume doubled in less than 12 months. In another 2 cases (1.1%) de novo metastasis developed within 1 year of initiating surveillance. Notably, these authors concluded that growth rate alone was insufficient to characterize the underlying biology of the SRM. The results of other published active surveillance cohorts reveal a 2.1% cumulative risk of regional or metastatic RCC while on surveillance although most suffer selection bias and limited followup.<sup>7</sup>

It may be tempting to dismiss the relatively low growth and metastasis rates of SRMs, but in younger healthier populations this is an unacceptable risk and treatment is clearly warranted. Risk stratified approaches have been proposed based on initial observation of SRM growth or renal biopsy. The ability to individualize treatment based on identification of aggressive phenotypes would be ideal oncologically. Unfortunately, no current strategy to date has been able to consistently identify SRMs with more aggressive biology. Radiographic features such as size, exophytic behavior and proximity to the collecting system/sinus have been incorporated into a preoperative nomogram to predict cancer versus benign as well as RCC grade with some degree of accuracy.<sup>8</sup> However, further external validation of this model is required and no current models predict the probability of progression to metastasis or RCC specific mortality in active surveillance cohorts. Even lack of linear growth on serial imaging does not rule out malignant potential, which indicates the substantial limitations of radiographic tools in characterizing the behavior of renal masses.<sup>7</sup>

What about biopsy? The accuracy of renal biopsies in diagnosing RCC has improved to more than 90% in recent years and yet the ability to accurately assess for tumor grade remains poor. Furthermore, recent studies on RCC pathological specimens have demonstrated marked heterogeneity in grade and molecular profile, limiting the theoretical ability of biopsy techniques to precisely detect tumor aggressiveness.<sup>9</sup> The ability to apply molecular techniques to renal biopsy or radiographic imaging may improve our ability to predict aggressive RCC phenotypes and, therefore, limit the cohort of patients who require surgical treatment. Until these methods are further developed and matured, surgery will continue to be performed for most small exophytic renal cancers in most patients.

Partial nephrectomy has largely supplanted radical nephrectomy as the mainstay of treatment for SRMs, decreasing the risk of chronic kidney disease with time.<sup>7</sup> Exophytic SRMs are ideally positioned for minimally invasive partial nephrectomy with resultant decrease in treatment related morbidity. Thus, the relative safety of treatments for SRMs provides further rationale for avoiding the oncologic risk of surveillance. Additionally, progression of SRMs initially under surveillance may result in tumor growth, causing an increase in technical difficulty or even inability to perform nephron sparing surgery. When patients present with incidentally discovered localized SRMs, they are not only at their most curable

state, but are likely also in the optimal state to tolerate surgery. Fitness for surgery does not improve with age and given that most renal masses will continue to grow with time, delaying surgery with active surveillance is unlikely to improve outcomes.

As always, patient selection is key and in those whose life expectancies are limited by age or comorbidity active surveillance may be a wise strategy. However, for the majority of patients with renal cancers of this size, we have the ability to virtually eliminate the risk of metastasis and death from RCC with minimal morbidity and treatment related risk. Until such time as consistently accurate diagnostic techniques can preclude aggressive treatment in those with assuredly indolent disease, partial nephrectomy remains the standard of care for cT1a renal masses as recommended by the National Comprehensive Cancer Network, American Urological Association and European Association of Urology.

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