Small renal masses in the elderly: Contemporary treatment approaches and comparative oncological outcomes of nonsurgical and surgical strategies

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Over the last decades, there has been a significant stage migration in renal cell carcinoma and especially older patients are getting diagnosed more frequently with low stage disease, such as small renal masses ≤4 cm of size. Considering the particular risk profile of an older population, often presenting with a nonnegligible comorbidity profile and progressive renal dysfunction, treatment approaches beyond aggressive radical surgical procedures have come to the fore. We sought to give a contemporary overview of the available different treatment strategies for incidental small renal masses in an elderly population with the focus on comparative oncological outcomes of nonsurgical and surgical modalities.

Keywords: Ablation techniques; Aged; Kidney neoplasms; Nephrectomy; Watchful waiting

INTRODUCTION

Malignant tumors of the kidney and the renal pelvis are among the ten leading cancer types in both, men and women, with an estimated 62,700 incident cases in the United States in 2016 [1]. The incidental detection of kidney lesions assumed to be renal cell carcinoma (RCC) has significantly increased in the past decades, which is mainly related to uprising imaging utilization for nonspecific abdominal issues or follow-up of other malignancies or diseases [2]. Specifically in small renal masses (SRM) ≤4 cm of size, incidence rates have increased significantly [2,3]. Remarkably, these trends are mostly upfront among the elderly adults, a patient subpopulation in which already higher rates of diagnoses

are reported [4]. The malignancy rate in SRM is related to the tumor size, as an increasing tumor size was shown to be associated with higher odds of having malignant disease than a benign lesion [5]. According to different reports, approximately 80%–90% of the incidentally diagnosed kidney tumors are malignant, whereas only 10%–20% present benign histology in pathological review [5,6]. Also, small tumors tend to be of low grade and less likely to present aggressive biology than larger renal masses. Notably, in spite of the constant use of aggressive treatment regimes, mortality rates among older patients with RCC and significant comorbidities have remained static over the past decades [3,7,8]. Given this discordance of aggressive approaches towards early stage lesions without a decline

in mortality, questions have risen regarding appropriate paradigms of treatment management. Furthermore, there is increasing evidence that benefits of distinct active treatment approaches are quite limited in a patient population ≥75 years of age, due to the physiologic process of aging, such as increasing comorbidities and predisposition for frailty [9]. Hence, several experts in the field of kidney cancer have endorsed less aggressive and morbid treatment options (i.e., active surveillance and ablative therapies) [7,10]. Due to the recent trend of reassessing the treatment effect of different approaches and a paradigm shift regarding the management of SRM, we sought to review and summarize contemporary treatment approaches for incidental small kidney tumors with a focus on an elderly, comorbid patient population and the oncological outcomes of treatment modalities which may be feasible in this patient subpopulation.

ACTIVE SURVEILLANCE

Active surveillance is defined as the initial systematic monitoring of kidney tumor size, which is provided by either ultrasound, computing tomography, or magnetic resonance guided abdominal imaging [11]. If any clinical progress is seen during the follow-up, those patients may be offered a delayed intervention [12].

The recent increase of active surveillance utilization in the treatment of SRM is fueled by 3 major factors. First, the general acceptance of percutaneous renal mass biopsy is growing and its role is expanding. The value of renal biopsy of kidney tumors has been subject to controversy for many years, but due to technical progress and improved histopathological review, this diagnostic procedure has come back to the fore in recent years. In order to gain a basis for reasonable risk stratification and treatment decisions, it is necessary to provide an adequate tissue sampling and subsequently a pathological review of the histology with excellent sensitivity and specificity [13]. Specifically, a renal biopsy can better classify patients who might be candidates for active surveillance. Percutaneous tumor biopsy is considered safe and useful for preoperative risk stratification with reasonable complication rates and a diagnostic accuracy of >90% [14,15]. Indeed, in a recent meta-analysis, 5,228 patients from 57 studies were assessed and the median concordance rate between histological subtype diagnosed at renal biopsy and that found on surgical pathology was 90%. After limiting the studies included to patients presenting with SRM, concordance even rose to 96% [16]. Hence, the authors concluded that renal biopsy provides a high diagnostic yield while only constituting a low risk of complications.

Ultimate goal of assuring diagnosis via percutaneous biopsy is the risk assessment and building ground for reasonable clinical decision-making regarding optimal and adequate treatment. Hence, the American Urological Association supports percutaneous tumor biopsy in SRM for clinical stage I, specifically in those patients who are considering different treatment options. Conversely, healthy patients who are unwilling to accept the potential remaining uncertainty after biopsy should not be counseled to undergo such [17]. In addition, by virtue of the high accuracy of abdominal imaging, patients with contrast-enhancing renal masses, for whom a surgical intervention is planned, are not eligible for preoperative biopsy [18]. Identifying patients for the adequate and most reasonable treatment strategy is still a multi-layered undertaking and implications of renal mass biopsy on treatment approaches for SRM remain partly elusive.

Second, a growing body of literature has devoted much effort into describing and understanding the natural history and the heterogeneity of SRM. Several reports confirm slow growth rates and low propensities of developing metastatic disease [19-21]. Mason et al. [21] analyzed 82 patients with 84 SRM undergoing active surveillance between 2001 and 2009 in a multi-institutional Canadian cohort (Table 1). Mean annual tumor growth rate was 0.25 cm/y and only one patient (1.2%) developed metastatic disease at a median follow-up of 36 months. By developing a diagnostic tool to predict growth rates, the authors found masses ≥2.45 cm at diagnosis to be growing faster than smaller tumors [21]. In a recent meta-analysis, Smaldone et al. [20] relied on 18 different series and included 880 patients with 936 SRM undergoing active surveillance (Table 1). In the overall cohort, a median growth rate of 0.3 cm/y was calculated at a median follow-up of 33 months. In only 2% (n=18) of patients, metastatic disease was diagnosed at a follow-up of 40 months. Of those, more detailed information was available for 11 patients and 73% (n=8) were diagnosed with distant visceral or bone metastasis, whereas 27% (n=3) had pathological lymph node involvement only. The majority of those metastatic patients were diagnosed with clear cell histology (67%), and 22% and 11% with papillary or mixed histology, respectively. When comparing SRM patients that progressed to metastasis to those, who did not, there were significant differences in initial tumor size (4.1 cm vs. 2.3 cm, p<0.001), mean linear (0.8 cm/y vs. 0.3 cm/y, p<0.001) and volumetric growth rate (27.1 cm^3/y vs. 6.2 cm^3/y, p<0.001), as well as patient age (75.1 years vs. 66.6 years, p=0.03) [20]. The authors concluded that progression to metastases occurs

Table 1. Selection of contemporary studies depicting considerations on intervention vs. surveillance for small renal masses in the elderly

Source	Study population	Main results	Main conclusions
Smaldone et al. [20]	Systematic review of 880 patients with SRM undergoing active surveillance.	Eighteen patients progressed to metastasis. Those were associated with an increased age, greater initial tumor dimension, and higher linear and volumetric growth rates, as compared to patients without developing metastasis.	A substantial proportion of SRM remained static after initial period of active surveillance. Progression to metastases occurred in a small percentage of patients. In patients with competing risks, radiographic surveillance is an acceptable approach. Delayed intervention should be reserved for patients who have tumors with significant linear or volumetric growth.
Mason et al. [21]	Prospective multi-institutional study of 82 patients with SRM undergoing active surveillance.	One patient progressed to metastasis. Maximum diameter at diagnosis was the only predictor of tumor growth rate. Masses ≥2.45 cm grow faster than smaller masses.	Most SRM grow slowly and carry low metastatic potential. Initial tumor size predicts tumor growth rate. SRM ≥2.45 cm at initial diagnosis grow faster than smaller tumors.
Kutikov et al. [25]	Retrospective SEER-Medicare study of 6,655 patients with localized RCC.	Age and comorbidity score strongly correlated with mortality and predicted other-cause mortality. Patients with localized and node negative RCC had low probability of cancer-specific mortality but higher risks of death from competing causes.	Informed consent treatment decisions must also integrate factors that predict noncancer deaths.
Lane et al. [8]	Retrospective single-institution study of 537 patients with cT1 RCC at age ≥75 years undergoing different treatment modalities.	Most common cause of death were cardiovascular events, cancer progression caused death in 4%. Age and comorbidity were predictors of overall survival, but not the treatment modality type.	Surgical management in patients with cT1 RCC ≥75 years does not increase overall survival. Patients mostly died of cardiovascular causes similar to the general elderly population. Further studies are needed to evaluate the advisability of different treatment options in patients with limited life expectancy.
Pierorazio et al. [27]	Prospective multi-institutional study of 497 patients with SRM undergoing primary vs. delayed intervention.	Equal cancer-specific survival rates at 5 years in both treatment groups. Active surveillance was not predictive of overall or cancer-specific survival in regression models.	Active surveillance with delayed intervention appears to be noninferior with regard to oncological outcomes for well-selected patients with SRM. Patients undergoing active surveillance are older, have more comorbid conditions, and smaller tumors on average.
Sun et al. [7]	Retrospective SEER-Medicare study of 10,595 patients with cT1 RCC undergoing surgical or nonsurgical treatment.	Patients treated with partial or radical nephrectomy had a lower risk of cancer-specific mortality compared to patients undergoing nonsurgical treatment. This difference in mortality vanished in patients ≥75 years.	The harms of surgery need to be weighed against the marginal survival benefit for some patients. The results corroborate recommendations from contemporary guidelines supporting the role of nonsurgical approaches in selected patients.

RCC, renal cell carcinoma; SEER, Surveillance, Epidemiology, and End Results; SRM, small renal mass.

only in a small subgroup of patients and that, specifically in older patients with severe competing health risks, active surveillance may be a reasonable treatment approach, considering the later option of delayed intervention in this population.

Third, competing causes in deaths in kidney cancer populations have found recognition and suggest a change of emphasis on balancing out the risks to die from cancer or other causes. The number of patients harboring clinically localized tumors but not being optimal surgical candidates because of older age or significant comorbidities has risen and several recent studies have shown a significant association of those cofactors and non-RCC-related mortality [8,22,23]. Indeed, in a study of 697 patients, it has been shown that in patients with localized, but surgically treated RCC, comorbidity, age, tumor stage, and tumor grade were predictive factors of overall survival [24]. Kutikov et al. [25] used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database to evaluate 6,655 patients with localized, lymph node negative RCC and found that the kidney cancer-specific mortality only overshadowed competing-risks mortality in patients with tumors >7 cm and Charlson comorbidity indices of 0 (Table 1). Interestingly, when evaluating patients treated for cT1 kidney cancer who were older than 75 years, in multivariate analyses it could be shown that age and comorbidity type were significantly associated with overall survival, whereas treatment approach (active surveillance vs. radical nephrectomy vs. nephron-sparing surgery) did not impact overall survival at all, and most patients in this investigation died from competing-risks, such as cardiovascular events [8] (Table 1).

Given the relative paucity of prospective data regarding the effectiveness of active surveillance compared to primary intervention in patients with SRM, recently the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry has been implemented with the purpose of (1) exploring oncological and medical outcomes in patients undergoing active surveillance for SRM, (2) identifying radiological and/or clinical parameters to predict local tumor growth and metastatic progression, and (3) comparing quality of life between patients undergoing active surveillance vs. primary intervention [26]. The registry's 5-year follow-up has been published in 2015 [27]. A total of 497 patients harboring cT1a kidney tumors were included and patients could choose from either active surveillance or primary intervention (partial nephrectomy or ablative procedures). Notably, active surveillance was not inferior to primary intervention, providing cancer-specific survival rates of 99% and 100% for primary intervention and active surveillance, respectively.

Patients undergoing active surveillance were older and more comorbid than their counterparts choosing primary intervention. Finally, the authors concluded that active surveillance with delayed intervention is to be considered as a noninferior treatment approach regarding short-to-intermediate-term oncologic outcomes in a well-selected cohort of patients harboring SRM [27] (Table 1). In a large-scale retrospective analysis relying on the SEER-Medicare linked database, this concept was furthermore corroborated by Becker et al. [28]. Overall, 6,237 patients with pT1a RCC were evaluated undergoing radical or partial nephrectomy as the final treatment. Interestingly, the authors found that a nephrectomy delay of >3 months was not significantly associated with a higher risk of cancer-specific mortality in multivariate analyses.

SURGICAL APPROACHES

Based on the available contemporary outcomes, partial nephrectomy as a nephron-sparing surgery procedure is considered as the standard of care in patients with SRM, who are eligible for surgery, based on equivalent cancer control but better preservation of long-term renal function [18]. Several studies have shown an increasing adoption of nephron-sparing surgery for localized RCC in Europe [29] and the United States [30,31]. Due to several benefits of wristed instruments regarding the dissection, suture techniques, and visual magnification, robotic-assisted laparoscopic partial nephrectomy (RAPN) has gained popularity and its utilization increased substantially over the last years. From 2008 to 2011, RAPN use increased to a peak of 14% accounting for approximately 47% of all partial nephrectomies and the authors of a recent trend analysis concluded that robotic technology might enable surgeons to more often perform nephron-sparing surgery [32]. Indeed, the emerging availability of robots is independently associated with increasing use of partial nephrectomy, as shown in a study by Kardos et al. [33]. However, long-term oncological outcomes from larger RAPN series, specifically in the SRM setting, are lacking. Early cancer outcomes were similar to open and robot-assisted approaches [34] and cancer-specific survival rates at 5 years are comparable using different surgical techniques, irrespective of utilization of either open surgical or laparoscopic techniques [35,36]. However, robotic surgery has not been evaluated in the latter studies. Nevertheless, the superiority of RAPN over traditional laparoscopic partial nephrectomy regarding warm ischemic time has been shown, which might significantly affect postoperative kidney function and thus, lead to measurable

survival benefits [37]. Notably, some population-based studies have compared surgical and nonsurgical procedures for SRM and significantly lower cancer-specific mortality rates are reported for surgical approaches [38]. In addition to oncological guidelines, general criteria for surgery incorporate the suitability for general anesthesia as well as the anticipated reduction in renal function. However, in the elderly, surgical intervention may not benefit patients with a limited life expectancy, as shown in retrospective competing-risks analyses by Sun et al. [7]. In 10,595 patients, partial nephrectomy and radical nephrectomy were compared to nonsurgical treatment and showed a cancer-specific survival benefit in patients <75 years. However, this effect completely vanished in patients ≥75 years with cT1a RCC. In a similar study, Lane et al. [8] evaluated 537 patients with localized kidney tumors at age ≥75 years and compared active surveillance, nephron-sparing interventions, and nephrectomy. Those patients did not benefit from surgical procedures, as overall survival was not increased in this particular subgroup of patients (Table 1). To the contrary, patients mainly died of cardiovascular causes and nephrectomy accelerated renal dysfunction, which - again - underlined the need for an adequate risk-assessment prior to intervention in comorbid, older subcohorts of patients [8].

In order to quantitate survival differences in older patients with SRM, efforts have been made to develop preinterventional tools to acquire reasonable treatment trade-off calculations for an effective shared decision-making. For example, Zastrow et al. [39] developed a comprehensive nomogram to integrate commonly available patient characteristics, such as age, tumor size, and American Society of Anesthesiologists physical status into a convenient tool for predicting synchronous metastatic disease. The nomogram was based on a multivariate logistic regression model, which yielded a significant c-index of 0.82 for aforementioned covariates. Another predictive model was developed by Kutikov et al. [40]. The authors integrated age, gender, tumor size, and race into a nomogram to compare and predict competing risks of death in patients with localized RCC.

ABLATIVE APPROACHES

In addition to active surveillance, ablative procedures have met growing interest as minimally invasive treatment for SRM due to the finding that the number of functional nephrons after a potential tumor resection or enucleation is directly related to survival [41]. Given that ablation hardly reduces the number of nephrons compared to

surgical treatment [42], it can be used in patients with SRM who suffer from impaired renal function. Indeed, in a retrospective review of three institutional databases, Woldu et al. [43] examined the renal parenchymal volume preservation after intervention in patients with SRM undergoing either thermal ablation or partial nephrectomy. Patients undergoing thermal ablation (radiofrequency ablation [RFA] or cryoablation) showed less renal parenchymal volume loss compared to their counterparts receiving partial nephrectomy (−8.1% vs. −16.5%, p<0.005) [43]. Additionally, since intraoperative ischemia is not required, the correlated parenchymal injury can be diminished. Thus, ablative approaches are mostly suitable for patients of older age and significant comorbidities who are not eligible for anesthesia and general surgery due to their poor general condition and are indeed an important extension of the armamentarium of potent treatments for locally confined renal tumors [44].

1. Radiofrequency ablation

RFA uses local heat to induce a coagulation necrosis of the tumor tissue and can be performed percutaneously or laparoscopically. It has been shown that necrosis is achieved by irreversible protein denaturation, which is guaranteed by applying a high-frequency alternating current (400–460 kHz) to the target tissue generating temperatures of 60°C to 100°C [45]. While the applied thermal energy also obliterates the tumor-supplying vessels, it has been recommended that, to ensure complete tumor ablation, a 3- to 5-mm margin of the nontumorous parenchyma around the malignancy should also be subjected to the RFA. The temperature-based techniques rely upon the final temperature reached by the probe while the impedance-based monitoring depends upon the tissue resistance to monitor the progress of RFA. The insertion of the RFA probes can be done under ultrasound or computed tomography guidance under sedation or general anesthesia. The efficacy of RFA is mostly dependent on the tumor size. Exophytic and posterior lesions ≤3 cm have been identified as optimal target tumors for RFA [45]. There are only a handful of studies using comparative methodology to evaluate oncological outcomes of RFA vs. surgical treatment. Takaki et al. [46] compared 51 patients undergoing RFA with 54 (10) patients undergoing radical (partial) nephrectomy in a population with SRM (stage cT1a). The authors found similar cancer-specific survival rates between the RFA subgroup and patients undergoing radical or partial nephrectomy (100% at 5 years vs. 100% at 5 years and 100% at 3 years, respectively). Patients who underwent RFA were significantly older and presented with more comorbidities,

relative to their counterparts undergoing surgery, which translated into a decreased overall survival in the former subgroup. Notably, the worsening postoperative renal function was significantly lower in the RFA group (median, 7.9%) vs. radical and partial nephrectomy groups (median, 29.0% and 11.5%, respectively). Olweny et al. [47] compared long-term oncologic outcomes in patients undergoing RFA vs. partial nephrectomy in a single-institution series of 37 patients in each group. No differences were shown in 5-year overall survival (97.2% vs. 100%, p=0.31) and cancer-specific survival (97.2% vs. 100%, p=0.31) between RFA and partial nephrectomy patients. Thus, the authors concluded that RFA can be used appropriately in selected patients with cT1a SRM [47]. Additionally, Stern et al. [48] published intermediate-term oncological outcomes with a follow-up of ≥2 years, comparing patients with cT1a RCC undergoing partial nephrectomy (n=37) or RFA (n=40). Corroborating studies above, cancer-specific survival was 100% in both groups and there was no difference in disease-free survival (95.8% vs. 93.4%, p=0.67) [48]. As of now, direct comparative evaluations of RFA vs. active surveillance are lacking and the aforementioned DISSRM study is the only one including patients undergoing ablative treatments into the primary intervention group. Since this treatment arm also incorporates patients undergoing surgery, results should be interpreted within its limitations and further comparative studies on RFA vs. active surveillance, specifically in the elderly, are needed.

2. Cryoablation

In contrast to RFA, cryoablation is based on destroying the tissue by freezing. A cryoprobe is inserted into the tumor and lowers the temperature in the tissue down to −40°C to −60°C. Analogous to RFA, the probe can be inserted by percutaneous or laparoscopic approach. The freezing of the tissue is generally monitored by ultrasound and it has been recommended that about 5 mm of the nontumorous surrounding parenchyma should also be ablated to achieve optimum results [45]. By providing repeated freeze-thaw cycles, cell organelles and cell structures are destroyed due to intracellular ice crystals, which then cause irreversible cell damage [44]. Similar to RFA, investigations comparing intermediate- and long-term outcomes of cryoablation vs. partial nephrectomy are scarce. Haber et al. [49] compared intermediate-term oncological outcomes of 48 patients undergoing laparoscopic partial nephrectomy to those of 30 patients undergoing laparoscopic cryoablation. Whereas overall survival was comparable between both groups at 3 and 5 years (p=0.74), cancer-specific survival was superior in

patients undergoing partial nephrectomy at 3 and 5 years (p<0.05) [49]. Klatte et al. [50] performed a matched-pair analysis of 41 cT1a RCC patients undergoing laparoscopic cryoablation vs. 82 patients undergoing partial nephrectomy. At 3-year follow-up, patients in the partial nephrectomy group showed a significantly better disease-free survival vs. patients in the cryoablation group (100% vs. 83%, p=0.015). Notably, none of the studies comparing cryoablation to partial nephrectomy showed an oncological benefit for cryoablation technique.

3. Other ablative techniques

There are other ablative techniques with underlying physics similar to those of RFA. However, as of now, laser ablation or high-intensity focused ultrasound ablation is considered experimental. Notably, there is emerging evidence for microwave ablation representing a feasible alternative approach in the treatment of SRM. Microwave ablation is applied percutaneously under image guidance. The technique also allows for the use of multiple probes simultaneously, enhancing its efficacy and the area of the zone of ablation. Thus, it can be postulated that microwave ablation has a better heat profile, can generate higher tissue temperature, can achieve better tissue penetration, and may even have higher ablative radius as compared to RFA [44].

Microwave ablation has been used extensively in the treatment of hepatic lesions. In a recent review of a randomized control trial and six retrospective studies, it was found that microwave ablation was feasible in larger hepatic neoplasms as compared to RFA [51]. The success of microwave ablation in hepatic neoplasms has laid the grounds for its use in SRM. The first randomized control trial that compared microwave ablation to partial nephrectomy was published in 2012. Overall, 54 patients underwent open or laparoscopic partial nephrectomy and intermediate-term oncological outcomes were compared with 48 patients that underwent open or laparoscopic microwave ablation [52]. No differences were seen regarding oncological outcomes between the groups, reporting a 91.3% and 96.0% disease-free survival at 3 years for microwave ablation and partial nephrectomy, respectively (p=0.5) [52].

CONCLUSIONS

Several factors have influenced and directed the contemporary relevance of reasonable treatment approaches in incidentally diagnosed SRM. Due to increasing cross-sectional abdominal imaging in the setting of different comorbid conditions, RCC diagnoses are likely to be made

at an early stage and particularly in an elderly population. Given the individual conditional profile of an aged patient, aggressive surgical approaches for SRM should not always considered by virtue of the morbidity of the procedure itself in relation to a relatively low risk of both progression and metastasis (Table 1). Radical surgical approach, specifically partial nephrectomy, should be the standard treatment for SRM, but increasing evidence suggests that open surgical procedures might be largely unnecessary in patients of advanced age, given their decreased life expectancy, higher comorbidity patterns, and decreased renal function. This is evident particularly in patients ≥75 years, and in this population alternative treatment approaches are available and should be taken into account, providing similar oncological outcomes and lower propensities of intervention-associated morbidity (Table 1). Active surveillance with the option of delayed intervention seems to be an adequate alternative to surgery in patients with cT1a kidney tumors who are unfit for surgery. Additionally, ablative treatments are feasible as minimally invasive modalities, providing sufficient oncological outcomes and an excellent preservation of renal function by sparing a maximal proportion of functional nephrons. However, whereas results for RFA are promising, there is still controversy regarding the oncological efficacy of cryoablation and experimental ablative strategies. Furthermore, specifically regarding an older and potentially more comorbid population, further comparative evaluations of different treatment approaches are needed. Undoubtedly, the present overview is based on mainly retrospective data and regarding the comparative effectiveness of both active surveillance and ablative strategies vs. surgical treatment in the elderly population, there is a clear mandate for large-scale randomized controlled trials due to lacking prospective evidence. Additionally, especially in the light of need for treatment decisions in the elderly, researchers should be encouraged to focus on prediction and preinterventional risk assessment tools to identify those patients who actually benefit from the different treatment approaches.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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