Active surveillance for small renal masses diagnosed in elderly or comorbid patients: Looking for the best treatment strategy

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Abstract

Introduction: Aim of this study is to provide our results after long-term active surveillance (AS) protocol for small renal masses (SRMs), and to report the outcomes of patients who remained in AS compared to those who underwent delayed surgical intervention.

Patients and methods: We retrospectively reviewed our database of 58 patients diagnosed with 60 contrast enhancing SRMs suspicious for renal cell carcinoma (RCC). All patients had clinical and radiological follow-up every 6 months. We evaluated the differences between patients who remained on AS and those who underwent surgical delayed intervention.

Results: The mean age was 75 years, the mean follow-up was 88.5 months. The median initial tumor size at presentation was 2.6 cm, and the median estimated tumor volume was 8.7 cm³. The median linear growth rate of the cohort was 0.7 cm/year, and the median volumetric growth rate was 8.8 cm³/year. Death for metastatic disease occurred in 2 patients (3.4%). No correlation was found between initial tumor size and size growth rate. The mean linear and volumetric growth rates of the group of patients who underwent surgery were higher than in those who remained on surveillance (1.9 vs. 0.4 cm/year and 16.1 vs. 4.6 cm³/year, respectively; \( p < .001 \)).

Conclusions: Most of SRMs demonstrate to have an indolent course and low metastatic potential. Malignant disease could have faster linear and volumetric growth rates, thus suggesting the need for a delayed surgical intervention. In properly selected patients with low life-expectancy, AS could be a reasonable option in the management of SRMs.

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PALABRAS CLAVE
Masas renales pequeñas; CÁNCER DE CÉLULAS RENALES; Vigilancia activa; Seguimiento

Vigilancia activa de masas renales pequeñas diagnosticadas en pacientes de edad avanzada o con comorbilidad: en busca de la mejor estrategia de tratamiento

Resumen
Introducción: El objetivo de este trabajo es proporcionar nuestros resultados tras un protocolo de vigilancia activa (VA) a largo plazo de masas renales pequeñas (MRP), e informar de los resultados obtenidos en pacientes que permanecieron bajo VA comparándolos con aquellos sometidos a intervenciones quirúrgicas tardías.

Paclientes y métodos: Se llevó a cabo una revisión retrospectiva de nuestra base de datos de 58 pacientes a los que se había diagnosticado 60 MRP captantes de contraste y con sospecha de cáncer de células renales (CCR). Todos los pacientes tenían una revisión de seguimiento clínico y radiológico cada 6 meses. Se evaluaron las diferencias entre los pacientes que permanecieron bajo VA y aquellos sometidos a intervenciones quirúrgicas tardías.

Resultados: La media de edad era de 75 años y la duración media del seguimiento fue de 88,5 meses. El tamaño medio del tumor en el inicio fue de 2,6 cm, y se estimó que el tamaño medio tumoral era de 8,7 cm³. La tasa media de crecimiento lineal del grupo fue de 0,7 cm/año y el crecimiento volumétrico medio fue de 8,8 cm³/año. Se produjo el fallecimiento de 2 pacientes debido a enfermedad metastásica (3,4%). No se encontró ninguna relación entre el tamaño tumoral inicial y el grado de crecimiento. Las tasas medias de crecimiento lineal y volumétrico del grupo de pacientes sometidos a cirugía fueron más elevadas que las de aquellos que permanecieron bajo vigilancia (1,9 frente a 0,4 cm/año y 16,1 frente a 4,6 cm³/año, respectivamente; p < 0,001).

Conclusiones: La mayoría de las MRP presentan una evolución poco activa y un potencial metastásico reducido. La enfermedad maligna podría presentar tasas de crecimiento lineal y volumétrico más rápidas, sugiriendo así la necesidad de una intervención quirúrgica tardía. En los pacientes adecuadamente seleccionados, con baja esperanza de vida, la VA podría ser una opción razonable en el manejo de las MRP.

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Introduction

The increasing utilization of noninvasive abdominal imaging (computed tomography, magnetic resonance imaging and ultrasonography) during the past 20 years has led to a significant growing number of incidentally detected small, asymptomatic, renal masses (SRMs).13 Most of these are classified in clinical stage T1a (≤4 cm in dimension), and in several cases they are diagnosed in elderly and co-morbid patients.3 Because of this increasing number of incidentally discovered renal masses, renal cell carcinoma (RCC) has been going through a stage and size migration.4 Traditionally, radical nephrectomy (RN) was the most common surgical treatment for renal cancer, regardless of the tumor size; more recently, nephron-sparing surgery (NSS) (performed by traditional open or minimally invasive approaches) has been considered the current standard of care for clinically localized RCC whenever technically feasible,3 with promising oncological results,4 lower renal function impairment7 when compared to RN, and low rate of positive surgical margins,8 even in the most challenging and complex procedures.3 Recent large surgical series indicate that 20–30% of SRMs are benign at final histology, with low metastatic potential,3 and only 20–25% of those renal masses have potentially aggressive behavior.10 Several retrospective and prospective reports showed that most of these masses grow slowly, with low risk of distant metastases (1–3%).11–13 The management of SRMs, especially in elderly and co-morbid patients, poses a frequent and controversial problem; thermal ablations (cryotherapy and radiofrequency ablation) and active surveillance (AS) are valid treatment strategies in selected patients who are not optimal surgical candidates or who may have a limited life expectancy.14 In patients initially managed with AS, the radiographic linear and volumetric growth pattern seems to be a useful indicator for aggressive behavior of SRM, thus suggesting the need for an active treatment of the tumor.15 With this retrospective study we provide our experience with long-term active surveillance management, and we report the oncological outcomes of patients in AS compared with those who underwent delayed surgical intervention.

Patients and methods

We retrospectively reviewed our database of 58 patients diagnosed with 60 contrast enhancing SRMs suspicious for renal cell carcinoma (RCC), detected during imaging procedures between January 1996 and December 2012. Indications for an active surveillance management were: relevant co-morbidities, advanced age, or patient refusal of surgery. Patients with Von Hippel–Lindau syndrome, history of hereditary RCC, and metastatic disease at presentation were not included in the cohort. Our follow-up protocol has been recently described.17 Briefly, we performed physical examination, blood sampling, and imaging studies every 3 or 6 months for the first year, and then annually; chest X-ray
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(evenly in the first years of study), chest and abdomen CT (5-mm slice thickness, with and without intravenous iodine contrast), magnetic resonance (MRI), or ultrasound were used for radiological evaluations. Tumor size was defined as the largest diameter of the tumor, measured in axial or coronal planes during nephrographic post-contrast imaging phase; whenever available, antero-posterior, transverse, and cranio-caudal diameters were measured. Tumor volume was calculated basing on the available dimensions reported on imaging studies. An ellipsoid volume formula \(0.5326xyz\) was used if three dimensions were present; the formula \(0.5326xy(x + y/2)\) was used if two dimensions were available, and the formula for the volume of a sphere \((0.5326x^2)\) was used if only one dimension was reported by radiologists'. We performed percutaneous CT-guided biopsy in 20 (34.5%) patients at the time of presentation or during follow-up, because of rapid growth rate of the physician's preference. The Charlson Comorbidity Index was determined in every patient. The end of the follow-up was defined by either patient death or surgical intervention.

Statistical analysis

Pearson’s correlation test was used to evaluate initial tumor size and linear or volumetric growth rate. Two-tailed \(p\) values less than 0.05 were considered statistically significant. Categorical and continuous data were evaluated by the Chi-square and the Student’s \(t\)-tests, respectively. The Wilcoxon/Kruskal–Wallis test was used for growth rate comparison between groups. SPSS version 17 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

The clinical, demographic and tumors’ characteristics are listed in Table 1. The mean and the median patients’ ages were 75 and 77 years, respectively (range: 65–90); of the entire cohort of patients, 38 were male (65.5%). The mean follow-up duration was 88.5 months (range: 10–204). Most of the SRMs (93.3%) were incidentally diagnosed during imaging procedures performed for other reasons; only 4 cases were diagnosed after US investigations on patients who complained of abdominal or back pain. The mean Charlson comorbidity index was 3 (range 1–6). Congestive heart failure, coronary artery disease, chronic renal failure, respiratory insufficiency, and dementia were the most common co-morbidities, affecting 20 (34.5%), 15 (25.9%), 9 (15.5), 7 (12%), and 5 (8.6%) patients, respectively; 2 patients, with no relevant comorbid condition, were scheduled for active surveillance only because of elderly age. At the time of diagnosis, the mean and the median tumor size were 2.0 and 2.6 cm, respectively (range: 1.6–4.3 cm), and the mean and median estimated tumor volume were 4.8 and 8.7 cm\(^3\), respectively (range: 1.8–42.3 cm\(^3\)). Moreover, the mean and the median linear growth rates of the overall population were 0.4 and 0.7 cm/year, respectively (range: 0.2–2.6 cm/year), and the mean and median volumetric growth rate were 4.6 and 8.8 cm\(^3/\)year, respectively (range: 0–19.6 cm\(^3/\)year). We performed percutaneous CT-guided biopsy of the renal mass in 7 cases at the time of diagnosis and in 18 cases during follow-up. The pathological examination of specimens revealed clear cell RCC in 13 (52%) cases, papillary RCC in 3 (12%) cases, benign findings in 7 (5 oncocytomas and 2 angiomylipomas) (28%), and inconclusive findings in 2 cases (8%). 4 patients underwent immediate nephron-sparing surgery after a positive percutaneous CT-guided biopsy; among these patients, 3 pT1a clear cell RCCs and 1 pT1a papillary-type 1 RCC were found. 14 (24%) patients were treated with delayed surgical excision, because of fast growth rate in 12 cases or patient’s preference in the remaining 2 cases; radical nephrectomy and partial nephrectomy were performed in 4 (28.5%) and 10 (71.4%) cases, respectively. All the 14 small renal masses were pathologically examined, and we found out 9 (64.3%) clear cell RCCs, 3 (21.4%) papillary renal cell carcinomas, and 2 (14.3%) benign oncocytomas. According to the TNM staging system, 11 patients were pT1a (78.6%), 2 patients were pT1b (14.3%), and only 1 patient was pT3a (7.1%). The mean follow-up of the group of patients who underwent surgical excision was 85.6 months (range: 28–185). No disease recurrence was found in all the 4 patients who underwent immediate partial nephrectomy after positive percutaneous biopsy; conversely, one patient died from metastatic lung and liver disease after 14 months from surgery; no evidence of disease recurrence or progression was found in the remaining 13 patients treated with delayed partial or radical nephrectomy. Globally, 40 patients (70%) were managed with an active surveillance protocol, according to our follow-up scheme. 18 patients (45%) died during the observation period; of them, 11 patients died because of acute coronary disease, 5 due to respiratory insufficiency, 1 because of pulmonary embolism, and 1 because of metastatic (liver and lung) disease after 20 months of follow-up. Interestingly, only in 2 patients (3.4%) of the entire

| Table 1 Clinical, demographic and tumors’ characteristics. |
|---------------------------|-----------------|-----------------|
| **Number of SRMs studied** | **60**          |
| **Total number of patients** | **58**          |
| **Number of males (%)** | 38 (65.5%)      |
| **Number of females (%)** | 20 (34.5%)      |
| **Mean/median age at presentation (range)** | 75/77 yrs (65–90) |
| **Number of incidentally detected SRMs** | **56** (93.3%) |
| **Mean follow-up duration (range)** | **88.5 months (10–204)** |
| **Mean/median tumor size at presentation (range)** | **2.0/2.6 cm (1.6–4.3)** |
| **Mean/median estimated tumor volume at presentation (range)** | **4.8/8.7 cm\(^3\) (1.8–42.3)** |
| **Mean/median linear growth rate (range)** | **0.4/0.7 cm/year (0.2–2.6)** |
| **Mean/median volumetric growth rate (range)** | **4.6/8.8 cm\(^3/\)year (0–19.6)** |
| **Mean Charlson Comorbidity Index (range)** | **3 (1–6)** |
Table 2  Comparison between patients who underwent delayed surgical intervention and those who were managed with active surveillance.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Delayed surgical intervention group (n = 14, 24%)</th>
<th>Active surveillance group (n = 40, 70%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean/median age at presentation (range)</td>
<td>75/76 years (64–88)</td>
<td>76/78 years (66–90)</td>
<td>0.09</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>3</td>
<td>3</td>
<td>0.56</td>
</tr>
<tr>
<td>Mean/median tumor size at presentation (range)</td>
<td>2.1/2.7 cm (1.7–4.3)</td>
<td>2.0–2.5 cm (1.5–4.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean/median estimated tumor volume at presentation (range)</td>
<td>4.9/8.9 cm³ (1.9–43)</td>
<td>4.6/8.4 cm³ (1.7–41.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Mean linear growth rate</td>
<td>1.9 cm/year</td>
<td>0.4 cm/year</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean volumetric growth rate</td>
<td>16.1 cm³/year</td>
<td>4.6 cm³/year</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Although the incidence of renal cell carcinoma has increased over the last decade, cancer-specific mortality has not significantly decreased,15 perhaps suggesting a potential cancer overdiagnosis.16 It has been discussed how some of these asymptomatic SRMs will prove to be benign after definitive pathological examination,16 even if the current imaging techniques alone are unable to definitively distinguish benign from malignant pathologic lesions.17 The increased detection of SRMs in elderly patients affected by relevant co-morbidities and, consequently, not ideal candidates for active surgical removal of the tumor, has enhanced the interest on alternative management options, such as thermal ablations (cryotherapy or radiofrequency ablation) and active surveillance protocols.18–20 Interestingly, in a retrospective evaluation of 537 patients aged ≥75 years diagnosed with suspicious RCC between January 2000 and December 2006, managed with radical nephrectomy, nephron-sparing surgery or active surveillance, Lane and collaborators did not find an improvement in overall survival of surgically treated patients when compared to those managed with active surveillance.21 The diagnosis of SRMs, especially in patients who are unfit for surgical management, often raises an important clinical dilemma: should we treat every patient, regardless of the tumor dimension and growth patterns? In a recent multi-institutional analysis of 82 patients diagnosed with 84 small renal masses (median dimension at diagnosis: 2.3 cm; median follow-up duration: 36 months), and who had been initially managed with active surveillance, Mason et al.22 found out that larger (>2.45 cm) renal masses will grow more quickly than smaller ones, with lower probability to remain in AS protocols and higher risk to develop metastatic disease. In our study, conversely, no statistically significant differences in initial tumor size (2.0 cm vs. 2.1 cm, p = 0.12) and tumor volume (4.6 cm³ vs. 4.9 cm³, p = 0.26) were found between patients who had been managed with AS and those who underwent delayed surgical intervention, respectively. On the contrary, the mean/median linear (1.9 cm/year vs. 0.4 cm/year, p < 0.001) and volumetric (16.1 cm³/year vs. 4.6 cm³/year, p < 0.001) growth rates of patients who underwent delayed surgical treatment were found to be statistically significantly higher compared to those measured in patients who remained in AS protocol. Several studies currently available in the literature demonstrated that small renal masses managed with active surveillance have a low metastatic potential, estimated at 1–2%.19,23,24 Similarly, in our cohort of 58 patients, progression to metastatic disease was reported in only 2 cases (3.4% of the entire cohort) after a long-term follow-up. These data are comparable to those emerged from the meta-analysis by Chawla et al.25: in a cohort of 286 small renal masses conservatively managed, the mean size at presentation was 2.6 cm (median: 2.48 cm), the mean follow-up was 34 months (median: 32 months; range: 26–39), and the mean growth rate was 0.28 cm/year. In this remarkable report, progression to metastatic disease was described in three patients, representing only 1% of the entire cohort of patients. According to the results of their study, the authors stated that most small enhancing renal masses, suspicious for RCC, will grow slowly when observed in a protocol of active surveillance. Although the biological behavior of small renal masses could be difficult to predict,19,23,24 the results of our study suggest that patients with a faster tumor linear or volumetric growth rates have a higher risk of potential malignancy, which may require delayed surgery. In fact, among patients who underwent delayed surgical intervention, those with malignant disease showed a faster mean linear and volumetric growth rate.
than those with benign disease. Furthermore, the mean linear and volumetric growth rates of the two patients who died from metastatic RCC during the follow-up were significantly faster than the mean value of 0.4 cm/year and 4.6 cm³/year that have been observed in the entire population. Faster tumor growth rates, because of the potential risk of disease progression and metastatic development, and, therefore, the risk of shortening the patients’ life expectancy, should recommend the surgeon to perform ablative strategies, such as delayed radical/partial nephrectomy or thermal ablations (cryotherapy and radiofrequency ablations). Although it appears that most renal masses will grow slowly and have low metastatic potential, these results should not be adapted to healthy and young patients, with lifelong expectancy and without contraindications to active surgical treatment; for those patients, nephron sparing surgery, whenever technically feasible, still remains the gold standard and highly recommended treatment, because it demonstrated to offer the best survival rates. Conversely, concerning elderly and/or co-morbid patients, with high operative risk (such as the patients included in our study cohort), most of the small, asymptomatic renal masses could be treated with ablative therapies or included in an active surveillance protocol, allowing to reduce the renal function impairment, the cumulative incidence of cardiovascular mortality and, therefore, potentially improving the overall survival outcomes.

Conclusions

Most of the small renal masses will grow slowly, and demonstrate to have an indolent course and low metastatic potential. Risk factors for malignancy and disease progression could be the fast linear and volumetric growth rates, and these events should suggest the need for a delayed surgical intervention in patients initially managed with active surveillance protocols. In properly selected patients with low life-expectancy, or with high operative risk due to relevant co-morbidities, active surveillance could be a reasonable option in the management of SRMs.

Other prospective studies with longer follow-up and larger cohort of patients are needed in order to define the criteria that make it possible to identify the best category of patients who could benefit from other treatments alternative to surgery, such as active surveillance or thermal ablations.

Conflict of interest

The authors declare that they have no conflict of interest.

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