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# Growth pattern of renal cell carcinoma (RCC) in patients with delayed surgical intervention

**Xue-Song Li · Lin Yao · Kan Gong · Wei Yu · Qun He · Li-Qun Zhou · Zhi-Song He**

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**Abstract**
*Purpose* Few studies have evaluated the growth pattern of renal cell carcinoma (RCC) in patients with delayed treatment. This report investigated the growth rate and stage progression of incidentally discovered RCC following a long period of active surveillance.
*Methods* Thirty-two patients who did not receive immediate surgical treatment for renal solid masses that later proved to be RCC were reviewed retrospectively. Annual tumor growth rates were calculated according to changes in the maximal diameter on CT or MRI. Clinical and pathological characteristics associated with tumor growth rate and stage progression were analyzed.
*Results* The median tumor size grow from 2.14 (range, 0.30–6.70) cm to 4.33 (range, 1.40–8.80) cm after a median 46.0 months observation period. The average tumor growth rate was 0.80 (range, 0.16–3.80) cm/year. Clear cell carcinoma (0.86 cm/year) tended to grow faster than papillary cell carcinoma (0.28 cm/year) ($P = 0.066$). The mean growth rate of grade 2 tumors (0.88 cm/year) was faster than that of grade 1 tumors (0.36 cm/year) ($P = 0.041$). Thirteen tumors (40.6%) were upstaged at a median 48 months after initial presentation. Cox regression analysis revealed initial tumor size as the only risk factor for upstaging ($P = 0.018$). No local and systemic recurrences were noted in our cohort after the intervention at a median of 47 (range, 6–248) months of follow-up.
*Conclusions* RCCs were found to be slow growing in a group of untreated renal cell carcinoma patients. However, some tumors progressed in stage under observation. The growth rate of RCC tended to correlate with histologic grade and histologic subtype.

**Keywords** Active surveillance · Delayed intervention · Growth rate · Kidney neoplasms · Natural history

## Introduction

Advanced US and CT allow us to detect more renal solid masses incidentally (Hock et al. 2002), and many of these masses have a high probability of eventually being diagnosed as renal cell carcinoma (RCC) (Volpe et al. 2004). Surgical excision remains the standard of care for localized renal tumors. The growth pattern or natural history of RCC has not been well established, because most masses are surgically excised shortly after diagnosis. However, some patients refuse surgery at the time of the initial diagnosis and may select an active surveillance approach. Thus, these patients provide a unique opportunity to characterize the natural history of RCC. Chawla et al. (2006) reviewed a contemporary active surveillance series and noted that the majority of tumors grow at a slow rate and had a low rate of progression to metastatic disease. However, pathological confirmation was only available in 46% of cases. Recent literature suggests that about 15–20% of these lesions are benign tumors, and elderly patients with small renal masses were up to 3.5 times more likely to have benign lesions than RCC (Rendon and Jewett 2006). Therefore, the natural history of RCC might have been misjudged.

Xue-Song Li and Lin Yao contributed equally to this article.

X.-S. Li · L. Yao · K. Gong · W. Yu · Q. He · L.-Q. Zhou · Z.-S. He (✉)
Department of Urology, First Hospital of Peking University, Institute of Urology, Peking University, National Urological Cancer Center, No. 8 Xishiku St, Xicheng District, Beijing 100034, China
e-mail: oncourology@sina.com

In this study, the growth pattern and natural history of incidentally diagnosed RCC were investigated during prolonged follow-up by reviewing 32 patients who had not received immediate surgical treatment for solid renal masses that were later histopathologically proven to be RCC. The growth rate, stage progression, and correlations between clinical and histological characteristics were examined.

## Materials and methods

### Identification of patients

The kidney cancer databases at the Institute of Urology, Peking University, were searched to identify enhancing renal masses for which treatment was delayed for at least 12 months from initial diagnosis between January 1990 and March 2010. Tumors without pathological results or benign kidney tumors were excluded.

A total of 41 patients who did not receive immediate surgical treatment for solid renal masses were found from among the 1,890 renal tumor cases. This study included only extirpated RCC cases. Of these, 32 patients underwent nephrectomy or partial nephrectomy after at least 12 months of active surveillance, and the pathological results verified RCC. In every case, the RCC was primary with no metastatic lesions.

### Methods

In these patients, CTs or MRIs were obtained and reviewed by a radiologist and urologic oncologist. The maximal dimension was used to determine tumor size and clinical stage. The annual tumor growth rate was calculated according to changes in the maximal diameter obtained from CT or MRI scan every 6 months or less. Where possible, the measurements were compared using the same imaging modality. Histologic subtypes of RCC were assigned according to the Heidelberg classification system (Kovacs et al. 1997). Clinical and pathological stages were determined using the 2002 American Joint Committee on Cancer/International Union Against Cancer TNM guidelines (Guinan et al. 1997). Histologic nuclear grade was assigned using the Furman score (Fuhrman et al. 1982).

The clinical and pathological characteristics associated with tumor growth rate and stage progression were analyzed. The patients were followed up after surgery every 3–6 months.

### Statistical analysis

The Mann–Whitney $U$ test was used to compare two groups; the Kruskal–Wallis $H$ test was used for three groups. The correlations between growth rate and clinical and histological characteristics were assessed by multiple linear regression. Kaplan–Meier survival estimates were used for upstage data analyses. Cox regression analysis was used to identify the risk factors for RCC upstaging. A $P$-value of $<0.05$ was considered significant. The SPSS v.14.0 software package (SPSS Inc, Chicago, IL, USA) was used to perform the calculations.

## Results

A total of 32 RCC patients who underwent delayed intervention after at least 12 months active surveillance were identified. Patient characteristics, pathological features, and growth rates are summarized in Table 1. The majority of patients were men (27 of 32 patients; 84.4%). Most tumors (29 of 32 patients; 90.6%) were $\leq$4 cm at presentation and categorized as small RCC. All tumors were solid. The mean period of observation was 46.0 (range, 12–155) months. All cases were followed up after the intervention. The median postoperative follow-up period was 47 (range, 6–248) months.

Most patients (27 of 32 patients; 84.4%) were referred to our institution after a period of surveillance elsewhere. The most common reason (21 of 32 patients; 65.6%) for delayed intervention was that the renal mass was small and the patient was unwilling to undergo surgery. Other reasons for delayed treatment included: six cases (18.8%) considered benign at presentation; two cases (6.3%) of bilateral disease; and two cases (6.3%) of concomitant malignancy. In one patient (3.1%), the tumor was incidentally detected on CT scan during follow-up of cholecystitis, and the renal mass was missed in earlier scans. Surgical intervention was pursued because of tumor growth. Twenty-two tumors (68.8%) were treated with radical nephrectomy, while 10 tumors (31.2%) were treated with partial nephrectomy. The pathological results confirmed RCC for all tumors confirmed. Twenty-eight tumors (87.5%) were clear cell carcinoma, three tumors (9.4%) were papillary cell carcinoma, and one tumor (3.1%) was mucinous tubular and spindle cell carcinoma.

The linear grow rate results are shown in Table 2. The mean growth rate was 0.80 (range, 0.16–3.80) cm/year. The mean growth rate of the 28 clear cell carcinomas was 0.86 (range, 0.16–3.80) cm/year. The mean growth rate of the three papillary cell carcinomas was 0.28 (range, 0.18–0.46) cm/year. The growth rate of the one mucinous tubular and spindle cell carcinoma was 0.33 cm/year. Most incidentally found RCCs were slow growing; 25 tumors (78.1%) had a growth rate $\leq$1.00 cm/year, and seven tumors (21.9%) had a growth rate $>$1.00 cm/year.

Clear cell carcinoma (0.86 cm/year) tended to grow faster than papillary cell carcinoma (0.28 cm/year)

**Table 1** Patient and tumor characteristics

| Case | Sex | Age (years) | Grade | Subtype | Initial tumor size (cm) | Tumor size at operation (cm) | Upstage | Duration of surveillance (months) | Growth rate (cm/year) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Male | 46 | G1 | Clear | 1.20 | 4.50 | Yes | 63 | 0.64 |
| 2 | Male | 68 | G2 | Clear | 1.60 | 4.40 | Yes | 155 | 0.20 |
| 3 | Male | 74 | G1 | Clear | 1.10 | 1.40 | No | 18 | 0.20 |
| 4 | Male | 49 | G2 | Clear | 1.90 | 7.80 | Yes | 108 | 0.60 |
| 5 | Male | 47 | G3 | Papillary | 0.80 | 4.00 | No | 84 | 0.41 |
| 6 | Male | 30 | G3 | Papillary | 2.00 | 3.50 | No | 90 | 0.18 |
| 7 | Male | 60 | G3 | Clear | 0.90 | 3.00 | No | 96 | 0.26 |
| 8 | Male | 60 | G2 | Clear | 2.40 | 3.30 | No | 13 | 1.02 |
| 9 | Male | 40 | G3 | Clear | 1.00 | 8.60 | Yes | 24 | 3.75 |
| 10 | Female | 59 | G2 | Clear | 3.60 | 7.00 | Yes | 32 | 1.01 |
| 11 | Male | 42 | G2 | Clear | 3.90 | 5.30 | Yes | 24 | 0.58 |
| 12 | Male | 43 | G1 | Clear | 1.30 | 1.55 | No | 19 | 0.17 |
| 13 | Male | 44 | G1 | Clear | 1.60 | 2.80 | No | 48 | 0.26 |
| 14 | Female | 67 | G2 | Papillary | 1.60 | 2.80 | No | 55 | 0.26 |
| 15 | Male | 58 | G2 | Clear | 1.3 | 5.00 | Yes | 137 | 0.29 |
| 16 | Male | 64 | G2 | Clear | 1.40 | 5.10 | Yes | 29 | 1.53 |
| 17 | Male | 38 | G2 | Clear | 2.00 | 3.80 | No | 13 | 1.20 |
| 18 | Male | 63 | G3 | Clear | 6.70 | 8.80 | Yes | 28 | 0.69 |
| 19 | Female | 53 | G2 | Clear | 3.10 | 6.80 | Yes | 63 | 0.63 |
| 20 | Male | 61 | G2 | Clear | 2.90 | 4.10 | Yes | 23 | 0.34 |
| 21 | Male | 43 | G2 | Clear | 1.50 | 4.00 | No | 13 | 2.08 |
| 22 | Male | 73 | G3 | Clear | 0.30 | 1.50 | No | 24 | 0.48 |
| 23 | Female | 38 | NA | Mucinous tubular and spindle cell | 4.00 | 6.00 | Yes | 70 | 0.33 |
| 24 | Male | 53 | G2 | Clear | 2.00 | 3.00 | No | 33 | 0.33 |
| 25 | Female | 42 | G2 | Clear | 0.90 | 1.90 | No | 12 | 1.00 |
| 26 | Male | 61 | G2 | Clear | 4.50 | 5.40 | No | 12 | 0.95 |
| 27 | Female | 26 | G2 | Clear | 1.50 | 2.30 | No | 48 | 0.16 |
| 28 | Male | 40 | G2 | Clear | 3.40 | 4.00 | No | 14 | 0.17 |
| 29 | Male | 51 | G2 | Clear | 1.00 | 4.6 | Yes | 48 | 0.90 |
| 30 | Male | 78 | G2 | Clear | 1.50 | 3.00 | No | 27 | 0.56 |
| 31 | Male | 46 | G1 | Clear | 4.40 | 5.40 | No | 24 | 0.40 |
| 32 | Male | 54 | G2 | Clear | 1.30 | 4.00 | No | 25 | 1.25 |
| Mean (median) | – | 52.2 (52.0) | – | – | 2.14 (1.60) | 4.33 (4.00) | – | 46.0 (28.5) | 0.80 (0.63) |

Clear = clear cell carcinoma, Papillary = papillary cell carcinoma, NA = not available

($P = 0.066$). The mean growth rate of grade 2 (0.88 cm/year) tumors was higher than that of grade 1 tumors (0.36 cm/year) ($P = 0.041$). The mean growth rate of grade 3 tumors (1.04 cm/year) tended to be faster than that of grade 1 and 2 tumors, but the difference was not significant. Multiple linear regression analysis revealed that tumor growth rate was not correlated with sex ($P = 0.484$), age ($P = 0.400$), and initial tumor size ($P = 0.829$).

cT classifications at presentation and at operation were compared with pT stage for all patients. Concordance of cT and pT at operation was identified in all tumors. Thirteen tumors (40.63%) were upstaged during active surveillance: 10 tumors were upstaged from T1a to T1b; two tumors were upstaged from T1a to T2; and one tumor was upstaged from T1b to T2 (Table 1). No patient had evidence of metastatic disease during active surveillance.

A comparison of the stage progression group and the stage stable group is shown in Table 3. Cox regression analysis revealed that only the initial tumor size ($P = 0.018$) was a risk factor for RCC upstaging. Of the 13 upstaged RCCs, the median upstage time was 48 months after the initial presentation (Fig. 1).

**Table 2** RCC growth rate

| | Growth rate (cm/year) mean/median (range) | *P* value |
|---|---|---|
| Overall ($n = 32$) | 0.80/0.63 (0.16–3.80) | |
| Histologic grade of clear cell RCC | | 0.041[a] |
| G1 ($n = 6$) | 0.36/0.33 (0.16–0.63) | |
| G2 ($n = 19$) | 0.88/0.70 (0.20–2.31) | |
| G3 ($n = 6$) | 1.04/0.53 (0.20–3.80) | |
| Histologic subtype | | 0.066[b] |
| Clear cell carcinoma ($n = 28$) | 0.86/0.66 (0.16–3.80) | |
| Papillary cell carcinoma ($n = 3$) | 0.28/0.20 (0.18–0.46) | |
| Mucinous tubular and spindle cell carcinoma ($n = 1$) | 0.33 | |

[a] *P* value is for the comparison of G1 and G2

[b] *P* value is for the comparison of clear cell carcinoma and papillary cell carcinoma

**Table 3** Comparison of stage progression group and stage stable group

| | Stage progression group (mean/SD) ($n = 13$) | Stage stable group (mean/SD) ($n = 19$) | *P* value |
|---|---|---|---|
| Age | 53.2/9.8 | 51.5/14.8 | 0.718 |
| Initial tumor size | 2.58/1.67 | 1.84/1.14 | 0.291 |
| Tumor size at operation | 6.00/1.64 | 3.19/1.17 | <0.001 |
| Duration of surveillance | 61.85/44.91 | 35.16/27.68 | 0.027 |
| Grow rate | 0.97/0.93 | 0.68/0.58 | 0.161 |

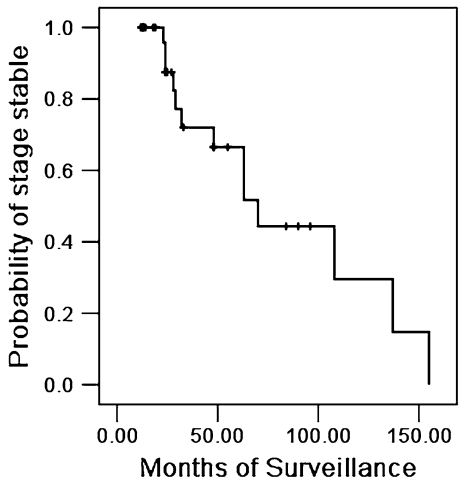


**Fig. 1** Overall Kaplan–Meier cancer upstaging in patients with RCC

No local and systemic recurrences were noted in our cohort after the intervention at a median of 47 (range, 6–248) months of follow-up. The estimated 1- and 3-year cancer recurrence-free survival rates for patients who underwent delayed treatment were both 100%. There were no cancer-related deaths, and no patient developed metastatic disease after intervention; only one patient died from a cerebrovascular event 25 months after surgery.

## Discussion

RCC is the most common malignancy of the kidney. The only established curative treatment for RCC remains surgery, with radical or partial nephrectomy (Hafez et al. 1999; Kunkle et al. 2008). Patient and surgeon often pursue prompt intervention immediately after renal cancer diagnosis. Thus, it has been difficult to evaluate the in vivo growth rate of the cancer in humans. However, the observation rate is increasing in the clinical management of small renal masses, especially for older patients with multiple medical comorbidities and limited life expectancies (Lamb et al. 2004; Abouassaly et al. 2008; Beisland et al. 2009). Many review papers have been published recently on the topic of active surveillance of RCC (Chawla et al. 2006; Van Poppel and Joniau 2007; Kunkle et al. 2008; Mattar et al. 2008; Jewett and Zuniga 2008; Cary and Sundaram 2009; Abou Youssif and Tanguay 2009). A meta-analysis of nine series with 234 renal tumors followed for 34 months revealed a mean growth rate of 0.28 cm/year. The mean growth rate of pathologically confirmed RCC variants was significantly higher (0.4 cm/year); three patients (1%) progressed to metastasis, representing the greatest risk of observation. Another recent meta-analysis evaluating excision, ablation, or observation of localized small renal masses (6,471 masses, mean tumor diameter 3.26 cm) demonstrated that ablation was not oncologically superior to active surveillance (Kunkle et al. 2008).

We also identified 13 reports from 13 single institutional series in the global literature regarding the natural history of renal masses (Table 4) (Volpe et al. 2004; Lamb et al. 2004; Beisland et al. 2009; Fujimoto et al. 1995; Bosniak et al. 1995; Oda et al. 2001; Wehle et al. 2004; Kato et al. 2004; Abou Youssif et al. 2007; Kouba et al. 2007; Siu et al. 2007; Fernando et al. 2007; Lee et al. 2008; Crispen et al. 2009). Collectively, these studies were reviewed and found to account for 570 analyzable lesions. Of the 570 analyzable lesions reviewed, 248 (43.5%) had pathological evaluations available, and 220 (38.6%) were RCC. The

**Table 4** Published series on the natural history of renal masses

| Reference | Year | No. | Age (years) | Mean lesion size (cm) | Mean follow-up (months) | Mean growth rate (cm/year) | No. of developed M+ disease | Pathologic RCC |
|---|---|---|---|---|---|---|---|---|
| Fujimoto et al. | 1995 | 6 | 59.7 | 2.47 | 24.0 | 0.47 | 0 | 5/5 |
| Bosniak et al. | 1995 | 40 | 65.5 | 1.73 | 39 | 0.36 | 0 | 22/26 |
| Oda et al. | 2001 | 16 | 54 | 2.0 | 25 | 0.54 | 0 | 16/16 |
| Volpe et al. | 2004 | 32 | 71 | 2.48 | 27.9 | 0.1 | 0 | 8/9 |
| Wehle et al. | 2004 | 29 | 70.0 | 1.83 | 32 | 0.12 | 0 | 3/4 |
| Kato et al. | 2004 | 18 | 56.5 | 2.0 | 27 | 0.42 | 0 | 18/18 |
| Lamb et al. | 2004 | 36 | 76.1 | 7.2 | 27.7 | 0.39 | 1 | 23/23 |
| Abou Youssif et al. | 2007 | 44 | 71.8 | 2.2 | 47.6 | 0.21 | 2 | 6/8 |
| Kouba et al. | 2007 | 46 | 67 | 2.92 | 32.8 | 0.7 | 0 | 12/14 |
| Siu et al. | 2007 | 47 | 68 | 2.0 | 29 | 0.27 | 1 | 10/16 |
| Fernando et al. | 2007 | 13 | 80.4 | 5.01 | 38.38 | 0.17 | 1 | 0 |
| Lee et al. | 2008 | 30 | 65.5 | 2.6 | 12.6 | 0.59 | 3 | 30/30 |
| Beisland et al. | 2009 | 41 | 76.3 | 4.3 | 33 | 0.66 | 2 | 15/18 |
| Crispen et al. | 2009 | 172 | 69.0 | 2.45 | 31 | 0.285 | 2 | 52/61 |

*No.* number, *M+* metastatic positive, *RCC* renal cell carcinoma

mean age ranged from 56.5 to 80.4 years, and the mean follow-up period ranged from 12.6 to 47.6 months. The mean grow rate ranged from 0.10 to 0.66 cm/year. Twelve (2.1%) of the 570 patients developed metastatic disease while under surveillance.

As in the present report, the available studies are mostly small, retrospective studies, with only a few prospective and well-defined series available (Volpe et al. 2004; Rendon et al. 2000). The most common limitation of these studies was a lack of pathologic results. The probability of a tumor being benign is inversely proportional to tumor size; as tumor size decreases, the probability of a tumor being benign increases (Kunkle et al. 2008). This may explain why some small tumors grow slowly or do not grow at all. The actual natural history of RCC might be misjudged with only radiologic diagnoses and short follow-up periods. In the present study, all tumors were surgically extirpated, and pathologic results verified RCC. In addition, the follow-up period of the present study is the longest of the available studies.

Although there was a large variation in the growth rates of small RCCs (the fastest increase in diameter was 30 times that of the slowest), most RCCs in the present study were slow growing. The growth rate of incidentally discovered RCCs ranged from 0.16 to 3.80 cm/year (mean, 0.80 cm/year). Most tumors (78.1%) had a growth rate $\leq$1.00 cm/year, and only 21.9% (7 of 32) had a growth rate $>$1.0 cm/year. When compared with other series, the growth rates seen in the present study were relatively rapid (Table 3). This may be due in part to the presence of non-RCC pathologies, older age, or the short follow-up period in other studies. Such a result may indicate that the growth rate of RCC in the present study more precisely reflects the natural course of incidentally discovered RCC.

Potential predictors of future tumor growth include sex, patient age (Kouba et al. 2007), tumor size, and pathological characteristics (Bosniak et al. 1995). The present study also attempted to identify factors that may be associated with a more rapid growth rate. Interestingly, sex, age, histologic subtype, and initial tumor size did not correlate with tumor growth rate in this population. However, tumor growth rate tended to correlate with the histologic grade.

All observed RCCs have the potential to metastasize, but the actual risk appears to be low. Only 12 (2.1%) of the 570 lesions reviewed in the previous studies developed metastatic disease. In our series, no patient developed metastatic disease. Nevertheless, stage progression was identified in 13 of 32 patients (40.6%) at a median of 48 months after the initial presentation. It is not surprising that initial tumor size is a risk factor for upstaging; this underlines the progressive nature of RCC. The low rate of observed metastatic progression, however, is obviously influenced by the relatively short follow-up, the indolent nature of a number of solid renal masses, the small tumor sizes in the published observation series, and the retrospective nature of such studies.

In summary, the results of this study showed that RCCs were slow growing in a group of untreated renal cell carcinoma patients. However, some cases showed tumor stage progression under observation. The RCC growth rate tended to correlate with histologic grade and histologic subtype. A large initial tumor size was a risk factor for RCC upstaging. Future investigations and development of

molecular and histologic markers of disease progression are needed, as well as randomized clinical trials investigating the efficacy of active surveillance and delayed management. These data provide some guidance in selecting patients for observational management of renal masses. More attention should be given to the natural history of RCC.

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