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ORIGINAL RESEARCH

Clinical outcome of incidentally discovered small renal cell carcinoma after delayed surgery

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Background: This study was undertaken to investigate the growth rate and clinical outcome of patients with a small renal mass (SRM) after delayed surgery.

Methods: We reviewed the clinical records of 34 patients with SRMs ≦ 4 cm at diagnosis, who underwent delayed surgical intervention during surveillance from January 2000 to December 2011. Radiographic evaluations using computed tomography (CT) scan and magnetic resonance imaging (MRI) were performed at least every 6 months, and the tumor size was determined at least twice.

Results: The mean follow-up time was 26.6 ± 18.6 months and mean tumor doubling time was 23.4 ± 16.0 months. Histopathological analysis revealed that 32 of the 34 patients were malignant in pT1aN0M0. Only one patient showed tumor recurrence, who subsequently died due to tumor progression.

Conclusion: The growth rate of the small renal mass was slow in the majority of our patients. Delayed intervention does not have a detrimental effect on cancer-specific outcomes.

Keywords: renal cell carcinoma, small renal mass, natural history, growth rate, delayed intervention

Background

Renal cell carcinoma (RCC) has been increasingly detected using noninvasive abdominal imaging techniques, such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI).[1–5]

A retrospective review has revealed that most small renal masses (SRMs) show a slow growth rate and low malignant potential.[6–8]

In this study, the growth rate and natural history of incidentally diagnosed RCC were investigated during prolonged follow-up in 34 patients who decided to postpone surgical treatment.

Methods

Thirty-four patients, each with an incidentally detected SRM ≦ 4 cm, were retrospectively reviewed at three centers from January 2000 to December 2011. All patients were operated on once the tumor growth was noted. They underwent at least two CT scans prior to surgical intervention.

The maximum tumor diameter and tumor volume were calculated at two points, using images yielded by the same diagnostic modality. Tumor volume (V) was calculated using the following equation, assuming the tumor had a spheroidal form:[9] $V = (4/3 \times \pi \times a \times b \times [a + b/2]) \times 1/8$, where a indicates the maximum tumor diameter and b denotes the minimum tumor diameter.

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The time to tumor doubling (TTD) was calculated using the following equation,[10,11] $TTD = (T - T_0) \times \log 2 / \log V - \log V_0$, where $T - T_0$ indicates the interval between the two time measurements and V_0 and V denote the tumor volume at T_0 and T, respectively.

Clinical and pathological stages were determined using the 2009 American Joint Committee on Cancer/International Union Against Cancer Classification of Malignant Tumors (TNM) guidelines.[12] Clinical and pathological characteristics that could be associated with tumor growth rates and stages were investigated. After surgery, a follow-up was conducted with the patients every 3–6 months. Patients under hemodialysis (due to end-stage renal disease) were not included in this study as they are at a greater risk of developing RCC than age-matched healthy controls.[13–15]

Survival curves were estimated using the Kaplan–Meier formulation. Also, data that were statistically significant were compared using the non-parametric Mann–Whitney U test.

Results

The mean age of the patients was 64.4 years (35–80). There were 26 men and eight women. Twenty-three patients underwent partial nephrectomy. Eleven patients underwent radical nephrectomy. In all patients, the tumors were ≦4 cm at diagnosis. Histopathological analysis revealed that 32 of the 34 patients were malignant in pT1aN0M0.

The mean observation period was 26.2 months (6.5–74.8) and the mean initial tumor volume was 6.2 ± 6.5 cm^3 (0.14–30.5). The mean preoperative tumor volume was 12.9 ± 11.9 cm^3 (0.7–47.4) and the mean TTD for the entire population was 23.4 months (23.0 months in men, 24.5 months in women, showing no significant difference between sexes). The mean growth rate was 3.9 mm/year (Table 1).

The pathological results confirmed the diagnosis of RCC for 32 of the 34 patients. 26 tumors (76.5%) were clear cell carcinomas, five (14.7%) were papillary cell

Table 1 Preoperative tumor volume and time to tumor doubling in size and growth rate

Case	Sex	Age (Years)	Preoperative follow up (months)	Initial tumor volume (cm^3)	Preoperative tumor volume (cm^3)	TTD (months)	Growth rate (mm/year)
1	Male	61	7.5	20.9	36.3	8.3	5.24
2	Female	75	16.4	2.04	3.93	7.1	2.96
3	Male	73	28.5	9.21	12.8	10.2	4.27
4	Male	78	22.8	4.32	8.66	28.6	2.13
5	Female	71	13.7	9.35	16.9	14.6	3.30
6	Male	75	8.6	9.49	25.3	17.7	2.93
7	Female	70	48.3	2.25	4.11	48.1	0.87
8	Male	60	52.8	1.55	5.46	61.3	3.61
9	Female	80	35.7	5.32	6.66	25.4	1.38
10	Male	76	54.2	30.5	44	62.3	1.71
11	Male	76	41.2	0.61	4.9	22.7	4.24
12	Female	73	19.1	11.5	27.1	58.2	1.47
13	Male	52	14.7	9.88	15.6	27.6	17.62
14	Female	35	56.6	11.2	13.4	18.8	1.94
15	Male	77	6.8	0.59	1.1	5.5	2.32
16	Male	72	6.5	0.14	0.7	31.5	2.79
17	Male	74	6.5	0.52	3.58	24.6	2.27
18	Male	65	6.6	11.6	19.2	9.9	5.71
19	Male	35	7.5	2.55	5.08	7.5	3.87
20	Male	57	59.9	1.9	11.7	22.8	5.71
21	Male	42	41.2	13.6	26.6	42.7	2.48
22	Male	59	6.9	8.62	11.5	16.7	2.25
23	Male	56	45.3	8.42	47.4	18.1	10.50
24	Male	50	23.1	1.2	3.45	15.1	2.82
25	Male	65	74.8	1.2	10.6	23.7	0.52
26	Male	58	23.1	1.05	3.23	14.2	2.74
27	Male	72	28.8	5.32	15.9	18.3	6.38
28	Male	61	20.2	1.6	3.94	15.6	3.20
29	Female	73	9.1	2.59	4.32	12.3	4.14
30	Male	70	39.9	0.48	1.78	21.1	1.38
31	Male	61	21.9	2.6	12.8	9.5	12.20
32	Male	65	11.3	8.16	14.4	13.7	5.68
33	Male	71	24.7	9.12	12.8	49.6	1.18
34	Female	52	6.9	2.83	4.32	11.4	0.64

Abbreviation: TTD, time to tumor doubling.

carcinomas, two (5.9%) were oncocytomas and one (2.9%) was a multilocular clear cell renal cell carcinoma. Thirteen tumors (40.6%) were of pathological grade 1, 13 (40.6%) were grade 2, four (12.5%) were grade 3, and two (6.3%) were of unknown grade. The mean postoperative follow-up time was 39.7 months (6.3–122.8). Three patients died: one due to RCC, another because of lung cancer, and the third due to pancreatic carcinoma (Table 2).

In fact, the 5-year overall survival rate (OSR) was 72.6%. The cancer-specific 5-year survival rate (CSSR) was 87.5%. The 5-year cancer recurrence-free rate (CRFR) was 96.2%.

A 72-year-old man died of cancer after an incidence of tumor recurrence. He had undergone an open partial nephrectomy. The histological stage of the RCC was clear cell type, pT1aN0N0 grade2. TTD was 18.3 months. Because local recurrence was found 29 months after the operation, radical nephrectomy was performed, but the patient died due to local recurrence at 54.3 months after the initial operation.

There is no significant difference of TTD according to histopathological grade and subtype. But a strong trend was evident with an almost significant $P = 0.068$ (Table 3).

Discussion

A greater number of small, asymptomatic renal tumors are being incidentally detected nowadays. The positive prognosis of incidental RCC is excellent as evidenced by the results of surgery.[16,17] Metastasis may occur in 1%–1.4% of patients with small renal cell carcinoma.[6,18]

Active surveillance is most commonly considered in early prostate cancer, however, recent advances regarding

Table 2 Histopathological diagnosis and clinical outcome

Case	Histological subtype	Grade	Tumor number	Postoperative follow up (months)	Clinical outcome recurrence (+/–)
1	Clear	2	1	25	–
2	Clear	2	1	15.2	–
3	Papillary	Unknown	1	12.4	–
4	Clear	Unknown	1	6.3	–
5	Clear	2	1	26.1	–
6	Papillary	3	1	37	–
7	Clear	1	1	33.6	–
8	Clear	1	1	35.7	–
9	Clear	1	1	32.3	–
10	Clear	1	1	33.4	–
11	Clear	1	1	28.6	–
12	Papillary	2	1	41.8	–
13	Clear	1	1	75.7	–
14	Clear	2	1	27.6	–
15	Clear	2	1	64.7	–
16	Clear	1	1	11.8	Death (LC)
17	Papillary	2	1	23.8	–
18	Clear	2	1	25.1	–
19	Clear	1	1	16.9	–
20	Papillary	3	1	19.6	–
21	Clear	2	1	32	–
22	Clear	2	1	30.1	–
23	Clear	1	1	30.3	–
24	Clear	1	1	45.7	–
25	Multilocular clear	3	1	42.3	–
26	Oncocytoma	–	1	–	–
27	Clear	2	1	54.3	Death (RCC)
28	Clear	1	1	56.5	Death (PC)
29	Oncocytoma	–	1	–	–
30	Clear	1	1	80.1	–
31	Clear	3	1	81.4	–
32	Clear	1	1	14.8	–
33	Clear	2	1	122.8	–
34	Clear	2	1	88.7	–

Abbreviations: Clear, clear cell carcinoma; LC, lung cancer; Multilocular clear, multilocular clear cell renal cell carcinoma; Papillary, papillary cell carcinoma; PC, pancreas carcinoma; RCC, renal cell carcinoma.

Table 3 Renal cell carcinoma growth rate

	TTD (months) mean (range)	*P* value
Total no of cases	34	
Histological grade of clear cell carcinoma		0.068*
Grade 1 (n = 13)	28.5 (7.5–62.3)	
Grade 2 (n = 11)	18.4 (5.5–149.6)	
Grade 3 (n = 1)	9.5	
Histologic subtype		ns**
Clear cell carcinoma (n = 26)	23.5 (5.5–62.3)	
Papillary cell carcinoma (n = 5)	26.7 (10.2–58.2)	
Multilocular clear cell (n = 1)	23.7	
Oncocytoma (n = 2)	13.3 (12.3–14.2)	

Notes: *Grade 1 versus grade 2; **clear cell carcinoma vs papillary cell carcinoma.
Abbreviations: ns, not significant; TTD, time to tumor doubling.

tumor detection tools such as ultrasound and high speed CT scans have made surveillance of RCC possible.[18–22] Active surveillance is becoming more common, in particular in elderly patients or patients with comorbidities, who may not be candidates for surgery. This approach is based on a retrospective cohort study of the growth rate and natural history of incidentally detected small renal tumors.[21–23]

Factors to be taken into account for SRM treatment involve tumor size at the time of diagnosis as well as tumor proliferation rate; 55% to 60% of SRMs are indolent RCC and 20% to 25% are progressive RCC.[24,25] Considering preoperative progression factors, these models allow quantitative detailing of the risks of recurrence, metastasis and survival. However, these tools have several limitations regarding highly qualified treatment decisions in the management of SRMs.[23]

In general, size is proportionate to the grade of malignancy.[26] In which case, when should tumors be treated proactively? How big must they be in diameter? In the case of SRMs smaller than 1.0 cm, 38%–46% are benign. On the other hand, for lesions larger than 7.0 cm, only 6.3%–7.1% are benign.[27] It has been reported that renal masses ≧ 3 cm in diameter have more aggressive potential, resulting in more metastatic cases.[28,29]

Moreover, the proliferation rate should also be considered. Renal masses < 2.45 cm at diagnosis were shown to have an average growth rate of 0.13 cm/year, while masses > 2.45 cm had an average growth rate of 0.40 cm/year.[22] Larger tumors and larger tumor volumes at diagnosis and at the conclusion of observation, tended to progress. Significant differences in both the average growth rate (0.80 cm/year versus 0.3 cm/year) and the average volumetric growth rate (27.1 cm^3/year versus 6.2 cm^3/year) have also been observed.[30]

Generally, local recurrence rates of RCC reportedly vary from 0% to 7%, and disease-specific survival probabilities range from 89% to 100%.[31] In our study 34 of 328 patients underwent delayed surgical intervention. In this study, there was no urgency to operate on patients with a TTD of more than 6 months. As a result, one of 34 patients died of local recurrence.

Active surveillance of SRMs offers oncological efficacy equivalent to surgery in the short/intermediate term.[32] In our study, although the 5-year OSR was rather low at 72.6%, the 5-year CSSR was 87.5%, and the 5-year CRFR was 96.2%; this was probably because surgery was sufficiently delayed considering the past medical history of each surgical case, although the small number of patients might also have influenced the results. It will be necessary to evaluate a large number of such patients to draw conclusions.

As for the treatment of RCC, if imaging findings suggest a typical malignant tumor or enlargement of the tumor is observed in images showing atypical findings, surgical intervention, such as partial nephrectomy to remove the tumor and preserve renal function, should be recommended to every patient, regardless of age. Finally, appropriate treatment should be decided considering age, past medical history and complications.

In conclusion, because short and intermediate term oncological outcomes of active surveillance for SRMs are the same,[32] active surveillance including delayed intervention surgery for small renal cell carcinoma may be considered a useful strategy by more institutions and become a treatment option in the future. However, surgical intervention should be considered in case of tumor growth to more than 3–4 cm or by more than 4–5 mm/year while on active surveillance.[29]

Disclosure

The authors report no conflicts of interest in this work.

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