Clinical Symptoms Predict Poor Overall Survival in Chronic-dialysis Patients with Renal Cell Carcinoma Associated with End-stage Renal Disease

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Objective: To evaluate which clinical symptoms predict the survival of patients with renal cell carcinoma associated with end-stage renal disease under chronic dialysis.

Methods: We retrospectively evaluated 401 patients with renal cell carcinoma associated with end-stage renal disease who underwent radical nephrectomy at our institute up through December 2012. Patients were divided into two groups: the symptomatic group and the incidental group, by diagnosis. We compared the clinicopathologic features and patient survival of the two groups and investigated prognostic factors using Cox multivariate analysis.

Results: Of the 401 patients, 124 (30.9%) were in the symptomatic group and 277 (69.0%) in the incidental group. The symptomatic group included more advanced tumors in terms of larger tumor size, higher stage and higher grade compared with the incidental group. The 5-year cancer-specific survival and overall survival of the symptomatic and incidental groups were 76.9 vs. 95.3% \((P < 0.001)\) and 64.2 vs. 84.9% \((P < 0.001)\), respectively. On multivariate analysis, the presence of symptoms, higher age, higher stage, diabetic nephropathy and longer hemodialysis duration were independent prognostic factors.

Conclusions: Symptomatic detection was significantly associated with worse overall survival in patients with renal cell carcinoma associated with end-stage renal disease as well as sporadic renal cell carcinoma. The high incidence of renal cell carcinoma as well as the poor oncologic outcome in patients with longer dialysis therapy may suggest an important role for routine screening in these patients.

Key words: renal cancer — symptoms — diagnosis — end-stage renal disease — hemodialysis

INTRODUCTION

The presence of symptoms at the time of diagnosis has been reported to be associated with an unfavorable prognosis in patients with sporadic renal cell carcinoma (RCC) compared with those with incidentally found tumors without symptoms in the general population \((1–3)\). In most studies, the poor prognosis of symptomatic tumors was associated with larger tumor size, higher stage and higher grade compared with patients with asymptomatic tumors \((1–4)\).

The number of patients with end-stage renal disease (ESRD) has been increasing globally due to the increase in patients with diabetes \((5,6)\). Moreover, the incidence of RCC occurring in patients with ESRD is 3.6- to 13.0-fold higher than that in sporadic RCC. In fact, the incidence of RCC is 3.9 times higher in patients with >10 years of dialysis than in patients with <10 years \((7–10)\). However, whether the presence of symptoms leading to poor prognosis can be applied to those patients with RCC-related to end-stage renal disease (ESRD-RCC) remains unclear. If poor prognosis can be linked to patients with ESRD who have symptoms of RCC, the importance of screening for RCC might be indicated.
Some reports have suggested the effectiveness of routine screening in improving the cancer-specific survival (CSS) and overall survival (OS) in patients with ESRD-RCC (11,12), but there are, as yet, few studies addressing this issue.

In the present study, we retrospectively analyzed patients with ESRD-RCC who underwent surgery in our department with respect to whether having symptoms or not is a predictor of patient survival.

**PATIENTS AND METHODS**

**Patients**

From September 1982 to December 2012, 401 patients with ESRD underwent radical nephrectomy for renal tumors that were pathologically confirmed as RCC in our department. We defined patients who had undergone dialysis therapy for longer than 6 months as ESRD-RCC. Therefore, patients who were diagnosed with RCC within half a year after induction of dialysis were not included in this study, since these tumors were considered unrelated to ESRD. Seventy-eight patients had staged bilateral nephrectomy for bilateral disease. The patients were divided into two groups according to the presence of symptoms at the time of diagnosis: those in whom symptoms related to RCC tumors resulted in diagnostic imaging studies (the symptomatic group) and those without symptoms in whom the tumors were found incidentally by routine screening or by screening for other diseases (the incidental group). Clinical and pathologic information was collected from medical records. The protocol for the screening varied among patients because each patient was screened at their particular dialysis center. Tumor stage was determined according to the 2009 TNM classification (13). Pathologic diagnosis was made in line with the 2004 World Health Organization classification (14). Patient characteristics are shown in Table 1. Postoperatively, we evaluated recurrence by computed tomography (CT) scan every 6–12 months.

**Statistical Analysis**

Patient survival was calculated using the Kaplan–Meier method and statistical difference was evaluated by the log-rank test and Wilcoxon analysis between the two groups. Each of the clinical and pathologic parameters was compared between the groups using the Mann–Whitney U-test. Univariate and multivariate analyses were performed using the Cox proportional hazard model to identify the prognostic factors. Statistical significance was considered as $P < 0.05$. All statistical analyses were performed using the JMP 8.0.2 software (SAS Institute, Cary, NC, USA).

**RESULTS**

**Patient Background**

Table 1 shows patient characteristics. The symptomatic group includes 124 patients (30.9%) and the incidental group 277 patients (69.1%). The duration of dialysis was significantly longer in the symptomatic group than that in the incidental group (16.4 vs. 14.1 years, $P < 0.01$). With regard to the primary diseases of chronic renal failure, chronic nephritis was highest in both groups (78.2 vs. 69.3%); diabetic nephropathy and nephrosclerosis were higher in the incidental group. More patients showed acquired cystic disease of the kidneys (ACDK) in the symptomatic group than in the incidental group. Initial symptoms in the symptomatic group included gross hematuria in the majority of the patients, abdominal pain and screening for metastatic disease.

Table 2 shows patient clinicopathologic findings according to groups. Most parameters confirmed that the tumors of the symptomatic group had higher malignant potential, including larger tumor size, higher pathologic stage and higher grade. The patient follow-up was similar between the groups, and recurrence, cancer death and overall death were found more frequently in the symptomatic group.

**Patient Survival**

Survival rates between groups were compared using the Kaplan–Meier method. Figure 1 shows the CSS and OS of patients with ESRD-RCC who underwent surgery in our department with respect to whether having symptoms or not is a predictor of patient survival.
patients in the two groups, revealing a significantly worse CSS in the symptomatic group than that in the incidental group \((P < 0.001)\). CSS of the symptomatic and incidental groups was 76.9 and 95.3\% at 5 years, and 76.9 and 93.1\% at 10 years. OS was also significantly worse in the symptomatic group than in the incidental group \((P < 0.001)\). OS of the symptomatic and incidental groups was 62.7 and 84.9\% at 5 years, and 55.7 and 66.6\% at 10 years.

### INFLUENCE OF THE PRESENCE OF SYMPTOMS ON PATIENT SURVIVAL

We further examined the prognostic factors influencing CSS and OS using the Cox proportional hazard model. With respect to CSS, higher age, higher pathologic stage, higher grade, larger tumor, longer dialysis duration and symptomatic tumor were significant factors, as shown by univariate analysis (Table 3). Higher stage, longer dialysis duration and symptomatic tumor were independent factors for CSS. The significant factors for OS as shown by univariate analysis were similar to those for CSS, but diabetes as the primary disease was also a significant factor. The multivariate analysis also showed higher age, higher stage, diabetic nephropathy, hemodialysis (HD) duration and symptomatic tumor as independent factors for OS. Our study proved that the presence of symptoms is a diagnostic predictor for poor prognosis in patients with ESRD-RCC.

### DISCUSSION

The incidence of incidentally detected sporadic RCC tumors has been increasing due to the advancements in imaging analysis \((4,15)\). Many studies have shown the incidental detection of tumors to be an independent prognostic factor \((1–3)\).

Whether the presence of symptoms is prognostic in ESRD-RCC remains controversial since there have been few reports addressing this issue. Sarasin et al. \((12)\) reported that incidental detection provided only limited benefit for patients with ESRD-RCC. The incidental detection of RCC by ultrasound or CT scan decreased cancer deaths by half and provided a 1.6 year gain in life expectancy only for patients with...
a life expectancy of 25 years or more (12). Their report, however, included a relatively high number of surgical deaths, which may have complicated their results. Ishikawa et al. (11) reported worse CSS and OS in ESRD-RCC patients with symptoms compared with patients whose ESRD-RCC was incidentally found, as we reported in this study. The incidental detection provided a survival benefit of 39 months (3.3 years) in death from all causes after adjustment for age and duration of dialysis, and this benefit appears to be more apparent in young patients (11). However, they did not perform a multivariate analysis, thus it remains unclear whether the incidental detection was an independent factor. Our present results demonstrate by multivariate analysis that the presence of symptoms is an independent prognostic factor not only for CSS but also for OS.

The necessity of routine screening for RCC in patients with ESRD should be discussed. In the general population, although the incidental detection is likely to be an independent prognostic factor (1–3), the role of routine screening for RCC appears to be insignificant since the incidence of RCC found by ultrasound was only 0.20% in patients without any urinary symptoms including hematuria (16). However, Terasawa et al. (17) showed that RCC was detected by ultrasound screening at the rate of 2.3% in patients on HD. This rate was 29 times as high as in healthy people at the same institution and reflected the high incidence rate in patients with ESRD (7–10). European studies showed that patients with ESRD-RCC may exhibit a more favorable outcome compared with RCC occurring in the general population (18). However, in their series, the mean period of HD before RCC diagnosis was only 65 ± 60 months. This short HD duration might have caused the favorable prognosis. According to our study, the rate of symptomatic RCC is higher in patients of >10 years’ HD duration (Fig. 2). In addition, the incidence in patients with dialysis therapy of >10 years was ~10 times higher than in the sporadic RCC, and these patients are likely to show a poor outcome (10,19). In Japan, 25.9% of the patients with ESRD had been receiving dialysis therapy for over 10 years (5). Thus, early detection of the tumor by routine screening may have a potential role in improving not only CSS but also OS in patients with ESRD-RCC.

Finally, we should emphasize the limitations of this study, including its retrospective and non-randomized nature and the small number of patients. In addition, the modalities used for detection varied at the different dialysis centers. A prospective multicenter study with a larger number of patients is required to confirm our data.

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#### Table 3. Prognostic factors for cancer-specific survival (CSS) and overall survival (OS)

| End point | CSS | | | OS | | |
|-----------|-----|-----|-----|-----|-----|-----|
|           | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|           | HR CI | P | HR CI | P | HR CI | P | HR CI | P |
| Age       | 1.04 1.00–1.07 | 0.01 | 1.03 0.99–1.08 | 0.08 | 1.06 1.04–1.09 | <0.01 | 1.07 1.04–1.09 | <0.01 |
| P-stage 2 or higher | 13.0 6.50–27.8 | <0.01 | 7.61 3.16–18.8 | <0.01 | 3.45 2.25–5.19 | <0.01 | 2.82 1.62–4.80 | <0.01 |
| Grade 3, 4 | 6.34 2.85–13.1 | <0.01 | 1.70 0.73–3.76 | 0.20 | 3.59 2.04–5.97 | <0.01 | 1.69 0.90–3.01 | 0.09 |
| Tumor size (mm) | 1.02 1.01–1.03 | <0.01 | 0.99 0.98–1.01 | 0.96 | 1.01 1.00–1.01 | <0.01 | 0.99 0.99–1.00 | 0.70 |
| Diabetic nephropathy | 1.45 0.23–4.84 | 0.62 | | | | | |
| HD duration (years) | 1.13 1.08–1.10 | <0.01 | 1.08 1.03–1.14 | <0.01 | 1.06 1.03–1.09 | <0.01 | 1.05 1.02–1.08 | <0.01 |
| Symptomatic | 3.93 1.99–8.06 | <0.01 | 2.57 1.23–5.54 | 0.01 | 1.90 1.27–2.84 | <0.01 | 1.75 1.14–2.66 | <0.01 |
| Papillary RCC | 1.23 0.49–2.68 | 0.63 | | | | | |
| Male | 0.98 0.3–2.63 | 0.97 | | | | | |
| Presence of ACDK | 1.05 0.48–2.61 | 0.90 | | | | | |

HR, hazard ratio; CI, confidence interval; P-stage, pathologic stage; RCC, renal cell carcinoma.
Conflict of interest
None declared.

References

1. Schips L, Lipsky K, Zigeuner R, et al. Impact of tumor-associated symptoms on the prognosis of patients with renal cell carcinoma: a single-center experience of 683 patients. *Urology* 2003;62:1024–8.
2. Lee CT, Katz J, Fearn PA, Russo P. Mode of presentation of renal cell carcinoma provides prognostic information. *Urol Oncol* 2002;7:135–40.
3. Palsdottir HB, Hardarson S, Petursdottir V, et al. Incidental detection of renal cell carcinoma is an independent prognostic marker: results of a long-term, whole population study. *J Urol* 2012;187:48–53.
4. Luciani LG, Cestari R, Tallarigo C. Incidental renal cell carcinoma—age and stage characterization and clinical implications: study of 1092 patients (1982–1997). *Urology* 2000;56:58–62.
5. Nakai S, Suzuki K, Masakane I, et al. Overview of regular dialysis treatment in Japan (as of 31 December 2008). *Ther Apher Dial* 2010;14:505–40.
6. Collins AJ, Foley RN, Chavers B, et al. United States renal data system 2011 annual data report: atlas of chronic kidney disease & end-stage renal disease in the United States. Introduction to volume two: atlas of end-stage renal disease in the United States. *Am J Kidney Dis* 2012;59;(Suppl. 1):e129–46.
7. Maisonneuve P, Gospodorwicz M, Wittekind G. Kidney (ICD-O C64). *TNM Classification of Malignant Tumours*. 7th edn. Oxford, UK: Wiley-Blackwell 2010; 255–7.
8. Denton MD, Magee CC, Ovuworie C, et al. Prevalence of renal cell carcinoma in patients with ESRD pre-transplantation: a pathologic analysis. *Kidney Int* 2002;61:2201–9.
9. Stewart JH, Bucciante G, Agodoa L, et al. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. *J Am Soc Nephrol* 2003;14:197–207.
10. Ishikawa I. Present status of renal cell carcinoma in dialysis patients in Japan: questionnaire study in 2002. *Nephron Clin Pract* 2004;97: c11–6.
11. Ishikawa I, Honda R, Yamada Y, Kakuma T. Renal cell carcinoma detected by screening shows better patient survival than that detected following symptoms in dialysis patients. *Ther Apher Dial* 2004;8: 468–73.
12. Sarasin FP, Wong JB, Levey AS, Meyer KB. Screening for acquired cystic kidney disease: a decision analytic perspective. *Kidney Int* 1995;48:207–19.
13. Sobin L, Gospodorwicz M, Wittekind G. Kidney (ICD-O C64). *TNM Classification of Malignant Tumours*. 7th edn. Oxford, UK: Wiley-Blackwell 2010; 255–7.
14. Ornstein DK. Pathology and genetics: tumours of the urinary system and male genital organs. *J Urol* 2004;172(Part 1):2511.
15. Lightfoot N, Conlon M, Kreiger N, et al. Impact of noninvasive imaging on increased incidental detection of renal cell carcinoma. *Eur Urol* 2000;37:521–7.
16. Haliloglu AH, Gulpinar O, Ozden E, Beduk Y. Urinary ultrasonography in screening incidental renal cell carcinoma: is it obligatory? *Int Urol Nephrol* 2011;43:687–90.
17. Terasawa Y, Fukuda Y, Suzuki Y, et al. Ultrasonic diagnosis of renal cell carcinoma in hemodialysis patients. *Nihon Hinyokika Gakkai Zasshi* Jpn J Urol 1993;84:2137–45.
18. Neuzillet Y, Tillou X, Mathieu R, et al. Renal cell carcinoma (RCC) in patients with end-stage renal disease exhibits many favourable clinical, pathologic, and outcome features compared with RCC in the general population. *Eur Urol* 2011;60:366–73.
19. Takagi T, Kondo T, Izuka J, et al. Prognosis and characteristics of renal cell carcinoma in hemodialysis patients: bilateral occurrence does not influence cancer-specific survival. *Int J Urol* 2011;18:806–12.