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Changes in Clinicopathological Characteristics of Renal Cell Carcinoma in the Past 25 Years: A Single-Center Experience

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Purpose: We examined changes in the clinicopathologic characteristics of renal cell carcinoma (RCC) in the past 25 years and aimed to obtain indicators for its diagnosis and treatment.

Materials and Methods: The medical records of 563 patients with confirmed primary RCC after surgical treatment from 1985 to 2010 at Seoul St. Mary's Hospital were retrospectively reviewed. Patient and tumor characteristics were compared over 3 time periods (period 1: 1985-1994, period 2: 1995-2004, period 3: 2005-2010).

Results: Period 1 included 65 patients, period 2 included 183 patients, and period 3 included 315 patients, showing an exponential growth in the number of patients. Frequency was highest in the late 50s age group. The review of clinical symptoms showed that incidental diagnosis increased significantly. The tumor size at diagnosis gradually decreased and the proportion of small tumors less than 4 cm increased remarkably. Concerning tumor spread, organ-confined tumors ($T_{1-2}N_0M_0$) increased and distant metastasis decreased. Histologically, the clear cell type made up the greatest proportion, about 90% in each period, but subtypes besides the clear cell type increased over the study period. The rate of nephron-sparing surgery increased, and exophytic masses were the most common.

Conclusions: Our review of the recent 25 year's worth of data on RCC from Seoul St. Mary's Hospital showed that the incidental diagnosis of RCC increased over the study period in accordance with the development of screening tests. Tumor size decreased in accordance with the progress in imaging modalities. In the future, multicenter research will be needed to analyze the characteristics of whole renal cancer in Korea.

Key Words: *Histology; Neoplasm staging; Renal cell carcinoma*

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INTRODUCTION

Renal cell carcinoma (RCC) represents 3% of all malignant tumors in adults and 85% of all primary malignant kidney tumors [1]. According to data from the Korea Central Cancer Registry (KCCR), in 2007, the incidence of RCC was 5.8 out of 100,000 persons and RCC constituted 1.8% of all cancers [2]. Moreover, the incidence is gradually increasing, and incidental diagnosis of early-stage disease is also increasing as the result of general health screening, ultrasonography, and computed tomography (CT) scanning [3-5]. Because the incidence of RCC grew considerably among domestic patients, increasing from 3.0 in 1999 to 5.8 out of 100,000 persons in 2007 [2], it is considerably important to study the characteristics of RCC in Korea through overall analysis to improve its treatment and prognosis. We intended to present guidelines for the diagnosis and treatment of RCC in Korea by studying changes in the clinicopathological characteristics of RCC over the past 25 years.

MATERIALS AND METHODS

The medical records of 563 patients with confirmed primary RCC after surgical treatment from 1985 to 2010 at Seoul St. Mary's Hospital were retrospectively reviewed. All patients underwent either radical nephrectomy (476 patients, 84.5%) or partial nephrectomy (87 patients, 15.5%).

The following variables were determined in each case: age at diagnosis, sex, clinical symptoms, tumor size, histologic subtype, TNM stage, Fuhrman grade, and surgical approach. Clinical symptoms were divided into 3 cases: the first was the case of incidental finding during a general health screening or during follow-up for other diseases, the second was the case of typical symptoms such as hematuria or flank pain, and the third was the case of being found during an examination for another abnormal medical symptom. Tumor size (largest diameter) was estimated from resected specimens. All histologic findings were reviewed retrospectively according to the 1997 UICC/AJCC classification of renal neoplasms (Storkel et al, 1997), whereas the Fuhrman four-grade scale (Fuhrman et al, 1982) was used to assess the histopathologic nuclear grade. The 2002 AJCC TNM staging system was used to classify cancer stage and tumor spread [6]. Open surgery and laparoscopic surgery were listed for the surgical approach, but robot-assisted laparoscopic surgery was added after the adoption of the da-Vinci® surgical system (Intuitive Surgical, Sunnyvale, CA, USA) at our hospital in 2009.

The 25-year study period was divided into three intervals (period 1: 1985-1994, period 2: 1995-2004, and period 3: 2005-2010) to investigate changes over time. The chi-square test and ANOVA regression analysis were used respectively for the comparison of qualitative and quantitative variable. Statistical significance was set at $p < 0.05$.

RESULTS

Of the 563 patients diagnosed as having RCC after surgical treatment over the past 25 years, 65 patients were included in period 1,183 patients were included in period 2, and 315 patients were included in period 3, showing an exponential growth in the number of patients.

The mean age of all patients was 55.6 years (range, 25-86 years), and the frequency of RCC was highest in the late 50s age group (Fig. 1). The mean age at diagnosis did not change over the time period (54.2±10.5 years, 55.2±12.2 years, and 56.1±11.8 years in the three periods, respectively, p=0.428). Also, the proportion of young (≤40 years old) patients was not statistically different among the groups (p=0.527). Reviewing the male to female ratio of all patients, disease occurrence was about two times greater in male than in female patients. There were 374 male patients and 189 female patients.

The proportion of incidentally diagnosed cases during general health screening or during follow-up for other diseases increased significantly over the time period (33.8%, 60.7%, and 72.7% in the three periods, respectively, $p < 0.001$). In the case of being found by typical symptoms, hematuria and flank pain were the most common symptoms reported. Palpable abdominal mass and bilateral varicocele were also found. In the case of being found during an examination for another abnormal medical condition, the symptoms reported included high fever, abdominal discomfort, poor oral intake, and anemia (Table 1).

According to the increase in incidentally diagnosed cases in early stages, tumor size decreased significantly over the

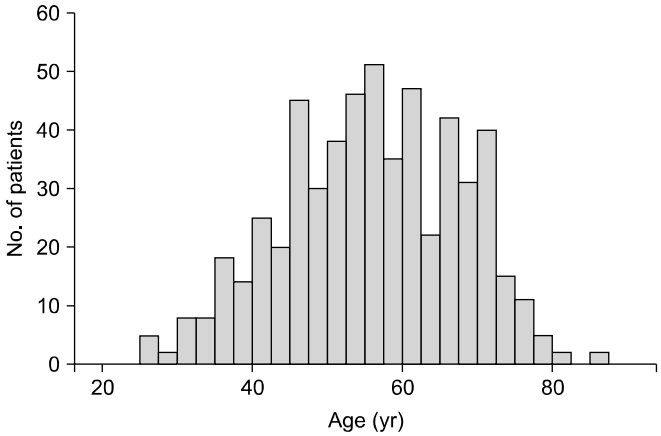

FIG. 1. Age distribution of the entire group of patients studied.

TABLE 1. Patient characteristics and distribution of clinical symptoms according to time period

Parameters	Period 1	Period 2	Period 3	p-value
No. of patients	65	183	315	
Mean age	54.2±10.5	55.2±12.2	56.1±11.8	0.428
Young age (≤40 yr)	7 (10.7%)	22 (12.0%)	28 (8.9%)	0.527
Sex (male:female)	1.24	2.10	2.12	0.134
Mean BMI	23.5±2.9	23.7±3.4	24.2±3.2	0.172
Clinical symptom				
Incidental (%)	22 (33.8)	111 (60.7)	229 (72.7)	<0.001
Symptomatic (%)	37 (56.9)	58 (31.7)	69 (21.9)	
Other medical condition (%)	6 (9.3)	14 (7.6)	17 (5.4)	

BMI: body mass index

time period studied (6.29±3.5 cm, 5.42±3.5 cm, and 4.69±3.12 cm, respectively, $p<0.001$), and the proportion of tumors less than 4 cm in size increased significantly (32.3%, 47.5%, and 53.0%, respectively, p=0.009).

In all patients, there were 492 patients (87.3%) with a TNM stage of T1-T2, which was far higher than the number with stage T3-T4 (71 patients, 12.7%). Regarding tumor spread, the incidence of organ-confined tumors ($T_{1-2}N_0M_0$) increased (60.0%, 68.3%, and 81.9%, respectively, $p<0.001$), whereas that of locally advanced tumors ($T_{3-4}N_0M_0$) and metastatic tumors ($T_{any}N_+M_0$ or $T_{any}N_0M_+$) decreased (Table 2).

Regarding histologic types, clear cell type patients were the most common (498 patients, 88.4%), and there was no chromophobe RCC, a newly established subtype of renal neoplasm, in period 1. However, we found that other histologic subtypes besides the clear cell type were increasing (9.2%, 9.3%, and 13.3%, respectively), although the increase was not statistically significant. The Fuhrman grade I/II was assigned to about three-fourths of the cases through all periods (76.9%, 73.2%, and 79.7%, respectively) (Table 3).

Concerning the surgical approach, open surgery decreased and laparoscopic surgery increased (0%, 38.8%, and 83.5%, respectively, $p<0.001$), and robot-assisted laparoscopic surgery increased after the adoption of the da-Vinci® surgical system (Intuitive Surgical, Sunnyvale, CA, USA).

As the tumor size became smaller, the rate of nephron-sparing surgery (NSS) increased (3.1%, 4.9%, and

TABLE 2. Tumor characteristics and stage according to time period

Parameters	Period 1	Period 2	Period 3	p-value
Laterality (Lt./Rt. ratio)	0.80	1.12	0.89	0.648
Tumor size (cm)	6.29±3.5	5.42±3.5	4.69±3.12	<0.001
Small tumor (≤4 cm)	21 (32.3%)	87 (47.5)	167 (53.0)	0.009
Tumor stage				
T1-T2 (%)	55 (84.6)	156 (85.2)	281 (89.2)	0.340
T3-T4 (%)	10 (15.4)	27 (14.8)	34 (10.8)	
Pathological nodal invasion (%)	1 (0.02)	9 (0.05)	7 (0.02)	0.284
Distant metastasis	20 (30.7)	49 (26.8)	40 (12.7)	<0.001
Tumor spread				
Organ confined (%)	39 (60.0)	125 (68.3)	258 (81.9)	<0.001
Locally advanced (%)	5 (7.7)	8 (4.4)	16 (5.1)	
Metastatic (%)	21 (32.3)	50 (27.3)	41 (13.0)	

TABLE 3. Histology of tumors according to time period

Parameters	Period 1	Period 2	Period 3	p-value
Histology				
Clear cell (%)	59 (90.8)	166 (90.7)	273 (86.7)	0.177
Papillary	2	9	13	
Chromophobe	0	3	14	
Sarcomatoid	3	2	4	
Others	1	3	10	
Fuhrman's grade				
Grade I/II (%)	50 (76.9)	135 (73.2)	251 (79.7)	0.297
Grade III/V (%)	15 (23.1)	48 (26.8)	64 (20.3)	

TABLE 4. Surgical approach according to time period

Parameters	Period 1	Period 2	Period 3	p-value
Approach of surgery				
Open (%)	65 (100)	112 (61.2)	25 (7.9)	<0.001
Laparoscopic (%)	0	71 (38.8)	263 (83.5)	
Robotic (%)	0	0	27 (8.6)	
Type of surgery				
Radical nephrectomy (%)	63 (96.9)	174 (95.1)	239 (75.9)	<0.001
NSS (%)	2 (3.1)	9 (4.9)	76 (24.1)	

NSS: nephron-sparing surgery

24.1%, respectively, $p < 0.001$), and exophytic masses were the most common tumor location (55.2%) (Table 4).

DISCUSSION

The incidence of RCC is consistently growing, and 30% of patients with RCC already have metastasis at the time of diagnosis. Among the remaining patients, metastasis occurs in about 30% to 50% after surgical treatment; thus, the death rate is not being reduced [7,8]. Therefore, guidelines for treatment need to be developed by studying the characteristics of RCC in Korea.

In this study, we, as have many other authors, observed a dramatic increase in the prevalence of incidental renal tumors, which progressed from 33.8% to 72.7% during a 25-year period. Sunela et al reported that the proportion of incidentally diagnosed cases increased from 12% in the 1980s to 19% in the 1990s ($p < 0.01$) [9], and Beisland et al also reported that the proportion of incidentally diagnosed cases increased from 21.1% in the 1980s to 37.4% in the 1990s ($p < 0.01$) [10]. The current domestic incidence of RCC is 5.8 out of 100,000 persons, which is 60% of that in the United States. Thus, ultrasonography and CT scanning for screening RCC may reduce cost-effectiveness. However, abdominal sonography or CT scanning should be recommended to adults older than 50, because abnormalities in other organs could be detected through these examinations [11,12].

Currently, the most frequent age of diagnosis of RCC is the 50s, although some authors have reported that the mean age at diagnosis is getting higher because of the wide application of screening tests in older men and prolonged life expectancy [13,14]. Luciani et al reported an increase in the mean age at diagnosis from 57 years in 1982-1983 to 62.6 years in 1996-1997 [13]. Patard et al also reported an increase in the mean age at diagnosis from 63 years in 1984-1992 to 65 years in 1998-2003 [14]. In this study, the mean age at diagnosis was 54.2 years in period 1, 55.2 years in period 2, and 56.1 years in period 3, which showed a slight increase over time, but the trend was not statistically significant. Furthermore, we found that domestic RCC occurred in more young patients than has been reported in European countries. Therefore, early screening tests must be activated and the distinctive characteristics of RCC in younger patients should be identified.

In the total group of patients, RCC occurred in about two times more males than females; there were 374 male patients and 189 female patients. KCCR data in 2007 also reported a male-to-female ratio of 2:1, and a higher occurrence in males than in females has also been reported in European countries [14,15]. Smoking, obesity, and hypertension are currently discussed as causes of RCC. In addition, studies on hormonal, environmental, and hereditary causes have been performed but not yet confirmed. Continued study on the causes of the high incidence in males is needed [16-18].

According to the increase in incidentally diagnosed cases in the early stages of disease, the tumor size at diagnosis has decreased and the rate of NSS increased [14,19]. Robotic support to the operator when laparoscopic surgery is being performed may be one reason for the increase in NSS. Regarding the tumor location after the performance of NSS, exophytic masses were the most common, and among those cases, the surgical margin was positive in only one. In the case of endophytic masses, however, it is hard to detect the exact border of the tumor, and the mass is difficult to resect. The development of surgical techniques in NSS is necessary.

Histologically, the highest proportion of tumors were of the clear cell type, about 90% in each period [20,21]. The proportion of subtypes other than the clear cell type increased gradually over the study period, but not significantly so. Nowadays, target therapy is mainly being performed for metastatic RCC, but medical insurance is being applied only to the clear cell type. In addition, studies on the clear cell type are being actively pursued, whereas the other histologic subtypes are poorly researched [22,23]. Golimbu et al reported that other histologic subtypes have a lower survival rate than does the clear cell type, but not significantly so [24]. Because the relative incidence of other histologic subtypes is still low, it is hard to make a simple comparison. Tumor grades should be considered, and opinions vary among researchers [25,26]. Recently, renal cell carcinoma is founded in small size compared to past, so prognostic factors for pT1a renal cell carcinoma will be more improtant in near future [27]. We suggest that a multicenter study would be needed to compare the survival rate and treatment effectiveness of the other histologic subtypes in Korea.

CONCLUSIONS

Our review of the recent 25 year's worth of data on RCC from Seoul St. Mary's Hospital showed that incidental diagnosis has increased in accordance with the development of screening tests, and the incidence of disease was highest in the late 50s age group. Tumor size at diagnosis became smaller in accordance with the progress in imaging modalities, and the number of small tumors should consistently increase in the future. NSS will play a predominant role in treatment. As histologic subtypes besides the clear cell type increase, studies of target therapy of them should be initiated. Because our study was a single-center experience, there were limits in representing whole renal cancer. In the future, multicenter research is needed to analyze the characteristics and trends of whole renal cancer in Korea.

Conflicts of Interest

The authors have nothing to disclose.

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