Impact of preoperative radiological and postoperative pathological findings on survival of patients after radical nephrectomy performed with the indication of renal cell carcinoma

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ABSTRACT

Objective: To evaluate the impact of preoperative radiological and postoperative pathological findings on survival of patients after radical nephrectomy because of renal cell carcinoma (RCC).

Material and methods: We performed 159 consecutive radical nephrectomy between December 2007 and January 2014. We evaluated age, gender, complaints, operation time, comorbidity, computed tomography (CT) and magnetic resonance graphy (MRG) results. Size of the mass, lymph node involvement, renal vein invasion, and presence of metastases were investigated. During histopathological examination, especially, pathological diagnosis, subtypes of RCC, lymph node involvement, lymphovascular, perineural invasion, and capsular, renal pelvis invasion, and renal vein involvement were sought. Follow-up periods of the patients were determined based on dates of death of the patients, and the study period.

Results: RCC was seen in 124 (78%) of patients. Mean estimated survival of RCC patients was 60 months and 5 year survival was 64%. Tumor size greater than 6.5 cm, lymph node involvement ($p=0.006$) and metastasis in radiological results ($p<0.001$), lymphovascular invasion ($p=0.015$) and stage of disease ($p<0.001$) found to be significantly affecting the survival. Lymph node involvement in radiological results ($p=0.0089$; HR: 4.6; CI 95%: 1.4753 -14.3523) and stage of the disease ($p=0.0129$; HR: 1.6; CI 95%: 1.1087-2.3461) were affecting the survival independently.

Conclusion: We found radiological lymph node involvement and stage of the disease as independent factors affecting the survival of RCC patients after radical nephrectomy.

Keywords: Kidney tumor; radical nephrectomy; renal cell carcinoma; survey analysis.

Introduction

Renal cell carcinoma (RCC) constitutes 2-3% of all types of cancer, and with increasing use of imaging modalities, the number of patients diagnosed as RCC are also increasing.^[1] It is more frequently seen between ages of 60, and 70, and also it is 1.5 times more frequently encountered in men rather than women.^[2]

Currently, more than 50% of the RCC patients are asymptomatic, and diagnosed incidentally during examinations performed for indications other than RCC.^[3-5] Most often imaging modalities as urinary system ultrasound, computed tomography (CT), and magnetic resonance examinations are sufficient to establish diagnosis of RCC. The most important criterion of detection of malignant mass lesions has

been demonstrated to be contrast uptake of the mass, and 15 Hounsfield unit increase in the intensity of contrast uptake after administration of the contrast agent has been considered significant finding as for malignancy.^[6]

The most frequently encountered subgroups of renal cell carcinomas are clear cell, papillary, and chromophobic RCCs, and they are seen at a rate of 80%, 12%, and 5%, respectively.^[7] In current guidelines, 5-year survival rates in these subgroups have been reported as 71, 91, and 88%, respectively.^[8]

In our study, we investigated data of 159 patients in whom we performed radical nephrectomy between December 2007, and January 2014 with the initial diagnosis of renal tumour. We aimed to search impact of preop-

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erative radiological and postoperative pathological findings on survival of patients with renal cell carcinoma.

Material and methods

Data of 159 consecutive patients who underwent radical nephrectomy between December 2007, and January 2014 were retrieved from electronic database of our hospital, and patient characteristics were retrospectively analyzed. Information about age, gender, complaints, date of operation, comorbidities, CT, and magnetic resonance imaging (MRI) results were obtained. Radiological examinations revealed size of the renal masses, lymph node involvement, renal vein invasion, and presence of metastases. Pathology reports were evaluated regarding pathological diagnosis, subtypes of RCC (if present), lymph node, and renal vein involvement, lymphovascular, perineural, and capsular invasion. Follow-up periods were calculated based on the date of death or surgery for deceased patients, while for survived patients date of the operation was taken into consideration.

Statistical analysis

In comparisons, chi-square test, two independent samples T-test, one-way ANOVA, and Mann-Whitney U tests were used. Overall survival rates were analysed with Kaplan-Meier survival analysis and Cox multivariate regression. In statistical analyses, values were expressed as numbers, standard deviation, percentages, and intervals.

Results

Median age of was 61.4 years, with a male/female ratio of 1.86:1. The patients were presented with complaints of pain (44%), bloody urine (12%), and 26% of them contracted the disease incidentally. Radiograms of a patient who consulted with arm pain revealed a mass on ulnar bone, and as a result of histopathological diagnosis of biopsy specimen, and further examinations, the patient was diagnosed as RCC. In a patient who consulted to the physician with visual impairment, multiple presumably metastatic cerebral lesions were detected, and more sophisticated examinations revealed the diagnosis of RCC. Median diameter of tumoral masses was 7.5 cm. Median diameter of incidentally detected tumoral masses was 6.4 cm, while median diameter of renal tumor diagnosed in patients who consulted with any complaint was 7.9 cm ($p=0.020$). Median follow-up period of the patients was 29.9 months. Histopathological results most frequently (78%) disclosed presence of RCC. Distribution of histopathological results of a total of 159 underwent radical nephrectomy patients are shown in Table 1.

Characteristics of 124 patients with RCC are summarized in Table 2. Median age of the patients with RCC at the time of diagnosis was 60.6 years with a male/female ratio of 1.95:1

Mean follow-up period was 28.20 ± 22.06 (range, 0.7-79.1 mos) months.

Comorbidities of patients with RCC are shown in Table 3. As comorbidities, hypertension (36%), and diabetes mellitus (12%) were observed, while 18 (14.5%) patients were current or former smokers. Ten percent of the patients had 3 or more than 3 comorbidities. In the presence of comorbidities survival times were affected adversely, and in the presence of 3 or more than 3 morbidities survival times decreased significantly. Twelve patients had three or more than three comorbidities.

Preoperative radiological examinations revealed lymph node positivity in 8 (6.5%), distant organ metastases in 7 (5.6%), and renal vein invasion in 5 (4%) patients with RCC. Preoperative evaluation results of the patients are shown in Table 4.

Based on histopathology reports of RCC patients, patients were classified as Fuhrman Grades 1 (8.8%), 2 (55.8%), 3 (29.2%), and 4 (6.2%). Most frequently observed RCC subtypes were clear-cell (66%), followed by chromofobe (10.5%), and papillary (7.3%) subtypes (Table 5).

Mean survival time was estimated as 60 ± 3.1 months in RCC patients, while 5-year-survival was calculated as 64 ± 0.3 percent. Mean survival time in patients with clear-cell subtype was 57.8 ± 3.7 months, while 5-year-survival rate was 61.7%. However because of limited number of patients in other types, survival times, and 5-year-survival rates could not be estimated.

Table 1. Distribution of the radically nephrectomized patients based on postoperative pathology results

Pathological diagnosis		%
Angiomyolipoma	3	1.86
Abscess	1	0.62
Mucinous tubular, and psindle-cell tumor	1	0.62
Hydatid cyst	1	0.62
Chronic pyelonephritis	1	0.62
Xanthogranulomatous pyelonephritis	1	0.62
Lymphoma	2	1.24
Mesenchymal tumor	1	0.62
Oncocytoma	4	2.48
RCC	124	77.0
RCC and angiomyolipoma	1	0.62
Transitional cell carcinoma	2	1.24
Histopathological data were not available	17	11.8
RCC: renal-cell carcinoma		

Table 2. General characteristics, and survival rates of the patients with histopathologically detected renal cell carcinoma

	n	% (range)
Total, n	124	
Age at the time of diagnosis (years)	60.6±12.3	
Mean tumor size (cm)	7.57±3.1	2.3-18 cm
Gender		
Male	82	67
Female	42	33
Laterality		
Right	58	
Left	66	
Complaints		
Flank pain	53	44.40
Anemia	2	1.60
Lower urinary tract symptoms	6	4.80
Dyspeptic complaints	1	0.80
Visual impairment	1	0.80
Lassitude	1	0.80
Hematuria	16	12.90
Weight loss	3	2.40
Arm pain	1	0.80
None, incidental	30	24.20
Survival		
Dead	27	21.80
Survived	97	78.20
Mean follow-up period (mos)	28.20±22.06	0.7-79.1

Tumor size greater than 6.5 cm, radiologically detected lymph node positivity, and presence of metastases, histopathologically revealed lymphovascular invasion, existence of more than 2 comorbidities, and disease-stage were found to be significant factors effective on survival. When cut-off value of 6.5 cm for tumor sizes was taken into consideration, then survival rates differed extremely between two groups ($p=0.001$). In Fuhrman grade 4 RCCs median survival time was 37.5 months shorter, but in log-rank comparisons this decrease was not found to be significant ($p=0.137$). In our series, 5-year-survival rates were 75% in stage 1, and 27% in stage 4 disease ($p<0.001$). As detected in radiological imaging, 8 patients with lymph node positivity had mean survival rates lower when compared with other patients ($p=0.006$). Metastases, and disease-stage were the most significant markers in the prediction of survival rates ($p<0.001$). Lymphovascular invasion was detected in 19 pathology specimens, and mean survival rates were significantly lower in these patients ($p=0.015$). Among histopathological data, perineural invasion ($p=0.340$), renal vein invasion ($p=0.954$), cap-

Table 3. Preoperative comorbidities seen in patients with histopathological diagnosis of renal cell carcinoma

	n	%
Rheumatoid arthritis	1	0.81
Liver cancer	1	0.81
Hepatic failure	1	0.81
Breast cancer	2	1.61
Chronic renal failure	1	0.81
Prostate cancer	1	0.81
Chronic obstructive pulmonary disease	12	9.68
Morbid obesity	2	1.61
Diabetes mellitus	15	12.10
Thyroid dysfunction	4	3.23
Cerebrovascular diseases	6	4.84
Coronary artery disease	21	16.94
Hypertension	45	36.29
Number of patients with comorbidities		
≤2	112	90
>2	12	10

Table 4. Radiological characteristics of the patients

Size	n	%
≤7 cm	69	56
>7 cm	55	44
Lymph node positivity	8	6.5
Distant organ metastases	7	5.6
Renal vein involvement	5	4

sular invasion ($p=0.372$), and renal pelvis invasion ($p=0.878$) were not found to be significant in the prediction of survival. Statistically significant factors effective on survival are summarized in Table 6.

In Cox regression analyses, more than 2 comorbidities, radiologically assessed lymph node positivity, and disease stage were found to be individually independent determinative factors for survival (Table 7). Radiologically detected lymph node positivity was observedly an independent predictive factor for survival ($p=0.0089$; HR: 4.6; CI 95%: 1.4753-14.3523). Disease stage was also one of the independent predictors for survival. ($p=0.0129$; HR: 1.6; CI 95%: 1.1087-2.3461).

Discussion

Renal cell carcinoma is implicated as the urinary system cancer with highest mortality rates.^[9,10] Approximately 90% of renal malignancies were detected to be RCC.^[11] In men it is 1.5 times

more frequently seen than women. Its incidence increases after 6. decade of life.^[12] Because of advances in imaging modalities, and their more frequent use, increasingly lesser sized-renal masses can be diagnosed.^[13] As was in our series incidentally detected masses were relatively smaller. In our study, although RCC was detected more frequently in men, the incidence of clear-cell type was lower than cited in the literature.

Currently accepted prognostic factors in patients with RCC have been indicated as anatomical factors (size, venous, and

capsular invasion, adrenal gland involvement, metastases into lymph nodes, and remote organs), histological characteristics (Fuhrman grade, RCC subtype, sarcomatous features, micro-vascular invasion, tumor necrosis, collecting system invasion), clinical characteristics (anemia, and various comorbidities), and molecular findings. It has been indicated that most widely accepted independent factor among histopathological characteristics is Fuhrman grade.^[14] Five-year survival rates in RCC, have been reported to be 81% in stage 1, and 6% in stage 4 disease.^[15] Median survival time in our study was found to

Table 5. Histopathological results of radically nephrectomized renal cell carcinoma patients with the indication of renal cell carcinoma

	n	%
Lymphovascular invasion	19	15.30
Perineural invasion	5	4.00
Renal vein invasion	8	6.50
Capsular invasion	38	30.60
Renal pelvis invasion	14	11.30
Lymph node positivity	3	2.40
Surgical margin positivity	5	4
T stage		
1a	15	12.00
1b	54	43.50
2a	28	22.60
2b	12	9.70
3a	12	9.70
3b	1	8.00
4	2	1.60
RCC subtypes		
Clear-cell	85	66.60
Clear-cell+ Chromophobe	4	3.20
Chromophobe	13	10.50
Papillary	9	7.30
Multilocular cystic	1	0.80
Sarcomatoid	1	0.80
Variant type	1	0.80
Stage		
1	68	55
2	54	28
3	12	10
4	9	7

RCC: renal cell carcinoma

Table 6. Factors statistically significantly effective on patients' survival rates

	Median survival (mos)	p value	Median age (mos)	p value
All patients	60.05		60.6	
Diameter		0.006		0.485
≤7 cm	66.50		61.3	
>7 cm	51.10		59.7	
Diameter				
≤6.5 cm	69.78	0.001	60.8	0.833
>6.5 cm	50.92		60.3	
Radiologically detected lymph node positivity		0.006		0.904
Present	21.20		59.6	
Absent	42.60		58.8	
Radiologically detected distant organ metaastases		<0.001		0.817
Present	27.80		62.1	
Absent	55.20		60.8	
Lymphovascular invasion		0.015		0.438
Present	29.80		60.3	
Absent	61.50		62.7	
Number of comorbidities		0.001		0.128
≤2	63.33		60.0	
>2	33.84		65.7	
Stage		<0.001		0.808
1	66.40		61.4	
2	52.89		58.9	
3	52.86		60.5	
4	27.04		61.3	

Table 7. Factors individually effective on survival in Cox regression analysis, and odds ratios (OR)

	p value	Odds ratio	95% confidence interval
Number of comorbidities >2	0.0008	4.801	1.9291-11.9485
Radiologically detected lymph node positivity	0.0089	4.6015	1.4753-14.3523
Disease stage	0.0129	1.6128	1.1087-2.3461

be 37.5 months in grade 4 RCC which was shorter relative to other groups without any statistically significant difference between groups. Five-year-survival rate in our study was 75% in stage 1, and 27% in stage 4 disease, and significant decrease was seen in survival rate in parallel with increase in disease stages. Disease stage is one of the factors which affected survival rates *per se*.

Many studies have investigated the significance of tumor size in the prediction of survival in patients with renal cell carcinomas. Klatte et al.^[16] investigated the effect of tumor size on prognosis, and followed up 902 patients with pathologic stage T2 for a median period of 52 months. The authors detected significantly higher 5, and 10-year-disease-free survival rates in the group of patients with renal masses smaller than the cut-off value of 11 mm. On the contrary, Ficarra et al.^[17] detected that cancer-related survival rates were significantly lower in 813 patients treated for localized RCC with tumor sizes larger than 5.5 cm. They revealed that the cut-off value of 7 cm accepted in the current TNM classification did not effect the survival rates significantly. In our study we have found that cut-off value of 6.5 cm for tumor size had demonstrated the highest level of significance in the prediction of survival rates. When cut-off value of 7 cm accepted in the current TNM classification was taken into consideration, significantly higher survival rates were detected in the group with smaller renal tumors. Contrary to other studies, all of our study group did not consist of patients with only localized disease.

Kondo et al.^[18] demonstrated independent effect of the presence of lymph node, and distant organ metastasis on survival, and reported 5-year-survival rate in 120 patients with RCC as 65 percent. Besides the authors also displayed significant effect of lymph node, and distant organ metastasis on survival in univariate analysis, however in multivariate analysis lymph node metastasis did not exert significant effect on survival *per se*. In their study, Takashi et al.^[19] found 5-year-survival rate of 121 operated RCC patients as 67% similar to previous study, in univariate analysis distant metastases, and lymph node metastases were significant predictors of survival, while in multivariate

analysis lymph node metastasis did not exert an important effect on survival rates. Similarly in a study by Giberti et al.^[20] the authors detected that the most important factor effective on prognosis was distant metastasis, while lymph node involvement had a minor effect. However in our series, median survival time of 8 patients with lymph node positivity was 21.2 months which was significantly lower relative to other patients. Since all three patients with lymph node positivity survived at the end of the median follow-up of 30.89 months, we didn't perform survival analysis in these patients. Distant organ metastases had a higher level of significance in the determination of survival. Median survival time in patients with distant metastases was nearly 27 months, however it wasn't a significant predictor for survival *per se*.

Belsante et al.^[21] examined the impact of lymphovascular invasion on survival, and detected the presence of lymphovascular invasion in 14% of 419 patients with clear-cell RCC, and revealed significantly lower rates of disease-free, and cancer-specific survival in patients with lymphovascular invasion. Katz et al.^[22] observed lymphovascular invasion in 11% of 841 patients, and revealed significantly lower metastasis-free, disease-specific, and overall survival rates in these patients. In our country, Türk et al.^[23] detected that grade, and histological subtype of the tumor were more significant in the determination of clinical behaviour of the tumor. The researchers also asserted that diameter of the tumoral mass, and incidence of metastatic lesions increased in line with higher tumor grade. In our study lymphovascular invasion was detected in 15.3% of pathologic specimens, and significantly lower overall survival rates were disclosed. However, invasion of perineural space, renal vein, capsule, and renal pelvis were not found to be significant in the prediction of survival.

Among limitations of our study, limited number of patients, and retrospective design of the study can be enumerated. Since exact causes of patients' death were not known, only overall survival rates could be estimated. Besides, operations, and histopathological examinations were performed by different surgeons which can be considered as other deficiencies of the study. However, consideration of comorbidities, and median age of the patient group in the calculation of the effects of imaging modalities, and pathological characteristics on overall survival rates are important features of the study.

Many debates have been made on actual effects of prognostic factors used to predict survival rates on prognosis. In our study, we detected that tumor size of 6.5 cm had exerted a significant impact on survival, and tumors greater than 6.5 cm in diameter significantly decreased survival rates. Besides lymph nodes detected during radiological studies, and stage of the tumor are predominant, and independent predictive factors of survival.

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Informed Consent: Due to its retrospective nature, written informed consent could not obtained from patients who participated to this study.

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