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MULTIVARIATE ANALYSIS OF PROGNOSTIC DETERMINANTS AFTER SURGERY FOR RENAL CELL CARCINOMA AT HIMEJI NATIONAL HOSPITAL

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A clinico-pathological study was performed retrospectively on 62 patients who underwent surgery for renal cell carcinoma between January 1992 and October 1998 at Himeji National Hospital to clarify the prognostic determinants for survival. The median follow-up peroid was 32 months and the cause-specific survival rates at 1, 3 and 5 years were 86.7, 81.3, 81.3%, respectively. Of the 62 patients, 11 (17.7%) patients died of renal cell carcinoma and 2 (3.2%) patients died of unrelated causes. Of the variables related to survival, presenting symptoms, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), alkaline phosphatase (ALP), tumor size, pathological tumor grade, infiltration pattern, pathological tumor stage, N classification and M classification were significant risk factors for survival by univariate analysis. However, ALP, N classification and M classification were significant for survival as determined by the step-wise procedure and M classification was the most significant factor according to Cox's proportional hazard model analysis.

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Key words : Renal cell carcinoma, Radical nephrectomy, Prognostic determinants

INTRODUCTION

Despite the use of biological response modifiers, surgery still remains the most effective and important treatment for renal cell carcinoma (RCC). Although there have been many reports on the prognostic relevance of clinical and pathological factors in RCC patients[1-9], we felt it was important to analyze clinicopathological factors by univariate or multivariate analysis to evaluate the relative importance of different factors that affect survival in RCC patients at Himeji National Hospital.

PATIENTS AND METHODS

Sixty two patients with renal cell carcinoma who underwent radical nephrectomy from January 1992 to October 1998 at Himeji National Hospital were examined retrospectively (Table 1). All data were obtained by reviewing the hospital medical records. Patient status was evaluated in November, 1999. The patients consisted of 46 males and 16 females. Ages ranged from 36 to 79 years with a mean of 59.7 ± (SD) 10.7 years. The right kidney was involved in 34 patients, the left kidney in 27 and both kidneys in one patient. Thirty-six patients underwent radical nephrectomy by a transabdominal approach, while 19 patients by a translumbar extraperitoneal approach. Six patients had nephron-sparing surgery and one patient, who had bilateral tumors, underwent a transabdominal radical nephrectomy for a huge tumor on the right and nephron-sparing surgery for the left side. Formal lymph node dissection was conducted if lymph node metastasis was strongly suspected preoperatively or during the surgical procedure itself. Patients with known distant metastasis underwent palliative surgery if the performance status was 0 or 1.

Clinicopathological prognostic factors were evaluated for their relationship to survival in the patients. Sex, age at the time of operation, tumor side, presenting symptoms, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and alkaline phosphatase (ALP) were evaluated as patient-related factors. Tumor size, pathological tumor grade, tumor cell type, infiltration pattern, venous involvement, pathological tumor stage, T classification, N classification and M classification were evaluated as tumor-related factors. Laboratory data were those obtained at the time of admission. Each specimen was independently reviewed by one pathologist (Y.K.). Pathological tumor grade and stage were classified according to the criteria of the Japanese

Table 1. Characteristics of 62 patients with renal cell carcinoma

Characteristics	No. of patients
Total	62 Age (range: 36–79, mean: 59.661±10.714)
Sex	Male: 46, Female: 16
Laterality	Right: 34, Left: 27, Bilateral: 1
Tumor size	<4.0 cm: 18, 4 cm≦, <7 cm: 17, 7 cm≦: 28 range: 1.5–15 cm, mean: 6.70 8±3.784 cm (bilateral case: right side=3.5 cm, left side=9.0 cm)
Cell type	Clear: 44, Granular: 14, Chromophobe: 2, Papillary: 1, Spindle: 1
Infiltration type	α: 52, β: 5, γ: 6
Pathological stage	I: 31, II: 15, III: 3, IV: 13
T classification	T1a: 18, T1b: 15, T2: 20, T3a: 7, T3b: 1, T4: 1
N classification	N0: 56, N1 or N2: 6
Metastatic sites	Lung: 10, Bone: 4, Liver: 2, Skin: 1

General Rules for Clinical and Pathological Studies on Renal Cell Carcinoma[10] Tumor size was defined by the diameter of the tumor at the largest point. Patients were divided into 2 groups for each factor. Laboratory data were categorized into normal and abnormal groups. For other factors in which normal values were difficult to define, patients were divided into 2 groups based on the most significant difference. The survival period was difined as the interval from the date of operation to death.

Statistical analysis of survival was calculated by Kaplan-Meier's method and differences in survival were evaluated by means of a log-rank test. Differences with a $p<0.05$ were considered significant. Significant laboratory and pathological factors were subjected to multivariate Cox's proportional hazards test by step-wise procedure to identify significant prognostic value. All these statistical analyses ware performed by computer, using the Stat View version J-5.0, SAS Institute Inc., USA.

RESULTS

The median follow-up period of the patients was 32 months. The cause-specific survival rates at 1, 3 and 5 years were 86.7, 81.3 and 81.3%, respectively (Tables 2 and 3). Eleven patients died of renal cancer during follow-up. Two patients died of unrelated causes with distant metastasis-one from a duodenal perforation due to a duodenal ulcer, and one from drowing in the bath. Thirty patients were free of disease, five patients were alive with distant metastasis or local recurrence. The data on clinical course of fourteen patients during the follow-up period were lacking.

Table 2. Summary of prognostic significance for survival by univarite analysis evaluated according to clinical and related data

Factors		No. of patients	Survival rate (1 year/3 year)	No. of cancer deaths	Missing data	Log-rank value
Total		62	86.7%/81.3%	11		
Pt. ages (ys)	<60	26	95.8%/91.5%	2	0	0.0950
	60≦	36	80.6%/74.5%	9		
Sex	Male	46	84.2%/81.8%	8	0	0.9895
	Female	16	93.8%/80.2%	3		
Laterality	Right	34	87.9%/84.4%	5	0	0.4469*
	Left	27	84.7%/76.8%	6		
	Bilateral	1	100%	0		
ESR (mm/hr)	<15	16	100 %/100 %	0	28	※
	15≦	18	70.6%/58.8%	7		
CRP	Negative	17	93.8%/93.8%	1	29	0.0345
	Positive	16	68.8%/62.5%	6		
ALP	Normal	49	91.5%/87.1%	6	6	<0.001
	Elevated	7	42.9%/28.6%	5		
Symptoms	Symptomatic	31	76.7%/69.8%	9	0	0.0158
	Asymptomatic	31	96.7%/92.9%	2		

* Bilateral case was excluded due to the limited number. ※ No case of death was seen during follow-up period in 16 cases whose ESR were less than 15 mm/hr.

Table 3. Summary of prognostic significance for survival by univariate analysis evaluated according to pathological findings and related data

Factors		No. of patients	Survival rate (1 year/3 year)	No. of cancer deaths	Missing data	Log-rank value
Total		62	86.7%/81.3%	11		
Tumor size	<70 mm	34	97.0%/93.7%	2	0	0.0039
	70 mm≦	28	74.1%/66.0%	9		
Tumor grade	1	35	94.1%/90.8%	3	0	0.0236
	2+3	27	77.2%/69.0%	8		
Infiltration pattern	α	52	94.0%/89.7%	5	0	<0.0001
	$\beta+\gamma$	10	50.0%/40.0%	6		
Cell type	Granular	14	85.7%/76.2%	3	0	0.6444*
	Clear	44	88.1%/83.2%	7		
N classification	N0	56	92.7%/87.0%	7	0	<0.0001
	N1+N2	6	20.0%/ 0.0%	4		
M classification	M0	49	95.8/%93.6%	3	0	<0.0001
	M1	13	41.7%/27.8%	8		
T classification	T1+T2	53	90.4%/84.4%	8	0	0.0532
	T3+T4	9	62.5%/62.5%	3		
Pathological stage	I+II	46	95.6%/93.2%	3	0	<0.0001
	III+IV	16	60.0%/44.4%	8		
v factor	Positive	7	71.4%/71.4%	2	0	0.3616
	Negative	55	88.7%/82.8%	9		

* Papillary, chromophobe and spindle cell type were excluded due to the limited number.

Table 4. Summary of prognostic significance for survival evaluated according to multivariate logistic regression analysis by the forward step-wise method

Factors		No. of patients (No. of deaths)	P-value	Odds ratio	95% confidence interval
ALP	Positive vs. negative	7 (5)/49 (6)	0.0049	13.745	2.213– 85.370
M classification	M1 vs. M0	10 (8)/46 (3)	0.0001	34.007	5.693–203.136
N classification	N1+2 vs. N0	5 (4)/51 (7)	0.0216	24.661	1.600–380.229
Symptoms	Symptomatic vs. asymptomatic	29 (9)/27 (2)	0.3559		
Tumor grade	2+3 vs. 1	22 (8)/34 (3)	0.2491		
Tumor infiltration	$\beta+\gamma$ vs. α	9 (6)/47 (5)	0.4319		
Tumor size	70 mm≦ vs. <70 mm	24 (9)/32 (2)	0.9424		

No other prognostic factors could be added to the multivariate logistic analystis since each P-value was greater than 0.05.

The prognostic factors that were significant for survival by univariate analysis were presenting symptoms, CRP, ESR, ALP, tumor size, pathological tumor grade, infiltration pattern, pathological tumor stage, N classification and M classification (Table 2, 3).

Among significant factors by univariate analysis, CRP and ESR were excluded from the multivariate analysis because of too much missing data. We selected 3 variables (ALP, N stage and distant metastasis) for Cox's proportional hazard model analysis by step-wise procedure to determine the value for survival. M classification was the most significant factor for survival (Table 4).

DISCUSSION

Numerous studies to identify morphologic and pathologic features that relate to the survival of patients treated for renal cell carcinoma have been published[1~9]. However, we investigated the prognostic factors influencing survival by univariate and multivariate analysis retrospectively.

Pathological tumor stage is the most significant variable identified as determining survival[1,3,5,6,8]. Patients with organ-confined disease removed surgically exhibit better prognosis than those with either lymph node involvement or distant metastasis[7] In addition to tumor stage, prognostic factors such as nuclear grade[9], histological pattern[7], cell type[11], and DNA content[12] have been reported to influence survival at various degrees. Demographic features, such as sex[11], performance status[1] and certain presenting symptoms[9] have also been implicated.

In our univariate analysis, presenting symptoms, CRP, ESR, ALP, tumor size, pathological tumor grade, infiltration pattern, pathological tumor stage, N classification and M classification were significant factors related to survival. For the multivariate analysis, we selected 7 factors that were significantly related to survival by the univariate analysis. Because 40% of CRP and ESR data were unavailable, we excluded them from the multivariate analysis. Among various pathological factors, pathological tumor stage is strongly related to T classification, N classification and M classification, so we excluded this factor even though it is generally regarded as an important factor for survival in renal cell carcinoma. The results of our multivariate analysis identified ALP, N classification and distant metastasis as significantly important predictors of survival, with distant metastasis being the most important.

Patients with distant metastasis have a dismal prognosis, with 5-year survival rates of 5% to 10%[13,14] Many investigators have tried to identify prognostic factors within the group of patients with distant metastasis in the hope of salvaging the better prognostic patient by aggresive immunotherapy or surgery. Site of metastasis, the number of metastatic lesions, the grade of primary tumor and associated weight loss have been reported to impact survival[13,14] According to the previous reports, a selected group of patients who are good surgical candidates with only a small number of metastatic lesions amenable to definitive therapy may benefit from nephrectomy or surgical extirpation of small-volume metastatic lesions[13,14] Although the small number of patients and short follow-up period made it difficult to evaluate the surgical therapy for our patients with metastatic disease, the results of the multivatiate analysis helped us to reflect on the selection of surgical candidates who have distant metastasis.

We consider that nodal involvement has an adverse impact on survival, but, the benefits of a lymphadenectomy are controversial. Bassil et al.[15] reported a retrospective analysis of 252 patients with renal cell carcinoma and compared the survival rate of the patients who underwent radical nephrectomy with that of those who underwent radical nephrectomy and extensive lymphadenectomy. The statistical differences between the two groups were not significant. Although Golimbu et al.[7] showed an improvement in survival associated with lymphadenectomy, the data was insufficient, and it was impossible to acertain whether the lymphadenectomy affectd survival.

Elevation of serum ALP is one manifestation of paraneoplastic syndrome in renal cell carcinoma with an estimated incidence of 10–20%. Chuang et al.[16] showed a prognostic significance of paraneoplastic serum ALP elevation with a statistical difference between normal and elevated serum ALP for overall survival in cases of renal cell carcinoma. Seven of our patients had elevation of serum alkaline phosphatase. Among them, two patients had bone metastasis. Even if we excluded them from statistical analysis, the statistical difference between normal and abnormal serum ALP for overall survival was significant ($p=0.0019$). In this respect, serum ALP may be regarded as a tumor marker in renal cell carcinoma.

In conclusion, our data suggest that distant metastasis is the most significant factor for survival, and three factors ALP, N classification and M classification, were interrelated statistically.

CONCLUSION

We evaluated the prognostic determinants for survival of 62 patients who underwent surgery for renal cell carcinoma at Himeji National Hospital. According to multivariant analysis, ALP, N classification and M classification were statistically significant for survival with M classification being the most significant factor.

REFERENCES

1) van der Poel HG, Muldeus PFA, Oosterhof GON, et al.: Prognostic value of karyometric and clinical characteristics in renal cell carcinoma. Cancer **72**: 2667–2674, 1993
2) Takahashi M, Nakano Y, Sakata T, et al.: Multivariate evaluation of prognostic determinants for renal cell carcinoma. Urol Int **50**: 6–12, 1993
3) Inomiya H, Isaka S, Okuno T, et al.: Prognostic factors in patients with non-metastatic renal cell carcinoma. Jpn J Urol **87**: 1099–1104, 1996
4) Satomi Y, Fukuda M, Hosaka M, et al.: Prognosis in 550 cases with renal cell carcinoma. Jpn J Urol **79**: 853–863, 1988
5) Giberti C, Oneto F, Martorana G, it al.: Radical nephrectomy for renal cell carcinoma: long-term results and prognostic factors on a series of 328 cases. Eur Urol **31**: 40–48, 1997
6) Masuda H, Kurita Y, Sudoko H, et al.: Prognostic factors after curative surgery for renal cell carcinoma: multivartiate analysis of 260 patients. Int J Clin Oncol **2**: 35–39, 1997
7) Golimbu M, Joshi P, Sperber A, et al.: Renal cell carcinoma: survival and prognostic factors. Urology **27**: 291–301, 1986
8) Thrasher JB and Paulson DF: Prognostic factors in renal cell cancer. Urol Clin North Am **20**: 247–262, 1993
9) Selli C, Hinshaw WM, Woodard BH, et al.: Stratification of risk factors in renal cell carcinoma. Cancer **52**: 899–903, 1983
10) Japanese Urological Association, Japanese Society

of Pathology and Japan Radiological Society: General Rules for Clinical and Pathological Studies on Renal Cell Carcinoma. 3rd ed., Kanahara Press, Tokyo, 1999

11) Dinney CN, Awad SA, Gajewski JB, et al.: Analysis of imaging modalities, staging systems, and prognostic indicators for renal cell carcinoma. Urology **39**: 122–129, 1992

12) Ljungberg B, Stenling R and Roos G: DNA content and prognosis in renal cell carcinoma: a comparison between primary tumors and metastases. Cancer **57**: 2346–2350, 1986

13) Maldazys JD and deKernion JB: Prognostic factors in metastatic renal carcinoma. J Urol **136**: 376–379, 1986

14) Neves RJ, Zincke H and Taylor WF: Metastatic renal cell cancer and radical nephrectomy: identification of prognostic factors and patient survival. J Urol **139**: 1173–1176, 1988

15) Bassil B, Dosoretz DE and Prout GR Jr: Validation of the tumor, nodes and metastasis classification of renal cell carcinoma. J Urol **134**: 450–454, 1985

16) Chuang Y-C, Lin ATL, Chen K-K, et al.: Paraneoplastic elevation of serum alkaline phosphatase in renal cell carcinoma: incidence and implication on prognosis. J Urol **158**: 1684–1687, 1997

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和文抄録

国立姫路病院にて原発巣に外科的治療を施行した腎細胞癌の予後因子に関する統計学的解析

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1992年1月から1998年10月までに，国立姫路病院にて原発巣に対し外科的治療を施行した62症例を対象に，その臨床的，病理学的予後因子の統計学的解析を行った．平均観察期間は32カ月であった．全体の1，3，5年疾患特異的生存率はそれぞれ86.7，81.3，81.3%であった．観察期間中，癌死した症例は11例（17.7%）で，2例（3.2%）は他因死した．単変量解析の結果，症状の有無，CRP，ESR，ALP，腫瘍径，組織学的細胞異型度，組織学的浸潤増殖様式，病理学的病期，N分類，M分類が有意な予後因子であったが，多変量解析では，ALP，N分類，M分類のみで有意に予後に関与しており，M分類が最も危険な因子であった．

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