Ⅳ.　研究成果の刊行（平成 25 年度）に関する一覧

様式第１９

学　会　等　発　表　実　績

委託業務題目「微小血管ネットワークを可視化する光音響画像化技術を用いた
前立腺がん検出システムの開発」

機関名　石原 美弥

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
深部機能画像診断のための光音響画像化技術の有用性検証	石原美弥	平成26年度厚生労働科学研究事業研究成果発表会	2015年2月	国内
Development of photoacoustic imaging technology overlaid on ultrasound imaging and its clinical application	Ishihara M, Tsujita K, Horiguchi A, Irisawa K, Komatsu T, Ayaori M, Hirasawa T, Kasamatsu T, Hirota K, Tsuda H, Ikewaki K, Asano T	SPIE Photonics West Biomedical Optics, BiOS 2015	2015年2月	国外
Photoacoustic imaging of small organic molecule-based photoacoustic probe in subcutaneous tumor using P(VDF-TrFE) acoustic sensor	Hirasawa T, Okawa S, Kamiya M, Urano Y, Ishihara M	SPIE Photonics West Biomedical Optics, BiOS 2015	2015年2月	国外
Influence of the light propagation models on a linearized photoacoustic imagereconstruction of the light absorption coefficient	Okawa S, Hirasawa T, Kushibiki T, Ishihara M	SPIE Photonics West Biomedical Optics, BiOS 2015	2015年2月	国外

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
State of the art photoacoustic measurements in biomedical application	Ishihara M	14th Japanese-American Frontiers of Science (JAFoS) Symposium	2014年12月	国外
統計学的モデルを用いた前立腺拡散MRI	新本弘	パラレルイメージングシンポジウム	2014年12月	国内
超音波画像に重畳でき、機能画像診断を可能にする光音響画像化技術の泌尿器科応用	石原美弥，辻田和宏，堀口明男，笠松直史，広田和弘，入澤覚，津田均，新本弘，浅野友彦	日本超音波医学会第41回関西地方会学術集会	2014年11月	国内
前立腺癌のMRI診断　-放射線科医が知っておくべきこと-	新本弘	城南ラジオロジー講演会	2014年11月	国内
安全確実に頚動脈内膜剥離術を完遂するための当院における手術戦略と治療成績	大谷直樹，和田孝次郎，長田秀夫，上野英明，戸村哲，富山新太，平沢壮，石原美弥，森健太郎	第73回日本脳神経外科学会総会	2014年10月	国内
【シンポジウム】生命科学研究における光音響イメージング技術	石原美弥	第23回日本バイオイメージング学会学術集会	2014年9月	国内

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
前立腺腹側癌におけるT2WI＋ADC mapの診断能：背側癌との比較	新本弘，田村千春，曽我茂義，岡村哲平，山田謙太郎，江戸博美，中森貴俊，加地辰美，堀口明男，浅野友彦	第42回日本磁気共鳴医学会大会	2014年9月	国内
前立腺癌の精嚢上皮内浸潤は，前立腺内精嚢／射精管からの進展よりも前立腺外精嚢筋層からの直接浸潤によって起こる	宮居弘輔，Kristiansen A，Egevad L，Pina-viedo S，Divatia MK，Shen SS，Ayala AG，Ro JY，津田均	第73回日本癌学会総会	2014年9月	国内
金ナノ粒子を用いた光音響信号増強に関する基礎的検討	石原美弥，平沢壮，佐藤良太，大川晋平，寺西利治	第2回光超音波画像研究会	2014年8月	国内
乳腺Ki-67計測定量化のための画像解析手法の検討	山下慶子，喜友名朝春，津田均，山口雅浩	第33回日本医用画像工学会大会(JAMIT2014)，2014.07.	2014年7月	国内
精巣胚細胞腫瘍の発生・進展過程におけるfatty acid synthaseの過剰発現の意義	宮居弘輔，岩屋啓一，玉井誠一，松原修，津田均	第103回日本病理学会総会	2014年4月	国内

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
Development of photoacoustic imaging technology overlaid on ultrasound imaging and its clinical application	Ishihara M, Tsujita K, Horiguchi A, Irisawa K, Komatsu T, Ayaori M, Hirasawa T, Kasamatsu T, Hirota K, Tsuda H, Ikewaki K, Asano T	Proceedings of SPIE [Epub ahead of print]	2015年3月	国外
Photoacoustic imaging of small organic molecule-based photoacoustic probe in subcutaneous tumor using P(VDF-TrFE) acoustic sensor	Hirasawa T, Okawa S, Kamiya M, Urano Y, Ishihara M	Proceedings of SPIE [Epub ahead of print]	2015年3月	国外
Influence of the light propagation models on a linearized photoacoustic imagereconstruction of the light absorption coefficient	Okawa S, Hirasawa T, Kushibiki T, Ishihara M	Proceedings of SPIE [Epub ahead of print]	2015年3月	国外
Image reconstruction of the absorption coefficients with l_1-norm minimization from photoacoustic measurements	Okawa S, Hirasawa T, Kushibiki T, Ishihara M	Quantitative Imaging in Medicine and Surgery, 5(1), p.78-85.	2015年2月	国外
深部機能画像診断のための光音響画像化技術の有用性検証	石原美弥	平成26年度厚生労働科学研究事業研究成果発表会, p.109-123.	2015年2月	国内

掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
Development of photoacoustic imaging technology for clinical applications	Ishihara M	11tn Igakuken International Symposiumu on Advances in Biomedical Optical Imaging Program & Abstracts, p. 23-24.	2015年2月	国内
分光を利用した光音響イメージング	石原美弥	電気学会研究会資料 光･量子デバイス研究会 OQD-15-007, p. 27-29.	2015年1月	国内
バイオメディカル・フォトニクス応用技術２ 2.3 光音響イメージング	石原美弥, バイオメディカル・オプティクス先端技術協同研究委員会編	電気学会技術報告 第1328号, p. 14-18.	2015年1月	国内
Clinical characteristics and prognosis of patients with renal cell carcinoma and liver metastasis	Hamada S, Ito K, Kuroda K, Sato A, Asakuma J, Horiguchi A, Seguchi K, Asano T	Molecular and Clinical Oncology, 3(1), p. 63-68.	2015年1月	国外
Tumor necrosis is a strong predictor for recurrence in patients with pathological T1a renal cell carcinoma	Ito K, Seguchi K, Shimazaki H, Takahashi E, Tasaki S, Kuroda K, Sato A, Asakuma J, Horiguchi A, Asano T	Oncology Letters, 9(1), p. 125-130.	2015年1月	国外

掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
Clinical significance of p21-activated kinase 1 expression level in patients with upper urinary tract urothelial carcinoma	Kuroda K, Asakuma J, Horiguchi A, Isono M, Tsujita Y, Sato A, Seguchi K, Ito K, Asano T	Japanese Journal of Clinical Oncology, 45(1), p.103-110.	2015年1月	国内
光音響イメージングの臨床価値を図る	石原美弥	超音波TECHNO, 26(6), p.21-24.	2014年12月	国内
Anterior Prostate Cancer: Diagnostic Performance of T2-weighted MR Imaging and Apparent Diffusion Coefficient Map	Shinmoto H, Tamura C, Soga S, Okamura T, Horiguchi A, Asano T, Kaji T	AJR Am J Roentgenol, [Accepted manuscript]	2014年12月	国外
Prognostic value of the number and size of venous invasions in pT3 colorectal cancer: A prospective observational study	Shinto E, Tsuda H, Ueno H, Shimazaki H, Yamamoto J, Hase K	World J. Surg, 38(12), p.3257-3264.	2014年12月	国外
Diffusion-weighted imaging of prostate cancer using a statistical model based on the gamma distribution	Shinmoto H, Oshio K, Tamura C, Soga S, Okamura T, Yamada K, Kaji T, Mulkern RV	J Magn Reson Imaging, doi. 10.1002/jmri.24761, [Epub ahead of print]	2014年9月	国外
Interpretation of diffusion MRI data using a gamma distribution model	Oshio K, Shinmoto H, Mulkern RV	Magn Reson Med Sci, 13(3), p.191-195.	2014年9月	国外

掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
Diffusion kurtosis imaging study of prostate cancer: Preliminary findings	Tamura C, Shinmoto H, Soga S, Okamura T, Sato H, Okuaki T, Pang Y, Kosuda S, Kaji T.	J Magn Reson Imaging, 40(3), p.723-729.	2014年8月	国外
The expression and clinical significance of connective tissue growth factor in advanced head and neck squamous cell cancer	Kikuchi R, Kikuchi Y, Tsuda H, Maekawa H, Kozaki K, Imoto I, Tamai S, Shiotani A, Iwaya K, Sakamoto M, Sekiya T, Matsubara O	Human Cell, 27(3), p.121-128.	2014年7月	国内
Histological growth pattern of and alpha-Actinin-4 expression in thyroid cancer	Tanaka N, Yamashita T, Yamamoto S, Tsuda H, Matsunobu T, Honda K, Yamada T, Tamai S, Shiotani A	Anticancer Res. 34(6), p.3157-3163.	2014年6月	国外
Widespread local extension and higher proliferation indices are characteristic features of symptomatic lobular neoplasias (LNs) and LNs with early invasive component	Katsurada Y, Yoshida M, Miyagi-Maeshima A, Ikeda K, Shibata T, Kinoshita T, Tsuda H	Histopathology, 64(7), p.994-1003.	2014年6月	国外

V. 研究成果の刊行・別刷

Clinical characteristics and prognosis of patients with renal cell carcinoma and liver metastasis

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Abstract. The prognosis of patients with renal cell carcinoma (RCC) and liver metastasis (LM) is poor. We evaluated the clinical characteristics, prognosis and prognostic factors of RCC patients with LM. A total of 25 patients who underwent radical or partial nephrectomy (Nx) for RCC between November, 1980 and April, 2013 at the National Defense Medical College, Tokorozawa, Saitama, Japan, with LM at initial presentation or following Nx, were included in this study. The association between prognosis following development of LM and clinicopathological parameters was analyzed. The Cox proportional hazards regression model was used to identify prognostic predictors. The median cancer-specific survival (CSS) following LM diagnosis was 10.6 months. The presence of sarcomatoid differentiation, Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2, C-reactive protein ≥1.0 mg/dl, corrected calcium ≥10 mg/dl and presence of multiple organ metastases, were identified as CSS predictors. The multivariate analysis identified ECOG PS ≥2 as an independent CSS predictor. Nine patients survived for >20 months following LM diagnosis and 1 patient, who received treatment with tyrosine kinase inhibitors (TKIs) for LM, exhibited stable disease for 5 years. Nine patients underwent local LM treatment. Two patients, who underwent hepatic resection, survived for 55.1 and 22 months, respectively. In conclusion, RCC patients with LM may benefit from local LM treatment if they have a limited number of metastases in addition to LM and if their ECOG PS is satisfactory. Indeed, a proportion of RCC patients with LM benefit from TKI therapy. Furthermore, RCC patients with LM and ECOG PS ≥2 apparently have a poor prognosis, regardless of local or systemic therapies.

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Key words: renal cell carcinoma, liver metastasis, prognosis, local treatment, tyrosine kinase inhibitor

Introduction

Approximately 30% of patients with renal cell carcinoma (RCC) exhibit distant metastasis at initial presentation, whereas a further 30% of the patients develop metastases following nephrectomy (Nx) (1). RCC patients develop metastases at various sites, including the lungs, lymph nodes, bone, brain and liver and their prognosis depends on the metastatic site. The frequency of liver metastasis (LM) in RCC patients is lower compared to that of metastasis to other sites, such as the lungs, lymph nodes and bone. The rate of LM was reported to be 9.3-18% (2-5). The prognosis of RCC patients with LM is poor and the median overall survival is 7.6-12 months, which is shorter compared to that of patients with metastasis to other sites (2-4). Patients with metastatic RCC were treated with interferon and/or interleukin-2 during the cytokine era; however, the response rate to cytokine therapy was reportedly only 10-20% (4). Cytokine therapy was occasionally effective for lung or lymph node metastases; however, it was generally not effective for liver, brain and bone metastases. Local treatments are reportedly effective in certain RCC patients with bone and brain metastases (6,7). Combination therapy with radiation and zoledronic acid was shown to decrease the rate of skeletal-related events in RCC patients; reossification was also reported in some patients (8). γ-knife surgery achieves good local control of brain metastasis from RCC. This procedure improves peritumoral edema and the survival rate of patients with multiple brain metastases (6,9). A definitive treatment for LM in RCC patients, however, has not been established. At present, tyrosine kinase inhibitors (TKIs) are used to treat metastatic RCC and the response is expected to be adequate when TKIs are used for organ metastases such as LM and brain metastases, which are considered to be extremely refractory to cytokine therapy (10,11). LM from RCC may grow rapidly and become life-threatening. Local treatments for LM may be beneficial for RCC patients. Long-term survival following surgical resection of a solitary LM was reported in RCC patients (12,13), although the efficacy of local treatments, such as surgical resection, radiofrequency ablation and transarterial embolization, was not fully evaluated. To the best of our knowledge, the number of studies focusing on the treatment of LM from RCC is currently limited.

In the present study, we evaluated the clinical characteristics, prognosis and prognostic factors in RCC patients with LM. We also aimed to determine the characteristics of RCC

Table I. Clinicopathological characteristics of 25 patients with liver metastasis (LM).

Variables	Values, mean ± SD
Gender	
Male	21
Female	4
Age at Nx, years (range)	59.4±12.4 (30-77)
Age at diagnosis of LM, years (range)	62.6±12.1 (30-79)
Tumor side[a]	
Right	9
Left	16
Tumor size[a], cm (range)	9.9±4.3 (3.5-18)
Cell type[a]	
Clear cell	24
Chromophobe	1
Histological grade[a]	
1	0
2	4
3	21
Fuhrman grade[a]	
1	0
2	0
3	6
4	18
NA	1
pT stage[a]	
1a	0
1b	8
2a	1
2b	4
3a	3
3b	4
3c	0
4	5
MVI[a]	
+	20
-	5
Tumor necrosis[a]	
+	14
-	11
No. of LM[b]	
Solitary	7
Multiple	14
NA	4
ECOG PS[b]	
0	12
1	3
2	2
3	5
4	1
NA	2
Hemoglobin[b], g/dl (range)	10.3±2.2 (6.1-13.5)
Platelet count[b], x10^4/mm^3 (range)	27.9±9.8 (5.8-43.8)
CRP[b], mg/dl (range)	6.8±8.3 (0.3-28)
LDH[b], IU/l (range)	323.9±286.3 (110-1,138)
Corrected calcium[b], mg/dl (range)	8.6±3.4 (8.4-12.7)

[a]Primary lesion. [b]At the diagnosis of LM. SD, standard deviation. Nx, nephrectomy; NA, not available; MVI, microvascular invasion; ECOG PS, Eastern Cooperative Oncology Group performance status; CRP, C-reactive protein; LDH, lactate dehydrogenase.

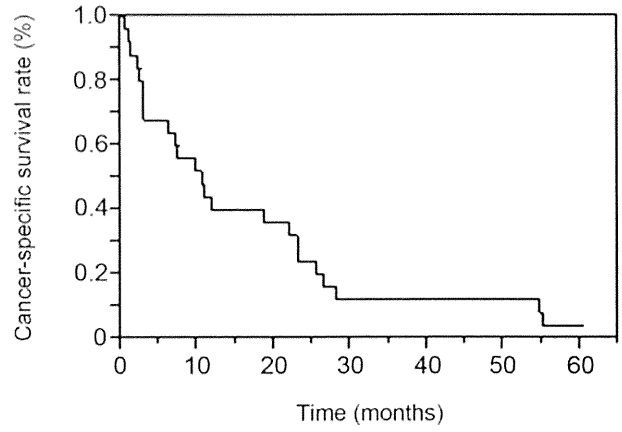

Figure 1. Cancer-specific survival of 25 patients with liver metastasis from renal cell carcinoma. The Kaplan-Meier method revealed 1-, 2- and 3-year survival rates of 40, 24 and 12%, respectively.

patients with LM who survived over a relatively long period, with particular focus on the clinical results of local treatments for RCC with LM.

Materials and methods

Patients and design. We retrospectively reviewed the records of all the patients who underwent radical nephrectomy (RNx) or partial Nx for RCC between November, 1980 and April, 2013 at the National Defense Medical College, Tokorozawa, Saitama, Japan. Our cohort included 25 patients (21 men and 4 women; age at Nx, 59.4±12.4 years; range, 30-77 years) with LM at initial presentation or who developed LM following Nx. The clinicopathological factors were assessed for each patient using the patient database or clinical records. The factors evaluated included gender, age, treatment after LM presentation, Eastern Cooperative Oncology Group performance status (ECOG PS), histological characteristics, tumor grade, Fuhrman grade, microvascular invasion, histological tumor necrosis, sarcomatoid differentiation and biochemical parameters, such as hemoglobin level, platelet count, lactate dehydrogenase level, corrected calcium (Ca) level and C-reactive protein (CRP) level. All 25 patients underwent RNx. Local recurrence and metastases were monitored by postoperative examination of each patient every 3-6 months for the first 5 years and every 6-12 months thereafter. The follow-up included physical examination, laboratory tests, chest radiography, abdominal

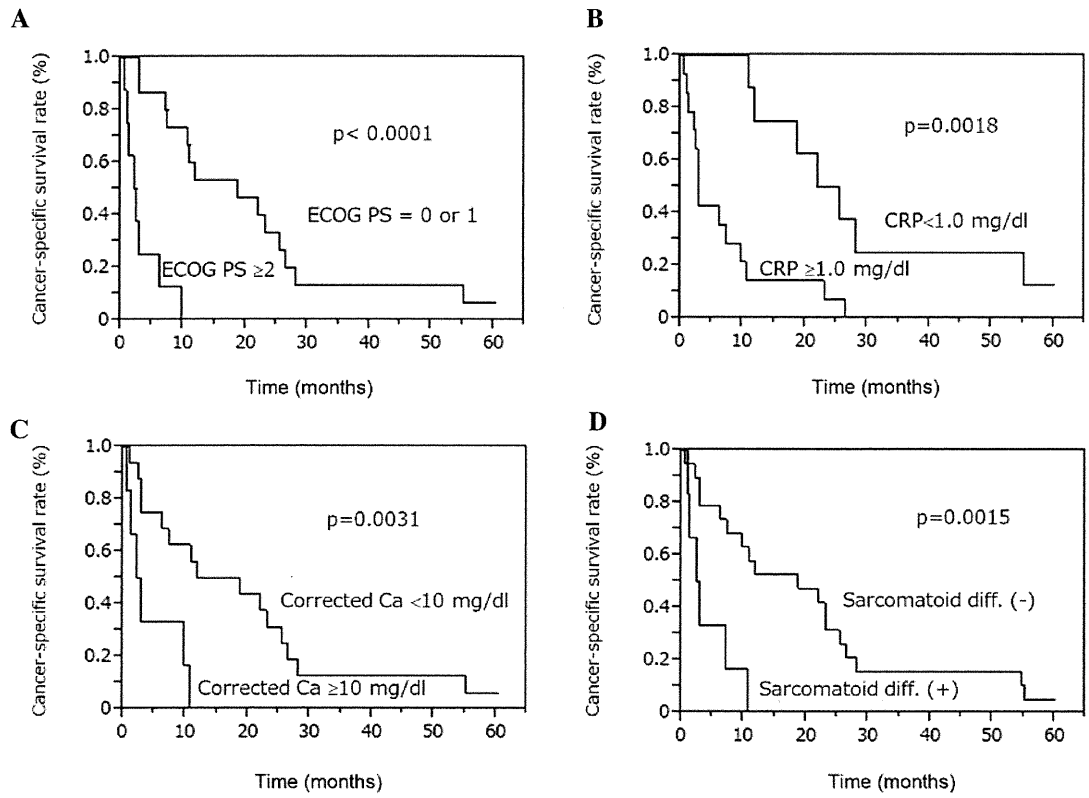

Figure 2. Cancer-specific survival rates for patients with liver metastasis from renal cell carcinoma. The Kaplan-Meier method revealed that patients with (A) ECOG PS ≥2, (B) CRP level ≥1.0 mg/dl, (C) corrected Ca level ≥10 mg/dl and (D) presence of sarcomatoid differentiation exhibited low cancer-specific survival rates. ECOG PS, Eastern Cooperative Oncology Group performance status; CRP, C-reactive protein; Ca, calcium.

and chest computed tomography (CT) and, if indicated, radionuclide bone scanning. LM was confirmed using CT or magnetic resonance imaging in all the patients. The median follow-up duration was 28.9 months (range, 2.7-180.1 months). Cancer-specific survival (CSS) was calculated from the date of Nx to the date of death or the date of the last follow-up. Tumor staging was performed according to the 2009 TNM classification of the Union for International Cancer Control (14). Tumor grades were assigned according to the General Rules for Clinical and Pathological Studies on Renal Cell Carcinoma in Japan (3-grade system) (15). Furmann nucleolar grading was also performed (16). This study was approved by the Ethics Committee of the National Defense Medical College (no. e-253). Consent was obtained for use of patient data.

Statistical analysis. All the calculations were performed using JMP 9.0 software for Windows (SAS Institute Inc., Cary, NC, USA). The results are expressed as means ± standard deviation. The CSS rates were calculated using the Kaplan-Meier method and compared using the log-rank test. $P<0.05$ was considered to indicate a statistically significant difference. The associations of clinicopathological parameters with death from RCC were assessed using the Cox proportional hazards regression model and summarized as hazard ratios (HRs) and 95% confidence intervals (CIs).

Results

Patient characteristics. The clinicopathological characteristics of the patients are listed in Table I. The histopathological types were clear cell RCC in 24 cases and chromophobe RCC in 1 case. A total of 21 patients (84%) had histological grade 3 disease, while 24 (96%) had grade ≥3 disease according to the Fuhrman classification. The mean age at LM diagnosis was 62.6±12.1 years (range, 30-79 years). The interval from Nx to LM appearance was 38.1±55.9 months (range, 0-175.3 months) and the follow-up period between LM appearance and outcome was 16.6±17.6 months (range, 0.4-60.2 months). LM was present at the time of Nx in 8 and developed following Nx in 17 patients. The median CSS following LM diagnosis was 10.6 months. The patient survival rates at 1, 2 and 3 years were 40, 24 and 12%, respectively (Fig. 1).

Factors affecting prognosis. We next attempted to identify the clinical factors affecting the prognosis of RCC patients with LM. The Kaplan-Meier method revealed that the CSS rates were lower in patients with sarcomatoid differentiation (P=0.0015), ECOG PS ≥2 (P<0.0001), CRP levels ≥1.0 mg/dl (P=0.0018) and corrected Ca levels ≥10 mg/dl (P=0.0031; Fig. 2). CSS was not significantly different between patients with LM at presentation and those who developed LM following Nx (P=0.1102), between patients with LM alone and those with multiple organ metastases (P=0.0578), between patients who were treated with TKIs and those who were not (P=0.7848) and between patients who underwent hepatic resection and those who did not (P=0.0912) (data not shown).

Univariate analysis of clinicopathological parameters and CSS. The results of the univariate analysis for the association between clinicopathological parameters and CSS are presented

Table II. Univariate analysis for cancer-specific survival following development of liver metastasis (LM).

Clinicopathological factors	P-value
Age[a], years (60> vs. 60≤)	0.1172
Sarcomatoid differentiation[b] (+ vs. -)	0.0067
Histological grade 3[b] (+ vs. -)	0.2898
Fuhrman grade[b] (<3 vs. 4)	0.4066
MVI[b] (+ vs. -)	0.9872
Tumor necrosis[b] (+ vs. -)	0.8618
Tumor size[b] (<10 vs. ≥10 cm)	0.9160
pT1 or 2 vs. pT3 or 4[b]	0.3196
Presence of LM at Nx (yes vs. no)	0.0992
No. of LM at presentation (1 vs. ≥2)	0.4447
ECOG PS[a] (0 or 1 vs. 2≤)	0.0002
CRP[a] (<1.0 vs. ≥1.0 mg/dl)	0.0019
LDH[a], IU/l (<338 vs. ≥338)	0.9019
Hemoglobin[a] (anemia vs. normal)	0.1704
Platelet count[a] (<35x10^4 vs. ≥35x10^4/mm^3)	0.3434
Corrected calcium[a] (<10 vs. ≥10 mg/dl)	0.0100
LM only (yes vs. no)	0.0367
Tyrosine kinase inhibitors (yes vs. no)	0.8848
Cytokine therapy (yes vs. no)	0.7278
Local treatment (yes vs. no)	0.8373
Hepatic resection (yes vs. no)	0.0528
Interval from Nx to LM, months (<24 vs. ≥24)	0.4218

[a]At the time of LM. [b]Primary lesion. MVI, microvascular invasion; Nx, nephrectomy; ECOG PS, Eastern Cooperative Oncology Group performance status; CRP, C-reactive protein; LDH, lactate dehydrogenase.

in Table II. The presence of sarcomatoid differentiation (P=0.0067), ECOG PS ≥2 (P=0.0002), CRP levels ≥1.0 mg/dl (P=0.0019), corrected Ca levels ≥10 mg/dl (P=0.0100) and presence of multiple organ metastases (P=0.0367) were identified as CSS predictors. The multivariate analysis (Table III) demonstrated that ECOG PS ≥2 (P=0.0063; HR=6.46; 95% CI: 1.67-32.8) was an independent CSS predictor.

Patients exhibiting long-term survival following LM. The characteristics of the 9 patients who survived for >20 months following LM diagnosis are summarized in Table IV. The longest survival time following development of LM was 60.2 months. Two patients who received treatment with TKIs for LM survived for ≥23 months. One patient remains alive after 5 years on sunitinib treatment, with prolonged stable disease. Another patient was treated with sorafenib for multiple metastases, including LM; however, the LM progressed. Two patients who received cytokine therapy for multiple organ metastases survived for >2 years and their tumors did not contain a high-grade component (both grade 2). Two patients who underwent hepatic resection and had no metastases to other organs survived for ≥22 months and one of these two patients survived for 55.1 months. One patient who received intra-arterial injection of styrene-maleic acid neocarzinostatin (SMANCS) and lipiodol (SMANCS/lipiodol) for LM treatment remained alive at 25.3 months. All the patients who survived for >20 months had ECOG PS ≤1.

Outcome with local treatment for LM. The characteristics of the 9 patients who underwent local treatment for LM are summarized in Table V. In patients 1 and 3, metastases were identified only in the liver and were completely eliminated; the survival duration was 55.1 and 22 months, respectively, as described above. Three patients who received local treatments but whose ECOG PS was >2 only survived for a short period of time. These data suggest that local treatment may be ineffective in patients with a poor ECOG PS. Four patients undergoing local treatment survived for >18 months. In those patients, the number of metastatic sites (patients 1, 2, 3 and 4) was relatively small. Two patients had a solitary LM, 1 had LM and local recurrence and 1 had LM, as well as lung and lymph node metastases.

Discussion

The prognosis of RCC patients with LM is extremely poor. Due to the poor prognosis, the clinical characteristics and treatment for LM have not been extensively investigated. Long-term survivors are rare among RCC patients with LM. However, it is crucial to investigate patients who have benefited from treatments such as local therapy and molecular-targeted therapy. During the cytokine era, there was no effective drug therapy for LM from RCC. TKIs are currently used for patients with metastatic RCC and patients with LM who have responded to TKIs have been reported (10,17). In the present study, 9 patients (36%) survived for ≥22 months following LM diagnosis. Of those 9 patients, 5 were treated with local LM therapies or TKIs. Local treatments and TKIs appeared to improve the prognosis of some RCC patients with LM. The multivariate analysis demonstrated that only ECOG PS ≥2 was an independent CSS predictor; therefore, patients with LM and ECOG PS ≥2 have a poor prognosis, even if they are treated with local and/or systemic therapies, including TKIs.

In this study, we observed that the median CSS following LM appearance was 10.6 months. In previous studies, the median CSS following LM was 7.6-12.6 months (2-4), while the 1-year survival was 38.3% (2). Those results are similar to ours. In the present study, however, we excluded patients who could not undergo Nx due to their deteriorated general condition caused by far-advanced disease, whereas the median CSS was only 10.6 months, indicating that the prognosis of RCC patients with LM is poor.

According to the multivariate analysis, ECOG PS ≥2 at LM appearance was an independent predictor of a shorter CSS. Among RCC patients with LM, those with a poor ECOG PS only survived for a short period of time. As shown in Table V, the 3 patients with ECOG PS ≥2 survived for <3 months following LM presentation. According to these results, all treatments appear to be ineffective for patients with ECOG PS ≥2.

In a proportion of patients with LM alone or a limited number of metastatic sites in addition to LM, local treatment of LM may prolong survival. We administered local treatments to 9 patients (36%) with LM (Table V) and their median

Table III. Univariate and multivariate analysis for cancer-specific survival following liver metastasis (LM).

	Univariate	Multivariate		
Variables	P-value	P-value	Hazard ratio	95% confidence interval
Sarcomatoid differentiation	0.0067	0.1759		
ECOG PS ≥2[a]	0.0002	0.0063	6.46	1.67-32.8
Multiple organ metastases	0.0367	0.3526		
CRP ≥1.0 mg/dl[a]	0.0019	0.3704		
Corrected calcium ≥10 mg/dl[a]	0.0100	0.3339		

[a]At the time of LM. ECOG PS, Eastern Cooperative Oncology Group performance status; CRP, C-reactive protein.

Table IV. Summary of the 9 cases who survived for >20 months following liver metastasis (LM).

Case	Age[a]/gender	ECOG PS[a]	CRP[a] (mg/dl)	Grade	Other metastatic sites at the time of LM	Treatment for LM	Survival after LM (months)
1	64/M	0	0.3	3	None	Sunitinib	60.2
2	61/M	1	0.6	3	None	Hepatic recection, Nx	55.1
3	71/F	NA	ND	3	Bone, lung	NA	54.6
4	54/M	0	0.6	2	Lung, pancreas, stomach, duodenum	Interferon-α	28.0
5	79/M	0	5.9	2	Lung	Interleukin-2	26.4
6	77/M	1	0.3	3	LR	SMANCS/lipiodol	25.3
7	57/F	0	28	3	Lung, bone, pleura, LN, cerebellum	Interferon-α, sorafenib	23.0
8	78/M	NA	ND	3	Lung	NA	23.0
9	77/M	1	0.6	3	None	Hepatic recection	22.0

[a]At the time of LM presentation. ECOG PS, Eastern Cooperative Oncology Group performance status; CRP, C-reactive protein; M, male; F, female; Nx, nephrectomy; NA, not available; ND, not determined; LR, local reccurence; SMANCS, stylene-maleic acid neocarzinostatin; LN, lymph node.

Table V. Summary of the 9 cases who underwent local treatment for liver metastasis (LM).

Case	Age[a]/gender	No. of LM[a]	ECOG PS[a]	Other metastatic sites	Treatment	Survival after LM (months)
1	61/M	2	1	None	Hepatic recection, Nx	55.1
2	77/M	3	1	LR	SMANCS/lipiodol	25.3
3	77/M	1	0	None	Hepatic recection	22.0
4	61/M	1	0	Lung, LN	SMANCS/lipiodol RFA	18.6
5	66/M	2	0	Pancreas, kidney, lung, jejunum	SMANCS/lipiodol	11.7
6	46/M	1	0	Lung, pleura, peritoneum, rib, pancreas, duodenum	TAE (lipiodol)	7.2
7	54/M	3	2	Lung, bone	RFA	2.8
8	45/F	1	2	Lung, bone, LN	SMANCS/lipiodol	2.3
9	64/M	3	4	LR, iliopsoas muscle	RFA	2.1

[a]At the time of LM presentation. ECOG PS, Eastern Cooperative Oncology Group performance status; M, male; F, female; Nx, nephrectomy; LR, local reccurence; SMANCS, stylene-maleic acid neocarzinostatin; LN, lymph node; RFA, radiofrequency ablation; TAE, transarterial embolization.

CSS was 11.7 months. The survival duration of patients with LM alone (patients 1 and 3) and those with LM and a limited number of additional metastases (patients 2 and 4) appeared to be longer compared to that of patients with far-advanced disease. We compared patients with LM alone to those with LM and metastases to other organ(s) and observed that CSS was longer in the former (median, 38.6 months) compared to that in the latter (median, 9.7 months), with the difference being borderline significant (P=0.0578). Two of the 4 patients (50%) with LM alone underwent local resection and their survival period following LM presentation was 55.1 and 22 months, respectively. LM from RCC occasionally grows rapidly and the patient's general condition deteriorates when LM becomes bulky. Therefore, local treatment of LM should be considered for patients with LM alone or those with LM and a limited number of additional metastases.

Two patients (patients 2 and 9; Table IV) survived for >20 months following hepatic resection for LM. Staehler *et al* (13) reported that the overall survival of RCC patients with LM alone who underwent hepatic resection was longer than that of those who did not undergo hepatic resection. Therefore, in RCC patients with LM alone, prognosis may be improved by hepatic resection. Furthermore, it was reported that in RCC patients, metachronous hepatic resection for LM prolonged overall survival compared to synchronous hepatic resection (18). Based on those reports, aggressive hepatic resection should be recommended if a radiological cancer-free status is achieved.

In the present study, the 2 patients who were treated with TKIs survived for >20 months. TKIs were used by 6 of the 25 patients (24%) following LM diagnosis. CSS was not significantly different between patients treated with TKIs and those who were not. However, 1 patient (case 1 in Table IV) appeared to benefit from TKI treatment, with the size of the LM remaining stable for 5 years. In the 2 patients who were treated with TKIs and survived for >20 months, ECOG PS was 0. A proportion of RCC patients with LM may indeed benefit from TKI treatment. Therefore, in patients with an ECOG PS of <1, TKI treatment may be a viable option.

Two patients received cytokine therapy for multiple metastases, including LM, and survived for >26 months. However, such patients are a rare finding. The histological grade of the primary lesions in those 2 patients was 2 (3-grade system), without a high-grade component. As the growth rate of the metastatic lesions is likely to be slow, such patients may survive over a long period of time on cytokine therapy alone.

There were several limitations to this study. First, this was a retrospective study conducted at a single institution with a small number of RCC patients with LM. LM is relatively rare in patients with RCC and it is difficult to collect a sufficient sample size at a single institution. Therefore, a multi-institutional joint study is required to verify our findings. Second, this study excluded patients who did not undergo Nx. There were certain patients with far-advanced RCC and LM who survived for only a short period of time. In addition, the efficacy of molecular-targeted therapies, including TKIs, for such patients mus be evaluated in the future. However, despite these limitations, our study may have generated useful clinical data on this understudied type of cancer.

In conclusion, RCC patients with LM may benefit from local treatment of LM, such as surgical resection, if they have a limited number of metastatic sites in addition to LM and if their ECOG PS is favorable and stable. Indeed, a proportion of RCC patients with LM benefit from TKI therapy. By contrast, RCC patients with LM and an ECOG PS ≥2 appear to have a poor prognosis, regardless of any local or systemic treatment.

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Tumor necrosis is a strong predictor for recurrence in patients with pathological T1a renal cell carcinoma

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Abstract. Patients with pT1aN0M0 renal cell carcinoma (RCC) generally have good prognosis, and recurrence is rare. However, metastasis develops postoperatively in a small number of patients with pT1aN0M0 RCC. The present study was undertaken to identify predictors for recurrence in patients with pT1aN0M0 RCC. We reviewed the clinicopathological factors of 133 patients with pT1aN0M0 RCC who underwent radical or partial nephrectomy at the Department of Urology, National Defense Medical College (Saitama, Japan). Clinicopathological factors, including age, gender, tumor size, histological subtype, tumor grade, microvascular invasion, histological tumor necrosis, C-reactive protein levels and performance status were reviewed. These factors were compared between patients with and without postoperative recurrence. Recurrence-free survival (RFS) and cause-specific survival (CSS) rates were calculated using the Kaplan-Meier method. Univariate and multivariate analyses were performed to determine independent factors predicting recurrence in patients with pT1aN0M0 RCC. The 5-year RFS and CSS rates were 97.2 and 99.1%, respectively. When clinicopathological factors were compared between patients with and without recurrence, tumor size (P=0.0390) and percentage of tumor necrosis (P<0.0001) were significantly different between groups. All patients with recurrence had primary lesions ≥3 cm. By univariate analysis, tumor size (P=0.0379) and the presence of tumor necrosis (P=0.0319) were significant predictors for recurrence; tumor necrosis was also an independent predictor for recurrence (P=0.0143). In patients with pT1b tumors ≤5 cm (recurrence rate, 16.8%; n=48), the percentage of tumor necrosis was significantly higher in patients with recurrence compared with those without (P=0.0261). This suggests that tumor necrosis may be an important predictor for recurrence in small RCCs. Although recurrence is rare in pT1a RCC, the presence of tumor necrosis may be an important predictor for recurrence. Particularly, patients presenting with pT1a RCC with histological tumor necrosis should undergo careful follow-up.

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Key words: renal cell carcinoma, pathological T1a, recurrence, predictor, tumor necrosis

Introduction

The prognosis of patients with T1aN0M0 renal cell carcinoma (RCC) is favorable, and recurrence is rare. Risk factors for recurrence in clinical T1a (cT1a) RCC have been previously evaluated (1-4). Takayama *et al* reported that symptomatic cancer, sarcomatoid component, and C-reactive protein (CRP) levels ≥0.4 mg/dl were risk factors for recurrence in cT1a RCC (1). In addition, Kume *et al* reported that microvascular invasion (MVI) was an independent predictor for distant metastasis of RCC with a diameter of ≤3 cm (2). Since patients with cT1a RCC include those with pathological T3a (pT3a) RCC, cT1a tumors theoretically, frequently include more aggressive tumors compared with patients with pT1a tumors. Although pT1a RCC tumors generally recur less frequently than cT1a, there are a small number of patients with pT1a disease recurrence.

Two studies have evaluated the predictors for recurrence in patients with pT1a RCC (5,6). Kim *et al* (5) revealed that MVI and tumor necrosis were independent predictors for recurrence. Nishikimi *et al* (6) evaluated RCC patients with clear cell RCC using multivariate analysis and found that Fuhrman grade, growth pattern and tumor necrosis were significantly associated with disease-free survival. As the majority of pT1a RCCs are less aggressive and recurrence is rare, longer follow-up intervals are generally accepted compared with RCCs at higher pathological stages (7). Kim *et al* (5) reported that 9 out of 93 pT1aN0M0 patients exhibited distant metastasis (mean follow-up duration, 63.6 months). Furthermore, Nishikimi *et al* (6) reported that 25 of 293 pT1aN0M0 patients exhibited distant metastasis (median follow-up duration, 62 months). If patients with pT1a RCC with a high risk of recurrence are identified, clinicians can monitor these patients closely and counsel them regarding the risk for recurrence.

The aim of the current study was to identify the risk factors for predicting recurrence in patients with pT1aN0M0 RCC. We evaluated the clinical characteristics of patients with pT1aN0M0 RCC in whom the disease recurred. In addition, we assessed the clinical characteristics of patients with pT1bN0M0 RCC ≤5 cm, who had a recurrence.

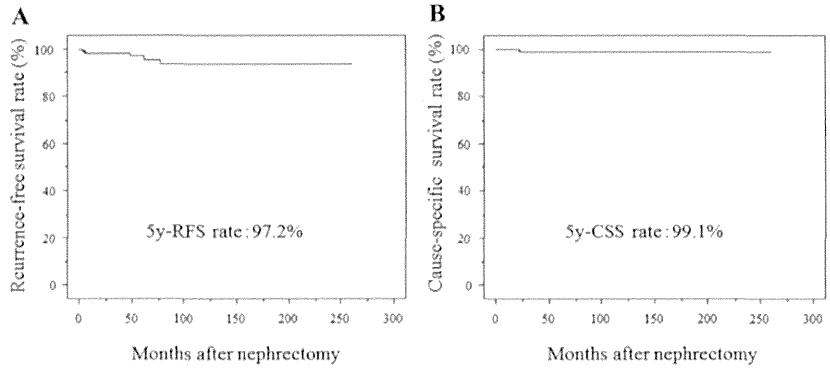

Figure 1. Kaplan-Meier curves analyzing recurrence-free survival (RFS) and cause-specific survival (CSS) in patients with pT1aN0M0 RCC. The 5-year (A) RFS and (B) CSS rates were 97.2 and 99.1%, respectively.

Patients and methods

We reviewed the medical records of patients with RCC undergoing radical nephrectomy (RN) or partial nephrectomy (PN) at the Department of Urology, National Defense Medical College (Saitama, Japan) between 1990 and 2011. The study cohort consisted of 133 patients in whom neither preoperative radiological or pathological examination of surgical specimens indicated distant or lymph node metastasis (N0M0 patients), and whose tumors were pathologically confirmed as pT1a. Of these patients, 101 underwent RN and 32 underwent PN. Their ages ranged from 32 to 89 years (mean, 60.8±12.2). Local recurrence and metastasis were monitored by examining each patient postoperatively at 3-6 month intervals for the first 5 years, and every 6-12 months thereafter. Follow-up included physical examination, laboratory tests, chest radiography, abdominal and chest computed tomography and, if necessary, radionuclide bone scanning. The total follow-up time ranged from 1 to 261 months (median, 57.8). Recurrence-free survival (RFS) was evaluated using the date at which local recurrence or metastatic disease was identified, and overall survival (OS) was determined using either the date of death or the date of the last follow-up examination.

The clinicopathological factors evaluated are listed in Table I, and included age, gender, tumor size, histological subtype, histological tumor grade, MVI, histological tumor necrosis, CRP levels, and Eastern Cooperative Oncology Group performance status (ECOG PS) (8). These factors were compared between patients with recurrence postoperatively (n=5, 3.8%), and those without (n=128). Tumors were staged according to the 2002 TNM classification system (9), and nucleolar grading in a three-grade system was determined (10). Tumor necrosis was defined as microscopic coagulative necrosis (6,11); the presence of necrosis that was apparent on gross examination was excluded. Preoperative elevation of CRP was defined as CRP ≥0.3 mg/dl, as previously described (12,13).

We also reviewed the clinicopathological factors of patients with pT1b tumors ≤5 cm, and of those with and without recurrence.

Statistical analysis. Results are presented as the mean ± standard deviation, and differences in variables between groups were compared using the Mann-Whitney U test. The independence of fit of categorical data was analyzed using the χ^2 test. Survival curves were constructed using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. To determine independent factors predicting recurrence in patients with pT1aN0M0 RCC, univariate and multivariate analyses were performed using the Cox proportional-hazards regression model. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Comparison of clinicopathological factors between patients with recurrence and those without.

Variables	Patients with rec. (n=5)	Patients without rec. (n=128)	P-value
Age (years)	61±12	67±8	0.2636
Gender (male/female)	3.2	91/37	0.5930
Side (right/left)	4/1	63/65	0.1769
Tumor size (cm)	3.5±0.4	2.8±0.7	0.0390
ECOG PS (0 vs. ≤1)	3/2	112/16	0.0778
Subtypes of RCC (clear cell vs. others)	5/0	112/6	0.6203
Grade 3 component (+ vs. -)	1/4	12/116	0.4325
MVI (+ vs. -)	2/3	18/110	0.1114
Tumor necrosis (+ vs. -)	3/2	4/124	<0.0001
CRP (>0.3 vs. ≤0.3)	2/3	14/113	0.0515

Rec., recurrence; ECOG PS, Eastern Cooperative Oncology Group performance status; RCC, renal cell carcinoma; MVI, microvascular invasion; CRP, C-reactive protein.

Results

Clinicopathological characteristics of patients with disease recurrence (Table I). Five out of 133 patients with pT1a (3.8%) exhibited disease recurrence (median follow-up, 57.8 months). The mean age of these five patients (three males and two females) was 60.8 years (56-75). Four patients underwent right nephrectomy and one underwent left nephrectomy. The mean diameter of the five tumors was 3.5 cm, and all were ≥3 cm. The ECOG PS in three patients was 0, in one patient was 1 and in the remaining patient was 3. Metastases were detected

Table II. Multivariate analysis for predicting recurrence in patients with pT1aN0M0 RCC (n=133).

	Univariate	Multivariate		
Variables	P-value	P-value	Odds ratio	Relative risk ratio 95% CI
Age	0.1591			
Gender	0.7189			
ECOG PS	0.1151			
Tumor side	0.2449			
Tumor size	0.0379	0.3622	2.355[a]	0.0373-14.866
Grade 3 component (+)	0.1353			
MVI (+)	0.0975			
Tumor necrosis (+)	0.0003	0.0143	14.286	1.701-125
CRP (≥0.3 mg/dl)	0.1061			

[a]By a 1 cm increase. RCC, renal cell carcinoma; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; MVI, microvascular invasion; CRP, C-reactive protein.

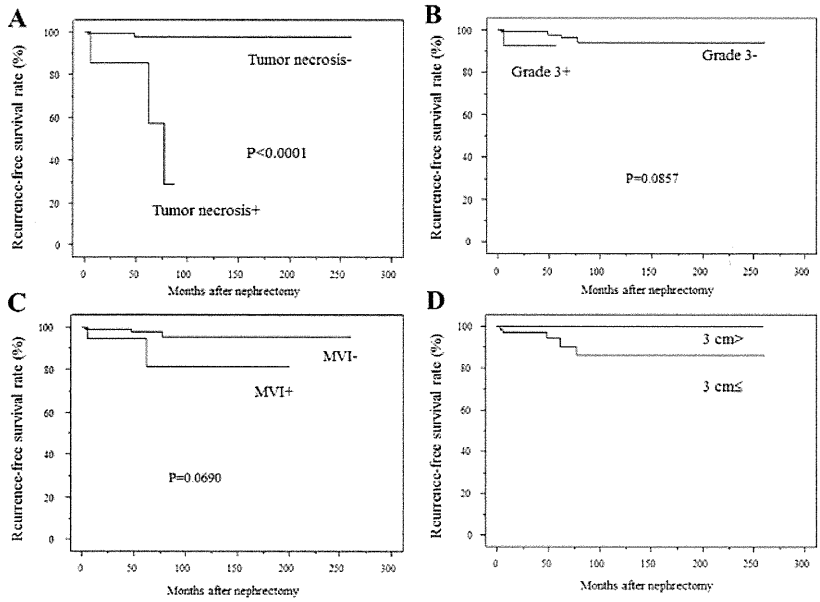

Figure 2. Kaplan-Meier curves analyzing recurrence-free survival (RFS). (A) Recurrence was significantly higher in patients with histological tumor necrosis than in those without. The 5- and 7-year RFS rates were 85.7 and 28.6% in patients with tumor necrosis, and were 97.9 and 97.9% in patients without tumor necrosis, respectively. (B) and (C) Recurrence rates were comparable between patients with and without a grade 3 component (B), and between patients with and without microvascular invasion (MVI) (C). (D) Patients with tumors <3 cm had no recurrence in the present study.

in the lungs of three patients, the mediastinal lymph node in one and the contralateral kidney of one patient. The time from nephrectomy to recurrence was <1 year in two patients (3.5 and 5.9 months), and >4 years in three patients (48.2, 61.2 and 77.5 months). All five patients had clear cell-type RCC; four tumors were histological grade 2 and one was grade 3. Two of the five tumors (40%) had microvascular invasion and three (60%) had histological tumor necrosis. Two patients (40%) had preoperative CRP levels ≥0.3 mg/dl. No patients had thrombocytosis.

Comparison of clinicopathological factors between patients with and without recurrence (Table I). Tumor size and the percentage of tumor necrosis were significantly higher in patients with recurrence than in those without. Age (P=0.2636), gender (P=0.5930), size of the tumor (P=0.1769), ECOG PS (P=0.0778), RCC subtype (P=0.6203), the presence of grade 3 component (P=0.4325), the presence of MVI (P=0.1114) and CRP (P=0.0515) were not significantly different between the two groups.

Impact of clinicopathological factors on recurrence in patients with pT1aN0M0 RCC. In all patients with pT1aN0M0 RCC, the 5-year RFS and CSS rates were 97.2 and 99.1%, respectively (Fig. 1). Kaplan-Meier analysis revealed that the recurrence rate was significantly higher in patients with histological tumor necrosis than in those without (P<0.0001) (Fig. 2A). The 5- and

Table III. Comparison of clinicopathological factors between pT1bN0M0 (≤5 cm) patients with recurrence and those without.

Variables	Patients with pT1b tumor (≤5 cm) (rec.+) (n=8)	Patients with pT1b tumor (≤5 cm) (rec.-) (n=40)	P-value
Age (years)	65±10	60±13	0.2509
Gender (male/female)	8/0	25/15	0.0367
Side (right/left)	3/5	21/19	0.4386
Tumor size (cm)	4.6±0.3	4.4±0.3	0.0563
ECOG PS (0 vs. 1)	0/8	6/33	0.2349
Grade 3 (+ vs. -)	3/5	14/26	0.8926
MVI (+ vs. -)	5/3	16/24	0.2416
Tumor necrosis (+ vs. -)	4/4	6/34	0.0261
CRP (0.3> vs. 0.3)	5/3	11/29	0.0552

ECOG PS, Eastern Cooperative Oncology Group performance status; MVI, microvascular invasion; CRP, C-reactive protein.

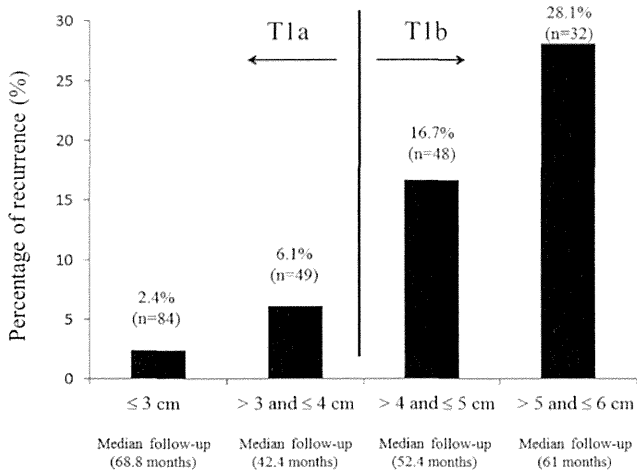

Figure 3. The percentage of renal cell carcinoma patients with different sized tumors. The percentage of patients with pT1aN0M0 >3 cm (n=49, median follow-up 42.4 months) was 6.1%, where as 16.7% of patients had pT1b ≤5 cm (n=48, median follow-up 52.4 months).

7-year RFS rates were 85.7 and 28.6% in patients with tumor necrosis, and 97.9 and 97.9% in patients without tumor necrosis, respectively. The recurrence rates were not significantly different between patients with a grade 3 component and those without (Fig. 2B), or between patients with and without MVI (Fig. 2C). Patients with a tumor size <3 cm had no recurrence (Fig. 2D).

Factors predicting recurrence in patients with pT1aN0M0 RCC. The Cox proportional-hazards regression model was used to evaluate factors predicting recurrence. Univariate analysis showed that tumor size (P=0.0379) and presence of tumor necrosis (P=0.0003) were significantly associated with RFS. Multivariate Cox proportional-hazards regression model analysis revealed that the presence of tumor necrosis was the only significant predictor of RFS (P=0.0143) (Table II).

Comparison of clinicopathological factors in patients with pT1b ≤5 cm with and without recurrence. We reviewed the clinicopathological factors of patients with tumors larger than pT1a tumors (pT1b tumors >4cm-≤5 cm) with and without recurrence. As shown in Fig. 3, the percentage of RCC patients with recurrence gradually increased according to tumor size. The percentage of patients with pT1aN0M0 >3 cm (n=49; median follow-up time, 42.4 months) was 6.1%, whereas the percentage of patients with pT1b ≤5 cm (n=48; median follow-up time, 52.4 months) was 16.7%. When the clinicopathological factors of patients with pT1b tumors ≤5 cm with and without recurrence were compared, the percentage of tumor necrosis (P=0.0261) and gender (P=0.0367) were significantly different (Table III), suggesting that tumor necrosis may be an important predictor for the recurrence of small RCCs.

Discussion

In the present study, five of 133 patients with pT1aN0M0 RCC (3.8%) experienced tumor recurrence (median follow-up time, 57.8 months). In previous studies, the 5-year RFS rates were 88-93% in patients with pT1aN0M0 RCC (5,6). The 5-year RFS rate in our study was higher than that in the previous studies. In the current study, patients with recurrence had a significantly increased tumor size and a higher percentage of tumor necrosis compared with patients without recurrence. Univariate analysis for the prediction of recurrence revealed that tumor size and necrosis were significant factors, but only tumor necrosis was an independent predictor for recurrence using multivariate analysis. When patients with pT1bN0M0 RCC with tumors sized ≤5 cm were evaluated, the percentage of tumor necrosis was higher in patients with recurrence compared with without recurrence. Therefore, tumor necrosis appeared to be a strong predictor for recurrence in small RCCs.

Predictors for recurrence and prognosis in cT1a RCC have been previously evaluated (1-4). Takayama *et al* (1) reported that symptomatic cancer and the presence of sarcomatoid components were independent risk factors for metachronous metastasis, and CRP levels of ≥0.4 mg/dl were an independent prognostic factor for overall survival. Kume *et al* (2) reported that MVI was an independent predictor for metastasis (2). Furthermore, cT1a RCC patients with tumors ≥3.1 cm exhibited lower recurrence-free survival rates than those

with tumor ≤3.0 cm, and patients with MVI exhibited lower recurrence-free survival rates than those without MVI (3). By contrast, tumor size not identified as an independent progostic factor in RCC patients with tumors ≤4 cm (4). We hypothesize that tumors in patients with cT1a RCC are theoretically more aggressive than those with pT1a RCC. In previous studies, the common site of recurrence in patients with cT1a RCC was the bone (1,2). Takayama *et al* reported that 65% of patients with cT1a with simultaneous or metachronus metastasis had bone metastasis (1). The authors also reported that the presence of a sarcomatoid component was an independent predictor for prognosis, and four out of the five patients with a sarcomatoid component exhibited bone metastases. Consistent with this, Nishikimi *et al* reported that the bone was a predominant site of recurrence (10 of 25 recurrent patients, 40%) in patients with pT1aN0M0 RCC (6). However, the mechanism for the preference of bone metastasis in cT1a RCC remains unclear. By contrast, there were no patients with bone recurrence in the present study. Kim *et al* reported that the lungs were the major site of recurrence in patients with pT1aN0M0RCC (four of nine patients), and only one patient had a recurrence in the bone (5). Therefore, it remains controversial whether the bone is a preferred site of recurrence in pT1aN0M0 RCC.

A small number of studies have set out to identify predictors for recurrence in pT1aN0M RCC. Nishikimi *et al* reported that Fuhrman nucleolar grade, growth pattern and tumor necrosis were independent predictors for recurrence in pT1aN0M0 clear cell RCC (6). In addition, Kim *et al* reported that microvascular invasion and tumor necrosis were independent predictors for distant metastasis in pT1aN0M0 RCC (5). Consistent with these two studies, the current study identified that tumor necrosis was an independent predictor for recurrence, suggesting that tumor necrosis may be an important predictor for the recurrence of pT1aN0M0 RCC.

In the present study, we also evaluated pT1bN0M0 RCC with a tumor size ≤5 cm. In this population with relatively small pT1b tumors, patients with a recurrence had a significantly higher percentage of tumor necrosis than those without recurrence (50 vs. 15%, P=0.0261). This suggests that tumor necrosis may predict the recurrence of small RCCs, which generally have low recurrence rates. Moreover, we have previously demonstrated that the non-normalization of postoperative CRP, pre-CRP elevation, microvascular invasion, and histological tumor necrosis were independent predictors for recurrence in N0M0 clear cell RCC (13). Therefore, tumor necrosis appears to accurately reflect biological activity, tumor grade and microvascular invasion; thus, it may predict recurrence of RCC.

MVI is an important predictor for recurrence in low clinical stage RCC (2,3,14). In our five patients with recurrence, two (40%) had MVI. In addition, four of the five patients with recurrence had distant visceral metastases, and one had LN metastasis. Distant and LN metastasis theoretically require MVI. Therefore, tumors with a small degree of MVI may be occasionally diagnosed as lacking MVI. In contrast, tumor necrosis usually occupies a relatively large area in RCC specimens compared with MVI. Therefore, the presence of tumor necrosis is unlikely to be missed during pathological diagnosis.

Identifying the risk factors for recurrence may be useful for determining the optimal follow-up period in patients with pT1a RCC. Antonelli *et al* defined a follow-up protocol based on the University of California Los Angelus Integrated Staging System (15) after surgery for N0M0 RCC (16). In their study, pT1 low-risk patients (pT1 and nucleolar grade 1-2, ECOG PS=0) required thoracic examination every 30 months and abdominal examination annually for 5 years after surgery. In addition, Hafez reported that annual follow-up with a medical history, physical examination, and select laboratory studies were sufficient for patients with RCC ≤2.5 cm (17). If we can establish a risk classification system that includes tumor necrosis as a predictor for recurrence, it may be possible to more effectively predict recurrence in patients with pT1a RCC. Therefore, risk classification may be useful for determining individual-based follow-up periods. Very few patients with pT1aN0M0 RCC have tumor necrosis in RCC specimens, which was demonstrated in the present study (7/133 patients) and a previous study (8/293 patients) (6). However, if tumor necrosis is detected, the patients should be followed more closely than patients without tumor necrosis.

The present study has several limitations. First, this is a non-randomized, retrospective, single-center study. Therefore, a prospective study including a large number of patients is required to confirm these observations. However, the current study revealed an important finding; tumor necrosis was an independent predictor for recurrence in pT1aN0M0 RCC.

Histological tumor necrosis was the only independent predictor for recurrence in patients with pT1aN0M0 RCC. The frequency of tumor necrosis was low in patients with pT1aN0M0 RCC. However, patients with tumor necrosis in RCC specimens had a significantly higher risk for recurrence compared with those without tumor necrosis. Therefore, the presence of tumor necrosis may reflect an aggressive biological activity and be an effective predictor for recurrence in small RCCs.

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