The Expression of Matrix Metalloproteinase 9 Associates with Microvessel Invasion in Renal Cell Carcinoma Specimen

Introduction and Objective: Association of microvessel invasion (MVI) with other clinico-pathologic prognostic factors remains unclear. Matrix metalloproteinases (MMPs) and its related proteins are often expressed in cancer tissue including RCC, and their strong expression is a prognostic factor of RCC. To determine which one of clinico-pathologic factors including immunoreactivity of MMPs associates to MVI, we performed an immunohistochemical study.
Materials and Methods: All studies presented here were approved by institutional review board at Nihon University School of Medicine. Surgical specimens were obtained from 249 cases with renal cell carcinoma in our institution. They consisted of 185 male and 64 female patients with an average age of 60.0 years old. The average observation period of them was 85.5 month. They included 135(54%) of Stage 1, 39(16%) of stage 2, 41(16%) of stage 3 and 34(14%) of stage 4. The histological classifications of them were 204(82%) cases of clear cell and 46(18%) of non-clear cell. We evaluated the status of immunohistochemical staining of MMP-2, MMP-9, membrane-type matrix metalloproteinase 1 (MT-MMP-1), tissue inhibitor of matrix metalloproteinase (TIMP)-1 and TIMP-2 for the renal specimen. The degree of immunoreactivity was semi-quantatively evaluated by one pathologist and classified to 4 grades (0, 1+, 2+, and 3+). Cell type, stage, Fuhrman's nuclear grade and micro-vessel invasion were also evaluated. For the statistical analysis, logistic regression test were used to determine significance.
Results: By the univariate analysis, all factors except TIMP-1 and TIMP-2 attained significance. The multivariate analysis identified MMP9 associates with MVI with an Odds ratio of 2.28 (95%CI: 1.508-4.934, p=0.0355). Pathological stage also had a significance with an Odds of 6.70 (95%CI: 3.514-12.730, p=0.0001) (Table).
Conclusions: Among the various MMPs and its related proteins that we examined, as well as clinic-pathologic factors, the expression of MMP9 and clinical stage associate with MVI.

Table
Multivariate analysis (n=249)

	category	Odd's ratio	95%CI	P value
Cell type	clear/non clear	1.626	0.751-3.522	0.2173
Fuhrman's grade	low(1, 2)/high(3 , 4)	0.808	0.367-1.781	0.5967
Stage	localized (1, 2)/advanced (3, 4)	6.689	3.514-12.730	**0.0001**
MMP-2	weak(0, 1+)/strong(2+, 3+)	1.410	0.709-2.802	0.3268
MMP-9	weak(0, 1+)/strong(2+, 3+)	2.284	1.508-4.934	**0.0355**
MT-MMP-1	weak(0, 1+)/strong(2+, 3+)	0.779	0.333-1.822	0.5650