—Reports on Experiments and Clinical Cases—

Evaluation of prognostic factors and PCNA expression for pulmonary metastatic tumors of colorectal carcinoma

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Abstract

The present study was conducted to evaluate clinicopathologically 26 patients whose primary colorectal carcinoma and resulting pulmonary metastatic tumors had been resected, and to determine the relationship between tumor progress and prognosis by PCNA immunostaining. Patients with solitary pulmonary metastasis were found to have much better prognoses than those with multiple metastasis. There was no correlation between tumor size of pulmonary metastasis and prognosis. Survival rates of patients with disease-free intervals (DFIs) of 2 years or longer were higher than for those with DFIs of less than 2 years. Mean PCNA expression of pulmonary metastatic lesions was significantly higher than that of primary lesions. It was suggested that the higher PCNA expression stemming from the relation between depth of tumor invasion and PCNA expression was greater with tumor progress. (J Nippon Med Sch 2000; 67: 28—31)

Key words : pulmonary metastatic tumor, colorectal carcinoma, PCNA, prognostic factor

Introduction

Prognostic correlations between clinico-pathological factors and PCNA expression of solid carcinoma have been studied extensively[1-3]. but such correlations with respect to pulmonary metastatic lesions are little understood. Clinicopathologically prognostic factors for colorectal carcinoma and pulmonary metastatic tumors were examined in this study, with particular attention to prognosis and PCNA expression, by immunohistochemically staining primary and metastatic lesions.

Materials and Methods

Twenty six patients with primary and pulmonary metastatic lesions participated in the present study. We investigated the following parameters: number and size of metastatic tumors, actuarial survival and disease-free periods (DFI: period between primary tumor control after operation and first observation of pulmonary metastasis), and PCNA (proliferating cell nuclear antigen) expression of primary and metastatic organs. PCNA immunohistochemical staining, using a monoclonal antibody (PC10) by the SAB method, of formalin-fixed, paraffin-embedded primary and metastatic tissues was carried out. Tissue PCNA labeling index (L. I.) was obtained by dividing the number of PCNA positive nuclei cells by the total number of tumor cell nuclei (1000 cells of each tissue sample were counted) and expressed as a percentage. Survival rates were computed by the Kaplan-Meier method and the Student's t-test, and generalized Wilcoxon method was used for statistical analysis. $P<0.05$ was considered significant.

Results

The patients in this study, 20 men and 6 women, ranged in age from 49 to 82 years (mean 60). The pri-

Table 1 Numbers and sizes of pulmonary metastases

Number	Cases	Size (mm)	Cases
		～10	1
1	14	11～20	3
2	6	21～30	10
3	3	31～40	5
4	3	41～50	0
		51～60	0
		61～	1

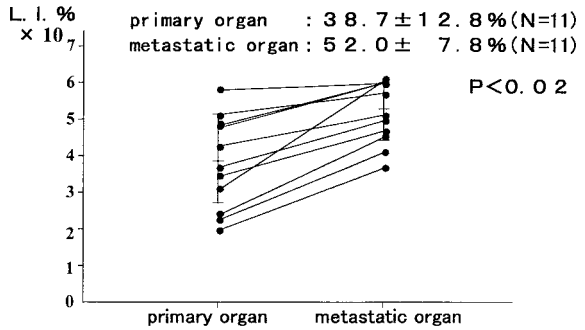

Fig. 1 Primary and metastatic tumor PCNA expression levels

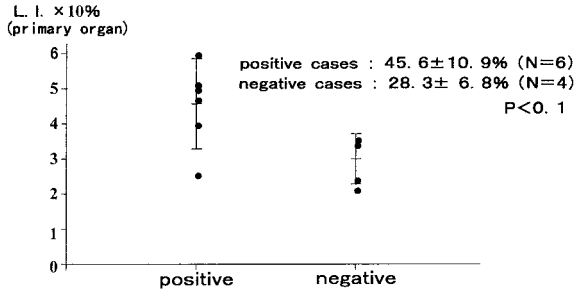

Fig. 2 PCNA expression by lymph node metastases and primay organ L.I. s

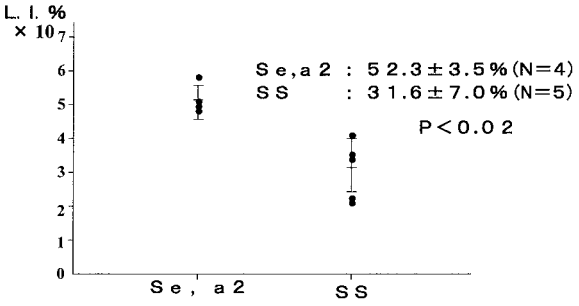

Fig. 3 PCNA expression and depth of tumor invasion (Se, a2 and SS)

mary colorectal carcinoma lesion occupied the ascending colon in 4 patients, descending colon in 2, sigmoid colon in 12 and rectum in 8. **Table 1** shows pulmonary metastasis number and size. Operative procedures to resect the pulmonary metastatic tumors were lobectomy in 16 patients, segmentectomy in 3 and partial resection in 7. Survival periods of patients with solitary and multiple metastases were compared. The 50 % survival period of 14 patients with solitary metastases was 3.1 years and that of 10 patients with multiple metastases, 1.4 years (P=0.055). The correlation of surgical procedure with survival period was not significant. There was no significant relationship between tumor size and survival period. The 50% survival period of patients with DFI for 2 years (N=7) was 1.5 years and that of patient with DFI of 2 years or longer (N=14), 4.5 years (P<0.1). PCNA expression of primary and metastatic lesions was as follows: mean L. I. of colorectal carcinoma tissue, 38.7 ± 12.8% (N=11) and that of pulmonary metastatic tissue, 52.0 ±7.8% (N=11); (P<0.02, **Fig. 1**). Primary organ L.I. of positive cases of lymph node metastasis increased compared to negative cases of lymph node metastasis (P<0.1, **Fig. 2**). The PCNA positive rate was lower than Se, a2 (N=4) for SS (N=5) of colorectal carcinoma (P<0.02, **Fig. 3**). There were no significant differences between PCNA positive rates and histological grades or stages.

Discussion

The effectiveness of chemotherapy and/or radiotherapy for pulmonary metastasis of colorectal carcinoma has yet to be evaluated. There is thus no progressive therapy other than surgical resection which is expected to prolong survival. The prognosis of solitary pulmonary metastasis is better than that of multiple metastases[4,5], as confirmed by the present study. The prognostic implications of tumor size of metastatic pulmonary lesions have been variously reported[6,7]. This study failed to disclose any significant prognostic factor in this parameter. The survival rates of DFIs of 2 years or longer exceeded those of DFIs shorter than 2 years. Four patients had recurrence after DFI of over 5 years, indicating the need for long-term follow up to detect late recurrences. There is still considerable disagreement regarding the prognostic implications of DFIs for survival[8,9].

PCNA is a nuclear protein synthesized during late G1 and S phases of the cell cycle. In this study, the prognostic factor of PCNA L.I. was examined by immunostaining for patients with pulmonary metastatic lesions of colorectal carcinoma. For colorectal carcinoma and pulmonary metastatic lesions, this paper is the first to examine prognostic implications based on PCNA expression evaluation. PCNA expression was found to be higher in metastatic than in primary lesions. Cellular proliferation of the metastatic lesion may thus possibly be higher than that of primary lesions. Lymph node metastasis positive cases showed higher PCNA L.I. for primary lesions than negative cases. Watanabe et al.[10] noted lymph node metastasis positive lesions of lung carcinoma to have significantly higher PCNA L.I. than primary lesions. Matsushima et al.[11] observed mediastinum lymph node positive lesions in pulmonary metastatic tumors to have higher lung PCNA L.I. compared to negative lesions. There would be thus likely to metastasize to the regional lymph node, for high PCNA L.I. of primary or/and metastatic lesions. Carley et al.[12] reported to be no significant differences in PCNA L.I. of mediastinum lymph node metastasis (N 2) and that of earlier stages (N 0/N 1) of lung carcinoma. SS carcinoma in this study showed lower PCNAL.I. than Se or a 2 carcinoma. Tanaka et al.[13] reported PCNA L.I. to increase with tumor progress from m to sm carcinoma, suggesting cell proliferative activity to be related to stromal invasion. Shirono et al.[14] found PCNA expression of Si and ai carcinoma to be higher than at other invasion depths, and furthermore reported hematogeneous metastasis-positive tumors (liver, lung, brain, and bone) to have higher PCNA expression than hematogeneous metastasis-negative tumors.

Present data on lymph node metastasis positive tumors indicate greater PCNA expression than those without such metastasis. Yamamoto et al[15] have presented similar results and metastatic lesions may thus affect cancer development by acting as productive clones. Sun et al.[16] noted PCNA accumulation to be related to the over-expression of c-erbB-2, p 53 and ras but PCNA expression itself not to provide additional clarification of the development of metastasis and prognosis. PCNA expression of primary lesions and metastatic lesions, were examined here and the prognostic implications were evaluated based on the results. Whether PCNA expression of pulmonary metastatic lesions is related to the biological behavior of primary lesions should be investigated in greater detail. The present results suggest tumors expressing high PCNA to possibly be more invasive and progressive compared to those with low expression. Clinicopathological findings indicated the prognosis of solitary pulmonary metastasis to be better than that of multiple metastases and that of patients with DFI 2 years or longer to be better than that of patients with DFI of less than 2 years. No correlation was found between prognosis and histological grade, tumor size, histological stage or surgical procedure. In summary, the present findings suggest the expression of PCNA protein may possibly be associated with tumor progress and prognostic implications, however, more detailed evaluation should be conducted.

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