Evaluation of Risk Factors for Metachronous Liver and Lung Metastasis in Colorectal Carcinoma

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Abstract Hepatic and lung recurrences are major determinants of survival for patients who have undergone a curative resection for colorectal carcinoma. The aim of this study was to assess the risk factors of metachronous liver and lung metastases from colorectal carcinoma. Method From January 1991 to April 2000, 705 patients with histologically confirmed adenocarcinoma of the colorectum and who had been operated on at our institution were retrospectively evaluated for this study. We investigated the risk factors of metachronous liver and lung metastases from colorectal carcinoma. Results According to a univariate analysis, lymph node metastasis, depth of invasion, and extramural lymphatic invasion were found to have a significant influence on the incidence of metachronous liver metastasis. Based on a multivariate logistic analysis, lymph node metastasis proved to be an independent recurrent factor. On the other hand, a univariate analysis showed lymph node metastasis, depth of invasion, and extramural lymphatic invasion to have a significant influence on lung metastasis. On multivariate logistic analysis, lymph node metastasis and lymphatic invasion proved to be independent recurrent factors. Conclusions Patients with not only positive results for lymph nodes metastasis but also positive results for lymphatic invasion should therefore be carefully followed and will likely be good candidates for postoperative adjuvant chemotherapy.

Key words Risk factors, Colon cancer, Metachronous liver metastasis, Metachronous lung metastasis

Introduction

Colorectal carcinoma is a worldwide public health concern and a frequent disease with increasing incidence. Its prognosis has recently improved because of the development of diagnostic and therapeutic procedures. However, optimized surgery with a curative intent may also be followed by an unfavorable course of the disease, primarily due to the occurrence of distant metastasis during the follow-up. In addition, distant metastases are the major cause of death for colorectal carcinoma patients. Patients with stage colon carcinoma have a −year survival of − after curative surgery, but it is difficult to identify the − of patients who will have recurrence. For stage patients with involvement of lymph nodes, the −year survival rate decreases to − . Some patients with stage disease are at high risk for recurrence and receive adjuvant chemotherapy, although its benefits remain unclear.

Liver metastasis is the most common site of recurrence in colon cancer patients, and lung metastatic patients are increasing. If the metastatic disease is left untreated, the median survival is − months. Whereas simple analyses of factors that appear to influence survival have been re-

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ported in many studies, there have been few attempts to use multivariate statistical methods to identify variables with independent effects on survival after resection of colorectal carcinoma. In addition, No risk factors for metachronous metastasis have been reported.

We herein report an investigation of the risk factors of metachronous liver and lung metastases from colorectal carcinoma.

Methods

Between January and April , patients with histologically confirmed adenocarcinoma of the colorectum who had been operated on at our institution were retrospectively evaluated for this study. All patients had undergone colorectal surgery. The patients who could not undergo surgery due to various reasons were excluded. According to the Japanese Society for Cancer of the Colon and Rectum [th] Edition , patients were pathologically staged as , as , as , as a, as b, and as . In patients, patients had synchronous liver metastasis and had metachronous liver metastasis. Seventeen patients had synchronous lung metastasis and had metachronous lung metastasis Table . The general epidemiologic data, clinical findings, treatment, histopathologic examination, and follow-up data were collected retrospectively. In this study, we evaluated the risk factors of liver metastasis and lung metastasis especially in metachronous metastasis.

The clinicopathological variables including sex, tumor gross appearance , type/ , type , lymph node metastasis, tumor depth, lymphatic invasion, venous invasion, and pathological grade were analyzed. The pearson chi-square test was used for comparison of sex, gross appearance, lymph node metastasis, tumor depth, lymphatic invasion, venous invasion and pathological grade. The Survival curves were generated by the Kaplan -Meier method. Differences in the survival rates were determined with the log-rank test. To identify independent prognostic factors for survival, multivariate analysis was performed using the Cox regression hazards model. We also used a multiple logistic regression to determine the risk factors for metachronous metastases. Level for statistical significance was set at . .

Results

The -year survival rate of patients without metastasis was . . Patients with metachronous liver metastasis had significantly higher -year survival rates than those with synchronous liver metastasis . , , p . , Fig. . In the same way, patients with metachronous lung metastasis had significantly higher -year survival rates than those with synchronous metastasis . , . , p . , Fig.

The incidence of synchronous liver metastasis was . and that of metachronous liver metastasis was . . Table shows the recurrent number according to each stage. In metachronous liver metastasis, the most frequent stage was found to be a . . The incidence of synchronous lung metastasis was . and that of metachronous lung metastasis was respectively Table . The most frequent stage was a in metachronous lung metastasis . . On univariate analysis Table , lymph node metastasis, depth of invasion, and extramural lymphatic invasion were found to have a significant influence on the incidence of metachronous liver metastasis. On

Table 1. Patient characteristics

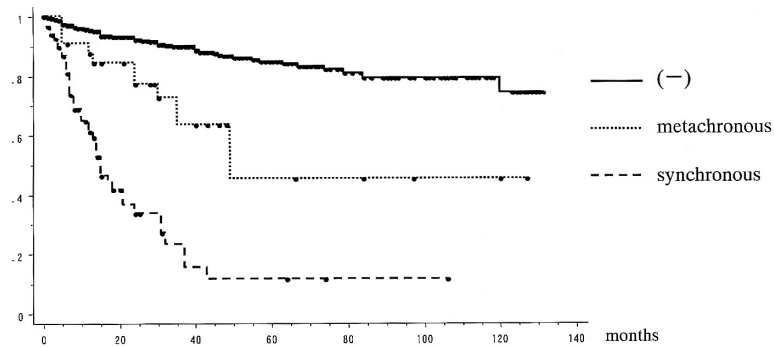| Stage	total	liver metastasis		lung metastasis	
		synchronous	metsachronous	synchronous	metachronous
a					
b					

Fig . The −year survival rate of metachronous liver metastatic patients
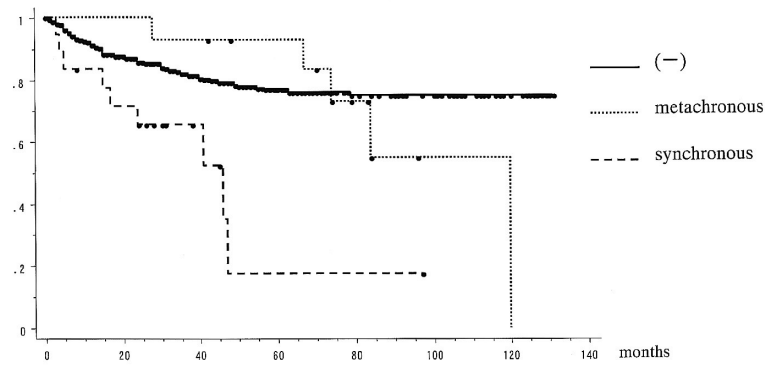was   .   and that of synchronous liver metastatic patients was
. p .

Fig . The −year survival rate of metachronous lung metastatic patients
was   .   and that of synchronous liver metastatic patients was
. . p .

Table . Risk factors for metachronous liver metastasis

metastasis			*p*−value
gender	/	/	.
gross apper '/	/	/	.
n factor	/	/	.
depth ss,a /	/	/	.
y factor /	/	/	.
v factor /	/	/	.
patho well/	/	/	.

Table . Risk factors for metachronous liver metastasis multivariate analysis

	odds ratio	*p*−value
n factor	.	.
depth	.	.
y factor	.	.
v factor	.	.

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.

Table . Risk factors for metachronous lung metastasis

metastasis			p-value
gender	/	/	.
gross apper '/	/	/	.
n factor	/	/	.
depth ss, a /	/	/	.
y factor /	/	/	.
v factor /	/	/	.
patho well/	/	/	.

Table . Risk factors for metachronous lung metastasis multivariate analysis

	odds ratio	p-value
n factor	.	.
depth	.	.
y factor	.	.
v factor	.	.

Discussion

Hepatic and lung metastases from colorectal carcinoma are major determinants of survival for patients who have undergone curative resection of colorectal carcinoma. Recent advances in surgery of the liver and lung have made surgical therapy common for the treatment of patients with metastases from colorectal carcinoma. Approximately of patients with isolated hepatic metastases resected curatively, and will survive for years with low morbidity and mortality. In addition, the lung is the most common extraabdominal site of metastases from colorectal carcinoma, and resectable metastatic disease is limited to the lung in approximately of patients after a resection of colorectal carcinoma.

Previous studies have indicated the survival for colon carcinoma and risk factors after resection of metastatic liver and lung tumors to be approximately years. To our knowledge, no previous studies have examined the risk factors for liver and lung metachronous metastasis. Liver and lung metastasis is one of the most important risk factors affecting the -year survival, therefore, an investigation of the risk factors for liver and lung metastasis would thus contribute significantly to an improved survival.

To date, no effective chemotherapeutic treatment is available for hepatic and lung metastases from colorectal carcinoma. Consequently, a surgical resection of hepatic and lung metastases has been accepted as the optimal therapy by many physicians.

In our institution, we also performed surgery if the metastatic liver and lung lesion was resectable. Nevertheless, the -year survival rate of metachronous liver cases was confined to . . The risk factors of metachronous liver metastases were found to be lymph node metastasis, depth of invasion, and extramural lymphatic invasion on univariate analysis. According to a multivariate logistic analysis, lymph node metastasis proved to be an independent recurrent factor. Generally, lymph node metastasis is the risk factor that most affects the survival rate. The more the lymph node-positive rate increases, the more staging increases. As a result, lymph node metastasis remains as the only factor affecting the staging background.

Regarding lung metastases, lymph node metastasis and lymphatic invasion proved to be independent recurrent factors on multivariate analysis. These results must indicate that cancer cells move via lymph vessels, not via the inferior mesenteric vein. Iizasa et al. reported using clinical factors that elevated the carcinoembryonic antigen level and the quantity of metastases are thus considered to be independent prognostic factors. In this study, we did not examine the CEA or metastatic counts.

The -year survival rate of metachronous lung

cases was . , which was better than the liver metastatic survival rate. This reason for this depended not only on the small number of lung metastastatic cases, but it was also due to the fact that the time of the metastasis onset was later than in liver metastatic cases.

In this series, two patients of stage   and   of stage   developed metachronous liver metastasis. Of the stage   patients,   developed metachronous lung metastasis. These results suggest that if a patient is positive for lymphatic invasion, then a follow-up is necessary even if the stage is relatively low.

Our data revealed that lymph node metastasis is the most important risk factor for liver and lung metastasis. Lymphatic invasion was also found to be an important factor for lung metastasis. In these cases, frequent examinations will be necessary and should contribute to improving the curability rate of metastasis and the overall survival.

Positive results for lymphatic invasion and lymph nodes during a curative resection are therefore considered to be useful for selecting colorectal cancer patients at high risk for developing lung and hepatic recurrence, and for identifying who may be good candidates for postoperative adjuvant chemotherapy.

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