Resection of Synchronous Liver Metastases from Colorectal Cancer

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Background: The prognosis for patients with liver metastases from colorectal cancer is still poor. Thus, patient selection for hepatic resection is essential to improve the poor results of the procedure. Some reports have shown that the prognosis for patients with synchronous liver metastases is worse than that for those with metachronous liver metastases. Therefore, determination of the factors that influence outcome after resection of synchronous liver metastases is more important than with metachronous liver metastasis.

Method: We studied patients who had been followed for more than 5 years after undergoing resection of synchronous liver metastases from colorectal cancer.

Results: Among the 12 prognostic factors studied (age, gender, adjuvant chemotherapy, tumor site, CEA level, tumor differentiation, tumor size, regional lymph node metastatic status, distribution of liver metastases, number of liver metastases, tumor size and pathological margin), regional lymph node metastatic status and pathological margin were significant prognostic factors by univariate analysis (p = 0.0002 and 0.005, respectively). Regional lymph node metastatic status was a significant prognostic factor by multivariate analysis (p = 0.031). The survival curve of patients with six or more regional lymph node metastases was similar to that of patients with non-resectable liver metastasis.

Conclusion: The resection of synchronous liver metastases in patients with six or more regional lymph node metastases is relatively contraindicated. For these patients, other treatment modalities should be considered.

Key words: colorectal cancer – synchronous liver metastasis – prognostic factor – lymph node metastasis

INTRODUCTION

The prognosis for patients with liver metastases from colorectal cancer is still poor. When liver metastases are not resectable, the median survival is 7–15 months and few patients survive more than 5 years (1–6). Even when liver metastases are resected, the 5-year survival rate is still only 20–40% (7–18). Hence patient selection for hepatic resection is essential to improve the poor results of the procedure. In multivariate analysis, some significant prognostic factors, including primary cancer stage, time of diagnosis of liver metastasis, number of liver tumors and size of liver tumors, have been reported (13,16,18). However, these factors are not sufficient for patient selection, because some patients with poor prognostic factors survive longer than expected. Some reports have shown that the prognosis for patients with synchronous liver metastases is worse than that for those with metachronous liver metastases (11,15,18). Therefore, determination of the factors that influence the outcome after resection of synchronous liver metastases is more important than for metachronous liver metastasis.

We studied patients who had been followed for more than 5 years after undergoing resection of synchronous liver metastases from colorectal cancer. From 1983 to 1992, a total of 176 patients underwent resection of liver metastases from colorectal cancer at the National Cancer Center Hospital. In 97 (55%) of these 176 patients, synchronous liver metastases diagnosed prior to the time of operation of the primary cancer were considered suitable for curative resection. The outcome for these patients has been investigated in terms of overall survival and prognostic factors.

MATERIALS AND METHODS

From 1983 to 1992, a total of 97 patients (53 male, 44 female) suffering from colorectal cancer and synchronous liver metas-
tases underwent curative surgical resection of primary tumor and liver metastases (curative group). Curative resection is defined as resection without residual tumors. During the same period, 102 patients (66 male, 36 female) had non-resectable or non-curative colorectal cancer and synchronous liver metastases (non-curative group). All the surviving patients were followed for more than 5 years. Our criteria for resection of synchronous liver metastases are as follows: (1) the primary lesion was resectable with curative intent; (2) preoperative and intraoperative examination revealed that all the liver tumors could be technically resected with conservation of adequate normal parenchyma; (3) there was no extrahepatic metastatic disease (11). When the patients met the criteria, hepatic resection and primary resection were performed at the same time.

Synchronous resection of liver metastases and primary tumor was performed in 83 patients (86%). In the other patients, resection of liver metastases was performed within 6 months after resection of the primary tumor, either because extensive hepatic resection was required or because the primary tumor was resected in other local hospitals. All the patients underwent computed tomographic (CT) examination of the liver before hepatic resection. Ultrasonographically guided partial resection with a surgical margin of more than 1 cm was performed to detect deposits not seen before operation, to confirm the relationship between tumors and intrahepatic vascular system and to retain an adequate surgical margin (11). Lobectomy or left lateral segmentectomy was performed when it was considered technically easier. Partial hepatic resection was performed in 62 patients (64%). The remaining 31 patients underwent segmentectomy or lobectomy.

Adjuvant chemotherapy using 5FU was given to 43 patients (44%) after hepatic resection. Because adjuvant treatment regimens were changed during the analyzed period, systemic therapy or intra-arterial or intraportal therapy was used as adjuvant chemotherapy. Patients were seen regularly every 3 months during the first 2 years after operation and every 6 months in the third year. Investigations for follow-up comprised physical examination, tumor marker, abdominal sonography and chest X-ray.

The survival rate was examined by the Kaplan–Meier method. Cox’s proportional hazards model was used in multivariate analysis to determine the significance of each variable, with survival as the end-point.

RESULTS

POSTOPERATIVE COMPLICATIONS

There were no deaths in the postoperative period. Operative complications occurred in 32 patients (33%). Postoperative hemorrhage, intra-abdominal abscess, bile leakage and anastomotic leakage occurred in four, two, one and one patient, respectively. The remaining 24 patients had minor complications including pleural effusion, wound abscess and bowel obstruction.

<table>
<thead>
<tr>
<th>Site</th>
<th>No.</th>
<th>%</th>
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<tbody>
<tr>
<td>Liver</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>Liver/lung</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Liver/local</td>
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<tr>
<td>Lung</td>
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<tr>
<td>Lung/local</td>
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<td>2</td>
</tr>
<tr>
<td>Local</td>
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<td>4</td>
</tr>
<tr>
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<tr>
<td>Total</td>
<td>68</td>
<td>70</td>
</tr>
</tbody>
</table>

*‘Others’ include bone, brain and peritoneal metastases.

Figure 1. Survival curves of patients with synchronous liver metastases from colorectal cancer. The 5-year survival rate and the median survival were 31% and 30 months, respectively.

PATTERNS OF RECURRENT AND SURVIVAL CURVES OF PATIENTS WITH SYNCHRONOUS LIVER METASTASIS

Patterns of recurrence are listed in Table 1. The most common site of recurrence is the liver remaining after the resection. Survival curves are shown in Fig. 1. The 5-year survival rate and the median survival were 31% and 30 months, respectively.

PROGNOSTIC FACTORS IN CURATIVE RESECTION OF LIVER METASTASIS

Gender, age, adjuvant chemotherapy and characteristics of the primary cancer (primary tumor site, CEA level, tumor differentiation, tumor size [pT of TNM classification (19)] and lymph node status (pN of TNM classification) and of the liver
metastasis (tumor distribution, number of metastases, tumor size and pathological margin) were considered as prognostic factors. The results of univariate analysis of these prognostic factors are summarized in Table 2. Lymph node status and pathological margin were significant prognostic factors for curative resection of synchronous liver metastasis ($p = 0.0002$ and 0.005, respectively). Multivariate analysis (Cox’s proportional hazards model) showed that lymph node status was the only significant prognostic factor (Table 3). None of the patients with six or more regional lymph node metastases of the primary cancer survived more than 5 years after resection of the primary tumour and the liver metastases; the survival curve of these patients was similar to that of the non-curative group. The most common site of recurrence in this group was the remaining liver (11 of 21 patients, 52%). The survival curve of this group was similar to that of the non-curative group (Fig. 2).

**DISCUSSION**

Surgical resection of hepatic metastases from colorectal cancer is considered to be effective therapy. The mortality rate of 0%, morbidity rate of 33% and 5-year survival rate of 31% in our studies are acceptable. Although the morbidity rate was higher than that of resection of metachronous liver metastases in our hospital during the same period (15%), the major complication rate was the same (8% vs. 6%). These results are similar to those achieved in other recent series (7–18) and provide further support for resection of synchronous liver metastases.
When liver metastases are resected with curative intent, the survival rate of patients with synchronous liver metastases is worse than that of patients with metachronous liver metastases. The poorer survival of patients with synchronous liver metastases might be caused by patient selection bias, because patients with metachronous liver metastases who are candidates for hepatic resection have already been selected during the follow-up period after resection of the primary cancer. The present study has shown that regional lymph node metastatic status is a significant prognostic factor in patients with synchronous liver metastasis. If patients are selected for this factor, the prognosis improves. For example, the 5-year survival rate of patients with five or fewer regional lymph node metastases is 40%, which is similar to that of patients with metachronous liver metastases.

Where possible, we perform combined resection of the primary cancer and the hepatic metastases. Because combined resection showed no mortality and only minor complications, there is no rationale for performing hepatic resection after surgery for the primary cancer. However, our results show that the number of lymph node metastases is the major prognostic factor. Hence macroscopic lymph node metastases should be examined by frozen section during surgery, because detection of positive nodes by manual palpation is sometimes difficult. When six or more regional lymph node metastases are detected, combined resection of the primary cancer and hepatic metastases is not recommended. In such patients, other modalities, including systemic and hepatic arterial infusion chemotherapy, should be considered. When recurrence is not seen in the follow-up period after the primary resection, consecutive hepatic resection is indicated.

Other large series that included metachronous liver resection have demonstrated that lymph node status of the primary cancer, depth of invasion, number of hepatic metastases, metastatic tumor size and pathological margin of the hepatic resection are prognostic factors (7,8,13,14,16,18). Because the indications for hepatic resection differ among the reports, the significant prognostic factors probably also differ. These prognostic factors should not be considered to be absolute contraindications to liver resection, because some patients with poor prognostic factors have unexpectedly long survival. For example, multiple liver metastases indicate a relatively poor prognosis, but several patients with such metastases survived for more than 5 years. Because chemotherapy cannot cure patients with liver metastases, hepatic resection should be considered even if patients have poor prognostic factors. However, our results demonstrated that the presence of six or more regional lymph node metastases is a relative contraindication for hepatic resection, because patients in this group showed a similar survival curve to that of patients in the non-curative group.

In some series, a positive pathological margin of the resected specimen has been related to recurrence (14,18,20–22). Our univariate analysis also indicated that a positive pathological margin is a significant prognostic factor. These results suggest that careful hepatic resection should be performed. Ultrasono-

References


