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Esophageal Cancer With Cirrhosis of the Liver: Results of Esophagectomy in 18 Consecutive Patients

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Backgrounds: Patients with cirrhosis of the liver sometimes are candidates for esophagectomy with extensive lymphadenectomy.

Materials and Methods: Of 271 patients with primary esophageal carcinoma, 19 patients (7.0%) had pathologically proven cirrhosis of the liver. Among those, 18 patients underwent esophagectomy with extensive lymph node dissection. Clinicopathologic characteristics of these 18 patients were retrospectively investigated.

Results: Pathological T stages were pT1 in 3 patients, pT2 in 9 patients, pT3 in 2 patients, and pT4 in 4 patients. Hepatitis C virus antibody was positive in 1 patient, and 14 patients were alcoholics. Three patients had cryptogenic cirrhosis. Seven patients were classified as Child-Turcotte B and 11 were Child-Turcotte A. Three patients had ICG-R 15 over 30%. Fifteen patients (83.3%) developed a total of 35 postoperative complications. Three patients currently are alive without recurrence. Fifteen patients have died: 7 from cancer recurrence; 5 of causes unrelated to esophageal cancer; and 3 of operative death (operative mortality: 16.7% in 18 cirrhotic patients vs. 5.7% in 227 non-cirrhotic patients; $P = .102$). The 1- and 3-year survival rates for 18 resected cirrhotic patients were 50% and 21%, respectively, and those for 227 resected non-cirrhotic patients were 67% and 42%, respectively ($P = .051$). When operative deaths were excluded from the analysis, the 1- and 3-year survival rates for 15 cirrhotic patients were 60% and 25%, respectively, whereas those for 214 non-cirrhotic patients were 68% and 43%, respectively ($P = .271$).

Conclusion: Although cirrhosis has a high morbidity and mortality rate, Child-Turcotte A and B cirrhosis may not contraindicate curative esophagectomy for esophageal carcinoma. However, these patients need meticulous perioperative care to avoid postoperative complications.

Key Words: Esophageal cancer—Cirrhosis of the liver—Esophagectomy—Prognosis.

Esophageal carcinoma is one of the most malignant tumors, with a dismal prognosis: half of the patients die within 2 years, and the overall 5-year survival rate is only 25% to 45%.[1–3] Among the available treatments, esophagectomy provides the best prospect of long-term survival. Since the early 1980s, three-field extensive lymph node dissection during esophagectomy has become a standard surgical procedure to obtain an accurate pathological staging and has done a great deal to improve surgical results in Japan[4–6]and the Western countries.[7,8]

In patients with cirrhosis of the liver, there is high operative mortality and morbidity after gastrointestinal and portal hypertension surgery.[9–12] Because of the etiologic relationship between alcohol consumption and cirrhosis of the liver and esophageal carcinoma, cirrhosis of the liver occasionally is encountered in candidates for esophageal cancer surgery.[13,14] Due to the attendant risk of liver dysfunction, extensive esophageal resections sometimes are contraindicated in cirrhotic patients. To our knowledge, there has been only one series that describes the mortality and morbidity of esophagogastrectomy for cirrhotic patients.[15,16] Those researchers reported limited esophagogastrectomy for this group of

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high-risk patients and did not perform extended lymph node dissection. Recent advances in perioperative patient care and surgical procedure, however, have reduced the morbidity and mortality associated with esophageal cancer surgery even after three-field lymphadenectomy[5,6] and, therefore, have produced optimism regarding the possibility of curative resection of esophageal carcinoma in cirrhotic patients. In this study, we have evaluated our experience of 18 esophageal resections along with extended lymph node dissection in cirrhotic patients and compared the results with those of 252 non-cirrhotic esophageal carcinoma patients.

PATIENTS AND METHODS

Between January 1981 and February 1999, 271 patients with primary esophageal carcinoma were admitted to the Second Department of Surgery, Shimane Medical University. Among those, 19 patients (7.0%) had pathologically proven cirrhosis of the liver; the remaining 252 patients did not.

Of the 19 patients with cirrhosis of the liver, 18 patients underwent esophagectomy (resectability rate 94.7%); the remaining patient refused any treatment. Seventeen patients underwent a right transthoracic subtotal esophagectomy and dissection of the three fields: the cervical (bilateral supraclavicular regions); mediastinal (periesophagus and around the trachea, including laryngeal recurrent nerve nodes): and abdominal (perigastric region and around the celiac axis) lymph nodes. During lymph node dissection, meticulous care was taken to ligate the small lymph channels to reduce lymphorrhea. Reconstruction was carried out with a gastric tube through the retrosternal route in 16 patients and with a right hemicolon through the subcutaneous route in one patient. Esophagogastrostomy was done using a cervical incision and laparotomy. The remaining patient, who had had a previous gastrectomy for peptic ulcer, underwent a left transthoracic lower esophagectomy with remnant stomach resection, and reconstruction was done with interposed transverse colon. The mean operative time of the 18 resected cases was 393 $\pm$ 108 minutes, and the mean amount of blood transfused was 8.6 $\pm$ 6.9 units of packed red blood cells derived from 200 ml of blood.

All patients were admitted to an intensive care unit for at least 2 days, with a minimum of 12 hours of mechanical ventilation. Postoperative management included enough water infusion on day 1 after esophagectomy and mild water and sodium restriction thereafter; infusion of albumin and fresh-frozen plasma to maintain the serum albumin at a level of at least 2.7 g/dl or prothrombin time at its preoperative level, and a diuretic agent, if necessary.

Clinicopathologic characteristics of these 19 cirrhotic patients and the 252 non-cirrhotic patients seen during the same period were investigated retrospectively based on the tumor, node, metastasis (TNM) classification of the malignant tumors.[17] Patients received regular outpatient follow-up, and all information was compiled within a database. An update inquiry about the current status of all surviving patients was done via telephone or letter contact in February of 1999. The patients who clearly died of recurrence were considered tumor-related deaths.

The standard χ^2 test, with or without Yates' correction, was used for comparative analyses. Survival rates were estimated using the Kaplan-Meier method,[18] and the statistical analysis was carried out by the log-rank test to test for equality of the survival curves. The level of significance was $P < .05$.

RESULTS

Patients With Cirrhosis of the Liver

All 19 patients had cirrhosis of the liver pathologically proven by either preoperative or intraoperative biopsy. All were men, with a mean age of 64.4 $\pm$ 8.3 years (range, 47–76). All patients had squamous cell carcinoma of the esophagus: 3 patients at the upper thoracic esophagus, 11 at the middle third, and 5 at the lower third. Eighteen patients underwent esophagogastrectomy, and one patient refused any treatment. The analyses discussed in the following sections were done for the 18 patients who underwent esophagectomy.

Clinicopathologic Characteristics of 18 Cirrhotic Patients Who Underwent Esophagectomy

The mean size of tumor was 6.1 $\pm$ 2.7 cm, ranging from 1.5 to 12.0 cm. Pathological T stages were pT1 in 3 patients, pT2 in 9 patients, pT3 in 2 patients, and pT4 in 4 patients. Hepatitis C virus (HCV) antibody was positive in one patient only, and 14 patients were alcoholics. Three patients had cryptogenic cirrhosis. Seven patients were classified as type B according to the Child-Turcotte classification, because of low serum albumin level ($\leq$ 3.5) in 6 patients and slight ascites in 1 patient. Four patients had weight loss of more than 10%. Indocyanine green (ICG)-R 15 was more than 30% in three patients: 30.6%, 34.3%, and 43.5%, respectively. Five patients had prolonged prothrombin time, and three had platelet counts lower than $10 \times 10^4/mm^3$ (Table 1). Only one patient underwent splenectomy, due to intractable bleeding from the spleen. As shown in Table 1, none of the cirrhotic patients in our series had thrombocytopenia.

TABLE 1. *Clinicopathologic features of esophageal cancer patients with liver cirrhosis who underwent esophagectomy (n = 18)*

Variable	m ±SD	(range)
Alcohol abuse	14	
HBAg-positive	0	
HCV-positive	1	(unknown 11)
Child-Turcotte classification A/B	11/7	
T-bilirubin	0.79 ± 0.34	(0.3–1.7)
Albumin	3.82 ± 0.50	(3.1–5.0)
>3.5 but <4.0	5	
≤3.5	6	
Weight loss (%)		
0	7	
>0, but ≤10	7	
>10	4	
ICG-R 15 min (%)	19.3 ± 9.4	(5.9–43.5)
≥10 but <20	8	
≥20 but <30	4	
≥30 but <40	2	
≥40	1	
PT (sec)		
<13.0	13	
>13.1	5	
Platelets ($\times 10^4/mm^3$)	16.2 ± 5.6	(7.4–24.0)
≥10.0 but <13.0	3	
<10.0	3	

ICG-R, indocyanine green test; m ±SD, mean ± standard deviation; PT, prothrombin time.

Operative Morbidity and Mortality

Three patients had an uneventful postoperative course. Fifteen patients (83.3%) developed a total of 35 postoperative complications (Table 2). Eight patients developed pleural effusion; of those, 4 patients developed persistent chylothorax as a cause of pleural effusion. Three of those died during the hospital stay—two due to septic complication associated with anastomotic leakage and one due to disseminated intravascular coagulopathy (DIC) (operative mortality, 16.7% in 18 resected cirrhotic patients vs. 5.7% in 227 resected non-cirrhotic patients; $P = .102$). When patients were stratified into two groups according to when they were seen (1981–1989 vs. 1990–1999), operative mortality rate in 227 non-cirrhotic patients was 7.8% (9/115) in the former period and 3.6% (4/112) in the latter. Of the cirrhotic patients, all three seen in the former period (3/9) died, whereas none seen during the latter period died (0/9). Similarly, in the cirrhotic group, estimated blood loss during esophagectomy in the former period was 2120 ± 1043 ml, dropping to 1257 ± 555 ml in the latter period ($P < .05$); in the non-cirrhotic group, those seen in the earlier period experienced blood loss of 1287 ± 873 ml, with a drop to 723 ± 479 ml in those seen in the latter period ($P < .01$). Table 3 lists clinicopathologic details of these three patients. All three patients had alcohol abuse. Two patients had severe weight loss (>10%) and were classified as Child-Turcotte B due to hypoalbuminemia. None of them had prolonged prothrombin time. Among 16 cirrhotic patients who had neither weight loss greater than 10% nor hypoalbuminemia (<3.4 g/dl), only one patient died of complications, whereas two patients who had both excessive weight loss and hypoalbuminemia died ($P < .05$).

TABLE 2. *Postoperative morbidity and mortality*

Variable	Morbidity (n = 15)	Mortality (n = 3)
Pulmonary		
Pneumonia	5	1 (20%)
Pleural effusion	8	–
Pneumothorax	2	–
Cardiac		
Arrhythmia	4	–
Cardiac failure	1	–
Technique-related		
Hemorrhage	4	–
Leakage	2	2 (100%)
Peritonitis, sepsis	3	2 (66.7%)
RNP	6	–
Others		
DIC	3	1 (33.3%)
Ascites	4	–
No complication	3	–

DIC, disseminated intravascular coagulopathy; RNP, recurrent laryngeal nerve paralysis.

Adjuvant Treatments

Five patients did not receive any adjuvant treatment because of superficial esophageal tumor (two patients), postoperative complications (two patients), and early tu-

TABLE 3. *Clinicopathologic backgrounds of three patients who died during the hospital stay after esophagectomy (in-hospital mortality)*

Patient characteristics	Case 1	Case 2	Case 3
Age (y)	67	57	76
Pathological stage	III	IV	IIA
Alcohol abuse	+	+	+
Weight loss (%)	21.0	19.0	0
Child class	B	B	A
Albumin	3.4	3.1	4.1
PT (sec)	12.2	10.5	10.5
Platelet	15.6	10.1	18.9
ICG-R 15 (%)	20.3	16.2	16.1
BSP 30′ (%)	–	17.0	35.9
Cause of death	Leakage[a] Sepsis	DIC	Leakage[b] Sepsis
Date of death	Day 20	Day 2	Day 12

DIC, disseminated intravascular coagulopathy; PT, prothrombin time.

[a] Pancreas juice leakage inducing left subphrenic abscess after splenectomy due to intraoperative injury.

[b] Leakage of ileotransversostomy of colon interposition.

mor progression (one patient). Four patients received postoperative chemotherapy alone. Of the remaining nine patients, five had both pre- and postoperative radiochemotherapy and four had postoperative radiochemotherapy only.

Outcome and Long-Term Survival in Cirrhotic vs. Non-Cirrhotic Patients

In 18 cirrhotic patients, 3 patients are still alive without cancer recurrence and 15 have died. Causes of death were in-hospital death in 3 patients; cancer recurrence in 7 patients; and causes unrelated to esophageal cancer in 5 patients—heart disease in 2 patients, and severe emaciation, choking accident, and synchronous hepatocellular carcinoma in 1 each. The long-term overall survival rates of 19 cirrhotic and 252 non-cirrhotic patients during the same period were compared. The 1-, 3-, and 5-year survival rates for 19 cirrhotic patients were 47.4%, 19.7%, and 19.7%, respectively, and those for 252 non-cirrhotic patients were 58.1%, 35.7%, and 29.9%, respectively ($P = .201$). The 1-, 3-, and 5-year survival rates for the 18 cirrhotic patients who had esophagectomy were 50%, 20.8%, and 20.8%, respectively, and those for the 27 non-cirrhotic patients were 67.1%, 42.1%, and 35.9%, respectively ($P = .050$) (Fig. 1). When 3 cirrhotic and 13 non-cirrhotic patients who died within 30 days after esophagectomy (operative death) were excluded from the analysis, the 1-, 3-, and 5-year survival rates for 15 cirrhotic patients were 60%, 25%, and 25%, whereas those for 214 non-cirrhotic patients were 68.4%, 42.9%, and 36.6%, respectively ($P = .271$) (Fig. 2). Thus, when postoperative complications were well managed, the cirrhotic patients had almost same long-term survival as that of non-cirrhotic patients.

DISCUSSION

Cirrhotic patients with esophageal cancer have been seen occasionally in the literature.[13,14] The incidence of cirrhosis in the present study was 7.0%, which is comparable to the 6.6% rate in a previous study by Fekete et al.[15] Although the major cause of chronic hepatitis or cirrhosis of the liver in Japan is viral infection,[19] most of the cirrhotic patients in this series were alcoholics. This may be attributable to the carcinogenic property of alcohol in esophageal squamous cell carcinoma,[20] which is the dominant histological type of esophageal cancer in Japan.[2]

Patients with only Child-Turcotte A and B cirrhosis[21] were the candidates for esophageal surgery in this series, which is different from the selection criteria in hepatocellular carcinoma patients in another study reported by Nagasue et al.[22,23] Hyperbilirubinemia (> 3.0 mg/dl) or the presence of uncontrollable ascites in Child-Turcotte C criteria, and severe weight loss ($>10\%$) with hypoalbuminemia are considered contraindications for esophagectomy. Of particular importance, we did not consider high rate of ICG-R 15 a contraindication for surgery. In fact, three patients had ICG-R 15 values over 30%, but none of them died of complications. Because the cirrhotic liver sometimes has portosystemic shunts, ICG-R 15 does not necessarily correlate with the functional reserve of cirrhotic liver. Moreover, having the surgery performed by an experienced liver surgeon who has clinical experience with a large number of cirrhotic patients may be an important factor in obtaining a successful outcome for cirrhotic patients with esophageal cancer. In fact, we have had no cases of in-hospital death in cirrhotic patients for the 9 years since a surgeon who

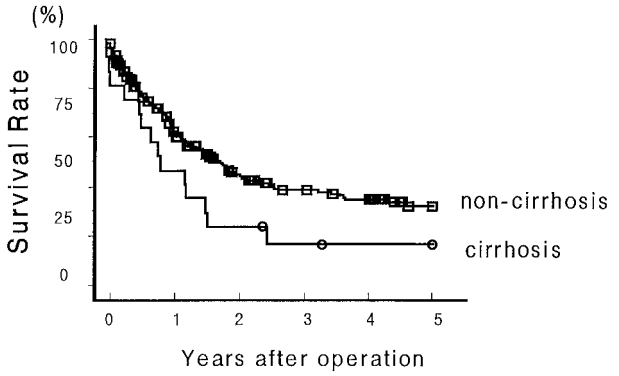

FIG. 1. Cumulative survival curves after esophagectomy for cirrhotic and non-cirrhotic patients. The 1-, 3-, and 5-year survival rates for 18 cirrhotic patients who underwent esophagectomy were 50%, 20.8%, and 20.8%, whereas those for 227 non-cirrhotic patients were 67.1%, 42.1%, and 35.9%, respectively ($P = .050$).

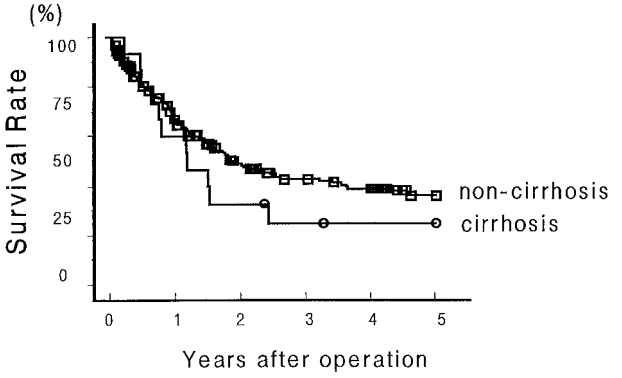

FIG. 2. Cumulative survival curves after esophagectomy for cirrhotic and non-cirrhotic patients when 3 cirrhotic and 13 non-cirrhotic patients who died within 30 days after esophagectomy were excluded from the analysis. The 1-, 3-, and 5-year survival rates after esophagectomy were 60%, 25%, and 25% for the 15 cirrhotic patients and 68.4%, 42.9%, and 36.6% for the 214 non-cirrhotic patients ($P = .271$).

also has extensive experience in operating on hepatocellular carcinoma patients joined the esophageal surgical team.

Among the miscellaneous postoperative complications we saw, pleural effusion and ascites occurred frequently, but were easily managed without any fatality. One possible reason for the high incidence of pleural effusion rather than ascites is that we performed extensive mediastinal lymphadenectomy, particularly around the trachea, which caused interruption of the lymph channels and subsequently caused massive lymphorrhea in the thorax. The incidence of hemorrhage (22.2%) apparently was higher than the rate previously reported for noncirrhotic patients.[9] Out of four who had hemorrhage, three patients had either prolongation of prothrombin time or depletion of platelet count, indicating that meticulous hemostasis may be important in cirrhotic patients. Anastomotic leakage that causes peritonitis or sepsis, or both, is one of the most serious complications after esophagectomy, with an incidence from 5% to 33% reported in the literature.[6,24–26] The mortality rates from leakage and from sepsis in cirrhotic patients in this study were 50% and 67%, respectively, and were reported to be 66% and 60%.[15] One possible reason for the high mortality rate due to septic complications is that cirrhotic patients have immunosuppressive conditions that cannot tolerate infection.[27] Pulmonary infection also is a well-known cause of in-hospital death after esophagectomy.[5,6,24–26] Pneumonia developed in 33.3% of the cirrhotic patients, but only one patient died because of it. Because esophagectomized patients are unable to cough in the postoperative period, we routinely perform cricothyroidotomy in all cases to facilitate suction of sputum without patient discomfort. This may be beneficial for reducing mortality by pulmonary infection.[28]

Three patients (16.7%) in the present study died of postoperative complications, a rate comparable to or lower than the rate previously reported.[15,16] Fekete et al.[15] reported that the only significant preoperative predictor of mortality after esophagectomy was a prothrombin time less than or equal to 60% of normal, but in this series, all three patients who died of complications had normal prothrombin times. Our data indicated, however, that patients who had both weight loss and hypoalbuminemia had a significantly higher mortality rate than those who did not. Therefore, patients with severe weight loss and hypoalbuminemia should be considered high-risk and are not suitable for an extended esophagectomy operation. A limited resection for palliation or adjuvant radiochemotherapy may be appropriate for these patients.

Although long-term survival of resected cirrhotic patients tended to be worse than that of resected noncirrhotic cases ($P = .050$), secondary to high operative mortality, these rates did not change when operative deaths were excluded ($P = .271$). These results may suggest that cirrhotic patients with esophageal cancer have the same chance of cure as do noncirrhotic patients when postoperative complications are managed well without mortality. Therefore, the mere presence of cirrhosis should not be considered a contraindication for curative extended esophagectomy operation. However, careful patient selection should be done to avoid postoperative liver failure and complication-related deaths. During the follow-up period, only one patient died of liver-associated disease (hepatoma) in our series, and Fekete et al.[15] also reported that none of their 23 patients after esophagectomy was dead due to cirrhosis- associated disease. On the other hand, the most frequent causes of death for cirrhotic patients after gastrectomy for gastric cancer were cirrhosis-related death, such as gastrointestinal bleeding or hepatic failure or hepatoma.[29,30] There are two possible explanations for why few patients die of liver-associated disease after esophagectomy. First, esophagogastrectomy involves a complete devascularization of the esophagogastric varices, which causes less gastrointestinal bleeding. Second, most patients develop loss of appetite after esophagectomy[31] and, consequently, reduce the alcohol consumption that is a major etiologic factor for cirrhosis in esophageal cancer patients. Thus, these patients might recover their postoperative liver function status.

In conclusion, our results indicate that cirrhosis provides a high probability of postoperative complications and a possible high mortality when compared with noncirrhosis in esophageal cancer surgery. Debilitated cirrhotic patients with excessive weight loss and hypoalbuminemia should be considered a high-risk group because of high postoperative mortality. Child-Turcotte A and B cirrhosis may not be a contraindication for curative esophagectomy for esophageal carcinoma; however, these patients need meticulous perioperative care to avoid postoperative complications.

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