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Prognosis After Surgical Resection of M1a/M1b Esophageal Squamous Cell Carcinoma

This study was undertaken to examine prognosis after resection for M1 disease in squamous cell esophageal carcinoma. Fifty-six patients with M1 esophageal cancer underwent esophageal resection with two or three-field nodal dissection from 1994 to 2001. Operative mortality occurred in 3 patients. Primary tumor sites were as follows; 10 upper, 23 middle, and 20 lower thoracic esophagus. They were found to have M1 disease by pathologic examination of dissected nodes, 24 M1a and 29 M1b. Forty-two patients (79%) were considered to have undergone curative resection. Chemotherapy and/or radiation therapy was given to 38 patients perioperatively. Recurrence was identified in 35 patients (66%) during a mean follow-up of 23 months. Overall median and 5-yr survivals were 19 months and 12.7%. Five-year survivals for M1a and M1b disease were 23.9% and 6.1%, respectively (p=0.0488). Curative resection tended to show better survival (p=0.3846). Chemotherapy and/or radiation therapy provided no advantage (p=0.5370). Multivariate analysis showed that M1b was significant risk factor over M1a disease. Our conclusion is that surgical resection can provide acceptable survival in thoracic squamous esophageal cancer with M1a disease. Survival differences between M1a and M1b disease support the current subclassification staging system.

Key Words : *Esophageal Neoplasm; Esophagectomy; Neoplasm Staging*

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INTRODUCTION

Distant metastatic disease from esophageal cancer is subclassified as M1a (distant, nonregional lymph node metastases) or M1b (other distant metastases). M1a disease is further classified by tumor location; M1a tumors of the upper thoracic esophagus metastatic to cervical nodes and M1a tumors of the lower thoracic esophagus metastatic to celiac lymph nodes. M1b tumors represent other distant metastases, namely, upper thoracic esophagus metastatic to noncervical nonregional lymph nodes or other distant sites, mid thoracic esophagus metastatic to either nonregional lymph nodes or other distant sites, and lower thoracic esophagus metastatic to nonceliac nonregional lymph nodes or other distant sites. Some reports have concerned the prognosis of M1a and M1b after the surgical resection of esophageal carcinoma. We report our surgical results of M1a and M1b esophageal squamous cell carcinoma and evaluate the clinical relevance of the M1a and M1b subclassification.

MATERIALS AND METHODS

We reviewed the data of the patients who had pathological M1a or M1b disease after esophageal resection and lymph node dissection. Fifty-six patients underwent esophageal resection and lymph node dissection from November 1994 to December 2001, composed of 4 transhiatal resections, 33 Ivor Lewis procedures, and 19 three-stage procedures, which included cervical anastomosis and node dissection. Operative mortality, including in-hospital deaths, occurred in 3 patients (5.4%). They had all undergone three-field lymph node dissection. Two patients died of respiratory failure and one patient died of sepsis. The remaining 53 patients were discharged, and their primary tumor sites were as follows; 10 upper, 23 middle, and 20 lower thoracic esophagus. The histologic type was squamous cell carcinoma in all patients, and all were found to have M1 disease by pathologic examination of the dissected lymph nodes, 24 M1a and 29 M1b (Table 1). Of the 29 M1b patients, three patients had intraoperative findings of pleural, hepatic, and satellite gastric metastasis respectively. The other 26 patients had metastases to the nonregional lymph nodes. Forty-two patients (79%) were considered to have undergone curative resection according to a tumor-negative resection margin. Chemotherapy and/or radiation therapy was given to 38 patients preoperatively or postoperatively. Recurrences and survivals were calculated for patients who were discharged. Survival was compared using the log rank test,

and the Cox regression test was used for univariate and multivariate analyses by using SPSS (ver. 10.0).

RESULTS

Recurrence was identified in 35 patients (66% of 53 patients) during follow-up for a mean 23 and a median 15.4 months (3 to 80 months). Locoregional recurrences were detected in 19, visceral distant metastases in 7, and locoregional recurrences with distant metastases in 9 (Table 2). When simultaneous locoregional recurrences and distant metastases were considered as distant relapse, locoregional relapse was more common in M1a than in M1b, but without statistical difference (p=0.123).

Table 1. Clinical characteristics of 53 patients with squamous esophageal carcinoma

Variable	All patients (% of 53)	M1a (% of 24)	M1b (% of 29)	p
Male Sex	52 (98)	24 (100)	28 (97)	1.000
EUS	30 (57)	17 (71)	13 (45)	0.057
PET	26 (49)	11 (46)	15 (52)	0.669
Tumor location				0.000
Upper	10 (19)	9 (38)	1 (3)	
Middle	23 (43)	0 (0)	23 (79)	
Lower	20 (38)	15 (62)	5 (17)	
Differentiation				0.274
Poor	12 (23)	3 (13)	9 (31)	
Moderate	29 (54)	15 (63)	14 (48)	
Well	12 (23)	6 (25)	6 (21)	
Preop. stage				0.649
IIA	4 (8)	1 (4)	3 (10)	
IIB	1 (2)	0 (0)	1 (3)	
III	38 (72)	18 (75)	20 (69)	
IV	10 (19)	5 (21)	5 (17)	
Type of operation				0.070
Ivor Lewis procedure	33 (62)	13 (54)	20 (69)	
Right thoracotomy and neck and abdominal incisions	16 (30)	7 (29)	9 (31)	
Transhiatal resection	4 (8)	4 (17)	0 (0)	
Resection margin				0.195
Negative	42 (80)	21 (88)	21 (72)	
Microscopically positive	5 (9)	1 (4)	4 (14)	
Grossly positive	6 (11)	2 (8)	4 (14)	
Preoperative treatment				0.877
RTx.	2 (4)	1 (4)	1 (3)	
CTx.	4 (8)	2 (8)	2 (7)	
RTx. and CTx.	3 (6)	2 (8)	1 (3)	
None	44 (83)	19 (79)	25 (86)	
Adjuvant therapy				0.866
RTx.	7 (13)	4 (17)	3 (10)	
CTx.	24 (45)	10 (42)	14 (48)	
RTx. and CTx.	3 (6)	1 (4)	2 (7)	
None	19 (36)	9 (38)	10 (34)	

EUS, esophageal ultrasound; PET, positron emission tomography; RTx., radiotherapy; CTx., chemotherapy.

Overall median survival, 3-, and 5-yr survivals were 19 months, 25.1%, and 12.7% (Fig. 1). Three-, and 5-yr survivals of M1a and M1b were 35.8%, 23.9% and 16.3%, 6.1%, respectively. Patients with M1a disease showed better survival than those with M1b disease by the log rank test (p=0.0488) as shown in Fig. 2. Well differentiated tumors showed better survivals than poorly differentiated tumors (p=0.0428). Curative resection showed better survival than incomplete resection but this lacked statistical significance (p=0.3846). Adjuvant chemotherapy and/or radiation therapy provided no advantage (p=0.5370). Clinical stage and type of operation had no effect according to the survival curve.

Univariate correlates of survival by Cox regression were analyzed in Table 3. Patients with poor differentiation and M1b disease had a higher risk than those with well differentiated M1a disease. Multivariate analysis was performed using likelihood-ratio statistics based on the conditional parameter estimate, and M1b disease was found to be the only significant risk factor in the prognosis of stage IV esophageal squamous cell carcinoma.

DISCUSSION

Involvement of the more distant lymph nodes (for example, the cervical or celiac nodes for intrathoracic tumors) is considered distant metastasis in the sixth edition of the American

Table 2. Initial site of relapse in M1a or M1b disease

Site of relapse	M1a	M1b	Total patients
Locoregional	12	7	19
Locoregional and distant	3	6	9
Distant	2	5	7
Total	17	18	35

Table 3. Univariate correlates of survival 53 patients with squamous esophageal carcinoma

Variable	Odds ratio	95% CI	p
Differentiation			
Moderate/well	2.15	0.87-5.28	0.096
Poor/well	3.05	1.11-8.37	0.031
Clinical stage			
III/II	0.84	0.29-2.43	0.746
IV/II	1.12	0.34-3.74	0.855
Type of operation			
three-field /I-L	1.18	0.36-3.92	0.787
transhiatal /I-L	1.14	0.32-4.06	0.840
Resection margin			
Positive/negative	1.39	0.64-3.01	0.411
Adjuvant therapy			
Done/none	1.23	0.64-2.37	0.539
M1a or M1b			
M1b/M1a	1.87	0.99-3.58	0.053

CI, confidence interval; I-L, Ivor Lewis procedure.

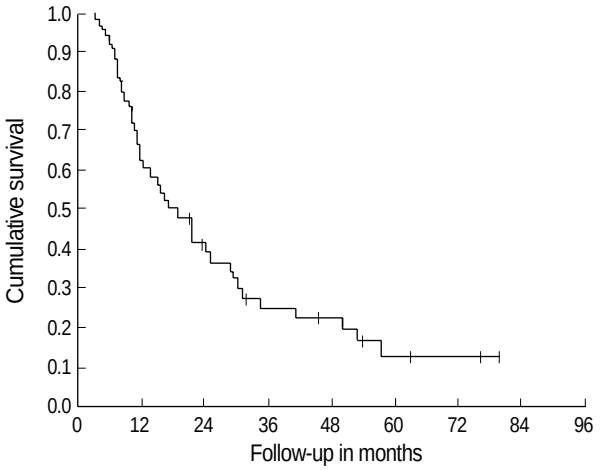

Fig. 1. Overall survival in 53 patients.

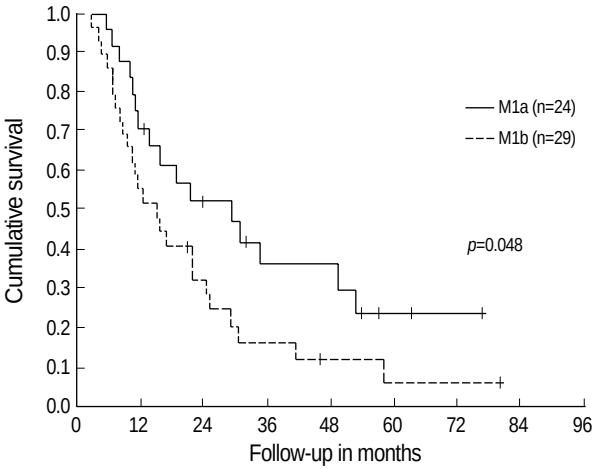

Fig. 2. Survival in patients with M1a or M1b disease. Three-year and 5-yr survivals for those with M1a were 35.8% and 23.9%.

Joint Committee on Cancer (AJCC) current staging (1). Previous reports suggested that nonregional metastases are resectable and that they are associated with a better survival than visceral metastases after surgical resection (2, 3). A recent report pointed out that the N1 versus M1a versus M1b descriptors do not accurately identify prognostically different groups (4). Christie and colleagues concluded that although there are statistically significant survival differences between M1a and M1b diseases, these differences are not clinically important due to a survival of less than 10% in both diseases (5). Their experiences mainly included adenocarcinoma of the distal thoracic esophagus and of the esophagogastric junction. Our data concerns only esophageal squamous cell carcinoma because of epidemiological characteristics in East Asian countries. It is not yet clear if the two cell types differ biologically or merely in location (6).

Operative results showed an acceptable range of operative and in-hospital mortality, but 81% of our patients were clinically stage II or III. We obtained an overall survival comparable to that of previous report (2). M1a disease showed better survival than M1b and this had clinical and statistical significance, which support the suggestion that the involvement of cervical or celiac nodes by intrathoracic tumors be classified as N2 disease rather than M1a. Ide and associates in Japan considered metastases from lower thoracic esophageal carcinomas to the celiac nodes as N2 rather than Ml disease (7). Such a change in classification requires further study. Moreover, our data would benefit from longer follow-up period.

Our results indicate that preoperative nodal staging is important because M1b disease has poor results after surgical resection. Preoperative accurate assessment of lymph nodes can be achieved by techniques like EUS-guided needle biopsies and PET. If lymph nodes are found to be positive, then whether the patients should be administered neoadjuvant therapy is another issue for study. Adjuvant chemotherapy and radiotherapy may or may not offer a survival advantage in patients with advanced esophageal cancer. Our data showed no advantage from adjuvant therapy, but this is not conclusive because of the heterogeneity and the small number of patients.

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