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 preoperatively. 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
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 ($p=0.123$).

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

| 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 |
| II A     | 4 (8) 1 (4) 3 (10) |
| III B    | 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) |

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

| Variable | M1a | M1b |
|----------|-----|-----|
| Site of relapse | 17 | 18 |
| Locoregional | 12 | 7 |
| Locoregional and distant | 6 | 9 |
| Distant | 2 | 5 |
| Total | 17 | 35 |

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

| Variable | Odds ratio | 95% CI | $p$ |
|----------|------------|--------|-----|
| Differentiation | 2.15 | 0.87-5.28 | 0.096 |
| Poor/well | 3.05 | 1.11-8.37 | 0.031 |
| Clinical stage | 0.84 | 0.29-2.43 | 0.746 |
| III/II | 1.12 | 0.34-3.74 | 0.855 |
| Type of operation | 1.18 | 0.36-9.92 | 0.787 |
| three-field /I-L | 1.14 | 0.32-4.06 | 0.840 |
| Resection margin | 0.866 |
| Positive/negative | 1.23 | 0.64-3.01 | 0.411 |
| Adjuvant therapy | 1.87 | 0.99-3.58 | 0.053 |

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

EUS, esophageal ultrasound; PET, positron emission tomography; RTx., radiotherapy; CTx., chemotherapy.
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 M1 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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