ANNALS OF SURGERY
Vol. 222, No. 5, 654–662

Mortality and Morbidity Rates, Postoperative Course, Quality of Life, and Prognosis After Extended Radical Lymphadenectomy for Esophageal Cancer

Comparison of Three-Field Lymphadenectomy with Two-Field Lymphadenectomy

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Purpose
The authors evaluated the efficacy of extended radical (three-field) lymphadenectomy for esophageal cancer compared with less radical (two-field) lymphadenectomy.

Study Subjects and Analytic Methods
The mortality and morbidity rates, postoperative courses, and survival rates were compared between 63 patients who underwent three-field lymph node dissection and 65 who underwent two-field lymph node dissection at Kurume University Hospital from 1986 to 1991. Long-term quality of life after surgery was compared between 37 patients who underwent three-field dissection and 35 who underwent two-field dissection from 1980 to 1991.

Results
Three-field dissection resulted in better survival for patients with positive lymph node metastasis from a carcinoma in the upper thoracic or midthoracic esophagus compared with two-field dissection. The mortality rates, postoperative courses and quality of life were the same for both procedures.

Conclusions
Three-field dissection is preferred for upper thoracic or midthoracic esophageal cancer because of improved survival, acceptable mortality and morbidity rates, and good postoperative course and quality of life.

Controversy remains over the efficacy of extended radical lymphadenectomy for esophageal cancer. The Consensus Conference in the International Gastro-Surgical Club 1994 in Munich concluded that extended radical lymphadenectomy for esophageal cancer offered the more correct staging and prevented regional lymph node recurrence. However, the conference could not agree that extended radical lymphadenectomy improved the survival of patients with esophageal cancer, largely because of the lack of a well-controlled randomized trial to evaluate this.[1]

Another controversy involves whether extended radical lymphadenectomy increases mortality and morbidity and disturbs long-term quality of life. Orringer reported low mortality and morbidity rates and a shorter hospital stay after transhiatal esophagectomy compared with transthoracic esophagectomy.[2] In contrast, according to a recent randomized control trial, Goldminc et al. reported no change in mortality and morbidity rates or duration of intensive care unit and hospital stay in a comparison of transhiatal and transthoracic esophagectomy.[3] Yoshida and Iwatsuka conducted a nonrandomized trial and found longer operation time, more blood loss, and higher mortality and morbidity rates after extended three-field dissection compared with after conventional two-field dissection.[4] In contrast, a randomized control study by Kato et al. revealed no change in mortality rate within 30 days and no change in morbidity rate or hospital stay in a comparison of three-field and two-field dissection.[5]

In the current study, we used a nonrandomized trial to compare the mortality and morbidity rates, postoperative courses, quality of life, and survival after three-field and two-field dissection for thoracic esophageal cancer. This study was not truly randomized because we used patient age and risk for complications as determinants for choosing three-field or two-field dissection.

PATIENTS AND METHODS

The study group consisted of all 128 patients who had undergone R0[6] subtotal esophagectomy for a squamous cell carcinoma in the thoracic esophagus between 1986 and 1991 at Kurume University Hospital. During this 6-year period, 262 patients with a carcinoma in the thoracic esophagus were admitted to our hospital, and 204 (77.9%) of these patients underwent esophagectomy: 133 for R0 curative transthoracic esophagectomy, 55 for R1 or R2[6] palliative transthoracic esophagectomy, and 16 for transhiatal esophagectomy. Five of these 133 patients were excluded from the study: two because of adenocarcinoma in the esophagus and three because of synchronous double primary carcinomas, the other tumor of which underwent palliative resection.

The male-to-female ratio of the study group was 112:16, and the average age was 60.9 years old. The location of the tumor was the upper thoracic esophagus for 11 patients, the midthoracic esophagus for 79 patients, and the lower thoracic esophagus for 38 patients. The distribution of the primary tumor was 1 with pTis, 29 with pT1, 19 with pT2, 73 with pT3, 5 with pT4, and 1 with undetermined pT because of preoperative treatment. Eighty-three patients had positive metastasis in the lymph nodes, including M1-Lym (TNM classification[6]), resulting in a metastatic rate of 64.8%. Eighteen patients had positive metastasis in the cervical and/or celiac nodes classified as M1-Lym, resulting in a metastatic rate of 14.1%. The average number of metastatic nodes per patient was 3.3 and of dissected nodes per patient, 65.5. The stage distribution was 1 at stage 0, 18 at stage I, 25 at stage IIA, 18 at stage IIB, 45 at stage III, 20 at stage IV, and 1 at an undetermined stage because of preoperative treatment.

Of the 128 patients, 63 underwent cervicothoracoabdominal three-field dissection through a right thoracotomy. The remaining 65 patients underwent thoracoabdominal two-field dissection: 54 through a right and 11 through a left thoracotomy. Three-field dissection was performed for patients who were age 70 years or younger and who were at a low risk for postoperative complications according to our original criteria for the risk analysis.[7] Background factors of the patients who underwent three-field and two-field dissection are shown in Table 1. Significant differences in background factors between the two groups were found, including patient age, approach, number of dissected lymph nodes, adjuvant therapies, and risk score for risk analysis.

Seventy-two patients had undergone R_0 subtotal esophagectomy with three-field or two-field dissection through a thoracotomy between 1980 to 1992 and had survived more than 2 years without recurrence. These patients were observed for long-term quality of life after surgery. Originally, a letter of inquiry about their postoperative conditions had been sent to each of 85 patients, and answers were received back from 72 (84.7%). Among these, 37 patients had undergone three-field dissection and 35 patients two-field dissection. The background factors of these two groups of patients are shown in Table 2. Significant differences between the two groups included the factors of age, adjuvant therapies, and follow-up period.

RESULTS

Mortality and Morbidity Rates

As shown in Table 3, the hospital mortality rates were 2% (1/63) after three-field dissection and 3% (2/65) after

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Accepted for publication March 9, 1995.

Table 1. CLINICAL CHARACTERISTICS OF PATIENTS WHO UNDERWENT 2-FIELD AND 3-FIELD LYMPHADENECTOMY FROM 1986 TO 1991

	2-Field	3-Field	p-Value
Sex (M/F)	55/10	57/6	NS
Age (yrs)	63.5 ± 8.8	58.3 ± 6.3	<0.001
Cancer location (upper/middle/lower)	3/44/18	8/35/20	NS
Tumor length (cm)	6.7 ± 3.2	7.3 ± 2.8	NS
Histology (G1/G2/G3/G4/unknown)	15/32/8/6/4	25/26/6/5/1	NS
pT (Tis/T1/T2/T3/T4/unknown)	1/17/9/33/4/1	0/12/10/41/0	NS
pN (N0/N1)	26/39	19/44	NS
pM-Lym (M0/M1)	58/7	52/11	NS
Stage (0/I/IIA/IIB/III/IV/unknown)	1/13/11/9/23/7/1	0/5/14/9/22/13/0	NS
Approach (right/left thoracotomy)	54/11	63/0	<0.01
Lymphadenectomy (metastatic nodes/dissected nodes)			
Neck	0.8 ± 4.5/2.7 ± 8.5	0.9 ± 2.9/26.6 ± 13.7	NS/<0.001
Upper mediastinum	0.8 ± 2.0/9.5 ± 10.4	0.8 ± 1.3/20.1 ± 9.9	NS/<0.001
Lower mediastinum	1.1 ± 1.8/15.2 ± 10.8	0.4 ± 0.8/19.3 ± 10.0	NS/<0.05
Abdomen	1.0 ± 1.5/19.1 ± 12.4	0.9 ± 1.5/18.9 ± 11.6	NS/NS
Total	3.6 ± 6.1/46.7 ± 26.1	3.0 ± 4.7/85.0 ± 28.7	NS/<0.001
Adjuvant therapy (surgery alone/pre R*/pre C†/post R‡/ post C†/pre R* + post R‡ pre R* + post C†/post R‡ + C†	30/6/1/1/18/0/2/7	25/0/0/3/32/1/1/1	<0.01
Risk analysis			
Risk score	2.5 ± 1.8	1.7 ± 1.4	<0.01
Karnovsky index	78.0 ± 16.3	82.4 ± 14.8	NS
Followup period (mos)	53.0 ± 22.6	46.0 ± 21.0	NS

* For the main tumor, 30 Gy.
† CDDP 70 mg/m^2 + VDS 3 mg/m^2 or 5Fu 700 mg/m^2, 2 courses.
‡ For the cervical and upper mediastinum, 50 Gy.

two-field lymphadenectomy, with no significant difference between them. No patients died within 30 days after either three-field or two-field dissection. During the average follow-up period of 46.0 months, 52% of the 63 patients who had undergone three-field dissection had died: 33% of recurrence, 14% of noncancerous causes,

Table 2. CLINICAL CHARACTERISTICS OF PATIENTS FOR WHOM QUALITY OF LIFE WERE EVALUATED

	2-Field	3-Field	p-Value
Sex (M/F)	26/9	34/3	<0.05
Age (yrs)	64.0 ± 7.7	57.9 ± 7.1	<0.001
Cancer location (upper/middle/lower)	1/24/10	3/20/14	NS
Histology (G1/G2/G3/G4/unknown)	11/16/4/3/1	13/14/5/4/1	NS
pT (Tis/T1/T2/T3/T4)	1/15/6/12/1	0/13/3/21/0	NS
pN (N0/N1)	24/11	19/18	NS
pM-Lym (M0/M1)	34/1	32/5	NS
Stage (0/I/IIA/IIB/III/IV)	1/13/10/4/6/1	0/6/13/6/7/5	NS
Adjuvant therapy (surgery alone/pre R*/pre R* + pre C†/ post R‡ + post C§/post R‡ + C§/pre R* + post R‡/ pre R* + post C§	20/3/1/2/6/1/1/1	16/1/0/1/18/0/0/1	<0.01
Followup period (mos)	65.6 ± 39.0	41.0 ± 23.0	<0.01

* For the main tumor, 30 Gy.
† CDDP 70 mg/m^2 + 5Fu 700 mg/m^2, 1 course.
‡ For the cervical and upper mediastinum, 50 Gy.
§ CDDP 70 mg/m^2 + VDS 3 mg/m^2 or 5Fu 700 mg/m^2, 2 courses.

Table 3. OPERATIVE RESULTS AFTER ESOPHAGECTOMY WITH EXTENDED RADICAL LYMPHADENECTOMY

	2-Field	3-Field	p-Value
Hospital mortality within 30 days	0	0	NS
Hospital mortality	2 (3%)	1 (2%)	NS
Died of recurrence	33 (51%)	21 (33%)	<0.05
Died without cancer	7 (11%)	9 (14%)	NS
Died of another cancer	0	2 (3%)	NS
Alive	23 (35%)	30 (48%)	NS

3% of other primary cancers, and 2% of postoperative complications. In contrast, during the average follow-up period of 53.0 months, 65% of the 65 patients who had undergone two-field dissection had died: 51% of recurrence, 11% of noncancerous causes after discharge, and 3% of postoperative complications. The ratio of patients who died of recurrence was significantly less after three-field dissection than after two-field dissection ($p < 0.05$).

Postoperative complications, such as recurrent nerve paralysis, leakage, aspiration pneumonia, tracheobronchial ulcer, hepatitis, and sepsis were common after three-field dissection, whereas complications such as recurrent nerve paralysis, aspiration pneumonia, hepatitis, sepsis, pyothorax, and leakage were common after two-field dissection (Table 4). Recurrent nerve paralysis occurred more often after three-field dissection than after two-field dissection (70% *vs.* 48%; $p < 0.05$). However, the incidence of permanent recurrent nerve paralysis did not differ between two groups (27% *vs.* 32%). Anastomotic leakage (33% *vs.* 11%; $p < 0.01$) and tracheobronchial ulcer (17% *vs.* 0%; $p < 0.01$) also were more common occurrences after three-field dissection.

Postoperative Courses

Table 5 shows the comparison of the postoperative courses between three-field and two-field dissection. Between both procedures there was no difference in any factor related to the postoperative course, such as weight gain immediately after esophagectomy (which is related to the volume of the third-space sequestration and the severity of the operation), length of time until a patient reached maximal weight, duration of assisted ventilation after surgery, proportion of patients with respiratory failure who had required assisted ventilation for more than 2 weeks, ratio of patients who underwent tracheostomy, duration of stay in an intensive care unit, and ratio of patients with complications who required intensive care for more than 2 weeks.

Survival Rates

Figure 1 shows the survival curves of patients who underwent three-field and two-field dissection. The 1-, 3-, and 5-year survival rates were 87%, 51%, and 40% after three-field dissection and 74%, 44%, and 36% after two-field dissection, with no significant difference between the two groups.

Figure 2 shows the survival curves of patients in subgroups according to cancer location and positivity of lymph node metastasis. Among patients with carcinoma in the upper thoracic or midthoracic esophagus with positive metastasis in the lymph nodes, survival after three-field dissection was significantly better than after two-field dissection ($p < 0.05$). However, no difference between the two procedures was found among patients with carcinoma in the lower thoracic esophagus or among patients with no metastasis in the lymph nodes.

Quality of Life

The postoperative conditions of patients who underwent three-field or two-field dissection was investigated by letter inquiry. Figure 3 shows the distribution of the performance status (PS)[8] of the 37 patients who underwent three-field dissection and 35 who underwent two-field dissection (Performance Status indicates the grading of physical activity, similar to Karnofsky index). Eighty-nine percent of patients were in PS-0 and 11% in PS-1 before three-field dissection, compared with 57% in PS-0, 41% in PS-1, and 3% in PS-2 after surgery. Conversely, 77% of patients were in PS-0, 17% in PS-1, and 6% in PS-2 before two-field dissection, compared with 29% in PS-0, 46% in PS-1, 20% in PS-2, 3% in PS-3, and 3% in PS-4 after surgery. The distribution of preoperative PS did not differ between three-field and two-field dissection, whereas postoperative PS was significantly better among patients after three-field dissection than after two-field dissection ($p < 0.01$).

Figure 4 shows the rates of patients who were employed. Sixty-nine percent of patients had worked before two-field dissection, 26% of whom could return to work after surgery. In comparison, 86% of patients had worked before three-field dissection, 56% of whom could return to work after surgery. Before surgery, the ratio of patients who worked did not differ between the two groups, whereas after surgery a significantly higher ratio was found after three-field dissection than after two-field dissection ($p < 0.05$).

Figure 5 shows the rates of patients reporting long-term problems after surgery. No difference was found between the two groups regarding patient reports of aspiration, hoarseness, or dyspnea, whereas severe pneumonia required hospitalization less often among patients who had undergone three-field dissection *versus* two-field dissection ($p < 0.05$).

Table 4. POSTOPERATIVE COMPLICATIONS

	2-Field	3-Field	p-Value
Recurrent nerve paralysis	31 (48%)	44 (70%)	<0.05
Permanent	21 (32%)	17 (27%)	—*
Temporary	11 (17%)	27 (43%)	—
Aspiration pneumonia	21 (32%)	17 (27%)	—
Hepatitis	13 (20%)	8 (13%)	—
Sepsis	9 (14%)	6 (10%)	—
Pyothorax	7 (11%)	5 (8%)	—
Anastomotic leakage	7 (11%)	21 (33%)	<0.01
Bronchopneumonia	4 (6%)	4 (6%)	—
Bleeding (reoperation)	4 (6%)	3 (5%)	—
Renal failure	3 (5%)	1 (2%)	—
Multiple organ failure	3 (5%)	0	—
Peptic ulcer	2 (3%)	2 (3%)	—
Anastomotic stricture	2 (3%)	5 (8%)	—
Alveolar fistula	2 (3%)	1 (2%)	—
Ileus	1 (2%)	2 (3%)	—
Subphrenic abscess	1 (2%)	1 (2%)	—
Tracheomalasia	1 (2%)	1 (2%)	—
Horner's syndrome	1 (2%)	1 (2%)	—
Tracheal ulcer	0	11 (17%)	<0.01
Purulent osteomyelitis	0	4 (6%)	—
Cholecystitis, pulmonary torsion, cardiac tamponade, meningitis, esophagotracheal fistula, hepatic failure, ARDS	Each 1	Fistula of the cervical thoracic duct, DIC, rupture of the common carotid artery	Each 1

ARDS = adult respiratory distress syndrome, DIC = disseminated intravascular coagulation.
* No significant difference.

Figure 6 shows the mental condition of the patients who underwent radical esophagectomy. Preoperative and postoperative mental activity was compared. No patients experienced more active or more positive mental activity after surgery. Thirty-eight percent of patients who underwent three-field dissection and 62% who underwent two-field dissection believed that mental activity had become more passive or negative. The degree of anxiety over their clinical state was evaluated. After three-field dissection, 6% of patients were always and 46% were occasionally anxious, whereas after two-field dissection, 12% were always and 52% were occasionally anxious. According to the patients' evaluation of treatment, of those patients who had undergone three-field dissection, 0% were dissatisfied and 59% were satisfied with the surgery; for those who had undergone two-field dissection, 6% were dissatisfied and 54% were satisfied with the surgery. In summary, no differences between the two groups were found regarding mental activity, anxiety over clinical state, or satisfaction with treatment.

DISCUSSION

In the current study, extended radical lymphadenectomy, that is, three-field dissection, did not increase number of deaths, although such postoperative complications as recurrent nerve paralysis, tracheal ischemic lesions, and anastomotic leakage were more common after three-field than after two-field dissection. Isono et al. found that recurrent nerve paralysis occurred more often after three-field than after two-field dissection, whereas the incidence of anastomotic leakage was the same after three-field dissection as after two-field dissection.[9] Kato et al. reported that anastomotic leakage was relatively more common after three-field than after two-field dissection (34% *vs.* 23%), whereas recurrent nerve paralysis occurred with equal frequency between the two groups.[5] In both of these studies, mortality rates did not differ between the three-field and two-field dissection groups, which is similar to our findings.

Noguchi et al. reported worse quality of life of patients who had undergone three-field dissection *versus* less radical lymphadenectomy based on more reports from the former group of adverse effects, depressed mental state, and inability to return to work. The researchers emphasized that the deterioration of quality of life was mainly caused by recurrent nerve paralysis.[10] In contrast, Nishihira et al. reported that the postoperative quality of life did not differ between patients with extensive *versus* conventional lymph node dissection, although recurrent nerve paralysis and tracheostomy were occurred more often after extensive lymph node dissection than after

Table 5. POSTOPERATIVE COURSES

	2-Field	3-Field	p-Value
Postoperative weight gain (kg)			
Mean	3.3 ± 2.2	3.8 ± 3.1	NS
Median	3.0	3.3	
POD of the maximal weight			
Mean	1.8 ± 1.5	1.4 ± 1.2	NS
Median	1	1	
Duration of assisted ventilation (days)			
Mean	5.9 ± 5.6	5.6 ± 5.1	NS
Median	4	4	
Assisted ventilation over 2 weeks	4 (6%)	5 (8%)	NS
Tracheostomy*	10 (15%)	13 (21%)	NS
Duration of ICU stay (days)	12.4 ± 8.6	11.6 ± 7.1	NS
Median	9	8	
ICU stay over 2 weeks	19 (29%)	13 (21%)	NS

POD = postoperative day.
* Patients who underwent preoperative tracheostomy are excluded.

conventional lymph node dissection.[11] In our study, recurrent nerve paralysis was found in 70% of patients who had undergone three-field dissection. However, in more than half of these patients, this effect was temporary and they recovered spontaneously. Moreover, for patients with permanent paralysis, vocal fold fixation therapy using silicone injection was performed based on the data of an electrolaryngogram during the primary hospitalization.[12] As a result, only 8% of the patients with long-term survival after three-field dissection reported severe hoarseness with difficulty speaking, and 16% reported mild hoarseness without difficulty in speaking. Regarding hoarseness among long-term survivors, no difference was found between the three-field and two-field dissection groups. Accordingly, we find taping of the left recurrent nerve to be necessary in completing dissection of the left paratracheal nodes to prevent irrecoverable injury to the nerve, even if averting temporary paralysis cannot be assured by this procedure. Preservation of the recurrent nerve and vocal fold fixation using silicone injection for any case of permanent paralysis is essential to quality of life after extended lymphadenectomy.

We reported that upper thoracic mediastinal lymph node dissection had to be considered carefully for preservation of the cardiopulmonary function.[13] During dissection of the upper thoracic mediastinal lymph nodes, we preserved the recurrent nerves, pulmonary branches, and cardiac branches of the vagus nerves, the right and left bronchial arteries, the inferior thyroidal arteries, the paratracheal sheath, and, if possible, the thoracic duct and the azygos arch. In contrast, during *en bloc* esophagectomy, pulmonary branches of the right vagus nerve, right bronchial artery, paratracheal sheath, thoracic duct, and azygos arch are resected.[14] We have indicated that preservation of the right bronchial artery and paratracheal sheath can prevent tracheal ischemia,[15] and preservation of the right bronchial artery and pulmonary branches of the right vagus nerve can help to avoid the dismal outcome (*i.e.*, severe adult respiratory distress syndrome or complication death) after pulmonary complications.[13] We therefore believe that preservation of the nerves and vessels related to cardiopulmonary function is essential for maintaining maximum safety when the extent of lymphadenectomy is expanded to perform more extended radical surgery.

Whether extended radical lymphadenectomy improves the survival of patients with esophageal cancer remains controversial. From the results of a randomized control trial, Kato et al. concluded that three-field dissection, compared with two-field dissection, improves survival after esophagectomy-based on a randomized control trial.[5] Isono et al. have reported similar results of a multi-institutional contemporary retrospective study.[16] However, the results of these studies have not been recognized internationally for several reasons. First, neither was a well-controlled study on the efficacy of extended lymphadenectomy. Second, there is great confusion regarding terminology of the extent of lymphadenectomy, especially for two-field dissection.[1] The difference in the survival rates between three-field and conventional two-field dissection has been attributed to the dissection of the cervical and upper mediastinal lymph nodes, particularly the lymph nodes along the recurrent laryngeal nerves.[17,18] Therefore, two-field dissection involving total mediastinal lymph node dissection

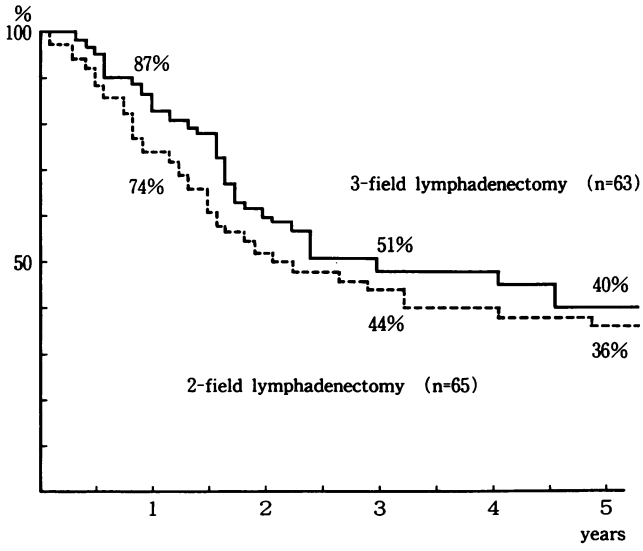

Figure 1. Survival curves of patients who underwent three-field or two-field lymphadenectomy.

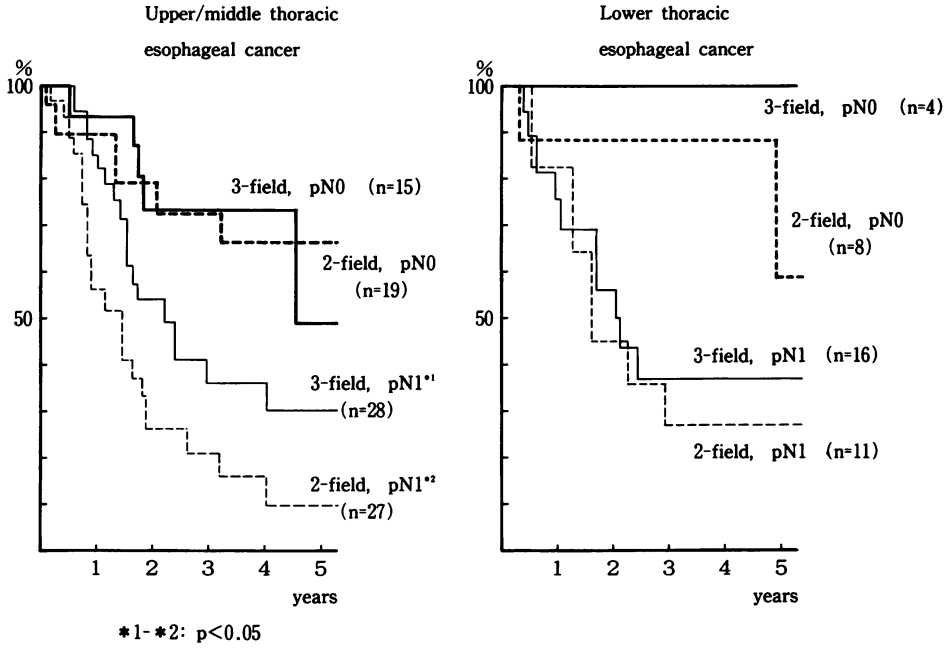

Figure 2. Survival curves of patients who underwent three-field or two-field lymphadenectomy with respect to lymph node metastasis and cancer location.

may show a similar survival rate to three-field dissection.[19] In our series, there was no difference in the overall survival rates between three-field and two-field dissection. However, our multivariate analysis revealed a significant difference in the modified survival curves between the two procedures.[20] In particular, there was a significant difference between the two groups regarding survival of patients with carcinoma in the upper thoracic or midthoracic esophagus with positive lymph node metastasis. We have reported that metastasis from a thoracic esophageal cancer was most common in the right recurrent nerve nodes, right paracardiac nodes, periesophageal nodes, and lesser curvature nodes.[21] We believe that three-field dissection is a reasonable procedure to use for resecting these nodes completely as well as for a carcinoma in the upper thoracic and/or midthoracic esophagus that is known to have frequent metastasis in the cervicothoracic junction nodes.

In our series during the same period, the 5-year-sur-

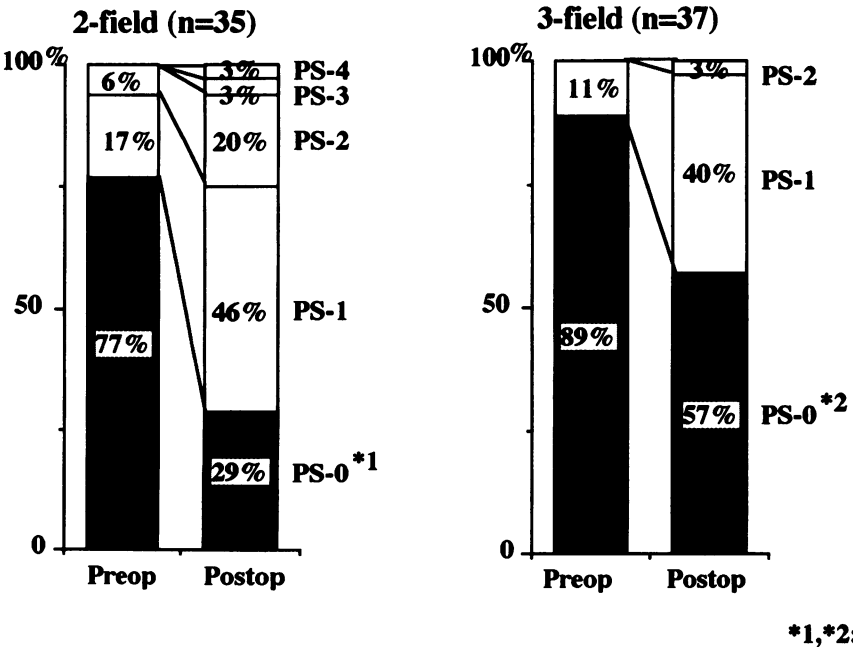

Figure 3. Performance status of patients who underwent three-field or two-field lymphadenectomy.

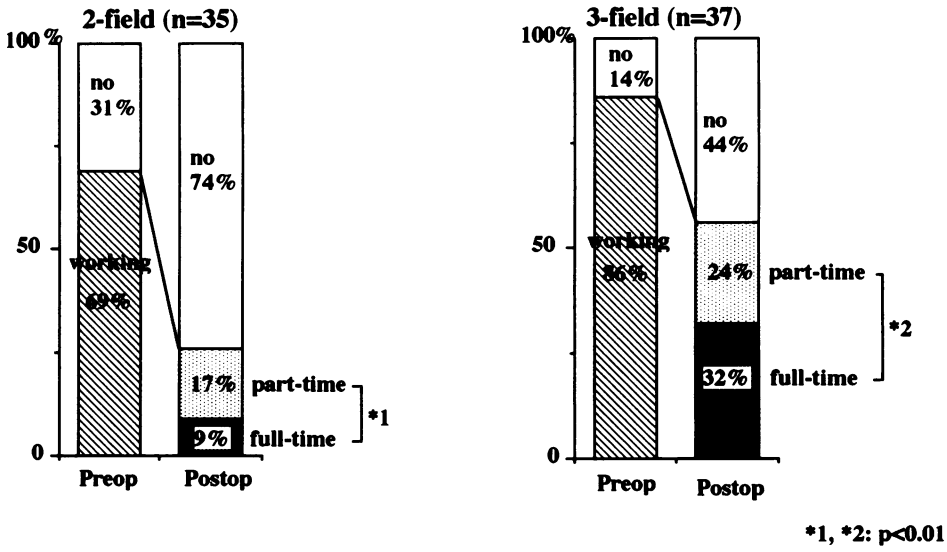

Figure 4. Rates of return to employment among patients who underwent three-field or two-field lymphadenectomy.

vival rate after R0 curative resection of esophageal cancer was 42%, whereas 5-year survival rates after R1 or R2 palliative resection or for patients with inoperable esophageal cancer were approximately 5%.[22] Siewert and Roder reported similar survival results and emphasized, based on multivariate analyses, that the most important prerequisite was an R0 resection.[23] We also consider R0 curative resection essential to improving survival rates after esophageal cancer surgery. Accordingly, the radical esophagectomy and lymphadenectomy should be performed more often, because the safety of our surgical treatment for esophageal cancer has been established. We have found that cancer recurrence more often disturbs quality of life than does an extended radical operation. As cited by Nishi,[24] absence of disease recurrence after a cancer operation is essential to good quality of life, but radicality sometimes has a negative effect on quality of life. We must strive to find a curative cancer treat-

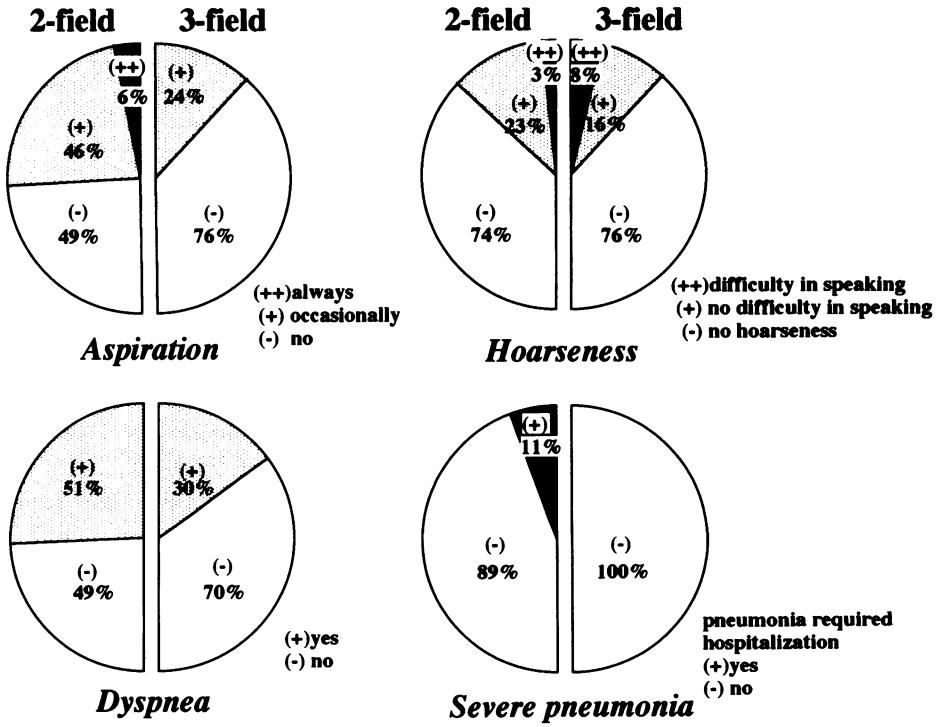

Figure 5. Postoperative problems in long-term survival after three-field or two-field lymphadenectomy.

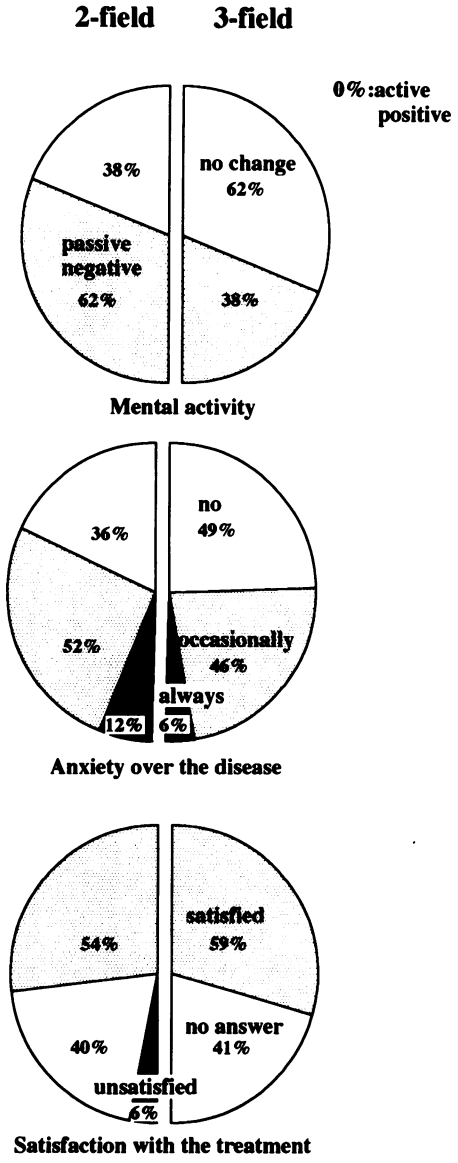

Figure 6. Mental conditions after three-field or two-field lymphadenectomy.

ment. To improve quality of life, we must aim for surgery that achieves radicality, safety, and fewer postoperative problems with physical functioning.

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