J Gastrointest Surg (2008) 12:802–810
DOI 10.1007/s11605-007-0385-7

Surgical Outcomes in Esophageal Cancer Patients with Tumor Recurrence After Curative Esophagectomy

Chikara Kunisaki · Hirochika Makino · Ryo Takagawa · Naoto Yamamoto · Yasuhiko Nagano · Syoichi Fujii · Takashi Kosaka · Hidetaka A. Ono · Yuichi Otsuka · Hirotoshi Akiyama · Yasushi Ichikawa · Hiroshi Shimada

Received: 24 August 2007 / Accepted: 3 October 2007 / Published online: 20 October 2007

Abstract This study aimed to identify predictive factors and to evaluate appropriate treatments for recurrence of esophageal cancer after curative esophagectomy. About 166 consecutive patients, who underwent curative esophagectomy, were enrolled between April 1994 and March 2003. Recurrence was classified as loco-regional or distant. Logistic regression analysis was used to identify predictive factors for recurrence. Prognostic factors were evaluated by Log-rank test and Cox proportional hazard regression analysis. The disease-specific 5-year survival was 56.8%. Recurrence was observed in 72 patients (43.4%), with 64 of these occurring within 3 years. The number of metastatic lymph nodes and lymphatic invasion independently predicted recurrence. There were significant differences in time to recurrence and survival time between loco-regional, distant recurrence, and combined recurrence. The 5-year survival time in patients with recurrence was 11.9%, and median survival time was 24 months. There was also a significant difference in survival after recurrence between treatment methods (no treatment vs chemo-radiotherapy, $p=0.0063$; chemotherapy, $p=0.0247$; and radiotherapy, $p<0.0001$). Meticulous, long-term follow-up is particularly necessary in patients with four or more metastatic lymph nodes to achieve early detection of recurrence. Randomized controlled trials should be used to develop effective modalities for each recurrence pattern to improve therapeutic outcomes.

Keywords Esophageal cancer · Lymph node dissection · Metastasis · Tumor recurrence

C. Kunisaki (✉) · H. Makino · R. Takagawa · N. Yamamoto · Y. Nagano · S. Fujii
Department of Surgery, Gastroenterological Center, Yokohama City University, 4-57, Urafune-cho, Minami-ku, Yokohama 232-0024, Japan
e-mail: s0714@med.yokohama-cu.ac.jp

T. Kosaka · H. A. Ono · Y. Otsuka · H. Akiyama · Y. Ichikawa · H. Shimada
Department of Gastroenteorlogical Surgery, Graduate School of Medicine, Yokohama City University, Yokohama, Japan

Introduction

Many esophageal carcinomas are found to be at the far advanced stage at the time of initial diagnosis[1,2] and cannot be treated curatively. Survival time in patients with advanced esophageal cancer is therefore unsatisfactory in spite of the development of operative procedures and perioperative managements.[3,4] Super-extended (three-field) or extended lymph node (two-field) dissection for esophageal cancer, however, offers favorable surgical outcomes,[5,6] whereas the significance of metastatic lymph nodes has been suggested as an independent prognostic factor in many reports.[7–9]

Some reports did not find preoperative chemoradiotherapy or chemotherapy to be efficacious,[10,11] and others suggested no survival benefits for adjuvant chemotherapy after curative surgery.[12,13] The recurrence rate after curative esophagectomy varies from 25 to 80%,[14–16] which is higher

than many other types of cancer, and patients can recur within only a few years after surgery. Therefore, it is important to understand the predictive factors and to assess the pattern and timing of recurrence after curative esophagectomy to improve therapeutic outcomes. This can also assist in the administration of appropriate treatment according to recurrence pattern. A previous report suggested that treatment response depends on type of recurrence, history of perioperative adjuvant therapy, time of recurrence, and laboratory data.[17] In this study, therapeutic outcomes in patients with recurrent esophageal cancer were retrospectively evaluated according to the pattern of recurrence to evaluate therapeutic strategies after curative esophagectomy.

Materials and Methods

Between April 1994 and March 2003, 166 patients with histologically proven squamous cell carcinoma or adenocarcinoma were enrolled in the study. The patient population was composed of 136 men and 30 women aged 30 to 85 years [mean age±standard deviation (SD)=63.7± 8.4 years]. Exclusion criteria included previous gastric resection, preoperative chemoradiotherapy and postoperative radiotherapy for esophageal cancer. The patients underwent transthoracic esophagectomy followed by esophagogastric anastomosis using the gastric conduit at the Department of Gastroenterological Surgery and the Department of Surgery, Gastroenterological Center, Yokohama City University, Japan. Preoperative diagnosis involving a barium-meal study, endoscopic examination with biopsy, and computed tomography (CT) was routinely carried out on all patients. Some patients underwent endoscopic ultrasonography to evaluate the depth of invasion.

Staging was principally based on the International Union Against Cancer (UICC)/TNM Classification of Malignant Tumors.[18] The quality of pathological diagnosis was controlled by experienced pathologists in each institution. About 72 patients had tumors located in the lower thoracic of the esophagus, 75 in the middle thoracic, and 19 in the upper thoracic. Pathological stage I of the disease was present in 30 patients, stage IIA in 27 patients, stage IIB in 47 patients, and stage III in 62 patients.

Well-defined tumors were macroscopically observed in 68 patients, ill-defined tumors in 64 patients, and superficial type (flat, slightly elevated, or slightly depressed) tumors were seen in the remaining 34 patients. The mean pathologic tumor diameter (±SD) was 56.2±19.6 mm. Two-field (thoraco-abdominal) lymph node dissection was performed in 123 patients and three-field (cervico-thoraco-abdominal) lymph node dissection in 43. Three-field lymph node dissection was selected for patients with a tumor in the upper or middle third near the upper third of the esophagus. Lymph node metastasis was observed in 102 patients (61.4%). All lymph nodes were defined in accordance with the TNM Classification of Malignant Tumors.

Adjuvant Chemotherapy

Adjuvant chemotherapy was performed in 59 (35.5%) patients with pathologically identified lymph node metastasis, good performance status, and who gave informed consent. About 600 mg/m^2 5-fluorouracil and 6 mg/m^2 cisplatin were intravenously administered for 2 weeks at 2-day intervals. The protocol was continued twice a year for 2 years.

Follow-up Protocol

All patients underwent a blood examination every 3 months, a CT scan every 6 months, and an annual endoscopic examination. If gastrointestinal symptoms were reported, an additional examination was carried out. After the fifth year, patients received an annual check-up at an outpatient clinic. The mean follow-up time was 44.9+31.3 months.

Definition of Recurrence

Loco-regional recurrence was defined as tumors occurring at lymph nodes in the neck, mediastinum including anastomotic site, or upper abdomen at the site of initial esophagectomy and lymph node dissection. Distant recurrence was defined as hematogenous metastasis within the solid organ, lymph nodes at the abdominal para-aorta, or peritoneal metastasis. Diagnosis of recurrence was made histologically, cytologically, and radiologically. Combined recurrence was defined as that both loco-regional and distant recurrence were detected simultaneously or within 30 days.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) program version 10.0 for Windows (SPSS, Chicago, IL, USA) was used for all statistical analyses. The chi-square test was used to evaluate the difference in proportions and the Student's t test was used to evaluate the continuous variables. All data were expressed as means±SD. The predictive factors of recurrence was evaluated by univariate analysis using the following 13 variables (age, gender, location of tumor, macroscopic appearance, tumor diameter, histologic type, depth of invasion, lymph node metastasis, number of metastatic lymph nodes, lymphatic invasion, venous invasion, type of lymph node dissection, and adju-

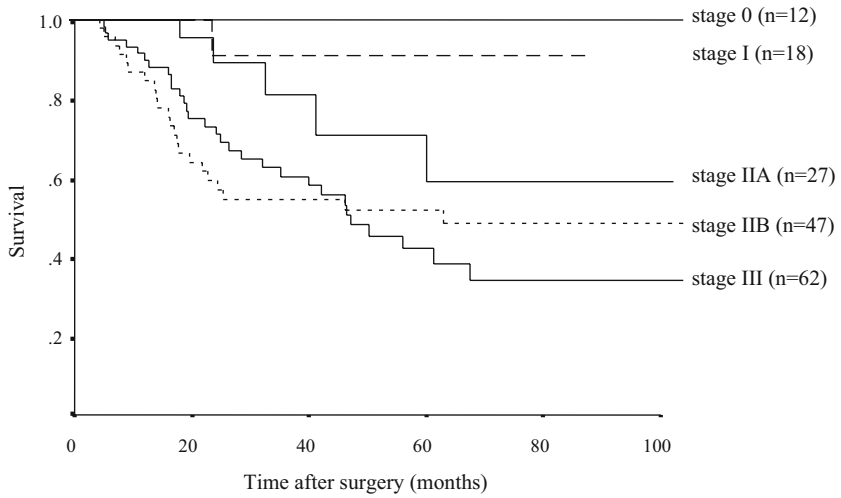

Figure 1 Disease-specific survival according to UICC/TNM classification.

vant chemotherapy). Of these 13 covariates, location of tumor, histological type, depth of invasion, and lymph node metastasis were employed based on UICC/TNM classification. Macroscopic appearance, lymphatic invasion, and venous invasion were principally according to the Japanese guidelines for clinical and pathological studies on carcinoma of the esophagus.[19] Number of metastatic lymph nodes,[8] type of lymph node dissection,[15] and adjuvant chemotherapy[20] were selected according to the previous studies. The logistic regression model was used for independent predictive factors of recurrence by using the variables selected as significant on univariate analysis. Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. Cox proportional regression analysis for disease-specific survival was applied using the following 12 variables (age, gender, location of tumor, macroscopic appearance, tumor diameter, histological type, depth of invasion, lymph node metastasis, number of metastatic lymph nodes, lymphatic invasion, venous invasion, and adjuvant chemotherapy). A p value of <0.05 was regarded as significant.

Treatments were selected after all possible alternative procedures had been explained to the patient and their informed consent had been obtained. Of the 166 patients, 89 patients gave informed consent who were alive when this retrospective study was conducted. The institutional review board approved this study.

Results

Pattern and Timing of Recurrence

Of the 166 patients registered, recurrence was observed in 72 (43.4%). A total of 38 patients (52.8%) recurred within the first year, 60 (83.3%) within 2 years, and 64 (88.9%)

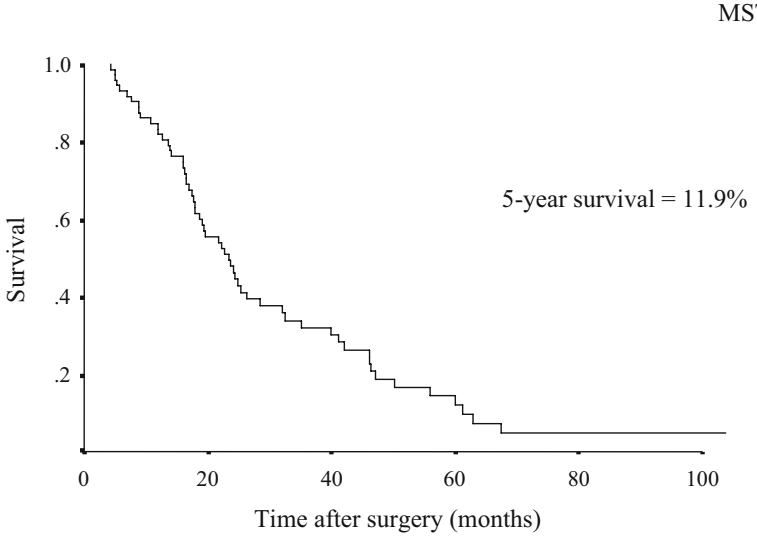

Figure 2 Disease-specific survival in patients with recurrence. *MST* Median survival time.

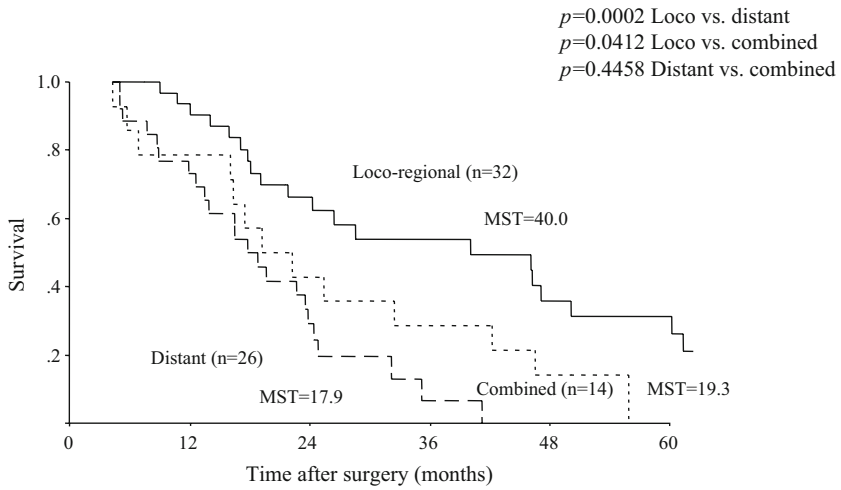

Figure 3 Disease-specific survival according to recurrence pattern. *MST* Median survival time.

within 3 years. Loco-regional recurrence was observed in 32 patients, distant recurrence in 26, and combined (loco-regional and distant) in 14. About 48 patients had a single site of recurrence, 21 had two recurrence sites, and 3 patients had three recurrence sites. There was no local recurrence amenable to re-resection. There was no significant difference in the 13 clinicopathological factors between patients with each pattern of recurrence. Time to recurrence in patients with loco-regional recurrence was 21.6± 16.3 months, that in patients with distant recurrence was 9.7±5.1 months, and that in patients with combined recurrence was 11.9±8.1 months. There were significant differences in time to recurrence between loco-regional and distant recurrence (p=0.0007) and combined recurrence (p=0.0409). Of 46 patients with loco-regional recurrence, 15 had cervical lymph nodes recurrence. Of 32 patients with only loco-regional recurrence, 9 had cervical lymph node recurrence. Moreover, only cervical lymph node recurrence was initially detected in 3 patients (9.4%) among 32. There was no significant difference in the incidence of cervical lymph node recurrence between patients receiving three-field and two-field lymph node dissection (5/11 vs 10/20) in 46 patients with loco-regional recurrence. Of the 32 patients who developed a loco-regional recurrence, 26 who developed distant recurrence and 14 with combined recurrence, 14, 6, and 6 had received adjuvant chemotherapy, respectively.

Survival

The 5-year disease-specific survival rate of the 166 patients was 56.8%. According to UICC/TNM classification, there were significant differences in survival between stage 0 and stages IIA and IIB, between stage I and stages IIB and III, and between stage IIA and stage III (Fig. 1). Of 72 patients with recurrence, 60 died of esophageal cancer during the

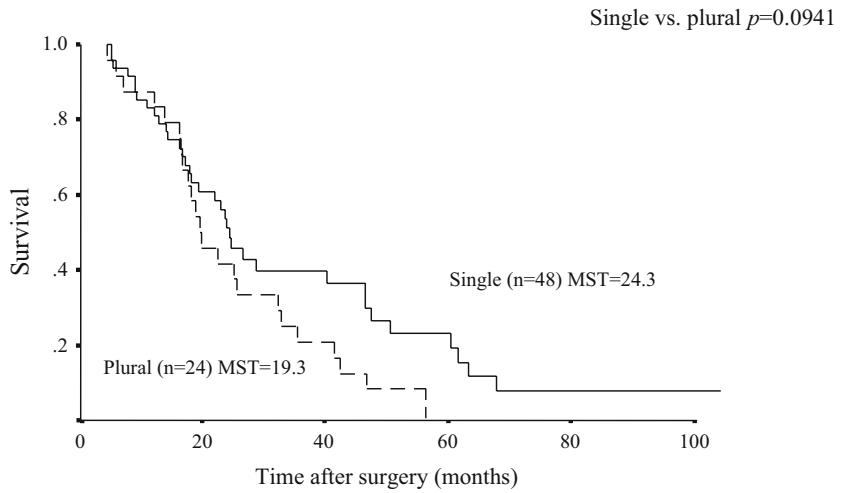

Figure 4 Disease-specific survival according to number of recurrence sites. *MST* Median survival time.

follow-up period. The remaining 12 patients who survived had only loco-regional recurrence (lymph node metastasis).

The 5-year survival time in patients with recurrence was 11.9%, and median survival time was 24 months (Fig. 2). Survival time according to the pattern of recurrence was calculated: median survival time in patients with loco-regional recurrence (n=32), distant recurrence (n=26), and combined recurrence (n=14) were 40.0, 17.9, and 19.3 months, respectively. There was a significant difference in survival between loco-regional recurrence and distant (p=0.0002) or combined recurrence (p=0.0412; Fig. 3). Survival time according to the number of recurrence sites was calculated, but the difference was shown to be non-significant (Fig. 4): Median survival time in patients with a single recurrence site was 24.3 months and that in patients with plural sites was 19.3 months.

Predictive Factors for Recurrence

Clinicopathological determinants were compared between patients with and without recurrence. A macroscopically ill-defined tumor type, deeply invading tumor, greater lymph node metastasis, presence of lymphatic invasion, and presence of venous invasion significantly predicted recurrence (Table 1). Of 13 clinicopathological factors used in univariate analysis, 6 factors (macroscopic appearance, depth of invasion, lymph node metastasis, number of metastatic lymph nodes, lymphatic invasion, and venous invasion) selected as significant were inserted into the logistic regression analysis. According to the logistic regression model, the number of metastatic lymph nodes and lymphatic invasion independently predicted recurrence. Similarly, presence of lymph node metastasis (UICC/TNM, N1) and lymphatic invasion

Table 1 Univariate Analysis of Recurrence After Curative Esohagectomy

Clinical variables	Recurrence (+)(72)	Recurrence (−)(94)	p value
Age (year)			0.7719
<70/≥70	58/14	74/20	
Gender			0.2202
Female/Male	10/62	20/74	
Location of tumor[a]			0.2390
Lower thoracic	26	46	
Middle thoracic	36	39	
Upper thoracic	10	9	
Macroscopic appearance[b]			0.0031
Superficial	6	28	
Well-defined	34	34	
Ill-defined	32	32	
Tumor diameter (mm)			0.1163
<50	32	57	
≥50 to <100	39	36	
≥100	1	1	
Histological type[a]			0.0516
Well diff. squamous	16	22	
Moderately diff. squamous	8	52	
Poorly diff. squamous	17	15	
Adenocarcinoma	11	5	
Depth of invasion[a]			0.0002
T1/T2/T3/T4	8/23/39/2	35/20/30/9	
Lymph node metastasis			<0.0001
N1	59	43	
Number of metastatic lymph nodes			<0.0001
0/≤3/≥4	13/37/22	51/5/8	
Lymphatic invasion[b]			<0.0001
Presence	56	38	
Venous invasion[b]			<0.0001
Presence	49	46	
Type of lymph node dissection			0.1200
Two-field	49	74	
Three-field	23	20	
Adjuvant chemotherapy			0.8934
Presence	26	33	

[a] TNM/UICC classification
[b] Japanese guidelines for clinical and pathological studies on carcinoma of the esophagus

Table 2 Logistic Regression Analysis of Recurrence After Curative Esophagectomy

Variable	χ^2	Odds ratio (95% CI[a])	p value
Number of metastatic lymph nodes	11.263		0.004
≤3/0		2.568 (1.109–5.947)	
≥4/0		6.249 (2.116–18.455)	
Lymphatic invasion	7.889		0.005
Presence/absence		3.038 (1.399–6.598)	
Lymph node metastasis[b]	8.199		0.004
N1/N0		3.226 (1.447–7.193)	
Lymphatic invasion	8.641		0.003
Presence/absence		3.155 (1.466–6.787)	

[a] 95% Confidence interval
[b] TNM/UICC classification

significantly predicted recurrence in another analysis using lymph node metastasis (UICC/TNM, N1) instead of the number of metastatic lymph nodes (Table 2).

Treatments for Recurrence

Chemoradiotherapy was employed in 29 patients, chemotherapy in 28, radiotherapy in 5, and no treatment was performed in 10 patients. Chemo-radiotherapy was performed in 24 patients with loco-regional recurrence and 9 patients with distant recurrence. Chemotherapy was performed in 22 patients with distant recurrence and 14 patients with loco-regional recurrence. Radiation alone was employed in five patients with loco-regional recurrence and one patient with distant recurrence. No treatment was performed in eight with distant recurrence and three with loco-regional recurrence. There was a significant difference in the correlation of recurrence site and treatments (p=0.0043).

Survival After Recurrence

The 5-year survival time after recurrence in 72 patients with recurrence was 14.3 months and median survival time was 10 months (Fig. 5).

Prognostic Factors for Disease-specific Survival After Recurrence

Cox proportional regression hazard model was used to evaluate prognostic factors after recurrence using 12 clinicopathological factors (age, gender, location of tumor, macroscopic appearance, tumor diameter, depth of invasion, lymph node metastasis, histological type, lymphatic invasion, venous invasion, pattern of recurrence, and treatment for recurrence). The treatment for recurrence was selected as an independent prognostic factor after recurrence. Each treatment significantly affected survival after recurrence (chemotherapy, hazard ratio=0.340 (0.158–0.733); radia-

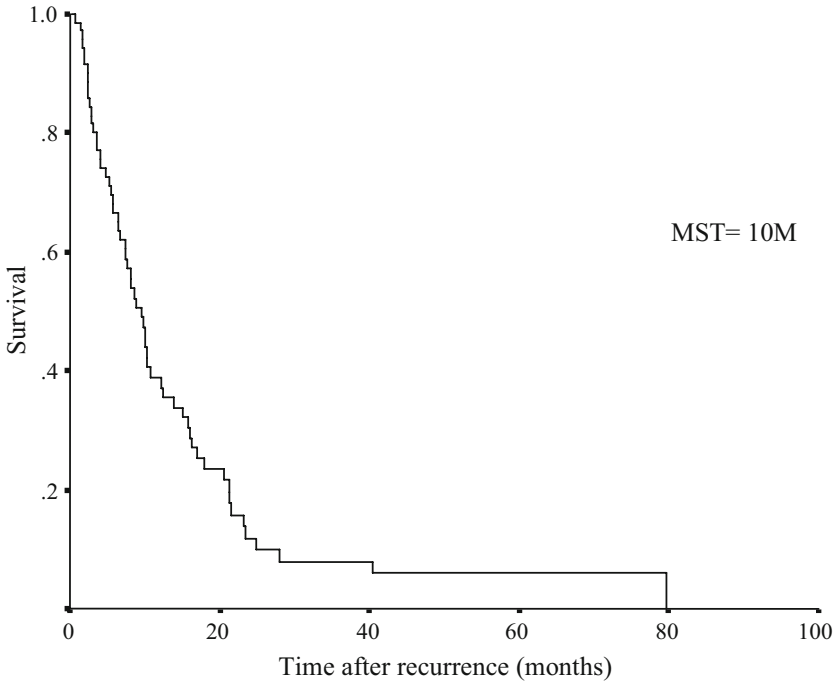

Figure 5 Disease-specific survival after recurrence. *MST* Median survival time.

tion, hazard ratio=0.180 (0.047–0.684); chemotherapy, hazard ratio=0.166 (0.073–0.375), $p<0.0001$).

Survival After Recurrence in Each Treatment

Median survival times in patients with chemoradiotherapy, chemotherapy, radiotherapy, and no treatment were 11, 8, 16, and 3 months, respectively. There were significant differences in survival between no treatment and chemoradiotherapy, chemotherapy, or radiotherapy ($p=0.0063$, $p=0.0247$, $p<0.0001$, respectively). Moreover, there was a significant difference in survival between chemoradiotherapy and chemotherapy ($p=0.0217$; Fig. 6).

Discussion

The current study shows that patients with four or more metastatic lymph nodes are likely to experience tumor recurrence after curative esophagectomy for esophageal cancer. It is therefore necessary to perform meticulous follow-up appointments for such patients. Patients with loco-regional recurrence may be treated effectively with chemoradiotherapy or radiotherapy, whereas new effective modalities for distant recurrence should be established.

Surgical resection with lymph node dissection is one of the most effective modalities for treatment of esophageal cancer.[5,6] In Japan, cervical lymph node dissection in addition to conventional thoraco-abdominal lymph node dissection, i.e., three-field lymph node dissection, has been advocated for the improvement of surgical outcomes at many institutions.[21,22] However, the efficacy of this operative procedure has not been widely accepted. As shown in the current study, the number of retrieved lymph nodes did not affect tumor recurrence after curative surgery. Moreover, the incidence of cervical lymph node recurrence was equal after both three-field and two-field lymph node dissection.

A previous study found that the incidence of cervical lymph node recurrence was 15% even after three-field lymph node dissection,[20] which is a similar value to that reported after two-field lymph node dissection.[23] Two-field lymph node dissection may therefore offer equal therapeutic outcomes to those achieved by three-field lymph node dissection when radiotherapy is performed for cervical lymph node recurrence.

As shown in the current study, the number of metastatic lymph nodes is an independent predictive factor of recurrence. Therefore, even super-extended lymph node dissections are limited in their improvement of survival for patients with multiple metastatic lymph nodes. Consequently, the oncological behavior of the tumor rather than the extension of lymph node dissection may affect survival outcomes.

More than 50% of tumor recurrences occurred within 12 months of curative esophagectomy in the present study. Moreover, occurrences were earlier and therapeutic outcomes worse in patients with distant recurrences compared with loco-regional recurrences. These findings contrast with previous reports that observed early distant recurrence after curative esophagectomy.[23,24]

A previous prospective study showed a high incidence of micrometastasis in the rib or the iliac bone.[25] Neither micrometastasis nor macrometastasis can be identified by current imaging tools and may already occur at the time of operation, after which they grow rapidly. Therefore, it is important to establish the usefulness of adjuvant chemotherapy, particularly as its significance has been questioned by the

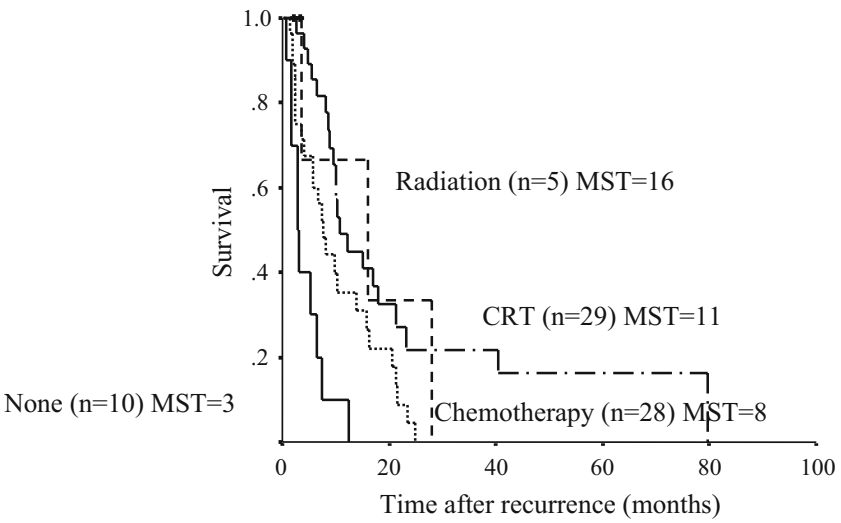

Figure 6 Disease-specific survival after recurrence in each treatment. *MST* Median survival time.

findings of some randomized controlled trials.[12] One study, however, revealed the therapeutic effect of adjuvant chemotherapy in patients with pN1 esophageal cancer,[13] whereas the NCCN esophageal cancer guidelines of 2007 suggested that adjuvant therapy has only category 2B level evidence.[26] In the current study, we also found that adjuvant chemotherapy did not influence tumor recurrence, but its usefulness should be examined in a larger volume study of patients with a high number of metastatic lymph nodes. Moreover, it is important to establish a detection method for the site of recurrence at the earliest opportunity and to develop effective chemotherapeutic agents to improve therapeutic results.

In the current study, many loco-regional recurrences were detected in the mediastinum, where lymph nodes had been dissected at the initial operation. Preoperative diagnosis by positron emission tomography/CT[27,28] or concept of sentinel node navigation surgery[29,30] may decrease the number of residual metastatic lymph nodes and improve surgical outcomes. In our study, chemoradiotherapy or radiotherapy were used for the treatment of loco-regional recurrence and offered favorable therapeutic outcomes. As blood flow to the remaining lymph nodes may be reduced after surgical lymph node dissection, chemotherapy alone may not be sufficient to deliver chemotherapeutic agents to the tumors. Chemoradiotherapy or radiotherapy, therefore, may be more effective for treatment of localized tumors. As loco-regional recurrence often occurs long after initial surgery, compared with distant recurrence, meticulous long-term follow-up of patients is necessary to achieve early detection.

In the current study, each treatment was selected as an independent prognostic factor after recurrence and resulted in a more favorable therapeutic outcome compared with no treatment. However, this study is retrospective and statistical bias may affect the outcomes. Patients who did not receive treatment had a poor performance status, were older, or gave no informed consent. Moreover, chemotherapy was frequently performed in patients with distant metastasis, whereas chemoradiotherapy was mainly employed in patients with loco-regional recurrence. Radiotherapy alone was chiefly advocated in patients with loco-regional lesions who had already been administered adjuvant chemotherapy. As the selection criteria for treatment were controlled by the physician, future work should focus on a randomized controlled trial conducted in patients who do and do not receive treatment.

Conclusion

Meticulous and long-time follow-ups are necessary, particularly for those patients with four or more metastatic lymph nodes, to achieve early detection of recurrence. It is also important to develop effective modalities for each recurrence pattern using randomized controlled trials to improve therapeutic outcomes.

References

1. Daly JM, Fray WA, Little AG, Winchester DP, McKee RF, Stewart AK, Fremgen AM. Esophageal cancer: results of an American College of Surgeons patient care evaluation study. J Am Coll Surg. 2000;190:562–573.
2. Lerut T, Nafteux P, Moons J, Coosemans W, Decker G, De Leyn P, Van Raemdonck D, Ectors N. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. Ann Surg. 2004;240:962–974.
3. Isono K, Ochiai T, Okuyama K, Onoda S. The treatment of lymph node metastasis esophageal cancer by extensive lymphadenectomy. Jpn J Surg. 1990;20:151–157.
4. Baba M, Aikou T, Yoshinaka H, Natsugoe S, Fukumoto T, Shimazu H, Akazawa K. Long-term results of subtotal esophagectomy with three-field lymphadenectomy for carcinoma of the thoracic esophagus. Ann Surg. 1994;219:310–316.
5. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg. 1994;220:364–372.
6. Law S, Wong J. Two-field dissection is enough for esophageal cancer. Dis Esophagus. 2001;14:98–103.
7. Kunisaki C, Shimada H, Akiyama H, Nomura M, Matsuda G, Ono H. Prognostic factors in esophageal cancer. Hepato-gastroenterol. 2004;51:736–740.
8. Osugi H, Takemura M, Takada N, Hirohashi K, Kinoshita H, Higashino M. Prognostic factors after oesophagectomy and extended lymphadenectomy for squamous oesophageal cancer. Br J Surg. 2002;89:909–913.
9. Wijnhoven BP, Tran KT, Esterman A, Watson DI, Tilanus HW. An evaluation of prognostic factors and tumor staging of resected carcinoma of the esophagus. Ann Surg. 2007;245:717–725.
10. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol. 2001;19:305–313.
11. Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, Ackland S, Gotley DC, Joseph D, Millar J, North J, Walpole ET, Denham JW, Trans-Tasman Radiation Oncology Group, Australasian Gastro-Intestinal Trials Group. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol. 2005;6:659–668.
12. Pouliquen X, Levard H, Hay JM, McGee K, Fingerhut A, Langlois-Zantin O. 5-Fluorouracil and cisplatin therapy after palliative surgical resection of squamous cell carcinoma of the esophagus. A multicenter randomized trial. French Associations for Surgical Research. Ann Surg. 1996;223:127–133.
13. Ando N, Iizuka T, Ide H, Ishida K, Shinoda M, Nishimaki T, Takiyama W, Watanabe H, Isono K, Aoyama N, Makuuchi H, Tanaka O, Yamana H, Ikeuchi S, Kabuto T, Nagai K, Shimada Y, Kinjo Y, Fukuda H. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study–JCOG9204. J Clin Oncol. 2003;21:4592–4596.
14. Mariette C, Balon JM, Piessen G, Fabre S, Van Seuningen I, Triboulet JP. Pattern of recurrence following complete resection of

esophageal carcinoma and factors predictive of recurrent disease. Cancer. 2003;97:1616–1623.
15. Dresner SM, Griffin SM. Pattern of recurrence following radical oesophagectomy with two-field lymphadenectomy. Br J Surg. 2000;87:1426–1433.
16. Tachibana M, Kinugasa S, Yoshimura H, Shibakita M, Tonomoto Y, Dhar DK, Nagasue N. Clinical outcomes of extended esophagectomy with three-field lymph node dissection for esophageal squamous cell carcinoma. Am J Surg. 2005;189:98–109.
17. Shimada H, Kitabayashi H, Nabeya Y, Okazumi S, Matsubara H, Funami Y, Miyazawa Y, Shiratori T, Uno T, Itoh H, Ochiai T. Treatment response and prognosis of patients after recurrence of esophageal cancer. Surgery. 2003;133:24–31.
18. Sobin LH, Wittekind CH. TNM: Classification of Malignant Tumours. 6th ed. New York: Wiley-Liss; 2002.
19. Japanese Society for Esophageal Disease. Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus. 9thth ed. Tokyo: Kanehara; 2001.
20. Chen G, Wang Z, Liu XY, Liu FY. Recurrence pattern of squamous cell carcinoma in the middle thoracic esophagus after modified Ivor-Lewis esohagectomy. World J Surg. 2007;31:1107–1114.
21. Fujita H, Sueyoshi S, Tanaka T, Shirouzu K. Three-field dissection for squamous cell carcinoma in the thoracic esophagus. Ann Thorac Cardiovasc Surg. 2002;8:328–335.
22. Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg. 2002;236:177–183.
23. Nakagawa S, Kanda T, Kosugi S, Ohashi M, Suzuki T, Hatakeyama K. Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. J Am Coll Surg. 2004;198:205–211.
24. Osugi H, Takemura M, Higashino M, Takada N, Lee S, Ueno M, Tanaka Y, Fukuhara K, Hashimoto Y, Fujiwara Y, Kinoshita H. Causes of death and pattern of recurrence after esophagectomy and extended lymphadenectomy for squamous cell carcinoma of the thoracic esophagus. Oncol Rep. 2003;10:81–87.
25. O'sullivan GC, Sheehan D, Clarke A, Stuart R, Kelly J, Kiely MD, Walsh T, Collins JK, Shanahan F. Micrometastases in esophagogastric cancer: high detection rate in resected rib segments. Gastroenterology. 1999;116:543–548.
26. Ajani J, Bekaii-Saab T, Gibson MK, Osarogiagbon RU. NCCN practice guidelines for esophageal cancer (Version 2.2007). http://www.nccn.org.
27. Gondi V, Bradley K, Mehta M, Howard A, Khuntia D, Ritter M, Tomé W. Impact of hybrid fluorodeoxyglucose positron-emission tomography/computed tomography on radiotherapy planning in esophageal and non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2007;67:187–195.
28. Wong WL, Chambers RJ. Role of PET/PET CT in the staging and restaging of thoracic oesophageal cancer and gastro-oesophageal cancer: a literature review. Abdom Imaging 2007 DOI 10.1007/s00261-007-9241-1.
29. Kitagawa Y, Kitajima M. Gastrointestinal cancer and sentinel node navigation surgery. J Surg Oncol. 2002;79:188–193.
30. Arima H, Natsugoe S, Uenosono Y, Arigami T, Ehi K, Yanagita S, Higashi H, Ishigami S, Hokita S, Aikou T. Area of nodal metastasis and radioisotope uptake in sentinel nodes of upper gastrointestinal cancer. J Surg Res. 2006;135:250–254.