Risk Factors for Local Recurrence and Optimal Length of Esophagectomy in Esophageal Squamous Cell Carcinoma

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Background. The risk factors for local recurrence in residual esophagus after esophagectomy have not been well documented. This study aimed to identify risk factors of local recurrence and optimal length of esophageal resection in esophageal cancer.

Methods. Patients who underwent curative esophagectomy with more than 2 years of follow-up were included. Patients who received preoperative chemoradiation or in whom the ex vivo length of proximal margin (LPM) from resected tumor was not documented in the pathologic report were excluded. A total of 551 patients from January 1995 to February 2013 were included.

Results. Complete resection was possible in 516 patients (94%), and mean LPM was 3.4 ± 2.5 cm. Sex, age, location of tumor, location of anastomosis, minimally invasive esophagectomy, three-field lymphadenectomy, cell type, differentiation, proximal resection margin status, tumor size, number of dissected lymph nodes, and T stages were not risk factors for local recurrence in multivariate analysis. The N stage ($p = 0.034$) and LPM ($p = 0.007$) were risk factors for local recurrence in multivariate analysis. The LPM was not related to local recurrence in N0, but 5-year freedom from local recurrence was higher for LPM of 5 cm or greater in N+ esophageal cancer (72% in LPM less than 5 cm versus 93% in LPM of 5 cm or greater, $p = 0.040$).

Conclusions. Local recurrence after esophagectomy in esophageal cancer is related to lymphatic metastasis rather than to proximal margin status, which raises the possibility that the main mechanism of local recurrence is submucosal lymphatic metastasis. Esophagectomy with LPM more than 5 cm is recommended for esophageal cancer with nodal metastasis.

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Surgical resection is a standard treatment for resectable esophageal cancer. Successful surgical treatment can be achieved by complete resection of the primary tumor and combined extirpation of draining lymphatic chains. Partial or total esophagectomy and two-field lymphadenectomy have been the most commonly performed operation in the treatment of esophageal cancer. If esophagectomy is considered as a procedure only for removal of primary tumor, the extent of esophagectomy could be limited to the length of negative resection margin in intraoperative frozen pathologic examination. However, submucosal lymphatic metastasis is a well-known phenomenon in esophageal cancer, and a proximal margin that is too short is associated with a high incidence of local recurrence (LR) in residual esophagus [1–3]. Therefore, esophagectomy should have a second role in the removal of hidden intramural metastasis in addition to removal of primary tumor.

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Risk factors for LR in residual esophagus after esophagectomy have not been well documented, and how long segment a esophagus should be resected has not been clearly suggested. In this study, we tried to identify risk factors for LR after esophagectomy and optimal length of esophagectomy to decrease LR.

Material and Methods

Patients and Inclusion Criteria

Medical records of patients who underwent esophagectomy owing to esophageal cancer were retrospectively reviewed. This study was approved by our Institutional Review Board. Permission from patients was waived. From January 1995 to February 2013, 672 patients received surgical resection of esophageal cancer in our hospital. The inclusion criteria were as follows: (1) squamous cell carcinoma; (2) esophagectomy for curative intent; (3) follow-up of more than 2 years; (4) no history of neoadjuvant chemotherapy or chemoradiation; and (5) documented ex vivo length of proximal margin (LPM) from resected tumor in the pathologic report. Finally, 551 patients were selected for the analysis.

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Definition of Terms

The location of tumor (upper, middle, or lower thoracic) was determined by the distance from incisors, not by anatomic landmark, using the staging definition of the seventh edition staging manual of the American Joint Committee on Cancer. An appreciable number of patients had mucosal or submucosal lesions that could not identified in chest computed tomography scan or positron emission tomography–computed tomography scan; in these lesions, the tumor could not be localized tumor by anatomic structure. Local recurrence was defined as recurrence confirmed by endoscopic evaluation at the residual esophagus or anastomosis site. Endoscopic surveillance was routinely performed annually in all patients for 2 years after operation or in symptomatic patients who had of newly developed dysphagia. The LPM was measured by pathologists in resected specimens. The length was measured by full traction of surgical specimen, and distance between end of resection and gross margin of primary tumor was measured. If the proximal border of primary tumor was not clear, microscopic evaluation of tumor infiltration was checked and LPM determined by the distance from microscopic margin of the tumor.

Statistical Analyses

Overall survival and freedom from recurrence were calculated from the date of operation. Survival and freedom from recurrence were calculated by the Kaplan-Meier method, and statistical significance was evaluated by the log rank test. The Cox proportional hazards regression model was used to analyze the prognostic significance of each factor in univariate and multivariate analyses. Statistical significance was considered when p was less than 0.05. Statistical analyses were performed using IBM SPSS version 22 software (IBM Corp, Armonk, NY).

Results

Patient Demographic and Operative Data

Demographic data of the patients are presented in Table 1. Most of the patients were male (n = 519, 94%), and most were former or current smokers (n = 421, 76%). Operations were performed in patients with good performance status; 99% of the patients (n = 548) had grade 0 or 1 performance status. Although the comorbidity rate was high (n = 350, 64%), a Charlson/Deyo comorbidity index of more than 1 was identified in 171 patients (31%). Operations were performed by thoracotomy in 461 patients (84%), robot-assisted surgery in 35 (6%), thoracoscopic surgery in 27 (5%), and transhiatial resection in 28 (5%). Stomach was used as an esophageal substitute in 515 patients (94%), colon in 35 (6%), and jejunum in 1 patient (0.2%). Thoracic and cervical anastomosis was performed in 391 patients (71%) and 160 patients (29%), respectively. Three-field lymph node dissection was performed in 30 patients (5%); the mean number of dissected lymph nodes was 29.1 ± 18.9 (range, 0 to 127). Adjuvant treatment was given in 138 patients (25%). Adjuvant radiation was administered in 70 patients (13%), adjuvant chemotherapy in 35 (6%) and chemoradiation in 33 (6%).

Table 1. Demographic Data

Variables	Values
Age, years	62.9 ± 8.2 (33–82)
Sex	
Male	519 (94)
Female	32 (6)
Body mass index, kg/m^2	22.5 ± 3.1 (13.6–32.1)
Dysphagia	
Absent	258 (47)
Present	293 (53)
Smoking history	
Former smoker	127 (23)
Current smoker	294 (53)
Performance status	
0	352 (64)
1	196 (35)
2	3 (1)
Comorbidity	350 (62)
Hypertension	456 (28)
Diabetes mellitus	71 (13)
Chronic liver disease	26 (5)
Chronic pulmonary disease	21 (4)
Coronary artery disease	22 (4)
Cerebrovascular disease	10 (2)
Renal disease	6 (1)
Peripheral vascular disease	7 (1)
Other cancer history	56 (10)
Charlson/Deyo comorbidity index ≥1	171 (31)
Predicted FEV_1%	99.5 ± 18.5 (39–150)

Values are mean ± SD (range) or n (%).

FEV_1 = forced expiratory volume in 1 second; SD = standard deviation.

Pathologic Data

The pathologic data are presented in Table 2. The most common location of the tumor was distal thoracic tumor in 343 patients (62%). R0 resection was performed in 516 patients (94%); R1 resection in 30 patients (5%); and R2 resection in 5 patients (0.9%). The causes of incomplete resection were positive proximal margin in 17 patients (3%), positive radial resection margin in 10 (2%), endolymphatic tumor in resection margin in 3 (0.5%), extranodal invasion in 3 (0.5%), and positive distal resection margin in 2 (0.3%). Among the 17 patients (3%) who had positive proximal resection margin, 10 patients received adjuvant radiation (59%) and 3 patients received adjuvant chemoradiation (18%).

Local Recurrence and Survival

Recurrence occurred in 268 patients (49%), and 295 patients (54%) died during follow-up. The 5-year freedom from recurrence was 46% (median 38.1 months, 95% confidence interval [CI]: 17.5 to 58.7), and 5-year

Table 2. Pathologic Data

Variables	Values
Differentiation	
Well	118 (21)
Moderate	326 (59)
Poor	46 (8)
Unknown	61 (11)
Size, cm	3.7 ± 2.0 (0.2–12)
Length of proximal margin, cm	3.4 ± 2.5 (0–20)
T stages	
T1	230 (42)
T2	70 (13)
T3	243 (44)
T4	8 (1)
N stages	
N0	306 (56)
N1	149 (27)
N2	68 (12)
N3	28 (5)
M stages	
M0	544 (99)
M1	7 (1)

Values are n (%) or mean ± SD (range).

SD = standard deviation.

overall survival was 46% (median 47.8 months, 95% CI: 35.2 to 60.3). There were 40 LRs (7%), 172 regional recurrences (31%), and 147 distant recurrences (27%). The 5-year freedom from LR was 90%, and median value was not reached.

Survival After Recurrence

The treatment for LR was heterogeneous. Among the 40 patients with LR, 13 patients (32%) were treated with radiation, 9 patients (22%) with chemotherapy, 5 patients (13%) with chemoradiation, 2 patients with surgery (5%), and 1 patient (3%) with stent insertion; 10 patients (25%) did not receive any treatment. The median survival after LR was 5.8 months (95% CI: 5.0 to 6.6 months). The survival of the patient with LR was shorter than that for patients with recurrences without LR (median survival 7.1 months, 95% CI: 5.7 to 8.4); however, the difference was marginally significant ($p = 0.073$; Fig 1).

Risk Factor Analysis and Determination of Optimal Length of Proximal Margin

Risk factors for LR were evaluated by Cox proportional hazards regression model. In univariate analysis, positive proximal margin ($p = 0.028$), T stage ($p = 0.008$), and N stage ($p < 0.001$ were risk factors for LR. In multivariate analysis, risk factors for LR were N stage ($p = 0.034$) and LPM ($p = 0.007$; Table 3). To determine optimal LPM for reducing local recurrence, hazard ratio and p value were calculated by Cox proportional hazard model with 1-cm intervals from 1 cm to 8 cm. An LPM of 5 cm or greater was statistically significant cutoff value for reducing

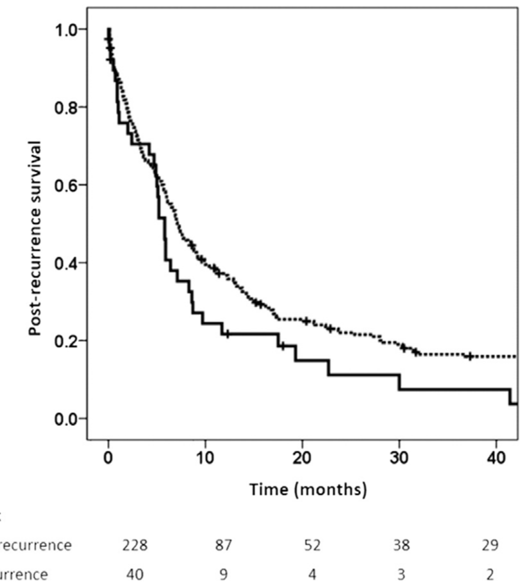

Fig 1. Postrecurrence survival, with local recurrence (solid line) versus without local recurrence (dotted line).

local recurrence (hazard ratio 0.45, 95% CI: 0.17 to 0.96, $p = 0.041$; Table 4).

Subgroup Analysis

In the 17 patients with positive proximal margin, 3 LRs occurred, and 5-year freedom from LR was 55%. Five-year freedom from LR was 94% in N0, 80% in N1, 76% in N2, and 70% in N3 patients ($p < 0.001$). Subgroup analysis was performed by status of nodal metastasis and LPM. In the N0 subgroup, freedom from LR was 93% for LPM less than 5 cm and 95% for LPM of 5 cm or greater, and there was no significant difference ($p = 0.609$). However, in the N+ group, freedom from LR was 72% for LPM less than 5 cm and 93% for LPM of 5 cm or greater, and the difference was statistically significant ($p = 0.040$; Fig 2). The LPM was not associated with extent of lymphadenectomy. The mean number of dissected lymph nodes was 29.0 ± 18.8 with LPM less than 5 cm and 29.6 ± 19.1 with LPM of 5 cm or greater, and there was no statistically significant difference ($p = 0.740$).

To rule out the influence of positive resection margin in LPM less than 5 cm subgroup, the patients who had positive resection margin were excluded and freedom from LR was calculated. The result was also similar for all patients. In the N0 subgroup, freedom from LR was 95% with LPM less than 5 cm and 95% with LPM of 5 cm or greater ($p = 0.980$); and in the N+ subgroup, freedom from LR was 72% with LPM less than 5 cm and 93% with LPM of 5 cm or greater ($p = 0.041$). The relationship between LR and LPM is plotted in Figure 3.

Comment

In this study, we analyzed risk factors for LR after esophagectomy in esophageal cancer. Local recurrence occurred in 40 of 551 patients, and 5-year freedom from

Table 3. Univariate and Multivariate Analyses of Risk Factors for Local Recurrence

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Sex						
Female	1			1		
Male	1.47	0.36–6.11	0.593	1.36	0.31–5.97	0.68
Age, years	1.00	0.96–1.03	0.830	1.01	0.97–1.05	0.733
Performance status						
0	1			1		
1, 2	1.74	0.92–3.29	0.089	1.06	0.52–2.17	0.867
CDCI ≥2						
No				1		
Yes	0.70	0.25–1.95	0.489	0.93	0.31–2.78	0.900
Location			0.640			0.378
Lower	1			1		
Mid	1.01	0.23–4.96	0.930	1.59	0.30–8.62	0.59
Upper	1.48	0.35–6.12	0.595	2.55	0.47–13.87	0.280
Anastomosis						
Thoracic	1			1		
Cervical	0.70	0.32–1.53	0.374	1.52	0.51–4.62	0.459
Minimally invasive surgery						
No	1					
Yes	0.60	0.21–1.68	0.327	1.07	0.29–3.90	0.921
LN dissection			0.098			0.267
One field	1			1		
Two field	0.67	0.32–1.36	0.260	0.79	0.32–1.94	0.599
Three field	1.95	0.61–6.21	0.260	1.29	0.31–5.43	0.730
Number dissected LN	1.00	0.99–1.02	0.854	0.91	0.72–1.14	0.069
Differentiation			0.238			0.232
Well	1			1		
Moderate	2.24	0.86–5.83	0.098	2.52	0.93–6.82	0.068
Poor	2.77	0.80–9.56	0.108	2.96	0.82–10.67	0.096
Unknown	1.14	0.27–4.76	0.861	1.86	0.42–8.17	0.410
Positive proximal margin						
No	1			1		
Yes	3.73	1.15–12.11	0.028	1.92	0.46–7.93	0.369
Size, cm	1.09	0.93–1.27	0.292	0.91	0.72–1.14	0.406
T stage			0.008			0.350
1	1			1		
2	1.87	0.65–5.39	0.245	1.76	0.57–5.47	0.327
3	3.37	1.64–6.96	0.001	2.37	0.92–6.08	0.073
4	5.66	0.73–44.07	0.098	3.32	0.29–38.07	0.335
N stage			<0.001			0.034
0	1			1		
1	3.23	1.56–6.71	0.002	2.77	1.20–6.39	0.017
2	5.01	2.11–12.30	<0.001	3.43	1.21–9.71	0.020
3	6.10	1.72–21.6	0.005	5.21	1.19–22.74	0.028
LPM, cm	0.88	0.76–1.01	0.077	0.80	0.67–0.94	0.007

CDCI = Charlson/Deyo comorbidity index; CI = confidence interval; HR = hazard ratio; LN = lymph node; LPM = length of proximal margin.

LR was 90%. Risk factors for LR were N stage and LPM. An LPM of 5 cm or greater was a favorable risk factor for LR. However, the protective effect of a long LPM was identified only in the patients with nodal metastasis, and LPM had no effect on LR in patients without nodal metastasis.

Recurrence after esophagectomy showed very poor prognosis despite treatment [4, 5]. The most common

Table 4. Hazard Ratios of Local Recurrence by Length of Proximal Resection Margin

Length of Proximal Margin	HR	95% CI	*p* Value
≥ 1 cm versus < 1 cm	0.51	0.21–1.26	0.142
≥ 2 cm versus < 2 cm	0.58	0.29–1.16	0.120
≥ 3 cm versus < 3 cm	0.73	0.38–1.41	0.356
≥ 4 cm versus < 4 cm	0.56	0.28–1.14	0.111
≥ 5 cm versus < 5 cm	0.40	0.17–0.96	0.041
≥ 6 cm versus < 6 cm	0.38	0.12–1.26	0.115
≥ 7 cm versus < 7 cm	0.64	0.19–2.13	0.466
≥ 8 cm versus < 8 cm	0.45	0.06–3.44	0.441

Hazard ratio (HR) was adjusted by pathologic stages and proximal margin status.

CI = confidence interval.

locations of recurrence in esophageal cancer are regional and distant recurrences; therefore, the importance of lymphadenectomy and multimodality treatment has been emphasized [6, 7]. Local recurrence is another important issue after esophagectomy. However, because of the relatively low incidence of recurrence, it has not been strongly emphasized in the literature. In case of LR, radiation therapy with or without chemotherapy is the most commonly performed treatment. Surgical re-resection can be tried. However, it is only possible for highly select patients. Local recurrence worsens the quality of life because of dysphagia and demonstrates poorer prognosis than the recurrences in other sites. Several studies reported LR is a poor prognostic factor for survival in patients with recurrence [8, 9]. The survival after radiation therapy for LR is poor, ranging from 7 to 21

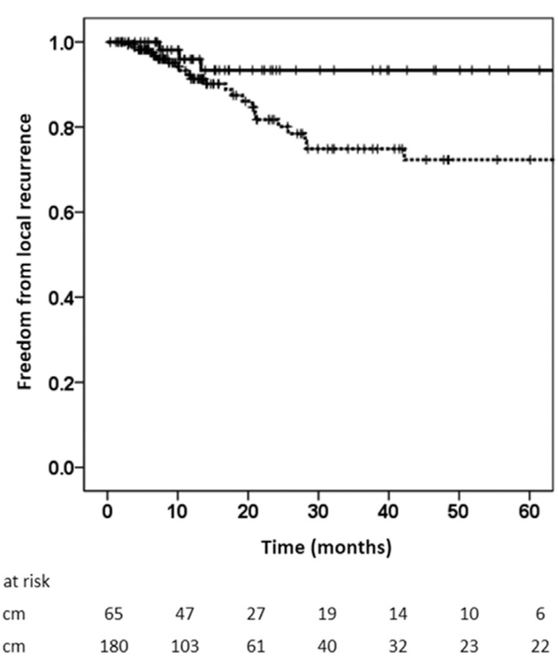

Fig 2. Freedom from local recurrence in the N+ patients with length of proximal margin (LPM) of 5 cm or greater (solid line) versus LPM less than 5 cm (dotted line).

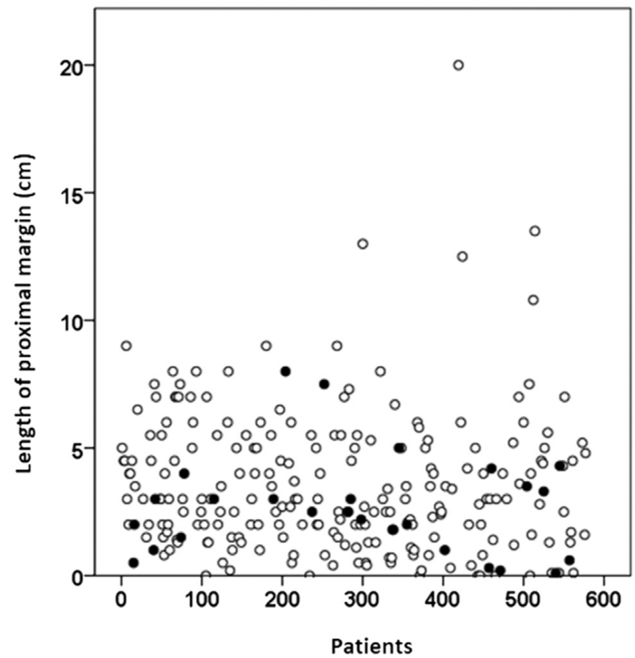

Fig 3. Relationship between local recurrence and length of proximal margin. Patient number is a serial number according to the date of operation. Open circles indicate without local recurrence; solid circles indicate with local recurrence.

months [5, 10]. In our study, the postrecurrence survival in the patients was very poor, with a median survival of 7 months, which was comparable to previous studies.

Traditionally, negative margin has been regarded as a mandatory condition to decrease LR after esophagectomy. However, it has been suggested that negative margin is not sufficient for the prevention of LR. Intramural metastasis is a very common phenomenon in esophageal cancer, and prevalence of intramural metastasis is related to lymph node metastasis [11, 12]. Intramural metastasis is usually found as a skip lesion in proximal or distal esophagus, and considering that distal esophagus can be resected completely in esophagectomy, intramural metastasis in remnant proximal esophagus is a concern. The LPM is reportedly associated with LR [1, 2]. In one study, a risk factor for LR was not positive resection margin, but rather the length of the resection margin [1]. Others have described that proximal margin length is a significant risk factor for overall survival [3]. In the current study, lymph node metastasis was a risk factor for LR and positive resection margin was not. Furthermore, a proximal margin of 5 cm or more in length was a favorable prognostic factor for LR. These findings suggest that the main mechanism of LR is intramural metastasis rather than residual tumor at the proximal resection margin, and that removal of intramural metastasis with sufficient length of proximal esophagus can decrease LR.

A safe length of proximal margin to prevent LR is unclear. In a study evaluating the location of intramural metastasis, the mean distance from tumor was 3.4 cm [11]. Therefore, a length exceeding 3 cm is usually recommended. The recommended length is diverse and ranges

from 3 cm to 10 cm [2, 13–15]. In the current study, a proximal margin length of 5 cm decreased LR. The LPM was a significant factor to decrease LR in multivariate analysis. However, the length was only significant in the patients with lymph node metastasis. We could not identify any correlation between the length and LR in patients without lymph node metastasis. Therefore, it can be suggested that the safe length of the proximal margin can differ based on the patient's N stage. Other studies have also indicated that the length of the resection margin is not important in T1 esophageal cancer [16], and that a short margin length is sufficient in T1-T2 esophageal cancer [14].

The most important limitation of this study is that LPM was measured ex vivo. Length of proximal resection margin is hard to evaluate in vivo before resection. Most of the studies evaluating LPM have used ex vivo LPM [1, 2, 11, 16, 17]. However, gastrointestinal organs may contract after resection, and ex vivo length of an organ may not represent the exact in vivo length. Evaluation of the correlation between in vivo and ex vivo length revealed than the total length of the esophagus contracted to 50% of its in vivo length, and the length of proximal margin to 44% [17]. We should be very cautious in interpreting the 5 cm LPM value. Although it was measured in a stretched condition, it almost certainly does not exactly reflect the in vivo length. Therefore, the optimum length of resection in vivo status will exceed 5 cm.

In summary, we evaluated risk factors for LR after esophagectomy. Lymph node metastasis and LPM less than 5 cm were risk factors for LR. The association between LPM and LR was identified only in patients with lymph node metastasis. Therefore, we suggest that ex vivo LPM should exceed 5 cm in patients with lymph node metastasis, whereas long LPM is not necessary in patients without lymph node metastasis.

References

1. Law S, Arcilla C, Chu KM, Wong J. The significance of histologically infiltrated resection margin after esophagectomy for esophageal cancer. Am J Surg 1998;176:286–90.
2. Tam PC, Siu KF, Cheung HC, Ma L, Wong J. Local recurrences after subtotal esophagectomy for squamous cell carcinoma. Ann Surg 1987;205:189–94.
3. Mine S, Sano T, Hiki N, et al. Proximal margin length with transhiatal gastrectomy for Siewert type II and III adenocarcinomas of the oesophagogastric junction. Br J Surg 2013;100:1050–4.
4. Blom RL, Lagarde SM, van Oudenaarde K, et al. Survival after recurrent esophageal carcinoma has not improved over the past 18 years. Ann Surg Oncol 2013;20:2693–8.
5. Zhang J, Peng F, Li N, et al. Salvage concurrent radiochemotherapy for post-operative local recurrence of squamous-cell esophageal cancer. Radiat Oncol 2012;7:93.
6. Little AG, Lerut AE, Harpole DH, et al. The Society of Thoracic Surgeons practice guidelines on the role of multimodality treatment for cancer of the esophagus and gastroesophageal junction. Ann Thorac Surg 2014;98:1880–5.
7. Rizk NP, Ishwaran H, Rice TW, et al. Optimum lymphadenectomy for esophageal cancer. Ann Surg 2010;251:46–50.
8. Jingu K, Matsushita H, Takeda K, et al. Long-term results of radiotherapy combined with nedaplatin and 5-fluorouracil for postoperative loco-regional recurrent esophageal cancer: update on a phase II study. BMC Cancer 2012;12:542.
9. Miyata H, Yamasaki M, Kurokawa Y, et al. Survival factors in patients with recurrence after curative resection of esophageal squamous cell carcinomas. Ann Surg Oncol 2011;18:3353–61.
10. Shioyama Y, Nakamura K, Ohga S, et al. Radiation therapy for recurrent esophageal cancer after surgery: clinical results and prognostic factors. Jpn J Clin Oncol 2007;37:918–23.
11. Lam KY, Ma LT, Wong J. Measurement of extent of spread of oesophageal squamous carcinoma by serial sectioning. J Clin Pathol 1996;49:124–9.
12. Takubo K, Sasajima K, Yamashita K, Tanaka Y, Fujita K. Prognostic significance of intramural metastasis in patients with esophageal carcinoma. Cancer 1990;65:1816–9.
13. Wong J. Esophageal resection for cancer: the rationale of current practice. Am J Surg 1987;153:18–24.
14. Tsutsui S, Kuwano H, Watanabe M, Kitamura M, Sugimachi K. Resection margin for squamous cell carcinoma of the esophagus. Ann Surg 1995;222:193–202.
15. Allum WH, Bonavina L, Cassivi SD, et al. Surgical treatments for esophageal cancers. Ann NY Acad Sci 2014;1325:242–68.
16. Barbour AP, Rizk NP, Gonen M, et al. Adenocarcinoma of the gastroesophageal junction: influence of esophageal resection margin and operative approach on outcome. Ann Surg 2007;246:1–8.
17. Siu KF, Cheung HC, Wong J. Shrinkage of the esophagus after resection for carcinoma. Ann Surgery 1986;203:173–6.

DISCUSSION

DR SHANDA H. BLACKMON (Rochester, MN): Why did no women get esophageal cancer? You only had 5 women, I think.

DR KANG: Yes, only a small number of women were included in this study.

DR BLACKMON: Do you know why? Is it that they do not want to have esophagectomy or is it because they do not get the cancer? Why?

DR KANG: Because there is cultural difference in Western and Eastern countries. Smoking and drinking alcohol in our Eastern culture is prohibited for women. Most of the squamous cell carcinoma is related to smoking and drinking alcohol. So there was only a small number.

DR STEVEN R. DEMEESTER (Los Angeles, CA): A more unique problem in the United States is the distal margin. You do not see that as being much of an issue with squamous tumors, but with adenocarcinomas of the gastroesophageal junction, a bigger issue for us is the distal margin, the gastric resection margin. Do you have any insights on that at all?

DR KANG: The distal margin is not quite that important in our data because, as you see, 95% of the patients had squamous cell carcinoma. Almost always the proximal margin is important. We had in some cases recurrence in the distal gastric margin area. I cannot remember the exact number. It was maybe 2 or 3 patients. It was very rare. So I think the proximal margin is more important in this type of study.

DR LISA M. BROWN (Sacramento, CA): Rather than dichotomizing the length of the proximal margin, did you find an inflection point beyond which you had no local recurrences—in other words, using length as a continuous variable?

DR KANG: Sorry, I could not understand it. Can you summarize again?

DR BROWN: For your length of the proximal margin, 5 cm, greater than or less than, did you look at all the lengths and see if there was a length beyond which there were no local recurrences at all?

DR KANG: All the lengths? I could not understand.

DR BREMNER: I think she is asking do you have an opinion of what the optimal length would be to reduce your risk of local recurrence.

DR KANG: It depends on the staging. An important feature that we are going to present is about the relationship between N stage and local recurrence. In the advanced stage, we should resect a long segment of the esophagus, but I think, in my personal opinion, more important is that the longer resection of the esophagus is not necessary in N0 patients, which means that a more reduced procedure or a lower-risk surgery can be applied to those patients. This is why endoscopic submucosal dissection and endoscopic mucosal resection are successful for such an early stage of esophageal cancer.

What is the optimal length? In my practice, if the tumor is located within 30 cm from the incisors, I do the anastomosis in the neck to get enough length of the margin, and if it is more than 30 cm, including gastroesophageal junction tumors, I do the anastomosis in the chest, and then it makes the mean length of the margin maybe around 4 cm or 5 cm.

DR ROSS M. BREMNER (Phoenix, AZ): And how would you treat a tumor at 20 cm from the incisors?

DR KANG: That is a problem. In such cases, and it all depends on the cases, we cannot get enough margin. However, in such cases, usually we deliver adjuvant treatment, concurrent chemoradiotherapy, or sometimes we do neoadjuvant concurrent chemoradiotherapy.

DR DONALD E. LOW (Seattle, WA): I think my question is much the same as Ross's. Most of your tumors were squamous cell carcinomas. The proximal resection margin is dictated as much by where the tumor is located rather than what you may wish your proximal margin to be. I notice that you had only a small proportion of three-field lymphadenectomies. Regarding proximal tumors, did you then treat them with neoadjuvant therapy before surgery and did you change your approach to lymph node dissection? What you showed was that the proximal margin was more significant in people who had positive lymph nodes, but if you have very proximal tumors and you are not sampling upper mediastinal or cervical nodes, then you may be understaging these patients as well.

DR KANG: With the upper thoracic esophageal cancer tumors, it is harder to decide what types of surgery we should do. Sometimes we do a three-field lymph node dissection. Sometimes we deliver neoadjuvant chemoradiation. In my practice, more and more I have come to use neoadjuvant treatment for upper mediastinal and cervical lymph node metastasis. Although we do not have any evidence of such practice, many centers in our country are starting to do neoadjuvant chemoradiation for cervical metastasis in squamous cell carcinoma. In my personal experience, I think overall survival is being improved by using neoadjuvant treatment because, as you see in the data, we cannot have enough primary tumor margin in upper thoracic esophageal cancer. The node metastasis to the neck means that the tumor cells can spread to the whole body. We have only a small margin for complete resection of the tumor, so in such a case I use neoadjuvant or adjuvant chemoradiation. However, these data are a mixture of many surgeons over a long time. Gradually we are changing, and we are going to gather some solid evidence for such a practice in the future.