



## Optimum Treatment Strategy for Superficial Esophageal Cancer: Endoscopic Mucosal Resection versus Radical Esophagectomy

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**Abstract.** This study was designed to determine the optimum treatment for a superficial esophageal cancer involving the mucosal or submucosal layer of the esophagus. The subjects were 150 patients with a superficial esophageal cancer who underwent endoscopic mucosal resection (EMR) or esophagectomy in Kurume University Hospital from 1981 to 1997. The mortality and morbidity rates, survival rate, and recurrence rate were retrospectively compared for (1) 35 patients who underwent EMR and 37 patients who underwent esophagectomy for a mucosal esophageal cancer and (2) 45 patients who underwent extended radical esophagectomy and 33 patients who underwent less radical esophagectomy for a submucosal esophageal cancer. Among the 72 patients with a mucosal cancer, lymph node metastasis/recurrence was observed in only one (1%); whereas of 78 patients with a submucosal cancer it was observed in 30 (38%). Among patients with a mucosal cancer the mortality and morbidity rates after EMR were lower than for those after esophagectomy. The survival rate after EMR was the same as that after esophagectomy. No recurrence was observed after either treatment modality. Among the patients with a submucosal cancer, the survival rate was higher and the recurrence rate lower after extended radical esophagectomy; than after less radical esophagectomy; the mortality and morbidity rates after extended radical esophagectomy were the same as those after less radical esophagectomy. Multivariate analysis demonstrated that the treatment modality (EMR versus esophagectomy) did not influence the survival of patients with a mucosal esophageal cancer, whereas it strongly influenced the survival of patients with a submucosal esophageal cancer. We concluded that EMR was the mainstay of treatment for a mucosal esophageal cancer, and extended radical esophagectomy was the mainstay of treatment for a submucosal esophageal cancer.

The incidence of a superficial esophageal cancer, including Tis and T1 lesions (UICC, 1997) [1], is increasing with advances in diagnostic modalities including endoscopy, endoscopic vital staining using iodine solution [2], and endoscopic ultrasonography [3]. There remains controversy over which treatment should be employed for a superficial esophageal cancer [4]. The treatment modalities for such a cancer vary from local excision, including endoscopic mucosal resection (EMR) [5–8], to extended radical

esophagectomy (three-field lymphadenectomy) [9]. Many have proposed their own treatment strategy for superficial esophageal cancer based on pathologic findings from surgically resected specimen [9–13]. Few have proposed a treatment strategy based on the comparative results between EMR and radical esophagectomy [14].

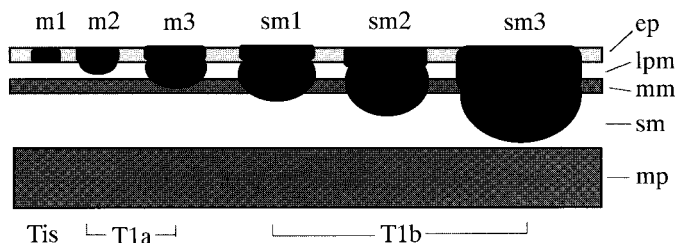
The purpose of this study was to evaluate the impact of EMR and extended radical esophagectomy on the outcome of superficial esophageal cancer. A retrospective trial compared the mortality and morbidity rates, survival rate, and recurrence rate for EMR and esophagectomy in regard to mucosal esophageal cancers and for extended radical esophagectomy and less radical esophagectomy in regard to submucosal esophageal cancers. The findings from this study provided useful information for determining the optimum treatment strategy for a superficial esophageal cancer.

### Patients and Methods

#### *Patient Population*

The study group consisted of 150 patients with a superficial squamous cell esophageal cancer who underwent esophagectomy, EMR, or both between 1981 and 1997 at Kurume University Hospital. During the same period, 640 patients underwent esophagectomy, EMR, or both for a squamous cell esophageal cancer. The ratio for superficial esophageal cancer was 23%. Altogether, 109 patients underwent esophagectomy; 37 patients underwent EMR; and 4 patients underwent esophagectomy following EMR. Among these patients, the depth of tumor invasion (T) [1] and the lymphatic or vascular invasion (Ly, V) [1] were pathologically confirmed in the resected specimen. Patients without histologic confirmation of the depth of invasion after laser vaporization or radiotherapy were excluded from this study.

There were 133 men and 17 women with an average age of 63



**Fig. 1.** Pathologic subclassification of superficial esophageal cancer. ep: epithelium; lpm: lamina propria mucosa; mm: muscularis mucosa; sm: submucosa; mp: muscularis propria; m1: ep (carcinoma in situ); m2: lpm; m3: mm; sm1: shallower one-third of sm; sm2: intermediate one-third of sm; sm3: deepest one-third of sm; Tis: m1; T1a: m1 + m2; T1b: sm (sm1 + sm2 + sm3).

**Table 1.** Relations between depth of invasion of superficial esophageal cancer and lymphatic or vascular invasion, lymph node metastasis, lymph node recurrence, and lymph node metastasis or recurrence.

Depth of invasion <sup>a</sup>	No. of patients	Ly/V	cNpN	Rec	N/Rec
m1 (Tis)	21	0	0	0	0
m2 (lpm)	28	2 (7%)	0	0	0
m3 (mm)	23	3 (13%)	1 (4%)	0	1 (4%)
sm1	16	9 (56%)	4 (25%)	3 (19%)	5 (31%)
sm2	27	18 (67%)	6 (22%)	2 (7%)	8 (30%)
sm3	35	28 (80%)	14 (40%)	5 (14%)	17 (49%)
Total	150	60 (40%)	25 (17%)	10 (7%)	31 (21%)

Ly/V: lymphatic and/or vascular invasion; cNpN: clinical lymph node metastasis at endoscopic mucosal resection (EMR) or pathologic lymph node metastasis at surgery; Rec: lymph node recurrence after EMR or surgery; N/Rec: clinical or pathologic lymph node metastasis, lymph node recurrence or both; m1 (Tis): carcinoma in situ; m2 (lpm): lamina propria mucosa; m3 (mm): muscularis mucosa; sm1: shallower one-third of submucosa; sm2: intermediate one-third of submucosa; sm3: deepest one-third of submucosa.

<sup>a</sup>Pathologic subclassification for superficial esophageal cancer (Fig. 1).

years at treatment. The location of the tumor according to the International Union Against Cancer (UICC) [1] was the cervical esophagus in 4 patients, the upper thoracic esophagus in 15, the mid-thoracic esophagus in 94, and the lower thoracic esophagus in 37. Based on the pathologic subclassification of superficial esophageal cancer (Fig. 1) [2, 10, 14], the distribution of the depth of tumor invasion was m1 (Tis) in 21 patients, m2 (lpm) in 28, m3 (mm) in 23, sm1 (shallowest one-third) in 16, sm2 (intermediate one-third) in 27, and sm3 (deepest one-third) in 35.

Table 1 summarizes the incidence of lymphatic and vascular invasion, lymph node metastasis at treatment, lymph node recurrence after treatment, and lymph node metastasis or recurrence at each depth of tumor invasion. Lymphatic or vascular invasion (or both) was observed in 60 patients (40%). Metastasis in the lymph nodes (pNcN1) [1] was found in 25 patients (17%) at surgery or EMR. In the present study pathologic lymph node metastasis (pN) could be assessed in patients who underwent esophagectomy, whereas clinical lymph node metastasis (cN) was substituted for pathologic lymph node metastasis in patients who underwent EMR. Clinical lymph node metastasis was assessed using physical examination, computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), and endoscopic ultra-

sonography (EUS). Lymph node recurrence was assessed using the same modalities and was found in 10 patients (7%) with a submucosal cancer. The rate of lymph node metastasis at treatment and of lymph node recurrence after treatment was only 1% (1/72) in patients with a mucosal esophageal cancer, whereas it was 38% (30/78) in those with a submucosal esophageal cancer.

Distant lymph node metastasis (M1-Lym) [1], including the cervical and celiac nodes, was observed at surgery in seven patients (9%) with a submucosal esophageal cancer. Recurrence in the distant lymph nodes was found in six (8%) patients with this cancer. Distant metastasis (M1-Org) [1] was not observed at surgery in any patient with a superficial esophageal cancer at treatment, whereas recurrence in distant organs was found in seven patients (9%) with a submucosal cancer. According to the TNM system [1], 22 were in stage 0, 103 in stage I, 0 in stage IIA, 18 in stage IIB, 0 in stage III, and 7 in stage IV.

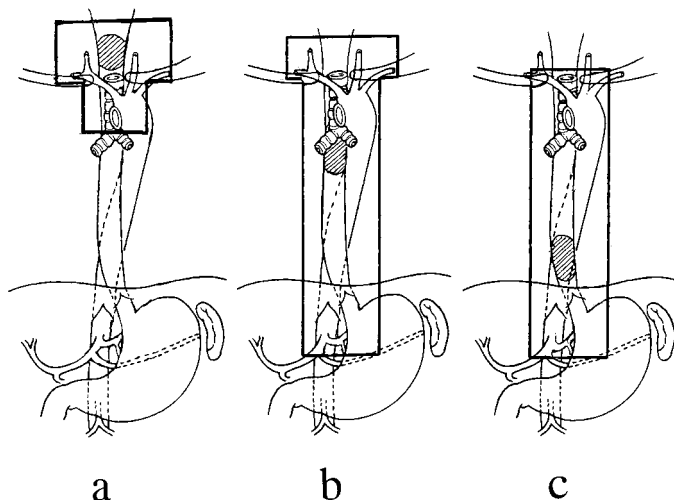
A total of 67 multiple primary cancers were observed in 55 patients (37%) with a superficial esophageal cancer; 36 synchronous double primary cancers were observed in 35 patients (23%); and 31 metachronous double primary cancers in 29 patients (19%). Multiple primary cancers with superficial esophageal cancer frequently occurred in the head/neck, stomach, colon/rectum, and lung.

The average follow-up period for all 150 patients was 45 ± 32 months (range 1–153 months). The overall 5- and 10-year survival rates for patients with a superficial esophageal cancer were 61% and 44%, respectively (Kaplan-Meier method); and the disease-specific 5- and 10-year survival rates for these patients were 90% and 88%, respectively.

*Treatment Modality*

Among those with a mucosal esophageal cancer, esophagectomy was employed in 35 patients (transthoracic esophagectomy with lymphadenectomy in 23, transhiatal esophagectomy without lymphadenectomy in 12) and EMR in the other 37 patients. Before 1993 all patients with a mucosal cancer underwent esophagectomy, regardless of the risk of postoperative mortality and morbidity. Since the technique of EMR was introduced at our hospital in 1993, we have started a team approach involving surgeons, endoscopists, and radiologists under a fixed strategy for superficial esophageal cancer. EMR was adopted mainly for patients with a localized mucosal cancer because we believe such a cancer rarely metastasizes to the lymph nodes, and it can be easily resected by EMR. Esophagectomy was adopted for patients with a superficial spreading type of mucosal cancer involving the whole circumference of the esophagus because we thought at that time that such a cancer could metastasize to the lymph nodes, and that esophageal stricture would subsequently occur after EMR for such a cancer. After 1993 approximately 78% (37/47) of patients with a mucosal cancer underwent EMR.

For those with submucosal esophageal cancer, esophagectomy was employed in 78 patients (extended radical esophagectomy in 45, less radical esophagectomy in 33). In the present study, extended radical esophagectomy was defined as (1) cervical esophagectomy with cervical and upper mediastinal lymphadenectomy for a cancer in the cervical esophagus; (2) right transthoracic subtotal esophagectomy with cervicothoracoabdominal lymphadenectomy (three-field dissection) for a cancer in the upper or mid-thoracic esophagus; and (3) right transthoracic subtotal



**Fig. 2.** Extended radical esophagectomy for a superficial esophageal cancer. **a:** Cervical esophagectomy through an upper median sternotomy with cervical and upper mediastinal lymphadenectomy for a cancer in the cervical esophagus. **b:** Subtotal esophagectomy through a right thoracotomy with cervicothoracoabdominal three-field lymphadenectomy for a cancer in the upper or mid-thoracic esophagus. **c:** Subtotal esophagectomy through a right thoracotomy with thoracoabdominal two-field lymphadenectomy for a cancer in the lower thoracic esophagus.

esophagectomy with thoracoabdominal lymphadenectomy (two-field dissection) for a cancer in the lower thoracic esophagus (Fig. 2). These surgical procedures have been our choices for advanced esophageal cancer [15, 16]. Less radical esophagectomy included all of these surgical modalities but a lesser extent of esophagectomy and a lesser extent of lymphadenectomy than extended radical esophagectomy. Before 1993 less radical esophagectomy was commonly employed for patients with a submucosal cancer, and after that times extended radical esophagectomy was employed for 79% (30/38) of patients with a submucosal cancer.

Curative (R0) resection [1] was performed in 135 patients and microscopic palliative (R1) resection in 15. The lateral surgical margin (proximal or distal surgical margin) was cancer-positive in 14 patients who underwent EMR and in 1 patient who underwent extended radical esophagectomy. No patients were cancer-positive at the deep surgical margin (external surgical margin). Among the 15 patients who were cancer-positive at the lateral surgical margin, repeated EMR, endoscopic laser vaporization, or radiotherapy followed.

Adjuvant therapy was administered to 28 patients, postoperative radiotherapy to 7, and postoperative chemotherapy to 21. Before 1985 a total dosage of 50 Gy radiotherapy was administered to the neck and upper mediastinum in two patients with lymph node metastasis (with informed consent); after that time two courses of chemotherapy (CDDP 70 mg/m<sup>2</sup> for 1 day and 5-fluorouracil 700 mg/m<sup>2</sup> for 5 days) were administered to 21 patients with lymph node metastasis (with informed consent). Four patients after palliative (R1) EMR underwent a total dosage of 50 Gy radiotherapy to the esophageal lesion because the EMR could not be repeated owing to esophageal varices or esophageal stricture. One patient underwent a total dosage of 50 Gy radiotherapy to the anastomotic line after palliative (R1) esophagectomy.

**Table 2.** Clinical characteristics of mucosal esophageal cancer.

Parameter	Esophagectomy (n = 35)	EMR (n = 37)	p
Gender (M/F)	30/5	33/4	NS
Age (years)	63 ± 11	65 ± 8	NS
Cancer location (cervical/ upper/mid/lower)	0/4/20/11	1/4/23/9	NS
Period (1981–1992/1993–1997)	25/10	0/37	< 0.001
pT (m1/m2/m3)	9/12/14	13/15/9	NS
pLyV (LyV0/LyV1)	31/4	36/1	NS
cNpN (N0/N1)	34/1	37/0	NS
cMpM (M0/M1-Lym/M-Org)	35/0/0	37/0/0	NS
pStage (St 0/I/IIA/IIIB/III/IV)	9/25/0/1/0/0	13/24/0/0/0/0	NS
R (R0/R1R2)	35/0	23/14	< 0.001
Complications (none–mild/severe) <sup>a</sup>	27/8	37/0	0.002
Adjuvant therapy (none/RTx/CTx)	34/0/1	33/4/0	NS
Multiple primary cancers (none/synchr/metachr/both)	19/6/7/3	21/10/5/1	NS

pT: pathologic subclassification; pLyV: pathologic lymphatic and/or vascular invasion; cMpM: clinical and pathologic distant metastasis; pStage: pathologic stage grouping, R: residual tumor classification; RTx: postoperative radiotherapy; CTx: postoperative chemotherapy; synchr: synchronous double primary cancer; metachr: metachronous double primary cancer; both: synchronous and metachronous double primary cancers.

<sup>a</sup>Multiple organ failure and respiratory failure in three patients each; renal failure and pyothorax subsequent to a perforated peptic ulcer in the gastric tube in one patient each.

#### Stratification

**Mucosal Esophageal Cancer.** To evaluate the effect of treatment modalities for a mucosal esophageal cancer, the incidence of mortality and morbidity, recurrence rate, and survival rate were compared for the patients who underwent esophagectomy and those who underwent EMR. Even though this was a retrospective study, except for a few factors there was no significant difference in background factors, including clinical characteristics and adjuvant therapies between the esophagectomy group and the EMR group (Table 2). The only notable differences were in the time period, residual tumor classification, and postoperative complications. According to the change in the treatment strategy for a mucosal esophageal cancer as noted above, all the patients with a mucosal cancer underwent esophagectomy before 1993, whereas almost all patients with such a cancer underwent EMR after 1993 ( $p < 0.001$ ). Among patients with a mucosal esophageal cancer no residual tumor (R0) was observed after esophagectomy, whereas a microscopic or macroscopic residual tumor (R1) was occasionally observed after EMR ( $p < 0.001$ ). As noted above, however, additional treatment was performed for such patients, so no patient died of recurrence. Severe complications, noted in Table 2, were frequently observed after esophagectomy, whereas a severe complication was never observed after EMR ( $p = 0.002$ ).

**Submucosal Esophageal Cancer.** For the group with a submucosal esophageal cancer, the mortality and morbidity incidence, recurrence rate, and survival rate were compared for patients who underwent extended radical esophagectomy and those who underwent less radical esophagectomy. There were no significant differences in the background factors for the extended radical

**Table 3.** Clinical characteristics of submucosal esophageal cancer.

Parameter	Extended radical esophagectomy (n = 45)	Less radical esophagectomy (n = 33)	p
Gender (M/F)	40/5	28/5	NS
Age (years)	61 ± 8	64 ± 9	NS
Cancer location (cervical/upper/middle/lower)	2/4/26/13	1/3/25/4	NS
Period (1981–1992/1993–1997)	15/30	25/8	< 0.001
pT (sm1/sm2/sm3)	10/11/24	6/16/11	NS
pLyV (LyV0/LyV1)	13/32	10/23	NS
cNpN (N0/N1)	28/17	26/7	NS
cMpM (M0/M1-Lym/M1-Org)	38/7/0	33/0/0	NS
pStage (St 0/I/IIA/IIB/III/IV)	0/28/0/10/0/7	0/26/0/7/0/0	NS
R (R0/R1)	44/1	33/0	NS
Complications (none–mild/severe) <sup>a</sup>	36/9	29/4	NS
Adjuvant therapy (none/RTx/CTx)	30/1/14	25/2/6	NS
Multiple primary cancers (none/synchr/metachr/both)	33/5/4/3	23/4/4/2	NS

<sup>a</sup>Multiple organ failure in four patients; respiratory failure in three; cardiac failure, renal failure, hepatic failure, rupture in the common carotid artery subsequent to tracheal necrosis, gastropericardial fistula due to penetrated peptic ulcer in the gastric tube, and gastrobronchial fistula due to penetrated peptic ulcer in the gastric tube in one patient each.

esophagectomy group and the less radical esophagectomy group except for the time period (Table 3). There was a change in the treatment strategy for a submucosal esophageal cancer, as noted above, at 1993: almost all patients with a submucosal cancer underwent less radical esophagectomy before 1993 and extended radical esophagectomy after 1993 ( $p < 0.001$ ).

The survival rates were calculated by the Kaplan-Meier method. The differences between survival curves were calculated by the Cox-Mantel test. The risk factors for prognosis of a superficial esophageal cancer were investigated using multivariate analysis by the logistic procedure in the SAS Computer Program [17]. The 15 factors—gender, age, cancer location, depth of invasion (T), lymphatic or vascular invasion (Ly/V), lymph node metastasis (N), distant organ metastasis (M), residual tumor classification (R), treatment modality (esophagectomy versus EMR for a mucosal cancer and extended radical esophagectomy versus less radical esophagectomy for a submucosal cancer), postoperative complications, radiotherapy, chemotherapy, synchronous double primary cancer, metachronous double primary cancer, time period—were each investigated as a potential risk factor for the prognosis using multivariate analysis.

**Results**

*Mucosal Esophageal Cancer*

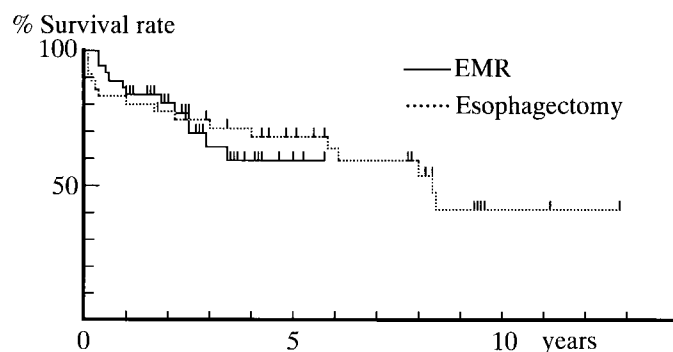
**Mortality and Morbidity Rates.** The morbidity rate after esophagectomy was 69% (24/35), whereas that after EMR was 7% (2/37), a significant difference ( $p < 0.001$ ). During the primary hospitalization five (14%) patients died after esophagectomy (hospital

**Table 4.** Operative results of mucosal esophageal cancer.

Parameter	Esophagectomy (n = 35)	EMR (n = 37)	p
Morbidity	24 (69%)	2 (7%)	< 0.001
Hospital mortality	5 (14%)	0	0.017
Cause of death after discharge			
Recurrence	0	0	NS
Other malignancies	7 (20%)	6 (16%)	NS
Without malignancy	3 (9%) <sup>a</sup>	5 (14%) <sup>b</sup>	NS
Alive	20 (57%)	26 (70%)	NS

<sup>a</sup>Trauma in two patients and ileus in one.

<sup>b</sup>Trauma, myocardial infarction, bleeding esophageal varix, esophago-tracheal fistula caused by esophageal dilatation for radiation esophageal stricture, and unknown cause in one patient each.



**Fig. 3.** Overall survival curves after endoscopic mucosal resection (EMR) and after esophagectomy for a mucosal esophageal cancer. There was no significant difference in the overall survival curves after EMR and after esophagectomy.

mortality): Before 1993 all patients underwent surgery regardless of the risk of postoperative mortality and morbidity. None of the 37 patients who underwent EMR died during hospitalization, a significant difference ( $p = 0.017$ ).

No patients with a mucosal cancer died of recurrence, although they commonly died of other malignancies. Causes of the deaths are given in Table 4. During the follow-up period the ratio of the alive patients after EMR was similar to that after esophagectomy.

**Survival Rates.** Among patients with a mucosal esophageal cancer, the overall 5-year survival rate after EMR was 61% and the 5- and 10-year-survival rates after esophagectomy were 71% and 42%, respectively. There was no difference in the overall survival rates after esophagectomy and after EMR (Fig. 3). For the disease-specific survival rates of these patients, there was no difference between esophagectomy and EMR because no patient died of recurrence.

**Lymph Node Metastasis and Recurrence.** Pathologic lymph node metastasis (pN) was observed in only 1 (3%) of 35 patients who underwent esophagectomy. No clinical lymph node metastasis (cN) was observed in the 37 patients who underwent EMR.

Recurrence was not observed in patients with a mucosal esophageal cancer after EMR during an average follow-up period of 32 months (4–68 months). It was also not seen after esophagectomy during an average follow-up period of 62 months (1–153 months).

**Table 5.** Risk factors for prognosis of mucosal esophageal cancer.

Factor	Odds ratio (at 95% confidence interval)	<i>p</i>
Postoperative complications		
None/mild	1	< 0.001
Severe	9 (4–23)	
Synchronous double primary cancer		
Absent	1	< 0.001
Present	5 (2–11)	

The other 13 factors, including gender, age, cancer location, depth of invasion (T), lymphatic and vascular invasion (Ly/V), lymph node metastasis (N), distant organ metastasis (M), residual tumor classification (R), treatment modality (esophagectomy versus EMR, radiotherapy, chemotherapy), metachronous double cancer, and time period were each determined not to be prognostic.

**Table 6.** Operative results of submucosal esophageal cancer.

Parameter	Extended radical esophagectomy ( <i>n</i> = 45)	Less radical esophagectomy ( <i>n</i> = 33)	<i>p</i>
Morbidity	41 (91%)	28 (85%)	NS
Hospital mortality	2 (4%)	2 (6%)	NS
Cause of death after discharge			
Recurrence	3 (7%)	7 (21%)	0.058
Other malignancies	5 (11%)	2 (6%)	NS
Without malignancy	1 (2%) <sup>a</sup>	10 (30%) <sup>b</sup>	< 0.001
Alive	34 (76%)	12 (36%)	0.001

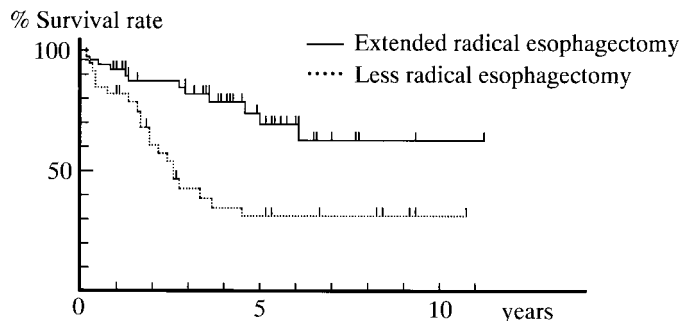
<sup>a</sup>Occlusion of the superior mesenteric artery in one patient.

<sup>b</sup>Aspiration pneumonia and ileus in two patients each; cardiac failure, fulminant hepatitis, and hypothyroidism in one patient each; unknown causes in three patients.

**Prognostic Factors.** The prognostic factors for patients with a mucosal esophageal cancer were determined using multivariate analysis. Survival of patients with mucosal esophageal cancer was strongly influenced by the postoperative complications and the presence of synchronous double primary cancers (Table 5). The treatment modality (EMR versus esophagectomy) was investigated and found not to be a risk factor for the prognosis of such patients.

#### Submucosal Esophageal Cancer

**Mortality and Morbidity Rates.** The morbidity rate was 91% (41/45) after extended radical esophagectomy and 85% (28/33) after less radical esophagectomy, with no significant difference. Of 45 patients who underwent extended radical esophagectomy, 2 (4%) died during the primary hospitalization (hospital mortality); and of the 38 patients who underwent less radical esophagectomy, 2 patients (6%) died (Table 6). The proportion of patients who died of recurrence and the patients who died without recurrence after discharge were significantly greater after less radical esophagectomy than after extended radical esophagectomy ( $p = 0.058$  and  $p < 0.001$ , respectively). The proportion of patients alive at the most recent check was significantly greater after extended radical esophagectomy than after less radical esophagectomy ( $p = 0.001$ ).



**Fig. 4.** Overall survival curves after extended radical esophagectomy and after less radical esophagectomy for submucosal esophageal cancer. The overall survival rate after extended radical esophagectomy was significantly better than that after less radical esophagectomy ( $p = 0.001$ , Cox-Mantel test).

**Survival Rates.** The overall survival rates for patients with a submucosal esophageal cancer are shown in Fig. 4. The overall 5- and 10-year survival rates after extended radical esophagectomy were 74% and 62%, respectively; and those after less radical esophagectomy were 31% and 31%, respectively. The overall survival rate after extended radical esophagectomy was significantly higher than that after less radical esophagectomy ( $p = 0.001$ ). The disease-specific 5- and 10-year survival rates after extended radical esophagectomy were 94% and 88%, respectively; and those after less radical esophagectomy were 57% and 57%, respectively. The disease-specific survival rate also was significantly different ( $p = 0.011$ ).

**Lymph Node Metastasis and Recurrence.** Pathologic lymph node metastasis was observed in 31% (24/78) of patients with a submucosal cancer who underwent esophagectomy, and lymph node recurrence was observed in 13% (10/78) of patients during an average follow-up period of 43 months (1–132 months). As a result, 38% (30/78) of patients with a submucosal cancer had lymph node metastasis at surgery, recurrence after surgery, or both.

Metastasis at surgery was observed in the upper mediastinal lymph nodes from a cancer in the upper thoracic esophagus; in the cervical, mediastinal, and abdominal nodes from a cancer in the mid-thoracic esophagus; and in the lower posterior mediastinal and abdominal nodes from a cancer in the lower thoracic esophagus. Recurrence after surgery was frequently observed in the cervical and upper mediastinal lymph nodes.

**Prognostic Factors.** The prognostic factors for patients with a submucosal esophageal cancer were determined using multivariate analysis. Among the 15 factors, the survival of such patients was strongly influenced by four factors: treatment modality, postoperative complications, synchronous double primary cancers, and lymphatic or vascular invasion (or both) (Table 7). Extended radical esophagectomy contributed significantly to improved survival of patients with a submucosal esophageal cancer compared with less radical esophagectomy ( $p < 0.001$ ).

**Table 7.** Risk factors for prognosis of submucosal esophageal cancer.

Factor	Odds ratio (at 95% confidence interval)	<i>p</i>
Treatment modality		
Extended radical esophagectomy	1	< 0.001
Less radical esophagectomy	6 (3–16)	
Postoperative complications		
None/mild	1	0.002
Severe	5 (2–14)	
Synchronous double primary cancer		
Absent	1	0.001
Present	3 (2–7)	
Lymphatic and/or vascular invasion		
Absent	1	0.022
Present	3 (1–7)	

The other 11 factors, including gender, age, cancer location, depth of invasion, lymph node metastasis, distant organ metastasis, residual tumor classification, radiotherapy, chemotherapy, metachronous double primary cancer, and time period, were each determined not to be prognostic.

## Discussion

### *Depth of Tumor Invasion and Lymph Node Metastasis in Superficial Esophageal Cancer*

To assess the depth of invasion of a superficial esophageal cancer, we routinely utilize esophagography, endoscopy, and EUS [2–4, 6, 11]. Diagnostic EMR is occasionally adopted for a borderline case to distinguish between a mucosal cancer and a submucosal cancer. We believe that the pathologic subclassification for superficial esophageal cancer [2, 10, 14] is effective for improving the diagnosis and treatment of this cancer. On the other hand, to assess lymph node metastasis from a superficial esophageal cancer, we routinely use US, EUS, CT, and MRI [4]. The incidence of lymph node metastasis from a superficial esophageal cancer is strongly correlated with the depth of tumor invasion. Based on nationwide questionnaire research, Kodama et al. [14] reported that the incidence of lymph node metastasis was 0% from an m1 cancer, 3.3% from an m2 cancer, 12.2% from an m3 cancer, 26.5% from an sm1 cancer, 35.8% from an sm2 cancer, and 45.9% from an sm3 cancer. These incidences are consistent with those reported by others [2, 7, 10–12] and in the present study.

Because lymphadenectomy was not performed in patients who underwent EMR, clinical lymph node metastasis (cN) was substituted for pathologic lymph node metastasis (pN) in the present study. Therefore to assess the actual incidence of lymph node metastasis, we calculated the sum of the incidence of lymph node metastasis at treatment and the incidence of lymph node recurrence after treatment. The present study revealed that the total incidence of lymph node metastasis, recurrence, or both was only 1% in patients with a mucosal cancer and 38% in patients with a submucosal cancer. To summarize: the incidence of lymph node metastasis from a mucosal cancer was insignificant, whereas that from a submucosal cancer was comparable to that from an advanced esophageal cancer. This fact indicated that only patients with a mucosal esophageal cancer should undergo endoscopic treatment for cancer excision.

### *Treatment Strategy for Mucosal Esophageal Cancer*

This study revealed that the incidence of lymph node metastasis from a mucosal cancer was only 1%, and there was no recurrence during the follow-up period after EMR or after esophagectomy. The lymph node metastatic rate was lower than the mortality rate after esophagectomy. The survival for patients with a mucosal cancer after EMR was equal to that after esophagectomy. Based on these results, we concluded that EMR was the mainstay of treatment for a mucosal esophageal cancer. We performed esophagectomy in four patients who underwent EMR because the specimen resected by EMR suggested lymphatic invasion from the mucosal esophageal cancer, but no lymph node metastasis was found.

Bonavina et al. [13] concluded that even though endoscopic modalities for cancer ablation were indicated only in patients with unequivocal intramucosal cancer surgery remained the mainstay of treatment of a superficial esophageal cancer because of the relative inaccuracy of current staging modalities, the low morbidity and mortality rates associated with surgical resection, and the frequent multifocality of squamous cell esophageal cancer. We, however, recommend EMR for borderline cases to distinguish between a mucosal cancer and a submucosal cancer for the purpose of combining diagnosis with treatment. We can more accurately assess the depth of tumor invasion (pT) this modality than with other diagnostic modalities. When the resected specimen reveals that the cancer is limited to the mucosa, we believe that a diagnostic EMR is adequate treatment for cure because of the unlikely possibility of lymph node metastasis. Because most multifocal esophageal cancers are also limited to the mucosa, repeated EMR can easily control such lesions. Accordingly, we conclude that almost all mucosal esophageal cancers can be controlled by EMR.

### *Treatment Strategy for Submucosal Esophageal Cancer*

Many have argued that esophagectomy with lymphadenectomy should be adopted for a submucosal esophageal cancer because of the high incidence of lymph node metastasis [2, 6, 7, 9–13]. Moreover, the patterns of lymph node metastasis from such a cancer were similar to those from advanced esophageal cancers [9]. Since 1993 we have applied extended radical lymphadenectomy for a submucosal esophageal cancer whenever possible. The present study has found that the mortality rate after extended radical esophagectomy was equal to that after less radical esophagectomy; the recurrence rate after extended radical esophagectomy was less than that after less radical esophagectomy; and the survival rate after extended radical esophagectomy was higher than that after less radical esophagectomy. Multivariate analysis demonstrated that the surgical procedure undertaken was one of the most important prognostic factors, and that extended radical esophagectomy improved the survival of patients with a submucosal cancer compared to less radical esophagectomy. Based on these results, we concluded that extended radical esophagectomy was the mainstay of treatment for patients with a submucosal esophageal cancer.

Soehendra et al. [8] performed curative resection using EMR on seven patients with a submucosal esophageal cancer and observed no recurrence during an average follow-up of 7 months. We have employed EMR in five patients with a submucosal

esophageal cancer. All five underwent palliative (R1) resection because of being cancer-positive at the lateral surgical margin or at the deep surgical margin; subsequent radiotherapy or chemoradiotherapy was needed. Of these five patients, three had recurrence in lymph nodes, distant organs, or both. During an average follow-up period of 28 months (18–62 months) two died of the recurrence, and the other two died from other malignancies. Accordingly, we concluded that EMR could not be employed for a submucosal esophageal cancer with curative intent. Bonavina et al. [13] also emphasized that the presence of lymph node metastasis undetected at preoperative investigation in patients with submucosal cancers would make endoscopic mucosectomy inadequate in these individuals.

#### *Treatment for Superficial Esophageal Cancer with Multiple Primary Cancers*

Of all 150 patients with a superficial esophageal cancer, 55 (37%) had synchronous or metachronous multiple primary cancers (or both). The multivariate analysis on the prognosis of patients with a mucosal esophageal cancer revealed that synchronous double primary cancers and postoperative complications were the only prognostic factors. Accordingly, we believe that EMR, as a less stressful treatment, should be employed in patients with a mucosal esophageal cancer who have synchronous double primary cancers. On the other hand, in patients with a submucosal esophageal cancer, the presence of synchronous double primary cancers and postoperative complications strongly influenced the prognosis of such patients, as did the surgical procedure. Therefore we believe that in patients with synchronous double primary cancers or at high risk of mortality and morbidity, less stressful treatment (e.g., chemoradiotherapy or less radical esophagectomy) is indicated even for those with a submucosal cancer. In particular, less invasive treatment should be employed when another primary cancer may decide the prognosis of the patient. Well balanced decision-making is required when treating patients with a superficial esophageal cancer who have synchronous double primary cancers or are at high risk of mortality and morbidity.

#### **Conclusions**

Until now, it has not always been clear which treatment should be adopted for a superficial esophageal cancer. The modalities of treatment for such a cancer has varied from EMR to extended radical esophagectomy with three-field lymphadenectomy. The present study was designed to determine which, among EMR, less radical esophagectomy, and extended radical esophagectomy, is indicated for a superficial esophageal cancer. The mortality and morbidity rates, survival rates, and the recurrence rates were compared for (1) 42 patients with a mucosa esophageal cancer who underwent EMR and 37 patients with such a cancer who underwent esophagectomy and (2) 45 patients with a submucosal esophageal cancer who underwent extended radical esophagectomy and 33 patients with such a cancer who underwent less radical surgery.

Of 72 patients with a mucosal esophageal cancer, lymph node metastasis or recurrence was found in only 1 (1%) patient. The mortality and morbidity rates after EMR in these patients were lower than in those after esophagectomy. The survival rate after

EMR was the same as that after esophagectomy. On the other hand, of 78 patients with a submucosal esophageal cancer, lymph node metastasis or recurrence was found in 30 (38%) patients. In these patients the survival rate was higher and the recurrence rate lower after extended radical esophagectomy than after less radical esophagectomy; the mortality rate after extended radical esophagectomy was the same as after less radical esophagectomy. Multivariate analysis demonstrated that the treatment modality (EMR versus esophagectomy) did not influence the survival of patients with a mucosal esophageal cancer, whereas it strongly influenced the survival of patients with a submucosal esophageal cancer.

Based on these results we concluded that EMR was the mainstay of treatment for a mucosal esophageal cancer, and extended radical esophagectomy was the mainstay for a submucosal esophageal cancer. A randomized controlled trial is needed to determine the optimal treatment for a superficial esophageal cancer.

#### **Résumé**

Le but de cette étude a été de déterminer le traitement optimal du cancer superficiel (muqueux ou sous-muqueux) de l'oesophage. 150 patients ayant un cancer superficiel de l'oesophage ont eu soit une résection endoscopique de la muqueuse (REM) ou une oesophagectomie à l'hôpital Universitaire de Kurume entre 1981 et 1997. La mortalité et la morbidité, la survie, le taux de récurrences ont été comparés rétrospectivement, d'une part, chez 72 patients ayant un cancer intramuqueux, 35 d'entre eux ayant eu une REM et 37, une oesophagectomie, et d'autre part, chez 78 patients ayant eu un cancer envahissant la sous-muqueuse, 45 ayant eu une oesophagectomie étendue radicale et 33, une oesophagectomie moins radicale. On a observé des métastases ganglionnaires et/ou une récurrence chez seulement un (<1%) des 72 patients ayant un cancer de la muqueuse, mais chez 30 des 78 patients (38%) ayant un cancer de la sous-muqueuse. Chez des patients ayant un cancer de la muqueuse, la mortalité et la morbidité après REM étaient plus basses qu'après oesophagectomie. La survie après REM était similaire à celle après oesophagectomie. On n'a pas observé de récurrence quel que soit le traitement proposé. Chez les patients ayant un cancer de la sous-muqueuse, la survie a été plus élevée, et le taux de récurrence plus bas, après oesophagectomie radicale étendue comparés à ceux qui ont eu une résection moins radicale, alors que la mortalité et la morbidité étaient similaires. Par analyse multifactorielle, on a démontré que la modalité thérapeutique—REM vs oesophagectomie—n'a pas influencé la survie des patients ayant un cancer de la muqueuse oesophagienne, alors que la modalité thérapeutique—oesophagectomie radicale étendue vs oesophagectomie moins radicale—a fortement influencé la survie des patients ayant un cancer envahissant la sous-muqueuse. Nous concluons que la résection endoscopique de la muqueuse est le traitement de choix du cancer de la muqueuse de l'oesophage, alors que pour les cancers envahissant la sous-muqueuse, il faut pratiquer une oesophagectomie radicale étendue.

#### **Resumen**

El presente estudio fue diseñado para determinar el tratamiento óptimo de un cáncer superficial del esófago que afecte la mucosa o la submucosa; se realizó sobre 150 pacientes con cáncer

superficial del esófago sometidos a resección endoscópica de la mucosa (REM) o a esofagectomía en el Hospital de la Universidad de Kurume en los años 1981 v 1997. Se compararon en forma retrospectiva las tasas de mortalidad y morbilidad y de supervivencia y recurrencia entre 35 pacientes con cáncer mucoso sometidos a REM y 37 sometidos a esofagectomía, con 45 con cáncer submucosa sometidos a esofagectomía radical ampliada y 33 sometidos a esofagectomía menos radical. De 72 pacientes con cáncer mucoso, se observaron metástasis ganglionares y/o recurrencia solamente en uno (1%), en tanto que en 78 con cáncer submucoso, ello ocurrió en 30 (38%). En los casos de cáncer mucoso, las tasas de mortalidad y morbilidad con la REM fueron menores que con la esofagectomía y la supervivencia fue igual. No se registraon recurrencias con ninguna de las dos modalidades terapéuticas. En los casos de cáncer submucoso, la tasa de supervivencia fue superior y la de recurrencia inferior con la esofagectomía radical ampliada en comparación con la esofagectomía menos radical, en tanto que las tasas de mortalidad y morbilidad fueron iguales. El análisis multivariable demostró que la modalidad terapéutica-REM versus esofagectomía- no tuvo influencia sobre la supervivencia en el cáncer mucoso, pero la modalidad de tratamiento-esofagectomía radical ampliada sí tuvo marcada influencia sobre la supervivencia de los pacientes con cáncer submucoso, con ventaja sobre la esofagectomía menos radical. Nuestra conclusión es que la resección de la mucosa es el mejor tratamiento para cáncer mucoso del esófago, y que la esofagectomía radical ampliada lo es para el cáncer submucoso.

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