

Clinicopathologic analysis of lymph node metastasis in surgically resected superficial cancer of the thoracic esophagus

M. Endo, K. Yoshino, T. Kawano, K. Nagai, H. Inoue

Department of Surgery, Tokyo Medical and Dental University 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

SUMMARY. We examined lymph node metastasis clinicopathologically in 236 cases of superficial cancer (T1, Tis) of the thoracic esophagus surgically resected at our department without adjuvant treatment. Mucosal cancer was observed in 112 cases (47%) and submucosal cancer in 124 cases (53%). Lymph node metastasis was present in 3% of mucosal cancer cases and 41% of submucosal cancer cases. By the recent pathologic subclassification of the extent of the cancerous invasion in superficial esophageal cancer, mucosal cancer and submucosal cancer were each divided into three subtypes according to the extent of invasion, i.e. m1, m2, m3, sm1, sm2 and sm3 cancers. There was no case of lymph node metastasis in m1 and m2 cases, but it was observed in 8% of m3 cases, in 11% of sm1 cases, in 30% of sm2 cases and in 61% of sm3 cases. The number of involved nodes was three or less in m3 and sm1 cases, however four or more involved nodes were observed in 14% of sm2 cases and in 24% of sm3 cases. Positive lymph nodes were found only in the mediastinum in m3 and sm1 cases. On the contrary, they were found extensively in the mediastinum, the abdomen and the neck and in two or more regions in 27% of sm2 cases and in 38% of sm3 cases. Considering the location of positive nodes, the recurrent nerve lymph nodes were most frequently involved, followed by the cardiac lymph nodes. A similar tendency was observed in cases with single node metastasis. The 5-year survival rate of cases from m1 to sm1 was similar. That of sm3 cases was significantly worse than that of other groups. Based on the clinical results, the therapeutic guidelines for superficial cancer of the thoracic esophagus are considered to be as follows: (i) in m1 and m2 cancer, endoscopic mucosal resection is generally indicated in principle, although transhiatal esophagectomy may be indicated in some cases; (ii) in m3 and sm1 cancer, endoscopic mucosal resection is performed initially, then subsequent treatment is selected if necessary; (iii) in sm2 and sm3 cancer, conventional transthoracic esophagectomy with systematic lymph node dissection is indicated.

Keywords: Thoracic esophageal cancer, Superficial cancer (T1) of the esophagus, Lymph node metastasis in superficial cancer of the esophagus, Pathologic subclassification of the superficial cancer of the esophagus

INTRODUCTION

Because of recent progress in endoscopic diagnosis, increasing numbers of superficial esophageal cancer lesions are being detected. In particular, an increase in the number of mucosal cancers has resulted from the increasing use of the endoscopic staining technique with Lugol's (iodine) solution. New therapeutic methods such as endoscopic mucosal resection have been developed and patients treated by this method are now increasing because of its lower invasiveness.

We examined lymph node metastasis clinicopathologically in superficial esophageal cancer cases treated by esophagectomy. Based on these findings, we attempted to establish the indications for treatment of superficial cancer of the thoracic esophagus.

MATERIALS AND METHODS

The 236 cases of superficial thoracic esophageal cancer (T1, Tis) resected at our department without adjuvant treatment from 1985 to 1997 constituted 34% of the total of resected thoracic esophageal cancer (696 cases). Of these, 215 cases (91%) were men and 21 (9%) were women. The ages ranged from 21 to 84 years and most were in the seventh decade (44%), followed by those in the sixth decade (Table 1).

Address correspondence to: M. Endo, Department of Surgery, Tokyo Medical and Dental University 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.

Table 1. Age distribution in superficial cancer cases of the thoracic esophagus

Age (years)	No. of patients (%)
≤39	4
40–49	17
50–59	63 (27)
60–69	104 (44)
70–79	46 (19)
≥80	2

Of these, 173 cases underwent transthoracic esophagectomy, 58 cases transhiatal esophagectomy, two cases thoracoscopy-assisted esophagectomy and three cases transperitoneal approaches. Mucosal cancer was observed in 112 cases (47%) and submucosal cancer in 124 cases (53%). Lymph node metastasis was present in 3% of mucosal cancer cases and 41% of submucosal cancer cases. Vascular invasion was present in 10% of mucosal cancer cases and 82% of submucosal cancer cases (Table 2). No lymph node metastasis was observed when the size of the maximum dimension of the lesion was under 1 cm. However, it was recognized in lesions of 1 cm or more in size. Lymph node metastasis tended to increase in accordance with the size of the lesion when the maximum dimension was more than 3 cm (Table 3).

Recently, the pathological subclassification of the extent of the cancerous invasion in superficial esophageal cancer has been commonly utilized. To evaluate accurately the depth of invasion, both mucosal cancer and submucosal cancer were each divided into three subtypes according to the extent of invasion, i.e. m1, m2, m3 cancers and sm1, sm2, sm3 cancers. Cases of m1 cancer included epithelial cancer, including cases in which it was questionable whether or not there was invasion to the lamina propria mucosae. Cancer invasive to the lamina propria mucosae was classified

as m2, and m3 cancer cases included cases with invasion in contact with or into the lamina muscularis mucosae. Submucosal cancers were also divided into three subtypes: sm1 cancer consisted of cases of invasion within the upper third stratum of the submucosa, invasion to the middle third stratum of the submucosa was classified as sm2 and invasion as far as the lower third stratum of the submucosa was classified as sm3 (Fig. 1).

Lymph node metastasis and vascular invasion in relation to the subclassification

Among m1 and m2 cancer cases, there was no case of lymph node metastasis, but vascular invasion was observed in 6% of m2 cancer cases. Lymph node metastasis was observed in 8% of m3 cancer cases and in 11% of sm1 cancer cases. Vascular invasion was observed in 25% of m3 cancer cases and in 44% of sm1 cancer cases. Figures for these two parameters increased roughly in accordance with increasing depth of invasion. The incidences of lymph node metastasis for the sm2 and sm3 cancer cases, 30% and 61% respectively, were clearly greater than the figure for the overall incidence (23%) in superficial esophageal cancer (Table 4). The subclassification subtypes were arranged in three groups according to incidence of lymph node metastasis, i.e. m1 and m2, m3 and sm1, and sm2 and sm3 groups. The incidence of lymph node metastasis was 9% in the m3 and sm1 group and 46% in the sm2 and sm3 group.

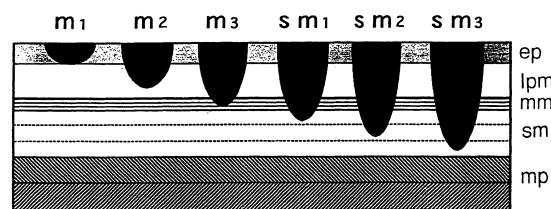


Fig. 1—Pathological subclassification on extent of invasion of superficial cancer of the thoracic esophagus. m1, invasion within the mucosal epithelium; m2, invasion to the lamina propria mucosae; m3, invasion in contact with or into the muscularis mucosa; sm1, invasion within the upper third stratum of the submucosal layer; sm2, invasion to the middle third stratum of the submucosal layer; sm3, invasion to the lower third stratum of the submucosal layer.

Table 2. Lymph node metastasis and vascular invasion in relation to cancerous depth in superficial cancer of the thoracic esophagus

Cancerous depth	No. of patients	No. of patients with positive nodes (%)	No. of patients with vascular invasion (%)
Mucosa	112	3 (3)	12 (11)
Submucosa	124	51 (41)	101 (81)
Total	236	54 (23)	113 (48)

Table 3. Lymph node metastasis in relation to size of the lesion in superficial cancer of the thoracic esophagus

Size of lesion (cm)	No. of cases	No. of cases with positive nodes (%)
≤0.9	9	0
1.0–1.9	50	7 (14)
2.0–2.9	50	4 (8)
3.0–3.9	38	9 (24)
4.0–4.9	31	11 (35)
≥5.0	58	23 (40)
Total	236	54 (23)

Table 4. Lymph node metastasis and vascular invasion in relation to the cancerous depth in superficial cancer of the esophagus

Depth of invasion (no. of cases)	Cases with lymph node metastasis (%)	Cases with vascular invasion (%)
m1 (29)	0	0
m2 (47)	0	3 (6)
m3 (36)	3 (8)	9 (25)
sm1 (18)	2 (11)	8 (44)
sm2 (50)	15 (30)	38 (76)
sm3 (56)	34 (61)	55 (98)

Clinical analysis of cases with positive lymph nodes according to the subclassification of the superficial esophageal cancer

Lymph node metastasis was observed in 54 cases of 236 cases of superficial cancer of the thoracic esophagus. Among the 54 cases, 52 cases were resected by transthoracic esophagectomy and a clinical analysis of lymph node metastasis was performed in these 52 cases.

Number of involved lymph nodes

There was no lymph node metastasis in m1 or m2 cancer cases. In cases with lymph node metastasis, the number of involved nodes increased in correlation with the depth of invasion. In m3 and sm1 cases, 1–3 involved nodes were observed. However, four or more involved nodes were observed in 14% of sm2 cases and in 24% of sm3 cases (Table 5).

Distribution of involved lymph nodes

Positive lymph nodes were found extensively in sm2 and sm3 cancers. These were observed not only in the mediastinum but also in the abdomen and sometimes in the neck. On the contrary, they were found only in the mediastinum in m3 and sm1 cancers (Table 6).

Involved lymph nodes were seen in more than two regions in 27% of sm2 cancer cases and in 38% of sm3 cancer cases.

Location of involved lymph nodes

The recurrent nerve lymph nodes were the most frequently involved in superficial esophageal cancer.

Table 5. Number of involved lymph nodes in relation to the cancerous depth in superficial cancer of the thoracic esophagus treated by thoracotomy

Number of positive nodes	m3 (3 cases)	sm1 (2 cases)	sm2 (15 cases) (%)	sm3 (32 cases) (%)
1	2	1	9 (60)	12 (38)
2–3	1	1	4 (26)	12 (38)
4–5			1 (7)	3 (8)
6 or more			1 (7)	5 (16)

In m3 and sm1 cancer cases, metastasis observed at the recurrent nerve lymph nodes and paraesophageal lymph nodes (Fig. 2). In sm2 and sm3 cancer cases, the recurrent nerve lymph nodes were most frequently involved (47%), followed by the left and right cardiac lymph nodes (30%, 15%). The left gastric artery lymph nodes (13%) and right supraclavicular lymph nodes (17%) were sometimes involved in sm2 and sm3 cancer cases (Fig. 3).

Considering 24 cases with simple lymph node metastasis in superficial cancer of the thoracic esophagus, a similar tendency was observed. Metastasis to the recurrent nerve lymph node was most frequently involved, in 38% of cases, followed by the cardiac lymph node in 29%. Furthermore, the lower thoracic paraesophageal lymph node, supraclavicular lymph node and left gastric artery lymph node were rarely involved.

Outcome of superficial cancer of the thoracic esophagus

The overall 5-year survival rate for superficial thoracic esophageal cancer was 67%. The 5-year survival rate of cases with invasion extending from m1 to sm1 was similar, 82–88%, and that of sm2 cancer cases was 77%. These were significantly better than the 52% of sm3 cancer cases ($p < 0.05$) (Fig. 4).

Causes of death in superficial cancer of the thoracic esophagus

In surgically resected cases of superficial cancer of the thoracic esophagus, there was one cancer death due to malignant melanoma among m1/sm1 cancer cases. There was no death due to esophageal cancer in squamous cell carcinoma cases in this group. Death due to esophageal cancer was observed in 27% of sm2/sm3 cancer cases. Incidence of death due to other diseases was similar in all groups. There was no case of death due to other primary cancer in sm2/sm3 cancer cases (Table 7).

Table 6. Region of involved lymph nodes in relation to the cancerous depth in superficial cancer of the thoracic esophagus treated by thoracotomy

Region of positive nodes	m3 (3 cases)	sm1 (2 cases)	sm2 (15 cases)	sm3 (32 cases)
One region				
Mediastinum	3	2	8	7
Abdomen			3	10
Neck			0	3
Two regions				
Mediastinum + Abdomen			3	3
Mediastinum + Neck			0	6
Abdomen + Neck			0	0
Three regions				
Mediastinum + Abdomen + Neck			1	3

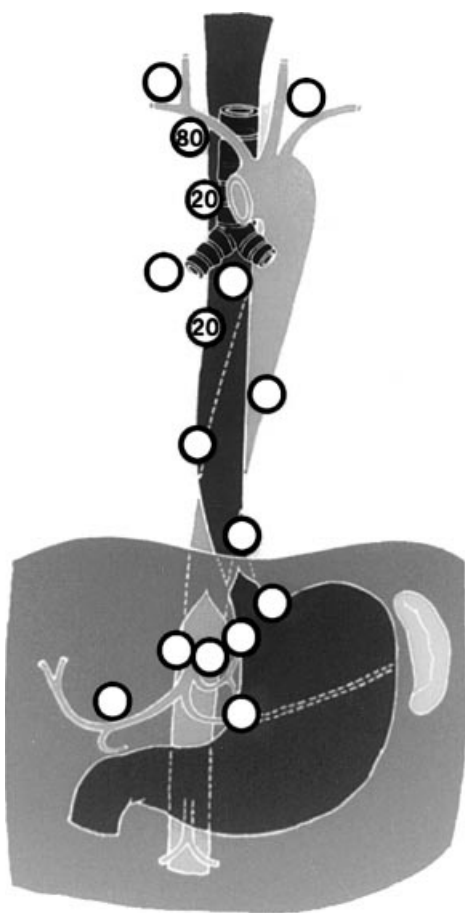


Fig. 2—Location of positive lymph nodes in m3 and sm1 cancers of the thoracic esophagus treated by thoracotomy (%) (five cases).

Therapeutic guidelines for superficial cancer of the thoracic esophagus

Based on the above-mentioned results, we consider the therapeutic guidelines for superficial cancer of the thoracic esophagus to be as follows: (i) when a lesion is suspected to be m1 or m2 cancer, endoscopic mucosal resection is generally indicated in principle, although transhiatal esophagectomy may be indicated in some cases; (ii) in m3 or sm1 cancer, endoscopic mucosal resection is performed initially, then subsequent treatment, i.e. chemoradiation or standard surgery, is selected if necessary; (iii) in sm2 or sm3 cancer, standard surgery with systematic lymph node dissection is indicated (Fig. 5).

DISCUSSION

Based on the depth of invasion, mucosal cancer and submucosal cancer have both been included as 'superficial cancer' of the thoracic esophagus, however there is a difference between mucosal cancer and submucosal cancer that is related to lymph node metastasis, vascular invasion and long-term survival rate. At present, we use the more detailed subclass-

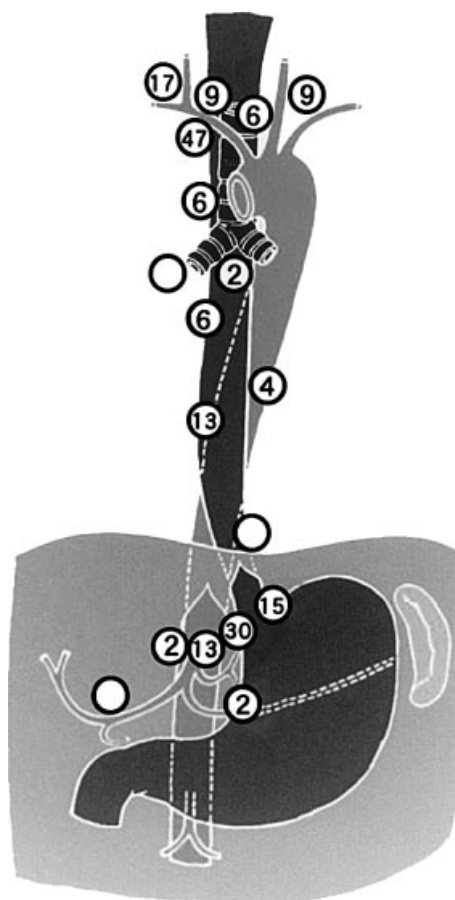


Fig. 3—Location of positive lymph nodes in sm2 and sm3 cancers of the thoracic esophagus treated by thoracotomy (%) (47 cases).

sification of superficial esophageal cancer. With respect to lymph node metastasis, no lymph node metastasis was observed in m1 epithelium (ep) cancer and m2 lamina propria mucosae (lpm) cancer cases. In cancer invasive to the muscularis mucosae (m3), lymph node metastasis was found in 8%. When cancer invaded as far as the shallow stratum of the submucosa (sm1), lymph node metastasis was found in 11%. In sm2 and sm3 cancers, the incidence of lymph node metastasis was reported to be 18–40% and 44–61%, respectively, including our own data.^{1–6} Considering the number of involved lymph nodes,

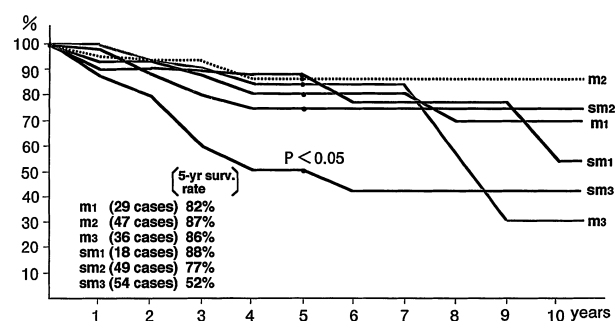
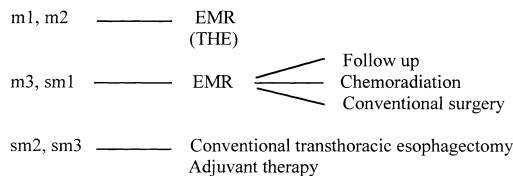


Fig. 4—Long-term survival rate of superficial cancer cases of the thoracic esophagus in relation to depth of invasion (1985–97).

Table 7. Cause of death in surgically resected superficial cancer cases of the thoracic esophagus

Cause of death	m1, m2 (76 cases) (%)	m3, sm1 (54 cases) (%)	sm2, sm3 (106 cases) (%)
Esophageal cancer	0	1 ^a (2)	29 (27)
Other disease	6 (8)	6 (11)	10 (9)
Other primary cancer	9 (12)	4 (7)	0
Unknown	1	0	0

^a Malignant melanoma**Fig. 5**—Therapeutic guidelines for superficial cancer of the thoracic esophagus.

1–3 involved nodes were observed in all of m3 and sm1 cases. On the contrary, four or more involved nodes were observed in 14% of sm2 cases and in 24% of sm3 cases. Positive lymph nodes were observed only in the mediastinum in m3 and sm1 cases. However, they were found extensively not only in the mediastinum but also in the abdomen, and sometimes in the neck in sm2 and sm3 cases. The 5-year survival rate was 82–88% in cases with invasion extending from m1 to sm1 and 72% in sm2 cancer cases, which was significantly better than the 52% of sm3 cancer cases.

From these results, the subtypes in histological subclassification were arranged in three groups, i.e. the m1 and m2 group, the m3 and sm1 group and the sm2 and sm3 group. Lymph node metastasis was not observed in the m1 and m2 group of superficial esophageal cancer but was seen in 9% of the m3 and sm1 group. However, 46% of the sm2 and sm3 group had lymph node metastasis. The number of positive nodes was three or less in the m3 and sm1 group, but four or more positive nodes were recognized in 22% of the sm2 and sm3 group. Positive nodes were located only in the mediastinum in the m3 and sm1 group, but in the sm2 and sm3 group they were observed not only in the mediastinum but also in the abdomen and neck. Moreover, positive nodes in 2–3 regions were recognized in 34% of sm2 and sm3 group. Considering the cause of death in surgically resected superficial cancer cases of the thoracic esophagus in relation to their subtypes, there was no death due to esophageal cancer in squamous cell carcinoma among m1/sm1 cases, except one cancer death due to malignant melanoma. Death due to esophageal cancer was observed in 27% of the sm2/sm3 group. Incidence of death due to other diseases was almost similar in all groups. There was no case of

death due to other primary cancer in the sm2/sm3 group.

Based on the above analysis of lymph node metastasis, the therapeutic guidelines for superficial esophageal cancer are considered to be as follows. For m1 and m2 cases, local therapy, i.e. endoscopic mucosal resection, is generally indicated, although transhiatal esophagectomy may be indicated when such lesions are large (three-quarters or more of the circumference of the esophagus) or are multicentric throughout the esophagus. For m3 and sm1 cases, endoscopic mucosal resection is performed as the initial procedure and then further therapy is performed if necessary after investigation of the resected specimen. The incidence of lymph node metastasis in the m3 and sm1 group was approximately 10% and the numbers of positive nodes were few. Moreover, the distribution of involved lymph nodes was localized in the upper and middle mediastinum. Therefore, conventional adjuvant chemoradiation can be applicable to the mediastinal and supraclavicular area. This therapeutic procedure was supported by experimental research showing that the esophageal glands, which are located in the middle stratum of the submucosa, could always be removed by conventional endoscopic resection after injection of physiologic saline solution in the submucosal layer.⁷ For sm2 and sm3 cancers, standard surgery with systematic lymph node dissection is indicated, in addition to adjuvant treatment.

Acknowledgement

The authors are indebted to Professor J. Patrick Barron of the International Medical Communications Center of Tokyo Medical College for his review of the manuscript.

References

1. Inoue H, Takeshita K, Hori H, et al. Endoscopic mucosal resection with a cap-fitted panendoscope for esophagus, stomach and colon mucosal lesions. *Gastrointest Endosc* 1993; 39: 58–62.
2. Endo M, Takeshita K, Kawano T, Inoue H. Endoscopic resection of intramucosal esophageal cancer. In: Peters J H, Demeester T R, eds. *Minimally invasive surgery of the foregut*. Missouri: Quality Medical Publishing, 1994; 245–249.
3. Endo M, Takeshita K, Kawano T, Inoue H. Local treatment of oesophageal cancer. *Min Invas Ther and Allied Technol* 1996; 5: 179–182.
4. Makuuchi H. Endoscopic mucosal resection for early esophageal cancer – indication and techniques. *Dig Endosc* 1996; 8: 175–179.
5. Makuuchi H, Shimada H, Mizutani K, et al. Clinical pathological analysis of surgically resected superficial esophageal carcinoma to determine criteria for deciding on treatment strategy. *Diagn and Ther Endosc* 1997; 3: 211–220.
6. Endo M, Kawano T. Detection and classification of early squamous cell esophageal cancer. *Dis Esoph* 1997; 10: 155–158.
7. Nagai K, Kawano T, Inoue H, et al. Histological depth in endoscopic mucosal resection in the experiment of dog (in Japanese). *Gastroenterol Endosc* 1994; 36: 949–957.