

Three Cases of Lymph Node Recurrence after a Long Disease-free Interval of Over 5 Years Following Curative Resection for Thoracic Esophageal Carcinoma

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Summary. Esophageal cancer recurring more than 5 years after esophagectomy is extremely rare. The clinicopathologic features of 3 cases in which esophageal cancer recurred 6.3, 6.5 and 13 years, respectively, after esophagectomy are reported. All three patients underwent curative resection and, with the exception of one patient who had histologic metastasis to one of the lymph nodes, there was no micrometastasis to the lymph nodes, which were simultaneously removed at surgery. The site of recurrence was the paratracheal lymph nodes, with hoarseness due to recurrent nerve palsy being the first clinical manifestation at the time of recurrence in all cases. Of the three patients, one survived 20 months and another continues to survive 45 months after radiotherapy for the recurrent disease. Chemoradiotherapy may be effective in prolonging patient survival in cases of late lymphatic recurrence after curative esophagectomy for esophageal cancer.

Key words—Esophageal neoplasm, late recurrence, tumor dormancy, chemoradiotherapy.

INTRODUCTION

Esophageal cancer is notorious for its early spread and poor prognosis after esophageal resection. Tumor recurrence, the main cause of death in patients with esophageal cancer after treatment, has been reported to occur in more than half of patients even after extended radical esophagectomy¹. The great majority of recurrent esophageal cancer

develops within 2 or 3 years after esophagectomy, not only at the esophagectomy site but also in distant organs². In contrast, tumor recurrence manifesting more than 5 years after esophageal resection is extremely rare. As a result, little is known about the clinical and pathologic features of such cases.

In this report, we describe the clinicopathologic details of 3 cases in which esophageal cancer recurred more than 5 years after curative esophagectomy, and discuss the characteristics of such late recurrence in patients who underwent esophageal resection for esophageal cancer.

CASE REPORTS

Case 1

A 59-year-old Japanese man was admitted to the First Department of Surgery of the Niigata University Medical Hospital on December 9, 1983, with a chief complaint of melena and progressive dysphagia. The physical examination and routine laboratory data were all normal. A barium swallow study revealed an irregular stricture of the mid-esophagus, measuring 4.4 cm in length. Endoscopic biopsy specimens taken from the tumor histologically showed a moderately differentiated squamous cell carcinoma.

The patient initially received one cycle of neoadjuvant chemotherapy consisting of peplomycin sulfate (5 mg/body on days 1-7, d. i. v.) and picibanil (2 KE/body on days 1-7, i. m.) combined with concurrent radiotherapy (30 Gy). Clinically, the tumor partially responded to the neoadjuvant treatment.

Subsequently, on January 17, 1984, the patient underwent a transthoracic esophagectomy with bilat-

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eral cervical, mediastinal, and upper abdominal lymphadenectomies, i.e., three-field lymphadenectomy and concomitant cervical esophagogastrotomy for reconstruction using a gastric tube via the retrosternal route.

The resected specimen histologically showed complete eradication of the tumor cells and only submucosal scar tissue present at the tumor site. Metastatic deposits were found in none of 59 lymph nodes removed at the time of surgery. Immunohistochemical examination using anti-cytokeratin antibodies (AE1/AE3) also failed to demonstrate microtumor cells in any of the removed lymph nodes.

The postoperative course was uncomplicated. The patient was discharged on March 15, 1984, after receiving additional radiotherapy (50 Gy) and oral administration of tegafur (600 mg/day).

After discharge, the patient was followed up regularly at intervals of 1 to 3 months with routine physical and laboratory examinations. Chest radiographs, computed tomography (CT), and ultrasonography were carried out every 3 or 6 months to detect any possible recurrence. Endoscopic examinations were performed when appropriate.

In February, 1997 (13 years after the esophagectomy), the patient experienced hoarseness and subsequently underwent gastro-intestinal and tracheo-broncheal endoscopic examinations. Esophagogastroscope revealed an edematous ulcer scar in the gastric tube 23 cm from the upper incisors, and bronchofiberscope showed right vocal cord paralysis and a subepithelial mass with an erosive change at the top of the tumor in the membranous portion of the trachea. Biopsy specimens taken from the erosive part of the tracheal mass showed a squamous cell carcinoma in the submucosal layer of the trachea. CT demonstrated a mass measuring 2.5 cm in diameter and expanding at the right-retro-tracheal space (Fig. 1) with a tumor of the left lung measuring 2.0 cm in diameter. The latter tumor was revealed by subsequent biopsy to be a primary adenocarcinoma of the lung.

The patient received 50 Gy radiotherapy for the retrotracheal tumor. After partial response to the radiotherapy, the patient died of hemoptysis and subsequent hemorrhagic shock on January 13, 1998.

Case 2

A 57-year-old Japanese man underwent transhiatal esophagectomy for a superficial tumor of the mid-esophagus on April 4, 1989. Reconstructive surgery was simultaneously performed using a gastric tube pulled up to the neck through the retrosternal route.

Metastatic disease was not evident in the preoperative staging by CT and percutaneous and endoscopic ultrasonography.

The resected specimen showed four superficial independent tumors located in the mid-esophagus, with respective diameters of 2.9 cm, 1.4 cm, 1.3 cm, and 0.7 cm. Histologically, two tumors were intramucosal invasive carcinomas, and the other two tumors were in-situ carcinomas. All four tumors were moderately differentiated squamous cell carcinomas with no evidence of vessel invasion. Metastatic tumor cells were not detected in eleven perigastric lymph nodes simultaneously removed by conventional histologic or immunohistochemical (cytokeratin staining) examination.

The postoperative course was uncomplicated and the patient was discharged on May 8, 1989. The patient was followed up regularly after discharge at intervals of 1 to 3 months.

On October 26, 1995 (6.5 years after the esophagectomy), this patient underwent magnetic resonance imaging (MRI) to determine the cause of hoarseness. The MRI revealed a mass lesion measuring 2.0 cm in diameter at the left side of the trachea and compression of the trachea by the tumor (Fig. 2). Broncheal endoscopy disclosed left vocal cord paralysis from left recurrent nerve palsy as the cause of the hoarseness. Surgical resection of the tumor was unsuccessful because the tumor had invaded strictly the thoracic vertebra and the trachea. Intraoperative biopsy of the tumor showed a squamous cell carcinoma.

The patient received radiotherapy for the tumor (66 Gy) with chemotherapy by 5-fluorouracil (440 mg/day, p. o.). Although the tumor showed only partial response to the chemoradiotherapy, the patient was alive and well, with the recurrent disease, at the time of this report (June 1, 1999).

Case 3

A 62-year-old Japanese man underwent transthoracic esophagectomy with three-field lymphadenectomy for a transmural tumor of the mid-esophagus measuring 6 cm in diameter on October 4, 1990. Reconstructive surgery was simultaneously performed using a gastric tube pulled up to the neck via the retrosternal route. Metastatic disease was not evident in preoperative staging by CT, or percutaneous and endoscopic ultrasonography. The tumor was completely resected and no metastatic tumor was found at the time of operation.

Histologically, the resected tumor was shown to be a well differentiated squamous cell carcinoma pene-

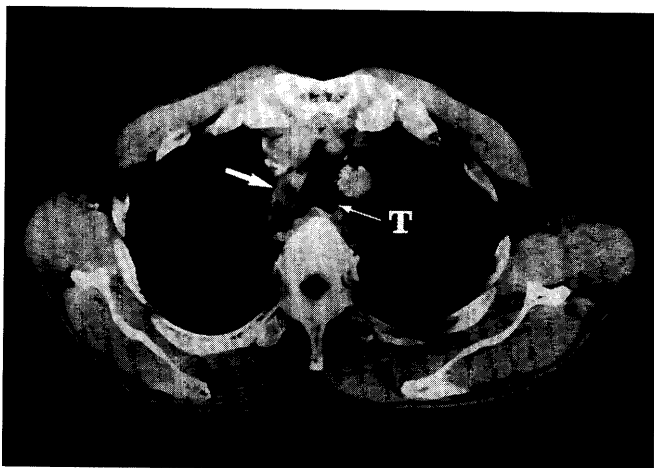


Fig. 1. CT showing a metastatic tumor (*arrow*) at the right retro-tracheal space. T indicates the trachea.

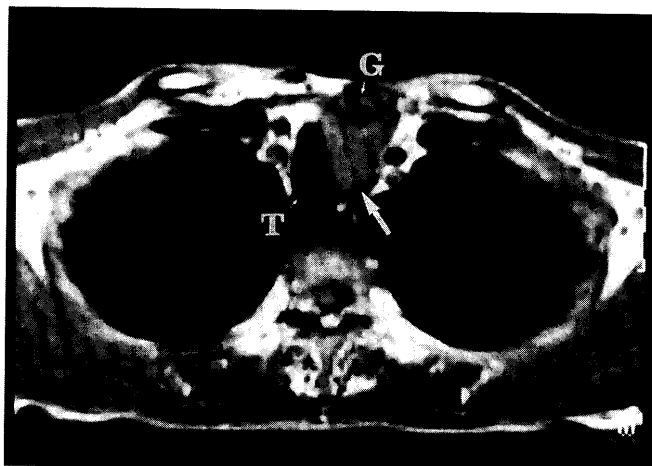


Fig. 2. MRI showing a metastatic tumor (*arrow*) at the left side of the trachea. T and G indicate the trachea and gastric tube, respectively.

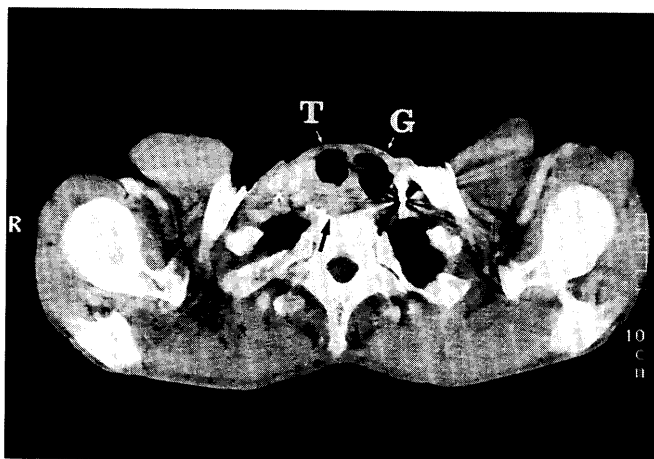


Fig. 3. CT showing a metastatic tumor (*arrow*) at the right side of the trachea. T and G indicate the trachea and gastric tube, respectively.

trating the esophageal wall. An undifferentiated carcinoma was found to be part of the invasive tumor. Marked vessel invasion was observed in the subepithelial layers around the tumor. A metastatic deposit was found in one of the left gastric artery lymph nodes of 101 lymph nodes removed at the time of surgery. Immunohistochemical examination using anti-cytokeratin antibodies failed to show micro-metastatic tumor cells in any of the 101 lymph nodes simultaneously removed.

The postoperative course was uncomplicated and the patient was discharged on November 23, 1990.

The patient was regularly followed up at intervals of 1 to 3 months.

In early February, 1997 (6.3 years after the esophagectomy), the patient experienced hoarseness, and underwent broncheal endoscopy and a CT search to determine its cause. Broncheal endoscopy revealed right vocal cord paralysis from right recurrent nerve palsy and CT revealed a mass lesion measuring 1.8 cm in diameter at the right side of the trachea (Fig. 3).

The patient received radiotherapy (70 Gy) for the recurrent tumor combined with chemotherapy by 5-fluorouracil (400 mg/day, p. o.), followed by 4 cycles

Table 1. Clinicopathologic features of the three cases at the time of esophagectomy

Case No.	Age	Sex	Primary site	Esophagectomy		Adjuvant therapy		TNM/Stage**	Nodal micro-metastasis
				Type*	Quality	Preoperative	Postoperative		
1.	59	Male	Mid-thoracic	TTE	Curative	Peplomycin, Picibanil 30Gy	Tegaful 50Gy	TO(T3)NOMO#/ (Stage II A)	Negative
2.	57	Male	Mid-thoracic	THE	Curative	None	None	T1NOMO/ Stage I	Negative
3.	62	Male	Mid-thoracic	TTE	Curative	None	None	T3N1MO/ Stage III	Negative

*TTE and THE indicate transthoracic esophagectomy and transhiatal esophagectomy, respectively.

**Disease state is based on the TNM classification of the International Union Against Cancer (UICC).

T category and stage grouping in parentheses indicate assessment modes prior to the preoperative treatment.

Table 2. Clinical features of the three cases at the time of tumor recurrence

Case No.	Clinical manifestation	Recurrence site	Disease-free period	Treatment	Outcome	
					Survival*period	Vital state
1.	Hoarseness, right recurrent nerve palsy	Right retrotracheal lymph node	13 years	50 Gy	11 months	Deceased
2.	Hoarseness, left recurrent nerve palsy	Left retrotracheal lymph node	6.5 years	5-fluorouracil 66 Gy	45 months	Surviving
3.	Hoarseness, right recurrent nerve palsy	Right retrotracheal lymph node	6.3 years	5-fluorouracil 70 Gy	20 months	Deceased

*Survival periods are expressed as time from the initiation of the treatment for recurrent tumors.

of chemotherapy consisting of cisplatin (5 mg/body on days 1-5, d.i.v.) and 5-fluorouracil (250 mg/body on days 1-5, d. i. v.). The patient died of respiratory dysfunction due to a broncho-gastric fistula caused by the tumor on October 9, 1998.

The clinicopathologic features of the three cases are summarized in Tables 1 and 2. Descriptions of disease stage are based on the TNM classification of the International Union Against Cancer (UICC)³.

DISCUSSION

Esophageal cancer is highly aggressive, and the prognosis of patients remains poor even after curative esophagectomy^{1,4}. Most of the deaths after esophagectomy are attributed to a recurrence of esophageal cancer either at the esophagectomy site and/or in distant organs.

of chemotherapy consisting of cisplatin (5 mg/body on days 1-5, d.i.v.) and 5-fluorouracil (250 mg/body on days 1-5, d. i. v.). The patient died of respiratory dysfunction due to a broncho-gastric fistula caused by the tumor on October 9, 1998.

The majority of recurrent disease manifests itself in the lymph nodes left behind at operation or in distant organs within 2 or 3 years after curative esophagectomy². Generally, esophageal cancer recurrences have been divided into two categories, lymphatic and hematogenous recurrences, which occur by different metastatic pathways⁵. Although some researchers have failed to find any differences in survival time after recurrence relative to the recurrence pattern⁶, other investigators have occasionally observed late manifestations of recurrence more than 3 years after esophagectomy in cases of lymphatic recurrence⁵. However incidences of recurrent esophageal cancer developing more than 5 years after esophagectomy are extremely rare. No such case

occurred among 90 patients who underwent extended radical esophagectomy, reported by Bhansali et al⁶. Morita et al. found such recurrence only in 2 (1.1%) of 187 patients receiving curative esophageal resection⁵.

All three patients herein reported underwent curative esophagectomy, and no micrometastasis was found in any of their lymph nodes, which were extensively removed, though one patient (Case 3) showed histologic metastasis in one lymph node at the time of esophagectomy (Table 1). These findings suggest that the metastatic potential might not be high in the present cases. Recurrence in these 3 patients occurred 6.3, 6.5, and 13 years, respectively, after esophagectomy. Hoarseness, a result of the involvement of the recurrent laryngeal nerves by the nodal metastatic tumors, was the first clinical manifestation of tumor recurrence in all 3 cases (Table 2).

Considering the natural history of general malignant tumors--i. e., that tumors first grow at local sites (T-categories), followed by metastases to the regional lymph nodes (N-categories), and finally to the distant organs (M-categories)--the tumors of the present cases might be at the midway stage of their natural history after curative esophagectomy, as hematogenous metastases to the distant organs were not evident in the clinical course after cervical recurrence in any of these cases. Although all three patients had tumor recurrence in the cervical lymph nodes along the recurrent laryngeal nerves, several recent studies have suggested that metastases to these lymph nodes may not be distant metastasis per se, based on the finding that the 5-year survival rates of patients with cervical lymph node metastasis did not differ from those of patients with mediastinal and perigastric, i.e., regional lymph node metastasis after extensive lymphadenectomy⁷. The absence of nodal micrometastasis in all three of the present cases may support this idea, because nodal micrometastasis is considered a significant indicator of latent metastasis to the distant organs in patients undergoing curative esophageal resection⁸.

The precise mechanisms by which esophageal cancer recurred more than 6 years after esophagectomy in the present cases remain unknown. However, one possible explanation is that some tumor cells that had already metastasized to the lymph nodes by the time of esophagectomy were in a dormant state for a considerably long time after operation in the present cases, notably, no evidence of metastatic mass was found in the neck area of any of these 3 patients during regular follow-ups lasting 6 to 13 years. It bears mentioning that two cases of late recurrence more than 5 years after esophagectomy reported by Morita et al. were both lymphatic⁵. The micro-

environment of a lymph node, which is an important organ in the host immune system, may be able to induce tumor dormancy in some cases of lymph node metastases.

Treatment of recurrent esophageal cancer generally fails to prolong patient survival⁶. However, Matsubara et al. have reported a better outcome in cases in which the recurrent lesions were resectable⁹. In accordance with these previous findings, one of the three patients in our series survived for 20 months after initiation of treatment for recurrence, and another patient continues to survive at 45 months after the radiotherapy at the time of this report. These findings suggest the possible validity of local treatments, including surgical resection and radiotherapy, in cases of late recurrence of esophageal cancer not accompanied by systemic dissemination.

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