Local Recurrences after Subtotal Esophagectomy for Squamous Cell Carcinoma

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From July 1982 to June 1985, 100 patients with squamous cell carcinoma of the thoracic esophagus had esophageal resection and reconstruction using an abdominal and right thoracotomy approach (Lewis–Tanner operation). Five patients died within 30 days. The remaining 95 patients were studied prospectively for evidence of local recurrences. It was found that anastomotic recurrences occurred in eight patients, and mediastinal recurrences involving the intrathoracic stomach occurred in seven patients over a mean follow-up period of 13 months. The total local recurrence rate was 16% (15 of 95 patients). The incidence of anastomotic recurrence was shown to be related only to the length of the proximal resection margin and not related to tumor differentiation or lymph node metastases. A proximal resection margin of less than 5 cm measured at operation had a 20% risk of developing an anastomotic recurrence, and a margin of between 5 to 10 cm had an 8% risk. Mediastinal recurrences that encroached on the intrathoracic stomach were found to be related more to the extent of lateral spread of the primary tumor in the mediastinum than to the length of the resection margins. Postoperative radiotherapy in patients with palliative resections decreased the incidence of local recurrences. To reduce the incidence and consequences of local recurrence after esophagectomy, it is suggested that (1) in patients with tumors in the upper thorax, a more complete esophagectomy is warranted, (2) postoperative radiotherapy should be given to patients with short resection margins, and (3) in patients with extensive mediastinal spread, use of the retrosternal route for reconstruction is preferred.

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BECAUSE MANY PATIENTS with carcinoma of the esophagus present only at a late stage, curative resection with long-term survival is possible in only a small minority. For most, the primary objective of treatment is to relieve dysphagia. Of the various modalities of treatment, resection offers the best form of palliation. Thus it is important to ensure that patients can swallow adequately after operation. A major disappointment to both the patient and the surgeon is the recurrence of dysphagia after operation. This may be from benign stricture at the anastomosis, recurrent growth at the anastomosis, or mediastinal recurrence causing external compression on the esophagoplasty near the anastomosis. We report a prospective study of the incidence of local recurrences after resection. These recurrences were also correlated with the clinicopathologic findings in an attempt to define the causes of this complication and thus minimize the risk.

Materials and Methods

From July 1982 to June 1985, 100 patients with squamous cell carcinoma of thoracic esophagus had esophagectomy and reconstruction with the whole stomach *via* a two-phase abdominal and right chest approach—the Lewis–Tanner operation[1-3]—in the Department of Surgery, University of Hong Kong, Queen Mary Hospital. Even for patients with advanced tumors, resection was attempted. Of the 100 patients, only 53 had a resection with curative intent when macroscopic clearance of tumor was achieved; the remaining 47 patients had a palliative resection for relief of dysphagia. Five patients died within 30 days after operation and were excluded from the study; the remaining 95 patients formed the basis of this study. There were 85 male and 10 female patients with a mean age of 60 years. Most tumors were located in the middle third of the thoracic esophagus (65 of 95 patients), whereas 32 tumors were at the lower third and in only one patient the tumor was in the upper third region.

During operation, the resection margins were measured *in-situ* before removing the esophagus.[4] As much of the esophagus as possible was removed through the right thoracotomy, leaving only sufficient length for an esophago-

a : **proximal resection margin**
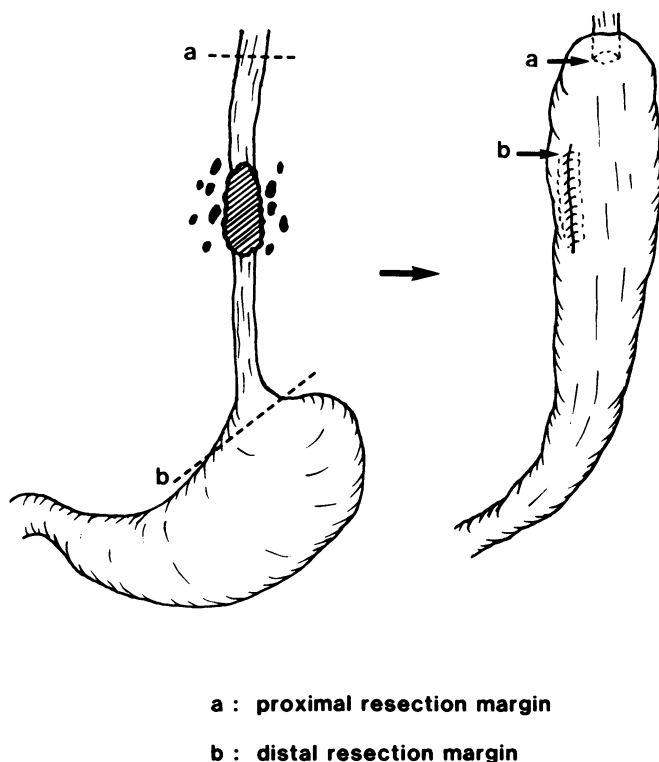
b : **distal resection margin**

FIG. 1. Esophagogastric anastomosis between remaining proximal esophagus and fundus of stomach.

gastric anastomosis to be made at the apex of the right chest. This anastomosis was made between the proximal remaining esophagus and the posterior wall of the fundus of the stomach (Fig. 1). The esophagogastric junction was used for the introduction of the stapler if this technique was used.[3] An average of 23.2 cm of esophagus was removed using this operative procedure.[4]

Mediastinal lymph nodes were removed *en bloc* with the esophagus. Tumor that had infiltrated the vertebrae, the chest wall, the aortic media, or the membranous parts of the tracheobronchial tree were left behind. The resected specimen was examined by serial sections. All lymph nodes were individually examined to determine the presence or absence of metastatic tumor. The resection margins, the proximal one being the "doughnut" or tissue ring retrieved from the stapling device and the distal one from the resected esophageal specimen, were particularly examined for evidence of tumor involvement.

All patients were followed up regularly after discharge at 1–3-month intervals. Those patients with recurrent dysphagia, hematemesis, or any other gastrointestinal symptoms were subjected to a flexible upper endoscopic examination, and any suspicious area was biopsied. Forty-eight patients (51%) had endoscopic examination at least once after operation. Tumor recurrences localized at the esophagogastric anastomosis only are categorized as anastomotic recurrences, whereas recurrent growths en-

croaching on the intrathoracic stomach or infiltrating through it are categorized as intrathoracic stomach recurrences. Either an anastomotic or an intrathoracic stomach recurrence are considered as local recurrence. At the time of analysis, 64 patients had died, mostly of metastatic disease. Postmortem examinations were requested in all patients, especially those with suspected recurrences. Cultural prejudices were responsible for refusal of most requests, and only 13 patients (20%) had autopsy.

Postoperative radiotherapy was not routinely given. Patients with positive resection margins, tumor invasion of adjacent organs, or lymph node metastases would be offered radiotherapy, provided that they were in satisfactory general conditions to tolerate this treatment. On the other hand, some patients with apparent curative resection would also receive radiotherapy with the hope that this might help to secure a radical cure.

Results

During a mean follow-up period of 13 months, 15 patients had local recurrences confirmed either at endoscopy, at subsequent operation, or at postmortem examination. Eight of these recurrences were anastomotic recurrences and seven were mediastinal recurrences encroaching on the intrathoracic stomach. The clinicopathologic features of this group of patients who had local recurrences were compared with the remaining patients. Particular attention was directed to the length and microscopic findings of the resection margins, the differentiation of the tumor, the lymph node status, and the extent of lateral spread of the primary tumor in the mediastinum. The effect of postoperative radiotherapy was also assessed.

In 94 of the 95 patients who were analyzed where the length of the proximal resection margin was determined at operation, it was found that the eight patients with an anastomotic recurrence had a mean proximal resection margin of 5.4 ± 3.0 cm (mean ±SD), whereas those without an anastomotic recurrence had a mean length of 8.5 ± 3.8 cm (mean ±SD). This difference was not statistically significant (p = 0.10). However, when the patients were grouped according to the length of the proximal resection margins, a definite trend towards a higher incidence of anastomotic recurrence with short resection margins was apparent (Fig. 2). When the *in-situ* resection margin was less than 5 cm, four of 20 patients (20%) had an anastomotic recurrence; when it was between 5 and 10 cm, four of 49 patients (8%) had anastomotic recurrences; and when it was greater than 10 cm, none of the 25 patients had a recurrence. The length of the distal resection margin was measured in 93 of the 95 patients. There was no difference in the mean lengths of the distal resection margins between those with and without an intrathoracic stomach recurrence, being 8.7 ± 5.0 cm (mean ±SD) and 8.4 ± 4.0 cm (mean ±SD), respectively. The mean values of the
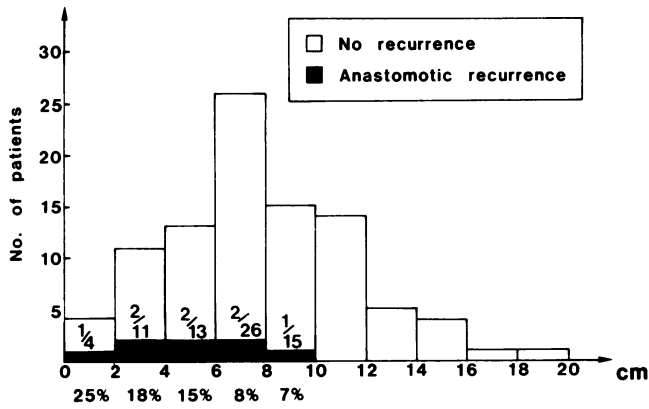
FIG. 2. Relation between length of proximal resection margin measured at operation and anastomotic recurrence.

resection margins in the different groups of local recurrence are shown in Table 1.

When the incidence of local recurrences was correlated with the pathologic factor of lymph node metastasis, degree of tumor differentiation, and extent of lateral spread, it was found that there was no increase in the incidence of any local recurrence when the regional lymph nodes were involved or when the tumor was poorly differentiated (Table 2). It was also noted that for tumors confined only to the muscular wall, none of the 14 patients had any local recurrence. This was in contrast to those patients with lateral spread of the tumor to beyond the adventitia where local recurrence developed in 37% (15 of 81 patients).

The effect of postoperative radiotherapy on the development of local recurrences in patients with both palliative and curative resection is shown in Table 3. The incidence of local recurrence after an apparent curative resection was not affected by postoperative irradiation, 18% (8 of 45 patients) and 17% (1 of 6 patients), respectively, had a local recurrence. When there was obvious residual tumor left behind (palliative resection), the difference was obvious; 18% (6 of 31 patients) of those without irradiation had local recurrence, whereas none of the 13 patients with irradiation had local recurrence. For the whole group, irrespective of whether resection was for palliation or apparent cure, none of the 19 patients who had irradiation had anastomotic recurrence and only one patient (5%) had an intrathoracic stomach recurrence. In contrast, for those who were not irradiated, 14 patients (19%) had local recurrences, eight as anastomotic recurrences and six as intrathoracic stomach recurrences. Furthermore, among those five patients with a positive proximal resection margin, two were not irradiated and anastomotic recurrences developed within 2 months and the patients died; whereas in the other three patients given postoperative irradiation, none of them had an anastomotic recurrence. Similarly, in the two patients with a positive distal resection margin,

one was irradiated and free from intrathoracic stomach recurrence, whereas the other patient was not irradiated and had intrathoracic stomach recurrence.

Among the eight patients with an anastomotic recurrence, tumor cells were present in the upper resection margins in two patients; both were found to have tumor emboli in the submucosal lymphatics. These two patients died within 2 months after operation. One of them had recurrent dysphagia and died of aspiration pneumonia; the other patient was not dysphagic and died of bronchopneumonia with the anastomotic recurrence confirmed only at postmortem examination. The remaining six patients had negative upper resection margins, and all except one had recurrent dysphagia with the development of an anastomotic recurrence. In these six patients, the intervals between resection and the occurrence of the anastomotic recurrence ranged from 5.5–24 months with a mean of 10.5 months. After detection of an anastomotic recurrence, most of them died within 3 months, with the longest survival of only 5.5 months (Fig. 3). All patients with anastomotic recurrences had died at the time of this re-

TABLE 1. *Average* (In-Situ) *Length of Resection Margins at Operation versus Local Recurrences* *

	Proximal Margin (cm)	Distal Margin (cm)
Anastomotic recurrence present	5.4 ± 3.0	10.3 ± 5.7
Anastomotic recurrence absent	8.5 ± 3.8	8.3 ± 3.8
Intrathoracic stomach recurrence present	9.6 ± 4.9	8.4 ± 4.0
Intrathoracic stomach recurrence absent	8.1 ± 3.7	8.7 ± 5.0

* Mean ± SD.

TABLE 2. *Influence of Pathologic Factors on Development of Anastomotic and Intrathoracic Stomach Recurrences*

	N	No. with Anastomotic Recurrence (%)	No. with Intrathoracic Stomach Recurrence (%)	No. with Any Local Recurrence (%)
Lymph node metastasis				
Negative	24	3 (13)	2 (8)	5 (21)
Positive	71	5 (7)	5 (7)	10 (14)
Tumor differentiation				
Well	27	1 (4)	2 (7)	3 (11)
Moderate	47	5 (11)	5 (11)	10 (21)
Poor	21	2 (10)	0 (0)	2 (10)
Depth of invasion				
Confined to muscular wall	14	0 (0)	0 (0)	0 (0)
Adventitia involved	42	5 (12)	3 (7)	8 (19)
Infiltrating adjacent structures	39	3 (7)	4 (10)	7 (18)

TABLE 3. *Influence of Postoperative Radiotherapy on the Development of Local Recurrence*

	N	No. with Anastomotic Recurrence (%)	No. with Intrathoracic Stomach Recurrence (%)	No. with Any Local Recurrence (%)
Palliative resection group				
No radiotherapy	31	4 (12)	2 (6)	6 (18)
Radiotherapy given	13	0 (0)	0 (0)	0 (0)
Curative resection group				
No radiotherapy	45	4 (9)	4 (9)	8 (18)
Radiotherapy given	6	0 (0)	1 (17)	1 (17)
Total				
No radiotherapy	76	8 (11)	6 (8)	14 (19)
Radiotherapy given	19	0 (0)	1 (5)	1 (5)

view; five patients died of aspiration pneumonia with the anastomotic recurrence as a significant contributing factor, one patient died of carcinomatosis, and the other two patients died of bronchopneumonia. There were three patients with positive proximal resection margins who did not have anastomotic recurrence. All of them received adjuvant postoperative radiotherapy and were free from any dysphagic symptom. One of them is still alive 36 months after operation.

Seven patients had intrathoracic stomach recurrences. The mean interval between resection and detection of gastric tumor recurrence was 11 months. None of the seven patients lived for more than 3 months after detection of the local recurrence, and the majority died within 4 weeks (Fig. 3). Among the seven patients with intrathoracic stomach recurrence, only two had recurrent dysphagia where the recurrent growth was found to be close to the anastomotic site at endoscopic examination. Three patients had gastrointestinal bleeding and the recurrence was only found at postmortem examination in the remaining two patients. All seven patients died of malignant cachexia from carcinomatosis; gastrointestinal bleeding from the ulcerative recurrent growth in the stomach contributed to death in three patients. Two patients had positive distal resection margin: one from tumor emboli in the submucosal lymphatics and the patient died of carcinomatosis 5 months after resection without recurrent dysphagia, the other patient was given adjuvant postoperative radiotherapy and did not have any intrathoracic stomach recurrence.

Two of our patients with anastomotic recurrences had colonic bypass operation in an attempt to further palliate dysphagia, and both patients died of bronchopneumonia about 3 weeks after the second operation. Two patients with intrathoracic stomach recurrences and three patients with anastomotic recurrences were given palliative irradiation after the diagnosis of local recurrence was made. The response was not satisfactory, and their median survival was about 2 months from the time of detection of
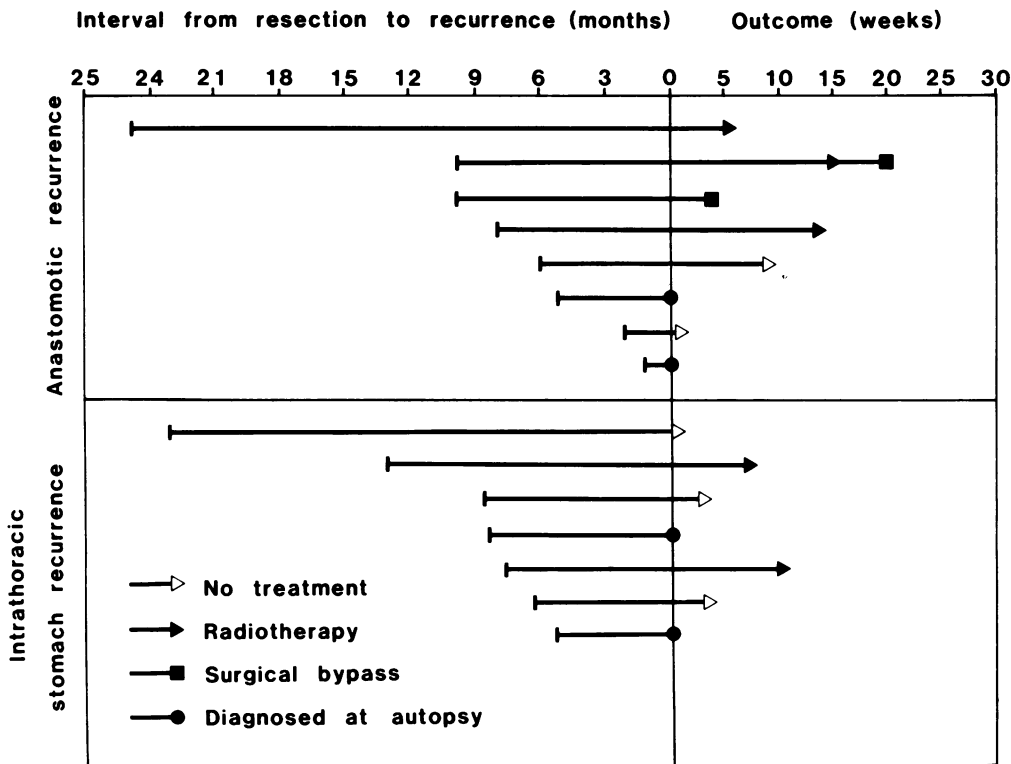

FIG. 3. Resection–recurrence interval and outcome of local recurrences.

the recurrence. Other patients did not receive any specific treatment, and the median survival was about 1 month.

Discussion

Recurrence of dysphagia defeats one of the main aims of resection for carcinoma of the esophagus. The reported incidence of anastomotic recurrence causing recurrent dysphagia ranged from 2–32%. Miller[5] reported 19 anastomotic recurrences (32%) among 60 resection survivors who had middle- and lower-third lesions. The majority of resections in this series were carried out through a left thoracotomy or thoracoabdominal approach, and about 80% of the anastomoses were subaortic. Twenty-two patients were considered to have inadequate excision because of the presence of tumor cells within 1 cm of the upper line of esophageal transection (measured on fixed specimens) and 17 of them had recurrences. Miller concluded that the main factor responsible for anastomotic recurrence was an inadequate resection margin.[5] McKeown[6] reported only one stomal recurrence (2%) among the 62 patients surviving a Lewis–Tanner operation, and recurrence did not occur in the 73 patients surviving the three-phase operation. Hennessy and O'Connell[7] reported eight anastomotic recurrences causing recurrent dysphagia (14.3%) among 56 resection survivors. A 5-cm longitudinal clearance was attempted in all patients. Microscopic involvement of proximal resection margin occurred in 11 patients, partly accounting for the relative high recurrence rate. In our current study, eight patients had anastomotic recurrences: six patients had dysphagia and were diagnosed at endoscopic examination, and two patients were not dysphagic and were diagnosed at postmortem examination. Thus, the incidence of anastomotic recurrence causing dysphagia is 6.3%.

The incidence of anastomotic recurrence seemed to be related to the margin of clearance achieved at operation. As the esophagus lies within a confined space in the mediastinum surrounded by vital organs, clearance in the lateral spread is much more limited than along the axial length of the esophagus. The latter, however, is dependent on the location of the tumor on the esophagus and the surgical approach used. It has been our practice to remove the entire thoracic esophagus leaving only a small stump to allow for reconstruction in the apex of the right chest. Securing an adequate resection margin longitudinally is important in decreasing anastomotic recurrences, which is one of the causes of recurrent dysphagia and ultimate fatality.

As the esophagogastric anastomosis is made between the proximal esophagus and the posterior wall of the fundus of the stomach, the length of the proximal resection margin would be more determinant than the distal resection margin in predicting anastomotic recurrences. On the other hand, any residual tumor along the distal resection margin would be expected to give rise to recurrences near the esophagogastric junction that may be indistinguishable from recurrences growing in from residual tumor in the mediastinum. A positive distal margin would in any case be rare since a partial gastrectomy could be easily added if there was any doubt on completeness of distal clearance.

In this study, anastomotic recurrences occurred in eight of 95 patients (8.4%), and all eight patients had a proximal resection margin of less than 10 cm at operation. Whatever the apparently clear margin obtained, an anastomotic recurrence represents an inadequate resection margin. In fixed specimens, Burgess et al.[8] found intramural spread up to 4 cm beyond the gross extent of the carcinoma, and this would represent at least a 12.5-cm in-situ length when extrapolated from our previous study on esophageal shrinkage after resection.[4]

Although the mean length of proximal resection margin between the patients with and without an anastomotic recurrence was not statistically different, there was a definite trend towards a higher incidence of anastomotic recurrence with shorter resection margins. The length of the proximal resection margin is obviously limited by the location of the tumor for a given exposure and procedure, as was the case in this study. With our current results, it seems that if a margin of more than 5 cm cannot be obtained with the two-phase operation, a high cervical anastomosis by a three-phase operation might be substituted, as advocated by McKeown[6] and Ong and Kwong.[9] Even so, there is a limit to the length of clearance obtainable for high thoracic tumors because the upper limit is the cricopharyngeus. To achieve longer margins would necessitate a pharyngolaryngectomy. Preservation of voice is thus weighed against the prospect of anastomotic recurrence and a reduced chance of cure.

Besides inadequate axial excision, growth of residual primary tumor or involved lymph nodes in the mediastinum may erode into the anastomosis and also appear as anastomotic recurrences. In some of these patients, however, the exact source of recurrent tumor cannot be determined with certainty. Nonetheless, the majority of our anastomotic recurrences probably arise from inadequate longitudinal resection, and most of the intrathoracic stomach recurrences represent mediastinal invasion from without rather than from residual tumor from the gastric cardia. This might explain why we could not demonstrate any significant difference in the length of the distal resection margins between patients with and without intrathoracic stomach recurrences.

Apart from resection margins, other pathologic features of the tumor did not seem to be important in the development of local recurrence. Though Sugimachi et al.[10] reported a higher incidence of tumor recurrence with high-

grade malignancy, lymph node metastases, or extensive local spread, their study was not specific for anastomotic recurrences, and patients with lymphatic and hematogenous metastases were included in the analysis. In our study, we could not demonstrate a positive correlation between anastomotic and intrathoracic stomach recurrences and lymph node status or degree of differentiation of the primary tumor. With regard to the depth of invasion of the tumor, local recurrences were noted when the tumor has invaded the adventitia. However, the risk was not found to be in direct proportion to the extent of this lateral spread.

As we believe that resection offers the best palliation for patients with esophageal cancer, about half of the operations were performed on patients with advanced disease, including those with mediastinal infiltration, extrathoracic lymphatic metastases, and patients with liver secondaries. Inevitably, in most of these patients residual tumors are present in the mediastinum after resection. This must have resulted in some of the intrathoracic stomach recurrences and increased the overall incidence of local recurrences. These residual tumors usually take some time to reach a mass of sufficient size to compress or invade into the intrathoracic stomach, by which time widespread metastases is already evident. Although these patients are usually able to eat until they die of malignant cachexia, some of them have gastrointestinal bleeding from the ulcerative growth. In patients with extensive mediastinal spread, use of retrosternal route for reconstruction may be preferable.

The role of radiotherapy in our patients could not be defined. Though Kasai et al.[11] have reported some successful results with postoperative irradiation, both in reducing local recurrences in the neck and mediastinum and in improving survival rate, we have refrained from giving routine postoperative irradiation to our severely debilitated patients who had just recovered from major surgery that only palliated the dysphagic symptoms and who had only a few more months to live. However, the results of selective treatment on the 19 patients who received postoperative radiotherapy suggest some benefit from this treatment. It seems that postoperative irradiation is effective in the prevention of local recurrence when there is obvious tumor present. These results, however, must be interpreted with caution because, as we have stated, patients were selected for radiotherapy according to their general condition.

The outcome of patients with local recurrence after esophagectomy is dismal. It is thus important to identify the causes of these local recurrences and initiate adjuvant therapy early.

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