

## Diagnosis and Treatment of Esophageal Neoplasms

Hoichi Kato

*Department of Surgery, National Cancer Center Hospital, 1-1 Tsukiji 5-chome, Chuo-ku, Tokyo 104*

During the last 10 years, the diagnosis and treatment of esophageal carcinoma have improved considerably. Endoscopy with Lugol staining and endoscopic ultrasonography have been newly introduced and used for early diagnosis and more accurate tumor staging. As a result, the number of patients with tumors at an early stage has increased remarkably (superficial carcinoma, 23%). In the field of treatment, surgical results have improved not only in the short term (30-day mortality rate, 4%) but also in the long term (5-year survival rate, 30%). The field of operation has been extended (3-field lymph node dissection), with lower morbidity and mortality. On the other hand, some techniques for limited treatment such as endoscopic mucosal resection, intraluminal radiotherapy, and laser irradiation have been introduced for the treatment of esophageal carcinoma at an early stage with curative intent. However, there are still many patients with esophageal carcinoma at an advanced stage for whom these treatments fail or are futile. The role of radiotherapy has been made more significant by the introduction of brachytherapy or in combination with other treatment modalities such as surgery, chemotherapy and hyperthermia. Response rates for existing anticancer drugs used as a single agent are 0-38%. Chemotherapy appears to have created significant improvements when used in combined modalities (response rate, 16-76%). However, chemotherapy for patients with esophageal carcinoma still offers an unsatisfactory survival benefit and remains experimental. Studies to evaluate multimodality treatments using chemotherapy, combined with radiotherapy and/or surgery have started. The contribution of molecular biology to the diagnosis and treatment of this disease is a subject for future investigation.

Key words: Review — Esophagus — Carcinoma — Diagnosis — Treatment

### Introduction

In his 1991 historical review of the surgical treatment of carcinoma of the esophagus, Hurt noted that, although this cancer was described in China over 2000 years ago, a considered and realistic assessment of this disease only 50 years ago was that it was beyond hope and help. He divided the history of the development of esophageal surgery into three different periods:

1877-1912—early procedures: period of excision without restoration of continuity

1913-1938—later procedures: period of excision and subsequent restoration of continuity

1938 onward—period of the ideal procedure of excision and immediate restoration of continuity

Hurt defined the period after 1945 as "the modern era," in which the operative mortality rate was 5-11% and the 5-year survival rate was 14-22% in the western world. He concluded that "the 5-year survival rate after resection for esophageal carcinoma is still poor," although he noted the remarkably low mortality rate reported in Japan as exceptional.<sup>1)</sup> Most of the articles he reviewed were published before 1989, so those esophagectomies would have been carried out up to five years before that.

Since then, the surgical results of esophagectomy in leading institutions around the world have improved greatly. These good results may largely be owing to recent developments in diagnostic and therapeutic measures. In this article, I will critically review recent advances in the diagnosis and treatment of esophageal neoplasms.

### Diagnosis

#### A. Screening

X-Ray examination with a barium meal has been a common diagnostic measure to identify upper gastrointestinal carcinoma in mass-screening programs or for examining patients with some digestive tract symptoms. However, there have been no reports of new applications for this screening technique.

For more than ten years, attempts have been made to identify occult esophageal carcinoma among high-risk populations. Balloon or brush cytology or endoscopy has been used for this purpose. Inhabitants of Linxian province of China or of the Caspian Sea littorals of Iran, or patients who have had previous head and neck cancers have been recognized to be high-risk populations for

esophageal carcinoma, and some of these people have been examined by mass-screening measures.

Dowlatshahi *et al.* used brush cytology in Chicago and found two asymptomatic esophageal carcinomas among 56 patients with upper aerodigestive tract tumor. He used a nylon brush placed in a nasogastric tube, and he smeared the trapped exfoliated cells. In his series, 40% of patients with upper aerodigestive tract malignancy showed positive esophageal cytology.<sup>2)</sup> Although he recommended this technique for detecting asymptomatic esophageal cancer in high-risk populations and for monitoring the treatment response of the upper aerodigestive tract tumor, it cannot be effectively used for the latter purpose because of its low positivity. This technique is simple, safe, and inexpensive, and so may be useful as a mass-screening measure for high-risk individuals.

The most reliable diagnostic measure that can be used today for mass screening of esophageal neoplasms may be endoscopy, although it is rather complicated, expensive, and invasive for that purpose. There is, however, a report expressing a negative opinion about the usefulness of such screening. Atabek *et al.* disputed the advantage of endoscopic screening for esophageal cancer in head and neck cancer patients because endoscopic screening for esophageal cancer did not improve their survival. Endoscopic screening in 574 head and neck cancer patients found 6 patients with one asymptomatic esophageal carcinoma. All but one of the patients died of esophageal cancer. They concluded that the survival rate for multiple primary patients actively screened by endoscopy was not greater than for those with subsequently diagnosed esophageal tumors.<sup>3)</sup> However, there are some questions about their patients and about the quality of the treatments they used for esophageal carcinoma. The survival rate for a very small number of head and neck cancer patients (six) in whom esophageal carcinoma was simultaneously identified by endoscopy cannot be compared with that of other larger groups of patients. All but one of those esophageal carcinomas were found in an advanced stage, in spite of "active screening." Further, all but one of their treatments of choice for esophageal carcinoma were chemotherapy or radiotherapy, with which better survival cannot be expected even when cases are diagnosed at an earlier stage. The only patient who was treated by surgery had an advanced esophageal carcinoma (T3 tumor).

We found a 10.0% 5-year survival rate for 41 patients with esophageal carcinoma as a second primary carcinoma among head and neck cancer patients. All of our patients were screened by endoscopy and most of them underwent surgery for esophageal carcinoma. Only one of eight patients who were treated without surgery survived more than two years.<sup>4)</sup> Adequate surgical treatment for second primary esophageal carcinoma, per-

formed by an experienced surgeon, may have improved the survival in some patients, which suggests there may be some survival advantage for endoscopic screening.

Early diagnosis of esophageal carcinoma is one of the most important factors for improving the patient's survival. Endoscopy has contributed greatly to this. Kuster and Foroozan indicated a high incidence of adenocarcinoma in Barrett's esophagus, and emphasized the importance of endoscopic examination for early diagnosis, and a better prognosis after surgical treatment for such tumors found at an early stage.<sup>5)</sup>

In Japan and in some leading institutions in other countries, Lugol spray has been widely used in combination with the standard esophageal endoscopy to identify minute or superficial esophageal carcinomas at a relatively early stage. Lugol solution stains glycogen in the normal squamous mucosa of the esophagus while the injured or cancerous mucosa is negatively stained, which grossly embosses the area of carcinoma in the esophagus. Sugimachi *et al.* emphasized the value of Lugol-combined endoscopic diagnosis by comparing the pathologic data of patients with esophageal carcinoma before and after introduction of this method. Detection of early-stage carcinoma clearly increased during the period when it was used.<sup>6)</sup> The importance of this method for early diagnosis and the possibility of its application as a screening measure for high-risk people were emphasized by Endo *et al.*<sup>7, 8)</sup>

The survival rate of patients whose esophageal carcinoma is found at an earlier stage is likely to be better than that of patients with tumors at a later stage.

## B. Staging

### 1. Staging system

One of the most important aspects of diagnosis is staging. We plan the type of treatment and predict the patient's prognosis according to the stage of the tumor. Germanov *et al.* substantiated the importance of staging, describing several diagnostic measures, selection of treatment according to the preoperative diagnosis, and the results.<sup>9)</sup> The TNM classification proposed by the International Union Against Cancer is well known and widely used for that purpose. In 1987, the TNM classification for esophageal malignant tumors was changed markedly.<sup>10)</sup> The Japanese Committee for Registration of Esophageal Carcinoma analyzed the registered records of patients from 1969 to 1980, and the chairman, Iizuka, reported the parameters which were linked to 10-year survival.<sup>11)</sup> Because the depth of tumor invasion correlated better with 10-year survival than the tumor length, they concluded that the new TNM classification had good prognostic value.

In 1992, when the new classification had been in use for five years, we evaluated its propriety in order to see

whether it could be improved. The survival curves for patients in each category were well separated, and properly reflected the patient's prognosis, except in some minor respects. We proposed putting stages IIA and IIB together, summing up all lymph node metastasis in N-categories and dividing these into N1 and N2 according to the number of positive nodes.<sup>12)</sup> On the other hand, Ellis *et al.* criticized the 1987 TNM classification and concluded that it provides no better discrimination of stages according to survival than the earlier version.<sup>13)</sup> Instead, they proposed a modified version of Skinner's WNM staging.<sup>14)</sup> The WNM staging closely resembles our proposal.

Several diagnostic measures are used today to determine the stage of esophageal carcinoma before treatment. The latest ones are esophagography, endoscopy, ultrasonography, radionuclide scanning, computed tomography (CT) scanning, magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS).

#### 2. CT scanning

The reliability of CT scanning for surgical indication has been controversial. There are two opposing evaluations of CT scanning in assessing resectability. Several authors found no value of CT to the surgeon, mainly because of its unreliability in the diagnosis of lymph node metastasis.<sup>15-17)</sup> Lehr *et al.* negatively evaluated both CT scanning and MRI for planning surgery because of their low sensitivity and specificity for the preoperative diagnosis of tumor infiltration into the adjacent structures or metastasis.<sup>18)</sup>

However, CT has been used frequently for tumor staging as an important diagnostic measure, especially in diagnosing tumor infiltration to other mediastinal structures. Consigliere *et al.* accepted the value of such scanning in predicting palliative or curative resection and in warning the surgeon about possible infiltration of adjacent structures.<sup>19)</sup>

#### 3. EUS

EUS is a relatively new diagnostic measure for staging esophageal carcinoma. It is often used today, for the preoperative diagnosis of tumor invasion depth and mediastinal and abdominal lymph node metastasis. According to studies comparing EUS and CT scanning, EUS is superior in evaluating tumor depth (accuracy: EUS 89-92%, CT 59-60%), especially in the early stages, and in assessing regional lymph node metastases (accuracy: EUS 80-88%, CT 51-74%), but EUS is less accurate than CT scanning in staging distant metastasis (EUS 68-70%, CT 82-90%).<sup>19-22)</sup> Although the diagnostic ability of EUS may be limited in cases with severe stenosis, it has become the standard imaging technique in staging before and after treatment in advanced institutions, as predicted by Tio *et al.*,<sup>20)</sup> because of its high accuracy and safety. The usefulness of EUS for diagnosis

of recurrent cancer at the surgical anastomosis has been reported (positive predictive accuracy 88%, negative predictive accuracy 92%).<sup>23)</sup> EUS may also be useful for evaluating the effect of treatment of recurrent tumor.<sup>24)</sup> Overall, the high diagnostic accuracy of EUS depends heavily on a combination of experienced endoscopic and equally experienced ultrasonographic technique.

#### 4. Other diagnostic measures

Esophagography, endoscopy and RI scintigraphy are the conventional diagnostic measures, and are still useful, though new articles concerning them have been relatively rare in the last decade. In 1985, Yamada and Kobayashi showed how to make diagnosis of early esophageal carcinoma by esophagography, and they emphasized the usefulness of double contrast pictures to delineate irregularity of the mucosa.<sup>25)</sup> The proposed technique may be quite useful for early diagnosis of esophageal carcinoma, but it seems too elaborate for general physicians. Since then, there has been no conspicuous development in this diagnostic measure.

One of the roles of endoscopy in the diagnosis of esophageal carcinoma today is to take the biopsy specimen, and the other is staging. Endo *et al.* classified endoscopic gross pictures of superficial esophageal carcinoma, and showed how to make diagnosis of depth of tumor invasion from the gross pictures.<sup>7,8)</sup> A similar endoscopic classification has been widely used in Japan as a part of the rules for endoscopic classification of the Japanese Society for Esophageal Diseases.

Scintigraphy may still be useful as a staging measure in some patients with esophageal carcinoma to diagnose bone metastasis. However, there has been no remarkable development during the last decade.

External ultrasonography is often used to investigate metastases to cervical and abdominal lymph nodes and abdominal organs. Ultrasound-guided fine-needle aspiration biopsy of the cervical lymph nodes has been used for staging of esophageal carcinoma.<sup>26)</sup> The procedure seems to be relatively simple and safe, although the indications for this examination are still controversial.

In staging esophageal carcinoma, we should not depend on only one diagnostic measure. Combined use of radiologic, endoscopic, radionuclide, and ultrasonographic examinations is recommended for staging, as stated by Germanov *et al.*<sup>9)</sup>

#### C. Peri-surgical diagnosis

Information obtained during surgery often plays a vital role in designing the treatment strategy. Tumor adhesion to other organs found during surgery may be definitely but incorrectly judged to be tumor infiltration. Based on the pathology reports on 39 excised lungs which were judged to have been invaded directly by esophageal tumors and which were resected during surgery, only 22

lesions invaded the pulmonary parenchyma (56%). This finding indicated the difficulty of gross diagnosis of esophageal tumor infiltration to adjacent organs.<sup>27)</sup>

Perioperative frozen sections of the distal esophagus are useful for determining the extent of esophageal resection, but, the rate of false negatives is not small. Normal epithelium of the esophagus contains glycogen in its superficial layers, whereas carcinomatous epithelium does not. This glycogen is stained with iodine-potassium iodide solution (Lugol's solution) (Fig. 1). Sugimachi *et al.* introduced the technique of Lugol staining of resected specimens from 1985 to 1989 and recommended it as a rapid, simple technique with a low false-negative rate for examining the spread of invasion in the mucosa macroscopically. Among 167 surgically excised esophagus specimens, carcinomatous infiltration at the surgical margin was found by Lugol staining in three cases.<sup>28)</sup> This technique has become widely accepted in Japan today. Researchers have also tried intraoperative endoscopic examination of the esophagus using Lugol staining to determine the resection line. Among eight patients, six had intraepithelial extensions of their tumors and two had

multiple carcinomas in the esophagus. However, all of the resected stumps were free of cancer and no recurrent disease occurred. They emphasized its usefulness in early cancer of the esophagus.<sup>29)</sup> This method may be useful in patients with multiple carcinomas in the esophagus or with proximal extension of the main lesion identified by preoperative endoscopy and who may have remaining carcinoma in the proximal esophagus. A retrospective evaluation of 239 patients with primary esophageal squamous cell carcinoma who underwent esophagectomy without preoperative treatment in our institution revealed 45 cases (18.8%) of multiple primary esophageal carcinoma. We emphasized the need for careful checking of the esophagus at the time of esophagectomy.<sup>30)</sup> However, most of the multiple lesions in our series had been recognized before surgery by endoscopy using the Lugol spray method, and sometimes we needed Lugol staining during surgery to confirm a free surgical margin. Intraoperative Lugol staining may be useful as a supportive measure to frozen section examination to find any grossly indistinct lesion in the remaining proximal esophagus. Preoperative detailed endoscopy using the Lugol spray method may also be useful to identify a lesion which is macroscopically unclear and situated around the planned surgical margin, and it is also recommended as a standard preoperative test.

In reconstruction of the esophageal replacement, circulation of the proximal end of the substitution will have a significant effect on the outcome of the anastomosis. Pulse oximetry has been used to assess the viability of the tubed stomach which would be used as an esophageal substitution. Because the number of patients who underwent this examination was small, a lower limit of oxygen saturation for safe anastomosis was not proposed.<sup>31)</sup> An accumulation of more cases may reveal whether the method is useful to assess the site of anastomosis.

## Treatments

### A. Surgery

#### I. General aspects

Among several treatment modalities, surgery has offered the best results for patients with esophageal carcinoma. In 1990, Muller *et al.*<sup>32)</sup> summarized the results of the surgical treatment of esophageal carcinoma, reviewing 174 articles published in West-European languages during 1980–1988. According to their literature, the average hospital mortality rate following esophagectomy was 13% (median 10%, range 40%); in Japan 6%, Italy 12%, France 16%, United States 12%, Great Britain 16%, Germany 21%. The average 5-year survival rate was 20% (range 6–61%). Comparing the results (SD) with a previous review of esophagectomy from 1953–1978 by Earlam and Cunha-Melo [resection mortality

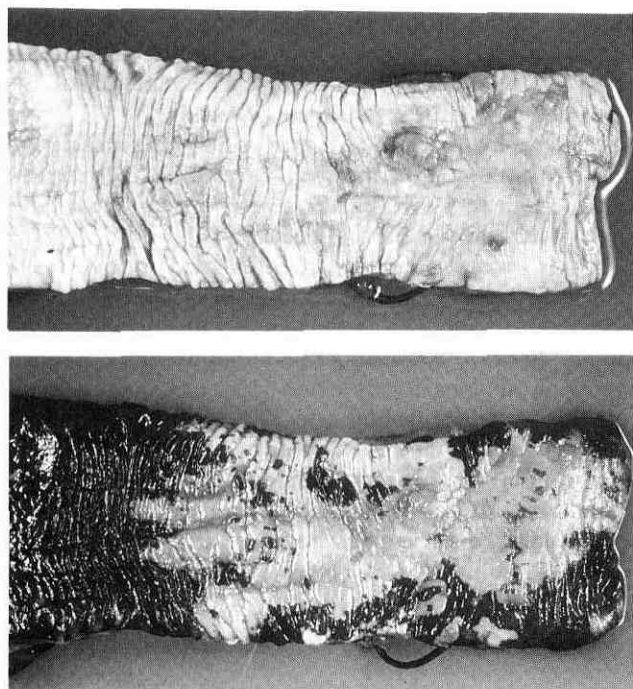


Fig. 1. Gross pictures of the excised esophagus before (upper) and after (lower) staining using Lugol solution. The normal mucosa acquires a dark mahogany brown color, while the area without normal squamous epithelium does not. Although the area of carcinoma is unclear in the upper picture, the lower picture clearly shows that the unstained area reaches the oral surgical margin of the esophagus.

rate 29%(16), 5-year survival rate 4%(3)],<sup>33)</sup> the authors concluded that all efforts to improve long-term survival have failed. However, this does not seem to be a valid assessment, since the average 5-year survival rate improved by 16%, which should be evaluated as a substantial improvement. Additionally, a detailed examination of the review revealed that the average 5-year survival rates reported in the last three years (1986–1988) of the period reached 22%. That may be an indication of further improvement of the survival rate. In 1991, Isono *et al.*<sup>34)</sup> summarized the results of questionnaires concerning 4590 carcinomas which were operated on between 1983 and 1989 in Japan. The 5-year survival rate was around 30%.

A retrospective study comparing 70 patients who underwent successful tumor resection and 62 who underwent curative irradiation showed significantly better results for the surgical patients. The authors concluded that if a patient was willing to accept the chance of dying from the operation, surgical treatment was preferable to radiation therapy, though when the initial inability to swallow was severe, irradiation was a better choice of treatment because this is a bad prognostic factor for survival.<sup>35)</sup> Certainly, recently reported results of surgery have been mostly superior to those of irradiation therapy. There is, however, no randomized control study comparing curative radiation therapy and true-curative surgery in which at least those fields included in radical radiotherapy are dissected (e.g. 3-field dissection<sup>32)</sup>). This may be because, after surgery, most patients with esophageal carcinoma died not of local recurrence, but of recurrent disease in the cervical, mediastinal or abdominal lymph nodes, or in other distant organs, so comparison of radiotherapy and surgery targeting only the primary tumor in the esophagus (e.g. transhiatal resection) is difficult. Similar survival may be surmised.

## 2. Techniques and results

Fundamental methods of esophagectomy were established before the 1970s. Today, there are two predominant trends of surgery for esophageal carcinoma. One is to find a way to keep the operative burden as small as possible and the other is to extend the operative field as far as possible. Most surgeons who prefer extended surgery believe that many esophageal carcinomas are curable in their hands. Surgeons favoring the more restricted surgeries consider that most esophageal carcinomas are hardly curable by surgery.

There are continuing arguments comparing transhiatal and transthoracic approaches for esophagectomy.<sup>36-39)</sup> In a prospective randomized trial to compare the transhiatal and transthoracic approaches, Goldminc *et al.* found no difference in the morbidity rate and similar long-term survivals.<sup>40)</sup> Of course, randomized trials in the field of esophageal surgery are noteworthy. However, the re-

ported survival rates after transthoracic esophagectomy seemed fairly low compared with those of other recent reports, which will be presented later. Although Goldminc *et al.* did not give an exact percentage of survival, the overall 3-year survival rate after transthoracic esophagectomy was nearly 15%.<sup>41)</sup> In evaluating a randomized study that compares surgical techniques, we should keep in mind that the results may have been greatly influenced by the quality of the surgical technique of the organizing surgeons, and that the specific results may not be generalizable to other surgeons.

Operative results may also be influenced by tumor location in the esophagus and the surgical procedure applied to it. When the tumor is located in the upper thoracic esophagus, lymph node metastasis is most common in the upper mediastinum and rare in the abdomen, whereas when it is located in the lower esophagus, the tumor metastasizes most frequently to the abdominal paracardiac lymph nodes.<sup>41)</sup> In the case of carcinoma of the cardia, upper mediastinal lymph node metastasis is rare. Recent reports from England and the U.S.A. indicate a rising incidence of adenocarcinoma of the esophagus, and it now represents a half of esophageal carcinomas in western countries, which has resulted in rising incidence rates of carcinoma of the lower esophagus and cardia.<sup>42, 43)</sup> In those cases, the survival after transhiatal esophagectomy with abdominal lymphadenectomy may be similar to that of transthoracic esophagectomy with mediastinal lymph node dissection, because most of these adenocarcinomas are located around the esophago-gastric junction or at most in the lower thoracic esophagus, and may rarely metastasize to the upper mediastinal lymph nodes. In Japan, adenocarcinoma accounts for 2.2% of all resected esophageal carcinomas according to the national registration from 1979–82; the percentage was similar in 1986. Accordingly, only 28% of esophageal tumors are located in the lower thoracic esophagus or around the cardia.<sup>44)</sup>

Results of surgery for esophageal carcinoma have improved drastically in recent years, especially in Japan and also in leading institutes in western countries. Launois *et al.* summarized the results of their surgical treatment, and, according to their report, the operative mortality in the 1970s was over 15%, but this improved to 2.6% in the 1980s; the 5-year survival rate was 5.5%.<sup>45)</sup> Hennessy and O'Connell reported a 12.9% overall operative mortality rate in their series of operation for esophageal carcinoma during the period 1976–1983, and the 5-year survival rate was 11.5%.<sup>46)</sup> Law *et al.* reported an overall hospital mortality of 16.5% and a 5-year survival rate of 15% for 625 patients with squamous cell carcinoma who were operated on between 1982 and 1989.<sup>47)</sup> In contrast, Isono *et al.* showed an overall 30-day mortality rate of 3.9%, and a 5-year survival rate of around 30% in 4590

patients in Japan.<sup>34)</sup> There may be a difference in the patients' backgrounds between Japan and western countries, but even in Europe, the results in some leading institutions have improved remarkably, even when results for patients at the same stage were compared. Lerut *et al.* reported surgical results in 257 patients who underwent esophagectomy from 1986 through 1988; the overall hospital mortality was 3%, and the overall 5-year survival rate was 30%.<sup>48)</sup>

The significance of lymph node dissection in surgery for esophageal carcinoma is still a subject of debate, since it is closely linked with the surgical procedures described above. The upper and middle mediastinal lymph nodes cannot be dissected completely without right thoracotomy. Skinner obtained an improvement in surgical results by *en bloc* esophagectomy, in which the lymphatics and the regional lymph nodes near the tumor were completely dissected by thoracotomy.<sup>49)</sup> Lerut *et al.* considered radical lymph node dissection by experienced hands as offering the best chance for curing the disease, based on analysis of their results using multivariate Cox regression analysis.<sup>48)</sup> From 1985 through 1989, 77 patients with thoracic esophageal carcinoma at the National Cancer Center Hospital underwent esophagectomy with cervical, mediastinal, and abdominal lymph node dissection (3-field dissection). In 1991, we demonstrated a positive effect of this lymph node dissection. Although the series included 20 stage IV patients (TNM classification), their 5-year survival rate was 48.7%, which demonstrated the efficacy of extended lymph node dissection in terms of patients' survival.<sup>50)</sup>

We also reported the results of 3-field lymph node dissection applied to 43 patients with superficial esophageal carcinoma of the thoracic esophagus. Histological examination revealed that 46.5% of the patients had metastasis-positive nodes. Among those patients with tumor invading the submucosa, 57.6% had positive nodes, which indicates the need for some treatment aimed at lymph node metastasis. In contrast, three pTis tumors had no lymph node metastasis, suggesting the possibility of such limited treatment as endoscopic resection.<sup>51)</sup> Nishimaki *et al.* have presented similar findings and opinions based on their experience,<sup>52)</sup> although Orringer found it difficult to support the assertion.<sup>53)</sup>

The quality of life and alimentary comfort of esophageal cancer patients who had been disease-free more than three years after esophagectomy were evaluated by a questionnaire. The major long-term complaints were a sensation of early fullness, dysphagia, diarrhea, cough-induced vomiting, and postprandial sweating. In this series, 76.5% of the patients led active lives. The investigators concluded that most disease-free patients may obtain a satisfactory quality of life after esophagectomy.<sup>54)</sup>

### 3. Special techniques

Orringer, who favors transhiatal esophagectomy, recommended partial sternotomy for blunt esophagectomy, segmental esophageal resection, drainage of perforation and extended cervical esophagectomy. Extending this idea, he introduced mediastinal tracheostomy, described the results, and evaluated it as useful in the treatment of selected patients with malignancies of the cervicothoracic esophagus.<sup>55, 56)</sup> Fujita *et al.*<sup>57)</sup> and we<sup>58)</sup> introduced a pectoralis major myocutaneous flap and some other techniques of plastic reconstructive surgery for mediastinal tracheostomy to prevent vessel blowout, a serious complication after this operation.

Some esophageal cancer patients will have previously undergone gastrectomy for gastric disease. In surgery for these patients, there are some problems in substituting the esophagus and in deciding how to manage the remaining lymph nodes in the abdomen. We analyzed the results of treatment of 50 of these patients at our institute and recommended abdominal lymph node dissection for patients with middle- or lower-thoracic esophageal carcinoma who have had previous gastrectomy without lymphadenectomy.<sup>59)</sup>

We reported the result of esophagectomy combined with resection of the lung directly invaded by the esophageal tumor. The operative mortality rate was 17.9%. The 5-year survival rate for patients whose tumor was completely removed was 21.1%. These results suggest that pulmonary resection and aggressive lymph node dissection are appropriate for patients with esophageal carcinoma invading the adjacent lung.<sup>27)</sup>

### 4. Thoracoscopic surgery

Recently thoracoscopy has been introduced into thoracic surgery, especially for benign diseases and for biopsy.<sup>60)</sup> Application of this technique today for the treatment of esophageal neoplasms must still be regarded as experimental. Collard *et al.* attempted subtotal esophagectomy in 13 patients by thoracoscopy.<sup>61)</sup> *En bloc* esophagectomy with extensive lymph node dissection was performed in seven patients with esophageal carcinoma. The thoracic procedure for the extensive *en bloc* resection required 240–390 minutes. Immediately after the thoracoscopic esophagectomy, the patients underwent a laparotomy and a cervicotomy for digestive continuity. One patient died of hepatic failure after the surgery. The technique needed a longer operating time, and seems to be more difficult than open thoracotomy. The greatest problem with this technique in the treatment of malignant diseases may be the possibility that it is insufficiently radical.

### B. Radiation therapy

#### 1. External beam radiotherapy

Esophagectomy or irradiation alone has traditionally been considered conventional therapy. In 1988, Menden-

hall *et al.* reported the result of radiation therapy alone for 34 patients with cervical esophageal carcinoma who were treated between 1966 and 1985. They had once-a-day fractions of 170 to 190 cGy, and the total doses ranged from 4715 to 7500 cGy. Four of these patients developed significant acute complications and another four developed significant late complications, three of whom required surgical intervention. The local control rate was 29.0%. Only four patients (all women) survived more than five years after treatment and one was saved by surgery for local recurrence. Accordingly, the researchers altered their treatment policy to use radiation therapy as a preoperative adjuvant therapy or with palliative intent.<sup>62)</sup>

Chakkaphak *et al.* retrospectively analyzed the records of 41 patients with carcinoma of the proximal esophagus (carcinoma within 24 cm of the incisor teeth). Ten out of the 23 patients who had radiation therapy could eat solid food, whereas all 12 of the survivors who had undergone resection were able to eat solid food. It was concluded that surgical treatment provides better palliation than radiation therapy and a reasonable survival time.<sup>63)</sup> Albertsson *et al.* reported the results of radiation therapy alone for 149 patients with thoracic esophageal carcinoma, among whom 81 were treated with palliative intent and 68 with curative intent. They also concluded that radiotherapy alone is an unsatisfactory method for treating potentially curable patients, because their actual 4-year survival rate was only 3%.<sup>64)</sup> Both Chakkaphak *et al.* and Albertsson *et al.* predicted better local control and survival with the combined use of irradiation and other treatments such as surgery or chemotherapy.

Although the history of radiation therapy for esophageal carcinoma is as long as that of surgery, there has been no randomized control trial comparing survival after radical radiotherapy and extended radical surgery. That kind of trial, however, has become more difficult to conduct on ethical grounds, because the latest results of esophagectomy in leading institutions are far better than those of radiation therapy.<sup>33, 48)</sup> There is no reported result on external beam irradiation alone for large numbers of patients with superficial esophageal carcinoma. Although three patients who underwent intraluminal brachytherapy and four who had combined chemotherapy were included, Okawa *et al.* reported a 61.7% cause-specific 5-year survival rate for 21 patients with superficial esophageal carcinoma after radiotherapy.<sup>65)</sup> They concluded that definitive radiotherapy can be applied as an alternative therapy to surgery for patients with superficial esophageal carcinoma. A combination of intracavitary brachytherapy and external beam irradiation might give even better results in some patients with pT1 tumor, because a half of them has no lymph node metastasis.<sup>49)</sup> Further accumulation of experience is

likely in the near future because of the recent increase in the diagnosis of the disease at that stage.

## 2. Intracavitary brachytherapy

Although the assessments of external-beam radiation therapy alone were pessimistic, there are several reports which have positively evaluated the effect of intracavitary brachytherapy. Hishikawa *et al.* reported on six patients with superficial esophageal carcinoma who were treated with intracavitary irradiation only. They used 18–24 Gy of high-dose-rate intracavitary irradiation, which caused radiation-induced ulceration of the esophagus in three patients. Local recurrence of the tumor was noticed in one patient, but all the patients survived 6–16 months.<sup>66)</sup>

Hareyama *et al.* reported 161 cases of intracavitary brachytherapy combined with external-beam irradiation for esophageal cancer patients. Their series included 30 stage I, 71 stage II, 30 stage III and 30 stage IV patients, according to the 1978 TNM classification. The overall complete response rate was 53.4%, although it did not differ according to the stage. No acute radiation injuries were noted, but benign radiation-induced esophageal ulceration or stricture developed in five long-term survivors. The actual 5-year survival rates for stage I, II, III, and IV patients were 43.3, 21.1, 0, and 0%, respectively. They recommended this therapy not only as a palliative therapy but also as a radical treatment for patients in the early stage.<sup>67)</sup> Because of its few complications and good palliation, Agrawal *et al.* also recommended this treatment based on their experiences with 70 patients who were unsuitable for surgery. Swallowing was restored in 92% of the patients, although four developed fistula.<sup>68)</sup>

Petrovich *et al.* analyzed the results of treatments including radiotherapy for 241 esophageal cancer patients. The treatments were external-beam radiotherapy (EBRT) alone in 137 patients, EBRT combined with brachytherapy in 46, chemotherapy alone in 3, resection alone in 9 and resection combined with radiotherapy in 46. Serious complications occurred in five patients treated with radiotherapy alone (2%) and four patients treated with surgery alone or combined with radiotherapy (7%). The best persistent local tumor control was obtained in patients treated with a combination of surgery and radiotherapy, and the worst local control in patients treated with surgery alone. The 5-year survival rate was 18% for patients treated by radiotherapy with surgery, 11% for EBRT with brachytherapy, 2% for EBRT alone, and 0% for surgery alone.<sup>69)</sup> Because the results for surgery alone in this series were unusually poor, their results after treatments which included surgery cannot be evaluated. The result of EBRT combined with brachytherapy, however, appears to be better than that of EBRT alone because of its low morbidity and the good correlation of survival with radiation dose.

C. Chemotherapy

Because the burden of esophagectomy for patients with esophageal carcinoma is generally huge and the results are often unsatisfactory, chemotherapy for esophageal carcinoma has been assessed in order to find an alternative treatment to surgery. There have been innumerable articles published on chemotherapy for esophageal carcinoma. Many chemotherapy regimens using a single agent for esophageal carcinoma were examined in the 1970s. In 1984, Kelsen summarized the reported results of single-agent chemotherapy for esophageal carcinoma.<sup>70)</sup> At that time, ten drugs (bleomycin, mitomycin C, Adriamycin, 5-fluorouracil (5-FU), methotrexate, chloroethyl-cycloethyl-nitrosourea, methyl-glyoxal bis, cisplatin, vindesine, and etoposide) had been adequately studied, and nine of them had been found to have modest to moderate activity with response rates of around 15% (Table I). Among these drugs, mitomycin and cisplatin had the best response rates (26 and 22%). Because of the modest activity of single agents, and with the knowledge that combination chemotherapy often seems to be more effective than single agents, multidrug chemotherapies have been studied.

Cisplatin-based combinations have been the mainstream chemotherapy for esophageal carcinoma in the past decade, and the response rates vary from 15.0 to 76.2%.<sup>71)</sup> In 1994, Ajani reviewed various chemotherapy studies, and concluded that the combination of cisplatin + 5-FU is the most useful chemotherapy currently available.<sup>72)</sup> Among the numerous combinations of chemotherapeutic agents, one of the most effective and tolerable regimens at present may be a combination of cisplatin/5-FU. Hilgenberg *et al.* reported a response rate of 57% and one (2.6%) serious toxic reaction with this combination used before surgery. Their regimen was cisplatin 100 mg/m<sup>2</sup> day 4, and 5-FU 1000 mg/m<sup>2</sup> infusion over 24 h

on days 1–4 given for 2 cycles 21 days apart. They concluded that this combination chemotherapy before surgery improved the intermediate-term survival of the patients.<sup>73)</sup> Iizuka *et al.* reported the results of a Phase II study on combination chemotherapy (cisplatin 70 mg/m<sup>2</sup> and 5-FU 700 mg/m<sup>2</sup> on days 1–5 for 2 cycles) in advanced squamous cell carcinoma of the esophagus, in which the overall response rate was 35.9% and the major toxicity was grade 3 or 4 myelosuppression in six patients (15.4%). They recommended this regimen as a postoperative chemotherapy because of its reasonable effect and mild adverse effects.<sup>74)</sup> Despite these numerous studies, it is still not clear whether chemotherapy alone is effective for improving survival.

D. Multimodality treatment

1. Radiation and surgery

Radiation therapy for surgical candidates was introduced before the 1980s to improve the resectability of esophageal carcinoma.<sup>75,76)</sup> But in the latter half of the 1980s there was a move to reevaluate the effect of irradiation as an adjuvant therapy before surgery. A multi-institutional randomized trial was carried out in Japan to evaluate the prognostic effect of preoperative irradiation. A total of 364 patients in eight institutions who underwent curative esophagectomy were divided into two groups. One group had preoperative irradiation (30 Gy), surgery, and postoperative irradiation (50 Gy), and the other had no treatment before surgery and underwent postoperative radiotherapy (50 Gy). Because the survival curve for patients who had no preoperative irradiation was better than that for patients who had it, the authors expressed doubt about the value of preoperative irradiation.<sup>77)</sup>

Arnott *et al.* compared two groups of patients who were randomly assigned to preoperative radiotherapy (20 Gy) or surgery alone. There was no significant difference between the survival rates of the two groups, and the researchers concluded that low-dose preoperative radiotherapy offered no advantage over surgery alone.<sup>78)</sup>

Two reports of randomized controlled studies of postoperative radiation therapy for esophageal carcinoma found no survival benefit, especially for patients who have undergone curative resection. Teniere *et al.* found a beneficial effect of postoperative radiotherapy (45–55 Gy) only in preventing a recurrence in patients without lymph node metastasis.<sup>79)</sup> Fok *et al.* accepted its role only in a specific group of patients with residual tumors in the mediastinum, because postoperative radiotherapy (52.5 Gy) reduced the incidence of recurrence in the tracheo-bronchial tree.<sup>80)</sup> These results indicate that postoperative radiation therapy may be unable to deal with lymph node metastasis, although it may have a limited positive effect on local residual tumors.

Table I. Response of Single Agent Trials in Esophageal Carcinoma<sup>68)</sup>

Agent	No. of patients evaluable	Response rate (%)
Bleomycin	80	15
Mitomycin C	58	26
Adriamycin	33	15
5-Fluorouracil	23	15
Methotrexate	26	12
CCNU <sup>a)</sup>	19	16
MGBG <sup>b)</sup>	18	17
Cisplatin	73	22
Vindesine	23	17
Etoposide	20	0

a) 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea.

b) Methylglyoxal bis(guanylhydrazone).



Nygaard *et al.* showed a positive effect of preoperative radiotherapy on survival in a randomized, multicenter study.<sup>81)</sup> The results, however, were criticized by DeMeester.<sup>82)</sup> Nygaard *et al.* divided a total of 186 evaluable patients into four groups: surgery alone, preoperative chemotherapy and surgery, preoperative radiotherapy and surgery, preoperative chemotherapy/radiotherapy and surgery. They reported that survival of patients with preoperative radiotherapy was better than that of patients without it. Although survival curves both for patients with radiotherapy and for patients with radiotherapy/chemotherapy were better than the curve for patients with preoperative chemotherapy, the differences of survival curves between the groups of patients with preoperative radiation and those without any adjuvant treatment were not significant.<sup>81)</sup> The numbers of patients included in each group seem rather small, and there are some serious factors in the patients' backgrounds that may have affected their survival as pointed out by DeMeester.<sup>82)</sup> There is no recent influential report that positively supports the effect of adjuvant radiation therapy by itself. Thus, conventional radiation therapy alone as an adjunct to surgery today should be judged to be ineffective in terms of survival of patients with esophageal carcinoma.

## 2. Chemotherapy and surgery

Because symptomatic esophageal carcinoma is regarded as a systemic disease, especially in many western countries, chemotherapy combined with surgery has been actively studied. When chemotherapy is given before surgery, the agents can be given to patients in good general condition and the effects can be confirmed histologically in the surgical specimens. The common denominator in chemotherapy studies today is cisplatin. The reported response rate ranges from 17 to 55%, the rate of resection is from 38–100%, the rate of operative mortality is from 0–45%, and the median survival is from 17–24 months.<sup>83)</sup>

Kelsen *et al.* reported the results of a randomized, controlled trial of preoperative treatments comparing preoperative chemotherapy (CHT) and radiation therapy (RT). Patients were assigned to receive either two intravenous cycles of cisplatin, vindesine, and bleomycin, or 55 Gy of external-beam irradiation before surgery. Postoperative crossover therapy (RT to those receiving preoperative CHT and vice versa) was given to patients with T3 or unresectable tumors. Objective response rates (RT 64%, CHT 55%), operability rates (RT 77%, CHT 75%), resection rates (RT 65%, CHT 58%), and operative mortality (RT 13.5%, CHT 11.1%) were similar. The median survival for all patients was 11 months, but analysis of survival according to the preoperative treatment arm alone was impossible because of the crossover design. The investigators concluded that research pro-

grams using preoperative chemotherapy as part of the initial treatment for localized esophageal cancer should continue, and that surgery alone or radiation alone should remain standard therapy outside of carefully designed clinical trials.<sup>84)</sup>

As noted by Kelsen, adjuvant chemotherapy for esophageal carcinoma is not a standard treatment arm today but remains an object of clinical study. A multicenter, randomized clinical trial comparing two groups of patients, one given a pre- and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin and a surgery-alone group, was carried out by Roth *et al.* The toxicity of the chemotherapy was judged to be acceptable. However, the overall resectability rates were similar for both groups, and there was no statistically significant difference between the actual survival curves of the two groups of patients. Overall survival was prolonged only for patients responding to preoperative chemotherapy.<sup>85)</sup> Carey *et al.* analyzed the results of preoperative chemotherapy for adenocarcinoma<sup>86)</sup> and for squamous cell carcinoma<sup>87)</sup> of the esophagus. Both groups of patients were studied using cisplatin and 5-FU as adjuvant chemotherapy. Patients with adenocarcinoma had pre- and postoperative chemotherapy or postoperative radiotherapy. The response rate for the preoperative chemotherapy group was 40%, and the resection rate was 73%. The median survival time was 18.5 months for all patients and 23.8 months for patients who underwent resection.<sup>86)</sup> As for the squamous cell carcinoma, the response rate was 66%, and the resection rate was 81%.<sup>87)</sup> The overall median survival was 21.9 months, and actual 5-year survival rate was 31% for all patients and 39% for resected patients, respectively.<sup>86, 87)</sup> Although these results showed that complete response to chemotherapy and successful resection of the lesion were correlated with better survival, it is still unclear whether adjuvant chemotherapy prolongs the patient's survival. Preoperative chemotherapy remains investigational and is the subject of ongoing random assignment trials comparing surgery to pre- and postoperative chemotherapy.

## 3. Chemotherapy and radiation

This approach has also been studied in the treatment of esophageal carcinoma with curative intent. Herskovic *et al.* reported the results of a recent phase III trial comparing two groups of patients who underwent radiation alone and who had radiation combined with chemotherapy using cisplatin and 5-FU. They showed that concurrent therapy with cisplatin and 5-FU and radiation is superior to radiation therapy alone as measured by control of local tumors, distant metastasis, and survival. However, severe and life-threatening side effects occurred in 44% of patients who received combined therapy. Survival rates at 12 and 24 months were 33% and 10%.<sup>88)</sup> As the combined chemotherapy and radiother-

apy in this series was superior to conventional radiotherapy alone in terms of survival and local control rates, this regimen requires further study. Although the survival and the cost of side effects in this combined treatment do not seem to be superior to those in the case of surgery, a controlled randomized trial comparing combined chemoradiation therapy with surgery alone may be required to prove this.

#### 4. Radiation, chemotherapy, and surgery

Because radiation therapy by conventional methods or chemotherapy using presently available drugs is largely ineffective as adjuvant treatment for surgery, studies to evaluate the effect of chemotherapy combined with radiation therapy as an adjuvant to surgery have begun. In the U.S.A., the Southwest Oncology Group performed a Phase II trial of a preoperative chemotherapy regimen of cisplatin (75 mg/m<sup>2</sup>/d, days 1 and 29) and 5-FU (continuous infusion 1000 mg/m<sup>2</sup>/d, days 1 to 4 and days 29 to 32), and radiation (3000 rad, days 1 to 19). The overall resectability rate was 49%, and the surgical mortality was 11%. The median survival was 12 months and the 2-year survival rate was 28%. The report's authors emphasized the need for a randomized comparison between combined-modality treatment and radiation therapy to determine definitively the usefulness of this aggressive approach.<sup>89)</sup> It is impossible to discuss the survival benefit of their combined-modality treatment, because the tumor stages of their patients were not clearly described, their survival data after surgery alone were not shown, and their historical data for survival had been reported nearly ten years before. Some members of the above study and others reported a 3-year survival rate, using the same regimen, of 8%. Their patients' tumor stages were four T1N0M0 (stage I), 35 T2N0M0 (stage II), and three T3N0M0 (stage III).<sup>90)</sup> Taking these tumor stages into consideration, survival does not seem to be improved by their regimen.

Some articles have discussed the survival benefits of preoperative chemotherapy and radiation therapy for esophageal carcinoma. The effect of several factors on the survival of patients who had preoperative treatments consisting of chemotherapy with 5-FU and mitomycin C combined with radiation were analyzed by multivariate analysis. The tumor stage was significantly correlated with survival and local relapse-free rate. The actual 5-year survival rate for patients with stage I or II was 18%.<sup>91)</sup> Orringer *et al.* reported the results of their treatment with cisplatin, vinblastine, and 5-FU chemotherapy concurrent with 4500 cGy radiation therapy for 21 days before transhiatal esophagectomy in 43 patients with esophageal carcinoma (21 adenocarcinoma and 22 squamous cell carcinoma). Their cumulative 3-year survival rate was 46%. Because the 2-year survival rate of this group was better than that of their historical control

group treated with transhiatal esophagectomy alone, they suggested that intensive combined-modality therapy improves the survival of patients with esophageal carcinoma.<sup>92)</sup> These same authors, however, have reported opposite results using a combination treatment with 49 Gy of preoperative radiation therapy and concurrent chemotherapy consisting of 5-FU for adenocarcinoma of the esophagus.<sup>93)</sup> In 1993, they reported the final results of the study of preoperative chemoradiation for esophageal carcinoma that had been reported in the former paper. The 5-year survival rates for adenocarcinoma and squamous cell carcinoma were 34% and 31%, respectively.<sup>94)</sup>

Naunheim *et al.* also reported the results of preoperative chemotherapy and radiotherapy for esophageal carcinoma. Of 47 patients, one patient (2%) died of complications related to the preoperative treatments. Thirty-four patients (83%) had resectable lesions at surgery. The operative mortality rate was 3%. Their actual survival was significantly better than that of historical control patients.<sup>95)</sup>

Wolfe *et al.* reported a 5-year survival rate of 25% for protocol patients who had preoperative chemotherapy and radiation therapy. They studied 93 patients with adenocarcinoma and 72 with squamous cell carcinoma, and the two diagnosis groups received different chemotherapy regimens. Three different methods of surgery were employed.<sup>96)</sup>

There appears to be a problem in the reports of Naunheim *et al.* and Wolfe *et al.* as to the various methods of surgery involved. In contrast to other treatments with a single regimen, the results of any surgery may be greatly affected by the type of procedure.

Although most of the above authors suggested the need for randomized controlled trials of those treatment modalities, the results of surgery alone may differ greatly among surgeons or institutions, or time periods. Surgery is not a quantitative but a technical field. A uniform dose of drug may be given to patients in a uniform manner; radiation may be conducted likewise. But surgery is not uniform among surgeons, and this presents a major problem in planning a multiinstitutional group study related to surgery or in comparing the results of combined-modality treatments that include surgery.

#### 5. Other combinations

Hyperthermia was introduced as a treatment modality for malignant tumors more than ten years ago. When the effect of it fell short of expectations, combined treatments that included hyperthermia were studied. Hou *et al.* reported 34 such cases. They used hyperthermia (44–48.5°C) by intracavitary microwave, chemotherapy with bleomycin and cisplatin, and radiation. Twenty-three patients (T1, 7; T2, 16) underwent the combined regimen as a primary treatment, eight had it as a treatment

for recurrent cancer, and three received surgery after it. The total response rate was 94%. The 2-year survival rate for the 23 primarily treated patients was 48%.<sup>97)</sup> Sugimachi *et al.* studied the effects of hyperthermia combined with chemotherapy and irradiation in treating patients with esophageal carcinoma.<sup>98, 99)</sup> Hyperthermia (42.5–44.0°C) was applied by a localized electromagnetic field in the esophagus using a radiofrequency system simultaneously with 5 mg bleomycin one hour after irradiation. Based on their historical data which showed better survival for patients with hyperthermochemoradiation therapy than for those with chemoradiation before surgery,<sup>98)</sup> a randomized trial was carried out to compare these two regimens.<sup>99)</sup> Although the subjective symptoms after preoperative treatment were significantly improved in patients who had hyperthermochemoradiation, there was no statistically significant difference in the response rates between the two groups. The survival results are not given in their published report.

In summary, there has been no report reliably demonstrating the superiority of preoperative hyperthermochemoradiation therapy over other simpler combination treatments in spite of its more complicated technical requirements.

#### E. Other treatment modalities

##### 1. Laser therapy

The neodymium yttrium aluminium garnet (Nd-YAG) laser plays a part in the treatment of esophageal neoplasm by smashing tumor tissue directly through the lumen, and is mainly used as a palliative therapy today. Krasner *et al.* reported their results of palliative laser therapy. A total of 76 patients with strictures caused by malignant tumors of the esophagus or gastric cardia were treated using a Nd-YAG laser. Among them, 36 had laser treatment only, 10 underwent intubation followed by laser treatment, 9 had laser treatment after surgery, 2 had laser therapy after radiotherapy, 14 had laser therapy followed by intubation, 2 had radiotherapy after laser therapy, and 1 underwent esophagectomy after laser therapy. Two patients had perforation related to laser treatment alone, two other patients had a perforation after laser treatment and dilatation, and three developed perforation during endoscopic intubation after previous laser therapy. The mortality of laser recanalization and associated treatments was 5%. After the treatment, 86% of patients improved sufficiently to take solid foods, and the improvement was maintained until death in 85% of them.<sup>100)</sup>

Nava *et al.* analyzed the retrospective data for 40 patients with esophageal malignancies treated by Nd-YAG laser or electrofulguration. All of their patients had malignant obstruction of the esophagus, and surgery was either contraindicated or refused. No esophageal per-

forations occurred. Retreatment was often required and was performed as indicated because no maximum dose has been established. Neither of these treatments precludes treatment with other modalities. Electrofulguration was capable of establishing luminal patency earlier than was Nd-YAG laser treatment.<sup>101)</sup> Considerable differences exist in the availability and cost of equipment between electrofulguration and Nd-YAG laser therapy. Thus, superiority of the Nd-YAG laser over the more conventional form of therapy (electrofulguration) was not demonstrated.

Segalin *et al.* reviewed the records of 732 patients who underwent several palliative regimens to evaluate the efficacy of those treatments. In their series, 50 patients had Nd-YAG or photodynamic laser therapy. In these patients, there were no procedure-related deaths. Their median survival was 4.1 months, and excellent or good palliations were obtained in 83% of them. Taking account of the higher cost of surgery and the lower mortality of therapies other than surgery, they concluded that other palliative treatments including laser therapy can achieve comparable survival, as well as quality of palliation, with lower morbidity and mortality.<sup>102)</sup>

Naveau *et al.* reported that the presence of an adenocarcinoma was positively correlated with the duration of symptom improvement in their experience of 144 patients with esophageal and cardiac carcinomas analyzed by stepwise regression analysis.<sup>103)</sup>

Although a small incidence of perforation related to laser therapy used for advanced esophageal carcinoma seems to be acceptable, it should be remembered that when a laser is used for superficial esophageal carcinoma, perforation may be more frequent because of the thinner esophageal wall. Hemorrhage, stricture, fistula, and bacteremia have been reported as complications of laser therapy. However, the occurrence of these complications solely related to laser therapy may be lower, because they are not rare in patients with advanced esophageal carcinoma not treated with a laser. The selection of laser therapy for palliation of esophageal carcinoma may largely depend on whether or not this expensive therapy is available.

##### 2. Photodynamic therapy (PDT)

Nonthermal laser light is used to initiate the process of photodynamic therapy not only in palliative treatment but also in the cure of early-stage esophageal carcinoma. Hematoporphyrin derivative is usually used as a light-sensitive drug that selectively concentrates in malignant tissue. Laser light is used to activate the drug, which induces vascular damage with subsequent tumor ischemia and necrosis. A tunable argon-pumped dye laser is often used to provide an output wavelength of 630 nm.

Esophageal perforation related to PDT is rare, except in cases of early cancer, because the typical tissue de-

struction with PDT is 5–10 mm. Sunburn effect is universal. Patients are intensively counselled to remain out of sunlight for one month, because such exposure could lead to a serious sunburn reaction.

Several authors have reported their experience of advanced esophageal carcinoma treated by PDT.<sup>104–107</sup> Most patients demonstrated a reduction in the degree of dysphagia. Patrice *et al.* described their experience of 11 complete responses, 8 partial responses, and 5 patients with no response in a group of 24 patients with squamous cell carcinoma of the esophagus.<sup>108</sup>

The most favorable results have been obtained in patients with superficial esophageal tumors.<sup>103, 105, 107, 108</sup> In 1986, Fujimaki and Nakayama summarized experience with PDT at eight institutions in Japan. Nine of 11 patients with superficial esophageal carcinoma treated with PDT alone had complete response. Two of 11 patients developed recurrent disease, were retreated, and had a complete response.<sup>109</sup> Tajiri *et al.* reported two patients who had PDT followed by esophagectomy. One had residual cancer in the resected specimen; the other was confirmed to have no residual tumor.<sup>110</sup> PDT alone or combined with other modalities is effective for treatment of limited esophageal carcinoma with curative intent.

### 3. Esophageal intubation

As a palliative treatment for esophageal carcinoma, esophageal intubation is an accepted measure for the relief of dysphagia. Angorn and Haffejee performed a prospective, randomized study to compare the palliative potential of esophageal intubation and retrosternal gastric bypass. A total of 106 patients with nonresectable carcinoma located in the upper thoracic esophagus were entered into the study. They used an armored, soft-latex rubber tube. Nutritional status following intubation and bypass was compared in terms of nitrogen balance, weight, serum albumin, and total iron-binding capacity. Intubation resulted in three deaths (5.5%) and gastric bypass in four deaths (7.8%). Palliation of dysphagia was achieved in 93% of patients following intubation and 92% of patients following bypass. Because of fewer complications and the lesser degree of postoperative catabolism, they concluded that esophageal intubation is the preferred palliative procedure.<sup>111</sup>

Oliver *et al.* analyzed their historic data for esophageal intubation and radiation therapy with or without intubation for patients with inoperable esophageal carcinoma. As survival in the radiation therapy group was not significantly greater than survival in the group treated by intubation alone, they concluded that the survival advantage associated with radiotherapy and intubation was small. However, they emphasized the need for a controlled trial of radiotherapy in these patients.<sup>112</sup> Because esophageal intubation is clearly a valuable treatment modality for unresectable esophageal carcinoma, the

effect of combined-treatment modality including intubation should be studied more in the future.

### 4. Endoscopic resection

Owing to recent advances in endoscopy, many cases of esophageal carcinoma are being found at an early stage. Some of these carcinomas can be cured by limited local treatment that is less invasive for the patient and costs less. Endoscopic treatment for esophageal tumors with curative intent has begun mainly in Japan, but the details of the technique have so far been described only in Japanese. In 1990, we proposed the use of local treatments, especially an endoscopic resection of the tumor, for superficial esophageal carcinoma. A total of 92 patients with superficial esophageal carcinoma underwent esophagectomy without any preoperative treatment. Their resected specimens showed that 24 tumors were limited to the mucosa and 23 (95.8%) of them had no lymph node metastasis, whereas, when tumors invade the submucosa, 35% of them have lymph node metastasis which will not be eradicated by the limited local treatment. Based on this result, we proposed an endoscopic mucosal resection for carcinoma diagnosed to be limited to the mucosa before treatment.<sup>113</sup> By examining the endoscopically resected specimen, the true depth of tumor invasion may be confirmed.

Eda *et al.* reported their experience with endoscopic treatments of submucosal tumors of the esophagus in 25 patients. All the tumors were leiomyomas. Submucosography and endoscopic ultrasonography were helpful in identifying the tumor location in the esophageal wall. Twenty tumors were resected using single-session electrocautery. Others underwent endoscopic injection of absolute ethanol into the tumor, which become necrotic and exfoliated during two months after the injection. There were no serious complications. Blood oozing occurred in three patients, and was stopped by topical injection of absolute ethanol. Local recurrence of a submucosal tumor was found in one patient and was retreated successfully.<sup>114</sup>

Some of these techniques may be very effective to minimize the treatment burden to patients with esophageal carcinoma, providing a new direction in this field.

### Future Directions

Diagnostic measures to find esophageal carcinoma at an early stage are quite well developed. The number of patients with esophageal carcinoma found at an earlier stage is expected to increase greatly, not only in Japan and China but also in western countries. An important theme in this field may be general education regarding the disease for physicians and for high-risk groups. The accuracy of endoscopic and external ultrasonography, of CT scanning, and of MRI imaging is expected to improve, providing better information on tumor extension.

Surgical treatments for esophageal carcinoma in leading institutions have been fully developed, but it is clear that there are still numerous diseases which cannot be cured in spite of fully extended surgery. More effective antitumor agents and better combination treatments are undoubtedly necessary. Future treatment strategies will need to take account of the tumor extension and the grade of malignancy, and will require a better under-

standing of the biochemistry and molecular biology of the disease.<sup>115, 116)</sup>

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