Current Status of Esophageal Cancer Treatment

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Abstract: The diagnosis and treatment of esophageal cancer has made remarkable progress in Japan. In terms of diagnosis, the number of early-stage superficial cancer cases detected by panendoscopy and iodine staining has increased, depth of cancer invasion can be diagnosed by EUS, the diagnosis of lymph node metastasis is becoming commonplace, and the diagnosis of tumor malignancies using a molecular biology approach has greatly advanced. In terms of treatment, treatment for mucosal cancer using endoscopic mucosal resection (EMR) has become widespread, the outcome of treatment has improved (5-year survival rate of more than 60%) as a result of the wider use of radical surgery with three-field (neck, chest, and abdomen) lymphadenectomy, chemoradiotherapy regimens have been reviewed, and the use of prosthesis insertion in inoperable cases has increasing rapidly. In particular, esophageal cancer is now classified as a curable cancer, thanks to improvements in the safety and performance of radical surgery. Some issues that require further investigation include improvements in the accuracy of detecting lymph node metastasis and prospective diagnoses of individual chemosensitivity.

Key words: Esophageal cancer; Endoscopic mucosal resection (EMR); Radical esophagectomy with three field lymph node dissection

Introduction

Recently, a rapidly increasing number of early-stage superficial esophageal cancers are being detected, thanks to improvements in diagnostic techniques for these cancers, especially the widespread use of panendoscopy and iodine staining. To determine an appropriate course of treatment for superficial esophageal cancers (mucosal [m] and submucosal [sm] cancers), a precise diagnosis regarding the depth of cancer invasion and the presence of lymph node metastasis is essential. In particular, determining whether endoscopic mucosal resection (EMR) is indicated is necessary to establish the lesion category: m1/m2 (from
Detection of esophageal cancer
Subjective symptoms, screening, contrast radiography, endoscopy (with pigment), and biopsy

<table>
<thead>
<tr>
<th>Preoperative examinations</th>
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<tbody>
<tr>
<td>Screening for cancers of other organs</td>
</tr>
<tr>
<td>Head and neck, stomach, colon, and others</td>
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</table>

**Diagnosis of the lesion**

1. **Extent of the lesion** (intraepithelial involvement and skip lesions)
   - Dye-spraying endoscopy examination
2. **Depth of invasion**
   - Dye-spraying endoscopy
   - Contrast radiography
   - Advanced cancer (T2, T3)
3. **Lymph node metastasis**
   - Ultrasonography: Neck and abdominal region, Mediastinum, Neck, chest, and abdominal region, PET (positron emission tomography)
4. **Organ metastasis**
   - Ultrasonography: Liver, Liver, lung, and others, Scintigraphy: Bone, PET: Lung, liver, bone and others

**Diagnosis of general condition**

1. **Pulmonary function**
   - Spirometer
   - Blood gases
2. **Heart function**
   - ECG, stress ECG
   - Ultrasound cardiology
   - Cardiac pool scanning
3. **Hepatic function**
   - Serum chemistry
   - ICG-R15
4. **Renal function**
   - General urinalysis
   - Urine biochemistry
   - Serum chemistry
5. **Nutritional status**
   - Serum chemistry
   - Rapid turnover protein
   - Body weight, height
6. **Immunological potential**
   - Lymphocyte count,
     - T cell and B cell counts
     - CD4, CD8
   - NK activity
   - PHA lymphocyte transformation potential
   - PPD intradermal reaction
   - Cytokines
7. **Other organs**
   - Upper and lower gastrointestinal endoscopy
   - Tumor markers
   - Ultrasonography, CT, MRI

**Fig. 1 Procedures for the diagnosis of esophageal cancer**

Mucosal epithelium to lamina propria mucosae, m3/sm1 (from lamina muscularis mucosae to surface of submucosa), or sm2/sm3 (middle layer of submucosa and deeper). If EMR is contraindicated for a given lesion, radical surgery is necessary. The difference in postoperative quality of life between the two treatments is significant and requires serious consideration. In Japan’s aging society, merely treating patients with esophageal cancer is not sufficient; every effort must be made to use minimally invasive procedures whenever possible. In some cases, the selection of innovative treatment methods that enable a better quality-of-life (QOL) is also important.

Surgical treatments for esophageal cancer have improved, and the five-year survival rate of patients who undergo extended radical surgery with a three-field (neck, chest, and abdomen) lymphadenectomy through a thoracoabdominal incision now exceeds 60%. As esophageal cancer becomes curable, a trend toward minimum intervention has arisen; this trend has been welcomed by Japan’s aging society. Endoscopic surgery is also becoming more popular.

Chemo and radiation therapies for esophageal cancer have been reviewed and trials (including molecular biology investigations) have been performed to establish the indications for combined therapy. The advent of EMR is noteworthy since this technique is
positioned at the interface between medical and surgical therapies; a substantial difference exists between EMR and surgery from the standpoint of operational intervention and post-operative QOL.

The ideal diagnostic criteria used to determine the indications or contraindications of these various therapies are described below.

Indications for Surgery and Non-Surgical Treatments

To determine an appropriate course of treatment, the tumor’s stage and the patient’s general health must be identified (Fig. 1).

1. Tumor staging
1) Diagnosing depth of invasion
i) Superficial cancer

Endoscopy: Endoscopy examinations enable the invasion of superficial cancers to be identified. Endoscopy is particularly useful when combined with iodine staining for the identification of type 0-IIb m1/m2 lesions.\(^1\) A summary of invasion depths is shown in Table 1. The accuracy rate of subclassification according to invasion depth is about 80%; when the cases are classified into m1/m2, m3/sm1, and sm2/sm3 lesions, the accuracy rate is more than 90%.\(^2,3\) Clinically, diagnosis using this classification system is important for determining an appropriate treatment plan.

<table>
<thead>
<tr>
<th>Depth of invasion</th>
<th>Number of cases</th>
<th>Vascular invasion</th>
<th>Lymph node metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>m1</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>m2</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>m3</td>
<td>11</td>
<td>6 (54.5)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>sm1</td>
<td>13</td>
<td>8 (61.5)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>sm2</td>
<td>20</td>
<td>16 (80.0)</td>
<td>8 (40.0)</td>
</tr>
<tr>
<td>sm3</td>
<td>34</td>
<td>28 (82.4)</td>
<td>15 (44.1)</td>
</tr>
</tbody>
</table>

Endoscopic Ultrasonography (EUS): EUS can barely identify m2 tumors using a 20 MHz thin probe and can easily identify sm tumors. Two types of EUS systems, linear and radial, are used. A skilled investigator can attain an accuracy rate of 80% or higher.\(^4\) The use of EUS is not widespread.

Contrast radiography: Typically, m3 lesions and deeper are discernible using contrast radiography, and the identification of sm cancers is relatively easy. The identification of m1 or m2 lesions is difficult unless a careful examination by a specialist is performed.\(^5\)

ii) Advanced cancer

The diagnosis of T4 lesions (infiltration into periesophageal organs) is clinically critical.

CT and MRI: CT and MRI are useful tools for diagnosing aortic and tracheobronchial infiltrations and can be useful for differentiation between T3 (infiltration into esophageal adventitia) and T4 lesions. CT is widely used.

Bronchoscopy: Bronchoscopy is helpful for diagnosing tracheobronchial infiltration and indispensable for identifying T4 lesions. Bronchoscopic ultrasonography and intravascular endoscopic ultrasonography are also used at some facilities.

EUS: T3 and T4 lesions can be diagnosed using the 7.5 MHz probe. EUS is carried performed from the tracheobronchial or aortic side.

Contrast radiography: Contrast radiography is useful for diagnosing T4 lesions.

2) Diagnosis of lymph node metastasis

EUS, CT, and MRI are currently used to diagnose lymph node metastasis. The accuracy rate is approximately 80%.

3) Diagnosis of distant organ metastasis

Ultrasoundography, CT, MRI, bone scintigraphy, PET, and other modalities are presently used to diagnose distant organ metastasis.

2. Patient’s general health

(1) Heart, pulmonary, hepatic, renal, and central nerve function tests are performed

(2) Metabolic disorders, like diabetes, are identified
3. Diagnosis of multiple cancers in other organs

The possible presence of head and neck cancer, gastric cancer, colon cancer, pulmonary cancer, and hepatic cancer is examined. In particular, a close relation has been found between head and neck cancer and esophageal cancer.

Treatment Strategy and Types of Treatment

1. Treatment strategy

As the number of radical resections of esophageal cancer increases, the pathology of this cancer is becoming clearer.

Esophageal cancers that are limited to within the mucosal epithelium (m1) or lamina propria mucosae (m2) seldom show lymph node metastases or vascular invasion. Lymph node metastases are found in 10–15% of cancers that infiltrate into the lamina muscularis mucosae (m3) or surface of the submucosa (sm1) and in 40% or more of cancers that infiltrate into the middle layer of the submucosa or deeper (sm2/sm3) (Table 1).

Based on the results of the various preoperative examinations described above, an appropriate treatment strategy is selected as shown in Fig. 2. Thus, preoperative examinations are essential to the process of selecting an appropriate treatment method.

a. EMR is performed for cancers whose depth of invasion is limited to m1 or m2.

b. EMR is performed for cancers with m3 or sm1 infiltration, that are not accompanied by enlarged lymph nodes, and that are technically operable. Radical surgery is selected as a treatment option after the histopathological findings of a resected specimen have been examined.

Patients with suspicious lymph node metastases usually undergo radical surgery with a three-field (neck, chest, and abdomen) lymphadenectomy.

c. Radical surgery is performed for cancers with a staging of up to T2 and with sm2 or sm3 infiltration.

Patients in poor general health and a high operative risk usually undergo a limiting esophagectomy. Patients with lesions located in the lower half of the lower intrathoracic esophagus (Lt) or abdominal esophagus...
(Ea) and who have poor pulmonary function usually undergo a transhiatal esophagectomy or esophagectomy without thoracotomy. For elderly patients, an esophagectomy is performed using a left thoracoabdominal approach or a right thoracoabdominal approach, and a lymphadenectomy in the neck and superior mediastinum is not performed completely.

Patients with several suspicious lymph node metastases identified during the preoperative diagnosis may undergo preoperative chemotherapy.

Patients with remote organ metastases usually undergo chemo and radiation therapy.

For patients with multiple cancers in other organs, a treatment protocol consisting of a well-balanced combination of chemo and radiation therapy is implemented.

2. Types of treatment

1) Endoscopic mucosal resection (EMR)

The development and spread of EMR has changed the face of the treatment of esophageal cancer and at the same time has promoted a great advance in diagnostic methods toward early detection, especially the detection of mucosal cancer.

Whether EMR is indicated in a particular case is determined by two factors: the characteristics of the lesion and the required technique. The characteristics of the lesion include the depth of invasion and the presence of lymph node metastasis, while the technique refers to whether the lesion can be certainly and safely removed. With regard to the lesion characteristics, an invasion depth of m1–m2 (mucosal epithelium and lamina propria mucosae), a tumor diameter of less than 3 cm, a lesion measuring 2/3 or less of the esophageal circumference, and the presence of 3–4 lesions are considered to be good indications for EMR. Since radical surgery for esophageal cancer is highly invasive and greatly affects postoperative QOL, the indications for EMR have been expanded to include tumors with an invasion depth of m3 (lamina muscularis mucosae) or sm1 (surface of submucosa), a diameter of up to about 5 cm, and those that have spread over the entire circumference of the esophagus.

EMR techniques currently used include the EEMR-tube (endoscopic esophageal mucosal resection-tube) method (Fig. 3), the strip biopsy method, and the EMR-C method. We have used the EEMR-tube method in 497 cases or 736 lesions as of December 2000 (Table 2). We experienced various complications including esophageal perforation in 5 cases, arterial bleeding in 16 cases, and esophageal stenosis in 9 cases, but none of the patients required surgical treatment and no operative or in-hospital deaths occurred. Local recurrence and chronologically different multiple cancers were observed in 2.4% and 8.3% of the cases, respectively; most of these patients underwent a second endoscopic treatment. Efforts have been made to devise techniques that will enable the indications for EMR to be expanded to include tumors in difficult-to-operate regions, such as the entrance of the esophagus, the back of the esophagus, the exclusion toward the left main bronchus, and the esophagogastric junction. To date, more than 1000 patients have undergone EMR in Japan.

2) Radical surgery

Since almost half of the cases of submucosal

Figure 3 EEMR-tube method
a. Iodine staining of the lesion. b. Lesion confirmation and injection of saline into the submucosal layer. c. Expand the snare on the lesion. d. Aspirate the mucosa into the tube using endoscopic suction. e. Squeeze the snare and resect the lesion using high-frequency current. f. Collect the mucosa containing the lesion for histopathological examination.
cancer are accompanied by lymph node metastasis, radical surgery with lymphadenectomy in three fields (neck, chest, and abdomen) must be performed in patients with lesions that infiltrate into the submucosa or deeper, since the first lymph node metastasis from esophageal cancer can develop in a wide area, from neck to abdomen. Nowadays, radical surgery with an expanded lymphadenectomy can be safely performed, with the operative death rate as low as 1.5%. As the risk of undergoing this surgical procedure has stabilized, the outcome has improved, with the 5-year survival rate now exceeding 60%.

Some attempts have been made to perform this surgery using a thoracoscope and a laparoscope. Kawahara, Inoue, Kohno, Akashi, Ozawa and other physicians have started to use this method in Japan, and the procedure is becoming well known. The technique reduces the effects of the procedure on breathing activity and is effective for preventing respiratory complications. Intrathoracic lymphadenectomies as well as thoracotomies can both be performed using a thoracoscope. Gastric tube reconstruction and intraabdominal lymphadenectomies can be performed using a laparoscope.

### 3) Chemo and Radiation Therapy

The main chemotherapeutic agents used for the treatment of esophageal cancer include cisplatin (CDDP), fluorouracil (5-FU), and calcium folinate (Leucovorin®). The chemotherapy regimen typically consists of 50–100 mg/m²/day of CDDP for 1 day and 500–1,000 mg/m²/day of 5-FU for 5 days; this regimen plus 10 mg/body of Leucovorin® and a regimen consisting of the continuous administration of low dosages of CDDP (10mg/body) and 5-FU (250mg/body) combined with concurrent radiation therapy (5 Gy/day×[5 days/week]×2 weeks) are currently used. Recently 2 Gy/day×[5 days/week]×6 weeks of irradiation for cervix, mediastinum and lesser curvature of

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**Table 2: Outcome of Endoscopic Esophageal Mucosal Resection**

<table>
<thead>
<tr>
<th></th>
<th>Total number of cases</th>
<th>Total number of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esophageal cancer</strong></td>
<td>497 cases</td>
<td>736 lesions</td>
</tr>
<tr>
<td>m1, m2</td>
<td>409 cases</td>
<td>623 lesions</td>
</tr>
<tr>
<td>m3, sm1</td>
<td>299</td>
<td>451</td>
</tr>
<tr>
<td>sm2, sm3</td>
<td>94</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td><strong>Dysplasia</strong></td>
<td>60 cases</td>
<td>78 lesions</td>
</tr>
<tr>
<td><strong>Benign lesion</strong></td>
<td>28 cases</td>
<td>35 lesions</td>
</tr>
<tr>
<td><strong>Death due to surgical operation</strong></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Death during hospitalization</strong></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal perforation</td>
<td>5 cases (0.7)</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Arterial bleeding</td>
<td>16 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Varicose bleeding</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Esophageal stenosis</td>
<td>9 (1.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Cases requiring surgery because of complications</strong></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Cases requiring surgery because of abnormal pathological findings</strong></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>Local recurrence</strong></td>
<td>15 lesions (2.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Chronologically different multiple cancers</strong></td>
<td>34 cases (8.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Five-year survival rate</strong></td>
<td>97.9%</td>
<td></td>
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</table>

(Keio Cancer Center, Tokai University; as of December 2000)
stomach combining with 2 courses of chemotherapy, 50 mg/m²/day of CDDP for 1 day and 500 mg/m²/day of 5-FU for 5 days are performed in some institutions in Japan.

REFERENCES


