

Present Status of Esophageal Cancer and its Treatment in Japan

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Epidemiology

In 2001, 10,677 people died of esophageal cancer in Japan, 9,026 were men and 1,651 women—demonstrating a male-to-female ratio of 5.5. The number of esophageal cancer deaths have been increasing, correlated with the aging of Japan's population. During the last two decades, the number of esophageal cancer deaths for men has increased by two-fold, and that for women 1.3-fold. The overall death rate in the general population from esophageal cancer in 2001 was 14.7 per 100,000 for men and 2.6 for women. This rate for Japanese men was double that for men in the USA or Western European countries, whilst that for Japanese women was similar to that for women in those countries.¹⁾

In western countries, the incidence of adenocarcinoma in Barrett's esophagus has been increasing, and has become approximately equal to that of squamous cell carcinoma (SCC) among cases of esophageal cancer.²⁾ According to the Comprehensive Registry of Esophageal Cancer in Japan published by the Japanese Society for Esophageal Diseases, the incidence of adenocarcinoma was 4.4% (32/734) in 1978,³⁾ 1.2% (16/1,382) in 1988,⁴⁾ and 1.6% (47/2,991) in 1998.⁵⁾ Although these incidence rates in Japan might include cardia cancer or gastric cancer with esophageal invasion, there has been no tendency towards any increase in the incidence of adenocarcinoma in Japan.

What kinds of treatment have been performed for Japanese patients with esophageal cancer? According to the Comprehensive Registry of Esophageal Cancer in Japan,⁵⁾ among 2,953 patients registered during 1999, 1,817 (61.5%) underwent esophagectomy, 231 (7.8%) underwent endoscopic resection, 840 (28.4%) did not undergo surgery but received chemotherapy and/or radiotherapy, and the other 65 (2.2%) underwent palliative surgery such

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as bypass. On the other hand, according to the Annual Report by the Japanese Association for Thoracic Surgery,⁶⁾ 7,440 patients with an esophageal cancer have been treated in designated hospitals during 2001. Of these, 4,794 (64.4%) underwent esophagectomy, 727 (9.8%) underwent endoscopic resection, and 1,919 (25.8%) received non-surgical therapy. The rates in these two registries were similar, probably due to the data having been collated from departments of surgery. Other esophageal patients may have been treated non-surgically and not seen at a department of surgery, in which case they were not enumerated in these registries. If we assume that all the unregistered patients were treated non-surgically, then the overall rate of surgical treatment for esophageal cancer in Japan would fall to less than 50%. According to the Comprehensive Registry of Esophageal Cancer in Japan, the resection rate was 61.0% (751/1,231) in 1978,³⁾ 78.3% (1,355/1,731) in 1988,⁴⁾ and 60.6% (1,883/3,109) in 1998.⁵⁾ The resection rate of esophageal cancer appears to have increased in the 1980s and early 1990s, and then subsequently to decrease.

Japan Esophageal Society

During the last several years, a major change has occurred for esophagologists in Japan. In 1999, the 9th edition of the Guidelines for Clinical and Pathologic Studies on Carcinoma in the Esophagus was published by the Japanese Society for Esophageal Diseases.⁷⁾ In this, the terminology and the definitions of regional lymph nodes of esophageal cancer, and lymph node grading—the grading of the clinical importance for each lymph node cluster—were described based on the results from three-field lymphadenectomy. The most important determination was the consensus among almost all Japanese surgeons concerning the cervical and upper mediastinal lymph nodes: in particular, the recurrent nerve chain nodes were defined as regional. The English version of the Guidelines for Clinical and Pathologic Studies on Carcinoma in the Esophagus was published in 2001.⁸⁾ In 2002, the Guidelines for Esophageal Cancer Treatment was also pub-

lished.⁹⁾ In these guidelines, the standard treatments at present were described according to each identifiable type and sub-type of esophageal cancer. In 2003, the Japanese Society for Esophageal Diseases changed its name to the Japan Esophageal Society, and the first volume of its official journal—The Esophagus—was published.

Superficial Esophageal Cancer

For superficial cancer, the sub-type classification of the depth of invasion has commonly been used in Japan.¹⁰⁾ The indication of endoscopic mucosal resection (EMR) is expanding from m1-m2 cancer to m3-sm1 cancer. There is, however, a controversy over which therapy—from among EMR, surgery, or chemoradiotherapy—should be chosen for m3-sm1 esophageal cancer. The most important consideration in deciding the optimal treatment for esophageal cancers is the relative risk to metastasis in the lymph nodes. Among m3-sm1 esophageal cancers, from 7% to 16% have been reported to have had metastasis in the lymph nodes. For borderline cases concerning the depth of invasion or lymph node metastasis, diagnostic EMR has been effective. The pathological findings such as lymph vessel and vascular invasion (ly/v), diffuse infiltration pattern (inf γ), and poorly-differentiated SCC in the EMR specimen are considered to be indicators of lymph node metastasis.¹¹⁾ The new technique of endoscopic resection of a superficial esophageal cancer—endoscopic submucosal dissection (ESD)—has been introduced. The specimen obtained by ESD is consequentially larger and en bloc, compared to that obtained by EMR, and pathological diagnosis is thus more accurate than by EMR.¹²⁾ The esophageal cancer study group of the Japan Clinical Oncology Group (JCOG) reported the results after the phase II trial of chemoradiotherapy (cisplatin [CDDP]/5-fluorouracil [5-FU]) for T1N0M0 Stage I esophageal cancer (JCOG 9708). The complete response (CR) rate was 96%, and the 2-year survival rate was 93%.¹³⁾ These results were similar to those after esophagectomy. Surgery therefore seems to be unnecessary for Stage I esophageal cancer, after it has been determined there is no lymph node metastasis.

Sentinel Node Navigation Surgery

Sentinel node navigation surgery using ⁹⁹Tc-Sn colloid was originally developed and applied for malignant melanoma or breast cancer. This has now been introduced in treatment for esophageal cancer in order to reduce the

extent of lymphadenectomy, and to decide the radiation field. Clinical investigations have been performed in several institutions in Japan. Preliminary findings have indicated a consensus that sentinel node navigation surgery can be effective for superficial esophageal cancer, while it is inapplicable for advanced esophageal cancers because the sentinel nodes are not clear in advanced esophageal cancers.¹⁴⁾ The overall efficacy of sentinel node navigation surgery for esophageal cancers is therefore still under investigation at present.

Micrometastasis in the Lymph Nodes

The pathological examination of micrometastasis (MM) in the lymph nodes using immunohistochemical staining with anticytokeratin antibody (AE1/AE3) has been introduced in esophageal cancers. Some have reported that the presence of MM was a prognostic indicator for esophageal cancers,^{15,16)} while others have reported that it was not.^{17,18)} Some authors distinguished MM from tumor cell microinvolvement (TCM) or cytokeratin deposit (CD), and have proposed that MM was prognostically equivalent to metastasis on hematoxylin-eosin staining, whereas TCM and CD were not prognostic indicators.^{15,16)} MM has also been examined using reverse transcriptase-polymerase chain reaction (RT-PCR) assay to detect carcinoembryonic antigen (CEA) messenger ribonucleic acid (mRNA). It has been reported that the sensitivity of RT-PCR to MM was several times greater than that of immunohistochemical staining.¹⁹⁾ The determination of lymph node micrometastasis using real-time rapid RT-PCR assay has been applied to decision-making for cervical lymph node dissection during esophageal cancer surgery.²⁰⁾ Namely, when metastasis to the recurrent nerve nodes is found by pathological examination or genetic analysis—RT-PCR assay, the dissection of the cervical lymph nodes is added, while it is omitted when it is not found.

Thoracoscopic Esophagectomy

In 1966, Akaishi et al. reported thoracoscopic esophagectomy with radical lymphadenectomy.²¹⁾ This was the first report of thoracoscopic esophagectomy with lymphadenectomy in the Japanese fashion. Now, such a procedure is performed in many Japanese institutions. Several types of thoracoscope and laparoscope procedures have since been designed. In the thoracic procedures, there are complete thoracoscopic esophagectomy,²¹⁾ video-as-

sisted thoracoscopic surgery (VATS),²²⁾ and hand-assisted thoracoscopic surgery (HATS).²³⁾ In the abdominal procedure, there are complete laparoscopic surgery and hand-assisted laparoscopic surgery (HALS). There is a consensus over the lesser invasiveness of thoracoscopic or laparoscopic surgery because of less wound pain, earlier recovery of pulmonary function, less impact on the lung, and other factors. There is, however, no consensus over whether radical lymphadenectomy can be performed by thoracoscopic surgery. Surgeons who support thoracoscopic esophagectomy maintain that the survival was not different between after thoracoscopic esophagectomy and after open thoracic esophagectomy.²²⁾ There has not yet been any well-planned trial comparing the short- and long-term outcomes between thoracoscopic esophagectomy and open thoracic esophagectomy. A randomized controlled trial is needed.

Adjuvant Therapy

Adjuvant therapy for potentially-resectable esophageal cancer in Japan has differed from that in western countries. In western countries, the mainstay has been preoperative treatment–neoadjuvant therapy. There still remains controversy over the efficacy of neoadjuvant chemotherapy, although many randomized controlled trials have been performed comparing chemotherapy followed by surgery versus surgery alone.²⁴⁾ On the other hand, the mainstay of adjuvant therapy in Japan has been postoperative treatment–adjuvant chemotherapy. There still remains controversy over the efficacy of adjuvant chemotherapy. There was no difference in the survival rate between surgery followed by chemotherapy and surgery alone, according to the randomized trial of the Japan Clinical Oncology Group (JCOG 9204).²⁵⁾ However, they have found a benefit from adjuvant chemotherapy in the disease-free survival rate mainly for patients with metastasis in the lymph nodes. Adjuvant chemotherapy using CDDP/5-FU seems to have a preventive efficacy against recurrence. The JCOG is currently performing a randomized trial comparing preoperative chemotherapy with postoperative chemotherapy (JCOG 9907).

Definitive Chemoradiotherapy

The clinical oncology group of the National Cancer Center Hospital East, Japan, has reported that definitive chemoradiotherapy has obtained the same survival for a potentially-resectable (Stages II/III) esophageal cancer as

esophagectomy, 51% after surgery versus 46% after definitive chemoradiotherapy, in 5-year survival rate.²⁶⁾ The phase II trial on definitive chemoradiotherapy for Stages II/III esophageal cancers (JCOG 9906) is now underway by the clinical oncology group for gastrointestinal cancer in JCOG. They have reported a preliminary CR rate of 65% (24/37).²⁷⁾ An increasing number of oncologists and radiologists in Japan now recognize the efficacy of definitive chemoradiotherapy without surgery for potentially-resectable esophageal cancer. The oncology group in the National Cancer Center Hospital however considers that definitive chemoradiotherapy leaves some risk to incomplete treatment and to later recurrence—more so in the long-term. They also emphasize that surgeons have to be more alert to the possible need for salvage surgery.²⁷⁾ After definitive chemoradiotherapy, meticulous follow-up examination is necessary to find any recurrence. Recently, positron emission tomography (PET) using ¹⁸F-fluorodeoxyglucose (FDG) has been used to evaluate the efficacy of chemoradiotherapy.²⁸⁾ On distinguishing CR from partial response (PR) and on detecting small recurrence, much more clinical experience is needed. Recently, randomized controlled trials have been performed in Western Europe to compare the survival between chemoradiotherapy followed by surgery and chemoradiotherapy alone. The outcome of two trials have gained wide notice, because they showed no difference in the survival rates between both groups.^{29,30)} We need a similar phase III trial in Japan.

Salvage Surgery

More than 50% of patients who have undergone definitive chemoradiotherapy have shown a residual tumor or recurrence after complete response. Esophagectomy after definitive chemoradiotherapy–salvage surgery—therefore is becoming more common in Japan. There is a consensus over the higher risk to postoperative complications such as pulmonary complications, infection and others after salvage surgery than after usual surgery,³¹⁾ while there is not yet a consensus over the definition, indication, surgical procedures, and the efficacy of salvage surgery. These are the current issues of concern raised by oncologists and radiologists.

The present status of esophageal cancer and its treatment in Japan is surveyed. Some novel movements such as gene therapy using p53 and new anticancer agents are not described here. Thoracoscopic and laparoscopic surgeries will become more common. Education and licens-

ing for endoscopic surgery will become an increasingly important issue for esophageal surgeons. In particular, a confrontation between esophagectomy—surgeons—and definitive chemoradiotherapy—oncologists/radiologists—for Stages II/III esophageal cancers will become the most important issue during the next decade.

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