Endoscopic Treatment for Early Esophageal Cancer

Sang Gyun Kim
Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea

Introduction

Early detection of esophageal cancer is difficult because the diagnosis is usually made in advanced stage. Although the national cancer screening program has recommended upper endoscopy or barium study biennially for normal population with the age over 40 years old in Korea, early detection and improvement of treatment outcome or survival are not yet definite in esophageal cancer unlike gastric cancer. Nevertheless, the improvement of endoscopic treatment and widespread upper endoscopy have enabled the endoscopic treatment for early esophageal cancer and expanded the indication of endoscopic treatment.

In this review, the indication of endoscopic treatment, method of endoscopic resection, and clinical outcome of endoscopic resection for early esophageal cancer would be discussed.

Definition of early esophageal cancer

Early gastric cancer is defined as a cancer confined to mucosa or submucosa irrespective of lymph node metastasis because the clinical prognosis of early gastric cancer is quite different from that of advanced gastric cancer. Likewise, the prognosis of early esophageal cancer should be different from that of advanced esophageal cancer to define the early esophageal cancer.

Although the cancer confined to mucosa or submucosa has been defined as a superficial esophageal cancer irrespective of lymph node metastasis, the prognosis has been variable according to the depth of tumor invasion unlike early gastric cancer.\textsuperscript{1,2} Although the lymph node metastasis is rare in the tumor confined epithelial layer (m1) or lamina propria (m2), lymph node metastasis is found in 10-21\% of tumor invasion to muscularis mucosa (m3), and more than in 30\% of submucosal cancer, which have poor prognosis compared with the tumor confined to epithelial layer or lamina propria.\textsuperscript{3-7} To be differentiated from advanced esophageal cancer in terms of prognosis, early esophageal cancer should be defined as 1) a tumor confined to epithelial layer or lamina propria among superficial esophageal cancer, 2) without the evidence of lymph node metastasis, 3) which can be a candidate of endoscopic resection. The 5-year survival rate of early esophageal cancer after curative resection has known to be over 95\%, whereas fall under 50 - 85\% in cases with a tumor invasion over submucosal layer or lymph node metastasis.\textsuperscript{8,9}

Indication of endoscopic resection for early esophageal cancer

The risk factors of lymph node metastasis in early gastric cancer are known to be tumor size, depth of tumor invasion, differentiation, and lymphovascular invasion, which play a role in esophageal cancer with same manner.

Tumor size can be measured by conventional endoscopy, chromoendoscopy, magnifying endoscopy, or narrow band imaging, and have higher risk of lymph node metastasis in cases with size over 2 cm.\textsuperscript{7} Also, undifferentiated histology and
lymphovascular tumor invasion have been considered as independent risk factors.\textsuperscript{10,11} Depth of tumor invasion can be also estimated by conventional endoscopy, chromoendoscopy, magnifying endoscopy, or narrow band imaging, but usually has a discrepancy with intra- and inter-observer variation.\textsuperscript{12,13}

Endoscopic ultrasonography (EUS) has been a most valuable method in the estimation of depth of tumor invasion in esophageal cancer. In early esophageal cancer, a miniature probe with high frequency over 12 MHz is usually used to estimate the depth of tumor invasion. The diagnostic accuracy was reported to be 81% in m1 and m2, 60% in m3 and sm1, 87% in sm2 and sm3, and 93% in the differentiation of m1 and m2 which could be a candidate of endoscopic resection from m3. The diagnostic accuracy of N staging was 69% in N0, and 89% in N1.\textsuperscript{14} EUS-guided fine needle aspiration can be used for histologic confirmation of regional lymph node metastasis, but it has a difficulty in terms of trans-tumoral approach.

Although computerized tomography (CT) has showed lower diagnostic accuracy in T staging and comparable N staging compared with EUS, positron emission tomography (PET) may be complementary in the improvement of diagnostic accuracy. In a study, diagnostic accuracy of N staging was 81% in EUS, 69% in CT, and 56% in PET.\textsuperscript{15}

In terms of risk factors, the indication of endoscopic resection of early esophageal cancer is 1) tumor size not more than 2 cm, 2) differentiated histology, 3) tumor confined to m1 or m2, and 4) no evidence of lymph node metastasis in staging work-up.

**Endoscopic resection for early esophageal cancer**

Endoscopic resection has been performed by conventional endoscopic mucosal resection (EMR), in which the lesion is changed to polypoid lesion by submucosal injection of mixture of normal saline and diluted epinephrine, and resected by grasper forcep and electrosurgical snare through 2-channel endoscope. Although the conventional EMR has been expanded into EMR-C (cap), EMR-P (precutting), EMR-L (ligation) to overcome many disadvantages, EMR method has had limitations in terms of low rate of complete resection in cases with large size or submucosal fibrosis.

To overcome the disadvantages of previous methods, endoscopic submucosal dissection (ESD) has been developed in late 1990’s. In ESD, circumferential incision and direct dissection of submucosal layer of the lesion has been possible with various knives, which has enabled en-bloc complete resection irrespective of tumor size or submucosal fibrosis.

Lugol’s solution is useful in determining the exact extent of the lesion prior to endoscopic resection. An 1% diluted solution is usually sprayed on the entire esophagus, and the abnormal neoplastic epithelium is not stained and in contrast to normal epithelium in a few minutes by non-binding with iodine in Lugol’s solution.

After spray of Lugol’s solution, marking around the lesion is made with electrocoagulation or argon plasma coagulation, and submucosal injection is made with various solutions such as normal saline with epinephrine, hypertonic saline, glycerol or hyaluronic acid to make submucosal cushion. The circumferential incision is made with various knives around the marking, and direct submucosal dissection is performed. Selection of knife is dependent on the lesion by each characteristic. Although most procedure is performed with one knife, various knives can be utilized for accurate and safe procedure by case by case. Decision factors of knife are location, morphology, size of the lesion and type of procedure. But most of all, familiarity to operator is most important. That is, most important factor of selection of knife is easiness and familiarity to operator.

Esophagus has a higher risk of perforation during procedure than stomach by a thinner wall and the absence of serosal barrier, and pneumomediastinum and/or subcutaneous emphysema can occur despite the absence of overt perforation by air leakage through proper muscle and adventitial layer. Although the supportive management can be made with oxygen
apply, intravenous nutrition and broad spectrum prophylactic antibiotics in case of pneumomediastinum and/or subcutaneous emphysema without overt perforation and the deterioration of vital sign, emergent surgery can be inevitable in case of overt perforation with a high risk of progression to mediastinitis or mediastinal abscess which has a high mortality rate.

Clinical outcome of endoscopic resection for early esophageal cancer

In conventional EMR era, clinical outcomes such as en bloc or curative resection were unsatisfactory especially in the lesion with larger size than 2 cm in diameter or submucosal fibrosis. However, with the improvements of instruments and treatment techniques, ESD has enabled en bloc and curative resection in almost all cases irrespective of tumor size, location, shape or submucosal fibrosis. In pathologic mapping, tumor size, differentiation, depth of tumor invasion, tumor involvement in resection margin, and presence of lymphovascular invasion should be evaluated. In cases with tumor involvement in lateral resection margin, additional surgical resection should be considered with the risk of residual tumor in remained esophagus. However, false positive tumor involvement can occur because of cautery effect of lateral resection margin, and any residual tumor cannot found in follow-up endoscopy especially in the cases with minimal tumor invasion to lateral resection margin.

If the mapping shows larger tumor size than 2 cm in diameter, undifferentiated histology, tumor invasion to the muscularis mucosa (m3) or more, or lymphovascular tumor invasion despite complete resection with margin free from tumor, additional surgical resection or adjuvant treatment should be considered with the risk of lymph node metastasis. However, additional treatment option may be held with minimal risk of lymph node metastasis in cases with curative resection for m3 cancer.

Conclusions

With the progress of endoscopic diagnosis and treatment, early diagnosis and minimally-invasive treatment have been increased for esophageal cancer. Technical and instrumental improvements of ESD have enabled curative resection for early esophageal cancer which was beyond the indication of endoscopic resection in the era of conventional EMR. In future, the improvement of quality of life as well as survival is anticipated by early detection and minimally-invasive endoscopic treatment of esophageal cancer in the same manner with EGC.

References