Editorial

An Appropriate Esophagectomy for Esophageal Cancer: A Lack of Evidence and a Growing Disparity between Western and Eastern Standards

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Definitive chemoradiotherapy has been demonstrated to offer a chance of cure for esophageal cancer as often as a radical esophagectomy.[1] However, it is generally accepted that an esophagectomy remains the mainstay of treatment for patients with resectable esophageal cancer, while chemoradiotherapy is the standard for patients with medically inoperable or surgically unresectable esophageal cancer. The mortality rates and the 5-year survival rates after an esophagectomy were 29% and 4%, respectively, in an early extensive reviews involving 122 English papers on esophageal cancer surgery published between 1960 and 1979.[2] The respective rates have improved to 6.7% and 27.9% in the most recent systematic reviews involving 312 papers published between 1990 and 2000.[3] The overall survival at 5 years was 36.1% after esophagectomy in 11,642 patients between 1988 and 1997 in Japan.[4]

A 3-field lymphadenectomy involving the 3 anatomical compartments of the neck, mediastinum, and abdomen was introduced as an important component of a curative esophageal resection in the early 1980s in Japan, and has been reported to be effective for improving not only the staging accuracy, but also the long-term survival in patients with esophageal cancer, with the average 5-year survival rate being 40 to 60%.[5] At present, 63% of all Japanese patients with esophageal cancer undergo an esophagectomy. Of these patients undergoing surgery, a 3-field and a conventional 2-field lymphadenectomy is performed in 35% and 33%, respectively.[5] Alternatively, a transhiatal esophagectomy without a systematic lymphadenectomy has become one of the preferred types of surgery for patients with esophageal cancer in Western countries.

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Although an esophagectomy remains the standard treatment of esophageal cancer and the majority of patients with this disease are still treated by this modality, there is little evidence concerning the adequate extent of an esophageal resection. Only 5 randomized clinical trials (RCTs) have been conducted so far: 3 studies comparing a transthoracic esophagectomy to a transhiatal esophagectomy, and 2 studies comparing a 3-field lymphadenectomy to a 2-field lymphadenectomy.[5] The positive impact of extended surgery on patient survival was detected in only a single RCT reported by Kato et al.[6] The superiority of a thransthoracic esophagectomy with 2-field lymphadenectomy over transhiatal esophagectomy could not be shown in Hulscher's study which recruited 220 patients: with a disease free survival at 5 years of 39% after a transthoracic esophagectomy vs. 27% after a transhiatal esophagectomy.[7] However, this negative result is considered to be attributable to the under-powered design of this RCT.

Adjuvant chemotherapy or radiotherapy either alone or in combination has frequently been performed either preoperatively or postoperatively in patients with esophageal cancer to improve the long-term survival with the aim of sterilizing occult micrometastasis in distant organs. Such adjuvant treatments have been performed in 30 to 40% of patients undergoing an esophagectomy in Japan.[4] However, the possible survival impact, if any, of adjuvant chemotherapy in comparison to surgery alone is most likely small because none of the 2 RCTs comparing the patients receiving postoperative adjuvant chemotherapy with those undergoing surgery alone failed to show any significant difference in the overall survival; only one of 7 RCTs conducted so far could detect any survival benefit of neoadjuvant, i.e. preoperative adjuvant chemotherapy in patients undergoing an esophagectomy.[5]

Recently, neoadjuvant chemoradiotherapy is increasingly performed for patients undergoing esophagectomy for esophageal cancer, particularly in Western countries in an attempt to improve both the local-regional control and long-term survival. The presence or absence of a sur-

vival benefit of neoadjuvant chemoradiotherapy over surgery alone has been tested in 8 RCTs so far.[5,8,9] Only one of the 8 RCTs demonstrated a positive survival impact of neoadjuvant chemoradiotherapy,[10] but this study was later criticized because the 3-year survival rate of patients randomized to surgery alone was much poorer than those in any other RCTs, thus casting doubt as to the reliability of this study. Therefore, no evidence indicating a survival benefit of neoadjuvant chemoradiotherapy has yet been shown in patients undergoing an esophagectomy for esophageal cancer.

Undoubtedly, the majority of surgeons believe that not only the extent of surgery but also the quality of a tumor resection strongly influences the postoperative outcome. An R0 resection, namely, both a macroscopically and microscopically complete removal of the tumor has been stressed to offer the best chance for a cure of esophageal cancer. However, how to achieve an R0 esophagectomy has not yet been standardized. Since most types of metastatic disease tend to be microscopic, a systematic lymphadenectomy of the regional lymph nodes is thus indispensable for an R0 resection of potentially curable esophageal cancer. Moreover, the standardization of an R0 resection is crucial for any RCTs in which an esophagectomy is one of the major treatment modalities for patients with esophageal cancer, because possible quality variations in an esophagectomy may interfere with the results of both control and investigational treatment modalities, thereby interfering with the reliability of such kind of RCTs. In fact, various types of esophagectomies have been performed in the above-mentioned RCTs when comparing adjuvant therapy to surgery alone, and in most such surgeries the extent and quality of the esophagectomy was not standardized.

During the last few decades, adenocarcinoma of the esophagus has shown a rapid increase in incidence in Western countries, while squamous cell carcinoma remains the predominant histology in Eastern countries. The former carcinoma is mostly located in the distal esophagus, whereas the latter carcinoma predominantly affects the mid-esophagus. The difference in tumor location may lead to the different patterns of lymphatic spread of the disease. Some studies have shown that mid-esophageal cancers frequently metastasize to the cervical, mediastinal, and abdominal lymph nodes, even in cases of potentially curable disease, while lower esophageal cancers predominantly metastasize to the lower mediastinal and abdominal lymph nodes.[11] These different patterns of lymphatic spread, in addition to the possible difference in tumor biology between esophageal adenocarcinoma and squamous cell carcinoma, may thus suggest a different extent of resection for the 2 tumors. Consequently, the treatment results reported from Western countries may no longer be applicable to the management of patients with esophageal cancer in Eastern countries due to the growing difference in the proportion of the 2 types of esophageal tumors between Western and Eastern countries. In fact, most RCTs recently conducted in Western countries in which an esophagectomy is one of the principal treatment modalities for esophageal cancer, have included either patients with adenocarcinoma alone or patients with adenocarcinoma in a large proportion of patients.

In conclusion, the standardization of resection quality is essential for evaluating the validity of an esophagectomy either with or without adjuvant treatment in patients with esophageal cancer. Further adequately powered large RCTs are thus needed to determine the appropriate extent of an R0 esophagectomy for esophageal cancer after stratification based on tumor histology.

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