Editorial

Surgery for limited-stage primary small cell carcinoma of the esophagus: is it feasible and for whom is it indicated?

Hirotoshi Kikuchi, Hiroya Takeuchi

Department of Surgery, Hamamatsu University School of Medicine, Hamamatsu, Japan

Correspondence to: Hiroya Takeuchi, MD, PhD. Department of Surgery, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan. Email: takeuchi@hama-med.ac.jp.

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Small cell carcinoma is a highly malignant cancer that most commonly arises in the lung. Small cell carcinoma arising from outside the lungs was first described by Duguid and Kennedy in 1930 and is referred to as extrapulmonary small cell carcinoma (EPSCC) (1). EPSCC is a rare neoplasm, accounting for 2% to 5% of all small cell carcinomas and 0.1% to 0.4% of all cancers, and it has been seen in nearly every organ system (2). EPSCC most commonly arises from the gastrointestinal tract, and primary small cell gastrointestinal carcinoma accounts for 0.1% to 1.0% of gastrointestinal cancers. Most primary small cell gastrointestinal carcinomas are derived from the esophagus.

Primary small cell carcinoma of the esophagus (PSCCE) was first described by McKeown in 1952 (3) and reportedly accounts for 0.5% to 2.8% of all esophageal cancers (4-7). PSCCE is characterized as a highly malignant cancer that often metastasizes early in its development and has a poor prognosis. However, because of its rarity, the clinical entity of PSCCE has not yet been clarified. To date, no randomized controlled trials have been performed to evaluate the treatment or recommended standard treatments of PSCCE. Because of its malignant nature, PSCCE is often diagnosed as an extensive disease involving a tumor outside locoregional boundaries; however, most cases of PSCCE are reportedly found as a limited disease involving a tumor confined within a localized anatomic region with or without regional lymph node metastases (4-8). No randomized controlled trials of PSCCE treatment have been performed, and it is difficult to draw conclusions from reported clinical series alone; therefore, treatment strategies for limited-stage PSCCE should be investigated by performing retrospective analyses with a relatively large number of cases.

Several retrospective studies have been conducted to analyze the prognostic factors of PSCCE and determine the optimal treatment strategies for limited-stage PSCCE. Situ *et al.* retrospectively analyzed 44 patients with limited-stage PSCCE who underwent esophagectomy with lymphadenectomy at the Cancer Center of Sun Yat-sen University in China to evaluate the significance of surgery for the treatment of limited-stage PSCCE. Because the survival analysis confirmed that regional lymph node metastasis was an independent prognostic factor, the authors concluded that radical esophagectomy with extended lymphadenectomy should be considered as the primary treatment for patients with limited-stage PSCCE (9).

Chen *et al.* reviewed 211 patients with PSCCE from 3 clinical databases of the Sun Yat-sen University Cancer Center, Peking Union Cancer Hospital and Shantou Cancer Hospital in China. Of these 211 patients, 148 (70.1%) had limited-stage PSCCE, and 85% of patients with stage I/II disease underwent surgery and showed improved survival. Because chemotherapy did not further improve survival in the analysis, the authors concluded that surgical procedures alone can be recommended for patients with stage I/IIA PSCCE and that chemotherapy should be the

main treatment approach for patients with stage IIB/III disease (8).

In a study by Wong *et al.*, the National Cancer Database was utilized to analyze the clinical features, treatment, and survival of 583 patients with PSCCE in a large, population-based dataset in the United States. Unlike patients in the above-mentioned Chinese database, most patients in the study by Wong *et al.* had stage IV disease (41.7%). Esophagectomy was associated with the best overall survival (OS) for patients with localized (node-negative) disease compared with chemotherapy alone or chemoradiation. Multivariate analysis revealed that esophagectomy was associated with improved OS compared with chemoradiation. The authors concluded that either esophagectomy or chemoradiation as part of multimodal treatment appear to improve OS for selected patients with nonmetastatic disease.

In contrast, some reports have suggested that PSCCE is a systemic disease and recommended systemic therapies for the treatment of all limited-stage PSCCE. Lv *et al.* retrospectively analyzed the clinical records of 126 patients with PSCCE that was diagnosed histologically and treated at the Cancer Hospital of Peking Union Medical College and the Chinese Academy of Medical Sciences in China. Of these 126 patients, 85 had limited-stage PSCCE, 5 underwent explorative resection, and 79 underwent esophagectomy with two-field lymph node dissection. Because the tumor stage, length of the primary lesion, and chemotherapy (but not surgery) were independent prognostic factors in the multivariate analysis, the authors concluded that systemic therapy based on chemotherapy with radiotherapy is recommended. Other studies from the Memorial Sloan-Kettering Cancer Center and Roswell Park Cancer Institute in the United States have also supported the use of chemotherapy or radiotherapy even for patients with early-stage PSCCE (4,6).

In a recent study, Xu *et al.* retrospectively analyzed the data of 152 consecutive patients with limited-stage PSCCE who received treatment at the Affiliated Cancer Hospital of Zhengzhou University in China (10). In this study, univariate and multivariate analyses showed that the treatment modality and N stage were independent prognostic factors (P=0.034 and P=0.002, respectively). In a subset analysis, 38 patients with stage I/IIA PSCCE who underwent surgery alone exhibited better survival than those who received nonsurgical treatment (P=0.031), and postoperative adjuvant therapy did not improve OS or disease-free survival. In a subset analysis of 39 patients with stage IIB PSCCE, there were no significant differences in OS among treatment courses with or without surgery and chemotherapy. The OS rate of 75 patients with stage III PSCCE who underwent neoadjuvant chemotherapy was significantly better than that of patients who underwent surgery alone or received nonsurgical treatment (P=0.021 and P=0.026, respectively). Based on their results, the authors recommended radical esophagectomy as the primary treatment for patients with stage I/IIA PSCCE and neoadjuvant chemotherapy followed by esophagectomy as an effective treatment option for stage III PSCCE. This study enrolled the largest number of patients among previous reports on limited-stage PSCCE and has thus impacted the treatment strategies for PSCCE. However, the study had some limitations. For example, it was a retrospective review of cases at a single institute, and selection bias for the treatment course may have existed. A previous report indicated that the demographic profile of patients with PSCCE in China seems quite different from that in other parts of the world, with a higher proportion of limited-stage disease in Chinese patients (11). In the study by Xu *et al.*, the histological diagnosis was pure SCCE in 66.4% of tumor specimens, whereas 11.7% of the specimens were combined with squamous cell carcinoma, 13.7% were combined with adenocarcinoma, and 8.2% were combined with adenosquamous carcinoma (10). Some differences in histological types that affect the response to chemotherapy may exist among studies, while no standard chemotherapy was established for PSCCE. Immunohistochemical information was available for only 95 (62.5%) patients, some of whom underwent staining for common neuroendocrine markers [chromogranin A, synaptophysin, neuron-specific enolase, lymphocyte antigen 56 (CD56), cytokeratin, and Ki-61] (10). The World Health Organization definition of neuroendocrine carcinoma (NEC), which is categorized into two morphological types (small and large cell type), includes positivity for endocrine markers such as chromogranin A, synaptophysin, and CD56. A Ki67 or mitotic index of ≥20% is also necessary for diagnosing NEC. Although the small cell type of NEC is more frequent (approximately 90% of all cases) and most cases formerly recognized as PSCCE were included, immunohistochemistry appears helpful for a more accurate analysis of the clinical data of PSCCE. The development of a worldwide registry of PSCCE with detailed histological information, including immunohistochemistry for chromogranin A, synaptophysin, and CD56, is expected to clarify the clinical entity of PSCCE and establish

individualized treatment strategies.

Although whether surgery can prolong the survival of patients with PSCCE remains controversial, it seems feasible at least in part for patients with stage I/IIA PSCCE. Further large cohort and multicenter studies are needed to confirm the feasibility of surgery for PSCCE, and basic and translational research will further help to select patients for whom surgery is indicated.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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