Primary small cell carcinoma of the esophagus: progression in the last decade

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Abstract: Primary small cell carcinoma of the esophagus (PSCCE) is a highly malignant tumor that is diagnosed by endoscopic biopsy and immunohistochemistry. Because of its low incidence, a high degree of malignancy, and rapid progress, it is difficult to conduct large, randomized controlled trials and to establish a standard treatment plan for this disease. In recent years, several retrospective studies have been reported, and with the rise of emerging therapies, PSCCE has gradually become a focus of thoracic surgery. This paper reviews progress in the diagnosis and treatment of PSCCE in recent years.

Keywords: Primary small cell carcinoma; esophagus; treatment

Introduction

Esophageal cancer is one of the most common digestive tract carcinomas in the world; a small cell carcinoma is a unique form of esophageal cancer (1-3). In 1952, McKeown first reported primary small cell carcinoma of the esophagus (PSCCE) (4), which often occurs in the lower and middle segments of the esophagus and accounts for 0.4–2.8% of all esophageal cancers (5,6). Because PSCCE is highly invasive and tends to metastasize, most patients are diagnosed with distant metastasis that often leads to poor prognosis (7,8); the 5-year overall survival (OS) rate is approximately 6.7–18% (9-13). However, due to the low incidence of PSCCE, there have been no large, randomized controlled trials, and the standard treatment is controversial. Considering the systemic nature of PSCCE, multidisciplinary systemic treatments are typically utilized (9,14,15). This article will summarize the recent PSCCE literature, supply insights for the

clinical management of PSCCE, and to focus on future treatment options.

General clinical characteristics

Clinical symptoms

The symptoms of patients with PSCCE are like those of esophageal squamous cell carcinoma (ESCC). The most common symptom is progressive dysphagia, and some patients present with symptoms such as pain during swallowing and weight loss (16,17). According to statistics, the average male to female ratio of PSCCE is approximately 3:1, although this ratio varies significantly around the globe (9,17). In China, PSCCE occurs most often in the middle esophagus, while in Western countries, PSCCE is most common in the lower esophagus (18). Similar to ESCC, besides drinking and smoking history, the risk factors for PSCCE are not defined (19-21).

Diagnosis

Most PSCCE cases present as ulcerative or diffuse types on gastroscopies; however, there are no specific differences between PSCCE, ESCC, and esophageal adenocarcinoma (EAC) in imaging examinations (5). Gastroscopy biopsy is the most used method for preoperative diagnosis. Unfortunately, the preoperative definite diagnosis rate is low, mainly due to the small volume of tissue collected during gastroscopy biopsies and the coexistence of small cell carcinoma, squamous cell carcinoma, and adenocarcinoma components in the same tumor tissue (22,23). Thus, when diagnosing complex small cell carcinomas, it may be difficult to distinguish them from poorly differentiated squamous cell carcinomas. To improve the diagnostic rate, some scholars recommend the use of fine-needle aspiration guided by ultrasonic gastroscopy to perform biopsies of submucosal lesions more accurately (5,24).

Tumor staging

Tumor staging is crucial for determining the best choice of treatment options. The American Joint Committee on Cancer (AJCC) staging system (25) and the Veterans Administration Lung Study Group staging system (VALSG) are generally used for PSCCE staging (26).

AJCC: According to the TNM staging system of esophageal cancer, patients are divided into T and M stages (8th edition 2017). Cases without regional lymph node metastasis are defined as N_0, cases with one to three regional lymph node metastases are defined as N_1, and cases with more than three regional lymph node metastases are defined as N_2.

VALSG: the VALSG staging system for primary pulmonary small cell carcinomas divides cases of PSCCE into limited disease (LD) and extensive disease (ED). LD is defined as a tumor confined to the esophagus or surrounding tissue, with or without regional lymph node metastasis. ED is defined as tumors outside the locoregional boundaries (17).

Some studies have combined the AJCC and VALSG staging systems to further divide the LD group into two groups: local disease and regional disease. Localized disease is defined as tumors confined to the esophagus without lymph node metastasis (T1-4aN0M0). The regional disease is defined as tumors that have directly invaded surrounding organs or tissues or have regional lymph node metastases (T4b/N+M0). ED is defined as tumors that extend to distant lymph nodes or organs (M1) (18).

Prognosis

PSCCE is a rare and extremely aggressive malignancy. The median survival time (MST) is approximately 14 to 28 months, with a 1-year OS of 56-86%, a 3-year OS of 27.3–35.7%, and a 5-year OS of 6.7–18% (5,27,28). Most studies indicate that patients with PSCCE are prone to lymph node metastasis, which is associated with poor prognosis (29,30). According to a study in patients with no lymph node metastasis, the MST is 44.9 months, and the 3-year OS was 50.5%; for patients with lymph node metastasis, the MST is 17.8 months, and the 3-year OS was 31.6% (27). Besides, some studies found that therapy, tumor size, and infiltration depth were also associated with poor prognosis (5,31).

Biological characteristics

Molecular-related biological characteristics

The molecular-related biological characteristics of PSCCE is significant for diagnosis and prognosis. The immunohistochemistry of specific neuroendocrine markers, such as synaptophysin (Syn), chromogranin A (CgA), neuron-specific enolase (NSE), cytokeratin (CK), and neuronal cell adhesion molecules (CD56), can help to distinguish PSCCE from neuroendocrine cells, poorly differentiated squamous cells, or adenocarcinoma cells to improve diagnosis (32). However, these markers are also associated with the patient's prognosis. A study on immunohistochemical markers included 73 patients with PSCCE and evaluation of thyroid transcription factor-1 (ttf-1), NSE, Syn, and CgA expression. Patients that were negative for all four markers had the worst prognosis, and patients with one positive marker had better prognoses than those with all negative markers (15.3 vs. 6.1 months, P=0.002) (33). Another study showed that patients with high CgA expression had increased survival times compared with those that were negative for CgA expression (34).

Moreover, the high expression of Ki-67 is a defining characteristic of small cell carcinoma. Ki-67 is generally labeling index is higher than 50% in small cell cancers and less than 25% in other types of tumors, which makes Ki-67 expression a valuable marker for the diagnosis of PSCCE (5,35,36). Besides, a retrospective study showed that high expression of Ki-67 was also a favorable prognostic factor in patients with PSCCE (P=0.012). Furthermore, in a stratified

analysis, adjuvant therapy resulted in significant survival benefits only for patients with high Ki-67 expression (37).

Prognosis-related biological characteristics

Prognosis evaluation is particularly crucial for PSCCE patients because it affects treatment options. Besides molecular-related biological characteristics, inflammation biomarkers and microRNA also play an essential role in evaluating the prognosis of patients.

Increased attention has been paid to the role of systemic inflammatory responses in tumor genesis, development, and metastasis (38,39) because, in the tumor microenvironment, inflammatory cells can be involved in angiogenesis, viability, mobility, and invasion (40). Inflammatory biomarkers are associated with the prognosis of different types of cancers, such as liver cancer, lung cancer, and ESCC, and patients' prognoses can be adequately assessed using pre-treatment hematologic biomarkers (40-42). A study retrospectively analyzed the independent prognostic factors for neutrophil-to-lymphocyte ratio in patients identified as having PSCCE (43). Another retrospective study found that a high platelet-to-lymphocyte ratio was an independent prognostic factor for poor OS (44).

With the in-depth study of microRNAs, evaluation of PSCCE patient prognosis via microRNA expression is receiving more attention. Okumura et al. used microarrays to detect the microRNA expression in PSCCE tumors. The expression of eight microRNAs (miR-4323, miR-625, miR-3619-3p, miR-4419b, miR-1249, miR-4648, miR-4664-3p, and miR-1203) was significantly correlated with tumor recurrence (P<0.01) (45).

Potential target-related molecules

Due to the low incidence of PSCCE, the study of esophageal cancer genes has focused on ESCC and EAC. However, with high-throughput genome technology, PSCCE has gradually received more attention. To understand the genetic basis of PSCCE, Wang et al. performed genomic profiling of 55 patients with PSCCE using whole-exome sequencing confirmed by ultra-deep targeted sequencing. Significant mutations were detected in eight genes (TP53, RB1, NOTCH1, FAT1, FBXW7, PDE3A, PTPRM, and CBLN2) that provided assistance for the development of new diagnostic and therapeutic tools for PSCCE therapy (46). Furthermore, Ishida et al. (47) found that loss of Rb1 gene expression and overexpression

of the SOX gene were crucial for the pathogenesis and differentiation of PSCCE. The incidence of phosphatase and tensin homolog deleted on revision 10 (PTEN) mutations in Chinese patients with PSCCE is high, and the over-expression of p21-activated kinase-1 (PAK-1) is associated with poor prognosis of patients with PSCCE. Thus, PTEN and PAK-1 may be potential targets for precise treatment of patients with PSCCE (48,49).

Treatment strategies

Traditional treatment strategy

Due to the low incidence of esophageal small cell carcinoma, the rapid occurrence of lymph node metastasis, and poor prognosis, it is difficult to carry out a large-scale randomized controlled trial to establish standard treatment options. Thus, most studies on PSCCE treatment have focused on retrospective studies. Furthermore, it is controversial whether surgery can help PSCCE patients. Many scholars believe that chemotherapy (CT) or radiotherapy should be the main treatment for PSCCE patients (6,10,12,50-52). However, some scholars hold an opposing view that surgical treatment plays an important role in the treatment of PSCCE (29,30). We believe that different multidisciplinary treatment regimens should be adopted for patients with different stages of PSCCE (53). Therefore, traditional treatment strategies for distinct stages of PSCCE are summarized.

Treatment strategies according to AJCC staging
Stages I and IIA
Some studies suggest that patients with early esophageal cancer could be considered for endoscopic treatment (54,55); however, there are currently no studies on endoscopic treatment of patients with early PSCCE. The FFCD 9901 trial showed that neoadjuvant therapy did not improve the productivity of patients with early esophageal cancer and that it could lead to an increase in postoperative mortality. Therefore, surgical treatment should be considered for early esophageal cancer (56). Similar conclusions have been reached in studies of stage I and IIA PSCCE, suggesting that early PSCCE should be treated first with surgery. Xu et al. (5) retrospectively analyzed 152 patients with PSCCE and found through stratified analysis that surgical treatment can result in survival benefits for patients with stage I and IIA; postoperative adjuvant therapy failed to improve patients' OS (P=0.522) and disease-free survival (DFS)

(P=0.368). Chen *et al.* (57) also suggested that surgery could lead to better MST for stage I and IIA patients (29 *vs.* 17.4 months, P=0.082). In conclusion, for patients with stage I and IIA, most scholars believe that surgical treatment should be the main treatment.

Stage IIB

The best treatment for patients with stage IIB PSCCE has been controversial. For patients with stage IIB PSCCE, Xu *et al.* (5) indicated that the OS and DFS were similar irrespective of whether the patients received only surgical treatment, postoperative CT, or chemoradiotherapy (CRT). However, Chen *et al.* (57) indicated that for patients with stage IIB PSCCE and above, postoperative CT can improve survival rates compared with surgical treatment alone (13 *vs.* 6.1 months, P=0.003), while the addition of RT also can improve survival benefits (16.8 *vs.* 9.5 months, P=0.076). A similar conclusion was reached by Ishida *et al.* (58), who concluded that non-surgical therapy was more beneficial for patients after stage II PSCCE than for patients with surgical therapy (16 *vs.* 11.5 months, P=0.097). Therefore, large-scale retrospective studies or randomized controlled trials are still needed to confirm the best treatment options for patients with stage IIB. Xu *et al.* (5) presented that the two patients who received neoadjuvant chemotherapy (nCT) had a longer survival time. However, due to the small sample size, it was not possible to further evaluate the efficacy of nCT in patients with stage IIB. Meanwhile, in the CROSS trial, van Hagen *et al.* (59) included a subset of patients with stage IIB esophageal cancer and showed that nCT improved survival (P=0.003). Hence, for patients with stage IIB PSCCE, the role of nCT in treatment must be further explored.

Stages III and IV

Most studies have shown CRT as the primary treatment for patients with stage III or above PSCCE. Chen *et al.* (57) showed that, compared with CT alone, CRT could improve the survival rate of stage IV patients (13.2 *vs.* 8.9 months, P=0.014). Similarly, a study by Wong *et al.* (27), which included PSCCE patients of whom 40% were stage IV, also found that CRT improved OS in patients with lymph node metastasis. However, a retrospective study by Hou *et al.* (9) involving 89 patients with stage III PSCCE found that surgical treatment combined with CRT resulted in longer survival times. Moreover, a randomized controlled study by Shapiro *et al.* (60) showed a greater survival benefit from nCT in patients with stage III or higher esophageal cancer than with surgery alone. A study of PSCCE patients by Xu *et al.* (5) reached a similar conclusion. However, the

determination of the best scheme of nCT needs further discussion.

Treatment strategies according to VALSG staging

VALSG staging is also a commonly used tumor staging method that classifies patients into LD and ED stages according to whether the tumor has distant metastases. Zhu *et al.* (22) used VALSG for staging in 64 patients with PSCCE; multivariate analysis showed that treatment modality was an independent prognostic factor (P=0.008). The combination of surgical treatment and CT helped the survival of LD patients, while combined CT had a significant impact on the MST of ED patients (P=0.0001). Furthermore, a recent study by Chen *et al.* (50) demonstrated that, for patients with stage LD PSCCE, combined CT and RT could improve prognosis (P=0.046), as well as increased radiation doses (≥56 Gy, P=0.027). However, this study did not examine whether surgical treatment resulted in increased survival benefits. Jeene *et al.* (6) proposed a contrary view, suggesting that lower radiation doses (<45 Gy) were associated with improved survival; their multivariate analysis showed that only the number of CT cycles was associated with better survival (P=0.006). However, both studies included only a small number of patients, so large-scale retrospective studies or randomized controlled studies are needed to clarify further the role of RT in the treatment of LD-PSCCE.

Considering that more accurate tumor staging could enable patients to obtain more accurate treatment regimens, Zou *et al.* (31) further subdivided patients: patients with T1-2N0M0 were defined as LD I, while patients with T3-4N0M0 or T1-4N1-2M0 were defined as LD II. Stratified analysis showed that for patients with LD I, surgical treatment was recommended, and there was no significant improvement in survival in patients with postoperative adjuvant CT or CRT. Alternatively, adjuvant CT improved the survival rate of PSCCE patients with fully resected LD II disease.

After using propensity score matching to balance demographic factors (patients treated in China and the United States), Xiao *et al.* (18) used VALSG staging to classify PSCCE patients, dividing them into LD and ED. The further classification was performed according to the presence of lymph node metastasis, LD is divided into focal lesions (T1-4aN0M0), and regional lesions (T4b/N+M0). The stratified analysis showed that, for patients with focal lesions, surgery could be beneficial, but CT does not improve survival. In patients with regional lesions, ED, RT,

and CT had improved OS.

In conclusion, for patients with early surgically resectable PSCCE, most studies support the use of surgical treatment to improve patient survival. For some patients, CT and RT can also be considered, but the choice of CT options and radiation doses still is controversial. For patients with advanced PSCCE (stage III and IV or ED), CT combined with RT can improve the survival rate. These patients may also consider nCT, as it may reduce the tumor stage; When tumor staging decreases, surgical treatment can increase survival benefits.

Emerging therapies

With the rise of targeted therapy and immunotherapy, several clinical trials are underway to study the application of these therapies in tumor therapy. Although studies on targeted therapy and immunotherapy for esophageal cancer have focused on ESCC and EAC, these emerging therapies may also be right for PSCCE, which is often a mixture of squamous and adenocarcinoma cells. The following section will briefly introduce the emerging therapies for esophageal cancer.

Targeted therapy

Except for trastuzumab, the development of targeted therapies for esophageal cancer over the past decade has been disappointing (61). Several large, international randomized trials have investigated drugs targeting the EGFR, MET/hGF, mTOR, VEGF, and FGFR pathways without satisfactory results (62-64). For example, cetuximab, a humanized mouse EGFR monoclonal antibody, combined with CT, significantly improved OS in patients with esophageal cancer in the phase II clinical study (65). However, other studies found that cetuximab combined with CT has no advantage over CT alone (63). Moreover, a phase III clinical study involving 450 patients with esophageal cancer assessed the role of gefitinib in the progression of esophageal cancer after CT and also found no improvement in OS (66).

On the other hand, trastuzumab, a drug that targets human epidermal growth factor receptor 2 (HER-2), has gained attention in different types of HER-2-overexpressing cancers because of its success in targeted breast cancer therapy (67). In a Japanese clinical study, trastuzumab combined with capecitabine/cisplatin or 5-fluorouracil/cisplatin improved OS in patients with advanced esophageal cancer compared to CT alone (68). Meanwhile, a phase II

study in Spain also found that trastuzumab combined with cisplatin as a first-line treatment for advanced esophageal cancer with positive HER-2 improved prognosis and had good safety (69). However, the overall development of targeted therapy for esophageal cancer has been prolonged. The emergence of next generation sequencing technology will supply a new direction for targeted therapy for esophageal cancer.

Immunotherapy

Immune checkpoint inhibitors

Programmed death ligand 1 (PD-L1) is expressed in up to 40% of esophageal cancers, and the expression of PD-L1 increases after conventional neoadjuvant CRT (19,70). Therefore, drugs targeting PD-L1 are considered useful in patients with PD-L1-positive esophageal cancer. Two PD-L1 inhibitors, pembrolizumab, and nivolumab have achieved satisfactory efficacy in esophageal cancer.

Pembrolizumab, a PD-1 inhibitor, was the first Food and Drug Administration (FDA)-approved immune checkpoint inhibitor for the treatment of advanced melanoma and was effective against esophageal cancer in several recent clinical trials. KEYNOTE-028 is a multi-cohort phase IB study designed to evaluate the safety and overall remission rate of pembrolizumab in advanced PD-L1-positive solid tumors. The study included 23 patients with PD-L1-positive advanced and metastatic esophageal cancer. The objective response rate was 30% [95% confidence interval (CI), 13–53%] with an average response duration of 15 months (ranging from 6 to ≥26 months). Treatment-related adverse events were present in 39% of patients (9 out of 23). The main adverse events included decreased appetite, decreased lymphocyte count, and a systemic rash. More than half of the patients showed tumor shrinkage. Overall, median progression-free survival was 1.8 months (95% CI, 1.7–2.9 months), and median OS was 7.0 months (95% CI, 4.3–17.7 months) (71,72). KEYNOTE-180 is a phase II single-arm study designed to evaluate the safety and efficacy of pembrolizumab. A total of 121 patients with advanced metastatic esophageal cancer who had progressed after a two-line treatment were enrolled. Compared to the previous traditional second-line treatment, the experimental results of this study were very satisfactory, with a median OS of 5.8 months and 6- and 12-month OS rates of 49% and 28%, respectively (62,72). The KEYNOTE-181 phase III clinical trial will assess pembrolizumab with CT as a second-line treatment of advanced esophageal cancer. Another phase III study (KEYNOTE-590) is comparing pembrolizumab

combined with CT and placebo combined with CT (72).

Nivolumab is a human monoclonal IgG4 antibody that inhibits PD-1 expression on activated T cells. Nivolumab is FDA approved for the treatment of metastatic melanoma, non-small cell lung cancer, and renal cell carcinoma (72). A randomized, double-blind, multicenter phase III trial in Japan was designed to evaluate the efficacy and safety of nivolumab in patients with advanced gastric or gastroesophageal junction cancer, who had previously received two or more CT regimens. That study suggested that nivolumab can lead to longer survival times (5.26 vs. 4.14 months, P<0.0001) (73). Moreover, CheckMate-032 demonstrated the safety and efficacy of nivolumab combined with ipilimumab in patients with advanced esophageal cancer; the combination was superior to nivolumab monotherapy (74).

Other immunotherapies

Other emerging immunotherapies such as peptide vaccines, adoptive T-cell transfer, and oncolytic viruses are also receiving increasing attention. Clinical trials are studying their applications in the treatment of esophageal cancer.

Since several immunogenic cancer antigens (ICA) have been shown on esophageal cancer cells and therapeutic cancer vaccines, they have received increasing attention. Cancer vaccines are designed to effectively induce ICA-specific cytotoxic T lymphocytes to enhance the immune response (72).

The adoptive T-cell transfer is another research hotspot. This treatment removes T cells from the patient, alters the T cells in vitro to increase their immunologic activity, and then reintroduces them into the patient to improve specific immune responses. Related studies have shown preliminary clinical benefits in patients with esophageal cancer (75).

Many scholars believe that oncolytic virus therapy may be the next breakthrough in cancer immunotherapy. Oncolytic viruses can selectively replicate in tumor cells and then induce tumor cell lysis (76,77). Recently, a phase I/II study showed the efficiency and tolerance of a novel telomerase-specific oncolytic virus (OBP-301) in elderly patients with esophageal cancer (78).

Conclusions

The incidence of PSCCE is low, but the progress is rapid, and the prognosis is poor. Despite the growing interest in PSCCE, research has focused on retrospective studies. Significant advancements will require extensive, randomized controlled studies to determine the best treatment strategy.

The survival rate of patients diagnosed with early PSCCE is notable; thus, early diagnosis is critical, requiring improved biopsy equipment and immunohistochemical tests. With a deepening understanding of the molecular biology and tumor microenvironment, the use of molecular biomarkers, inflammatory biomarkers, and microRNAs to help improve the diagnostic accuracy and evaluate the prognosis of PSCCE patients has received more attention.

Additionally, proper tumor staging is vital for the choice of treatment options for PSCCE patients. Surgical treatment is the preferred treatment for early-stage patients without lymph node metastasis. However, the benefits of neoadjuvant therapy in patients with partial lymph node metastasis or large tumors requires further study. For patients with advanced PSCCE, systemic treatment, such as radiotherapy and CT, should be considered first. If nCT can reduce tumor staging, surgical treatment may be considered to maximize the survival benefit. With targeted therapy and immunotherapy becoming the focus of cancer therapy and despite current research focusing on ESCC and EAC, future PSCCE patients will have new treatment options.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.03.214). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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