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Extensive Stage Small Cell Lung Cancer and its Systemic Therapy Approaches

Anita, Shilpi*

Himachal Institute of Pharmacy, Paonta Sahib, Himachal Pradesh, India

**Correspondence*
Dr. Shilpi, H.O.D, Himachal Institute of Pharmacy, Paonta Sahib, Himachal Pradesh, India.
E-mail: shilpyaroara111@gmail.com

Abstract
ES-SCLC represents 60-80% of all SCLC cases. These tumors exhibits aggressive growth characteristics and an early propensity to metastasize, resulting in an unfavourable prognosis. The OS is limited to 9-12 months. Currently, systemic therapy is used as treatment, which has progressed from chemotherapy combinations ofplatinum+ etoposide to chemo immunotherapy.Optimal induction regimen is defined by recent studies such as IMpower133 and CASPIAN, recommending carboplatin/cisplatin plus etoposide with addition of PD-L1 inhibitors (atezolizumab or durvalumab). This combination leads to an increase in OS by 2-4 months and PFS benefit, with response rates ranging from 60-70%. Maintenance therapy has seen several improvements recently. Most notably, atezolizumab + lurbinectedin was approved by FDA in 2025 based on the results from IMforte trial which showed improvement in PFS by 46% and lower mortality risk by 27% compared to placebo, subsequently being granted NCCN category 2A recommendation as the preferred option following induction. Novel therapeutic avenues are being explored, such as tarlatamab, a bispecific antibody targeting DLL3, and multi-agent trials involving benmelstobart+ anlotinib or apatinib, both of which are anti-angiogenic agents, demonstrating encouraging results within biomarker-selected patient populations. Furthermore, consolidative thoracic radiotherapy, administered after chemoimmunotherapy or in conjunction with novel agents like Ifinatamab- deruxtecan (I-DXd), has shown objective response rates (ORR) of 55% and effective intracranial control. Future research will focus on combination intensification strategies, the utilization of liquid biopsies for resistance monitoring and clinical trials incorporating PARP inhibitors or antibody-drug conjugates (ADCs) to overcome the limitations of immunotherapy.

Keywords: Extensive stage SCLC, systemic therapy, chemoimmunotherapy, platinum-etoposide, immune checkpoint inhibitors, tarlatamab, radiotherapy, anti-angiogenics.

Introduction

Cancer occurs when our body cells start to grow out of control and spread to other body parts. Our normal cells grow and multiply through a process known as cell division to make new cells. When these cells become damaged and grow out of control, they can spread to other parts of the body via bloodstream or lymphatic system to form new tumors.[1]
Cancerous tumor spread or invade nearby tissues and travel to distant places in the body to form new tumors by process metastasis. Many cancers form solid tumors but cancer of blood called leukemia can spread throughout the body via blood transmission.[2]

Cancer is an extremely fatal disease, not only in developed but also in developing countries.Cancer cells arise due to the imbalance in the body functions and they invade and infect the normal cells.[3]
The common causes of cancer are Inherited gene mutations, different age groups, tobacco, smoking, lifestyle, alcohol, pollution, lack of exercise, radiation, infections and household chemicals.[4]

Type of Cancer Tumors

- **Malignant tumor:** Also called as cancerous tumor characterized by rapid, uncontrolled cell proliferation that invades tissues and metastasizes to other parts of the body via bloodstream and lymphatic system.[5]

- **Benign tumor:** Also called as non-cancerous tumor and do not spread or invade nearby tissues. Usually don't grow back when removed but can cause serious symptoms or life threatening such as benign tumor in the brain.[6]

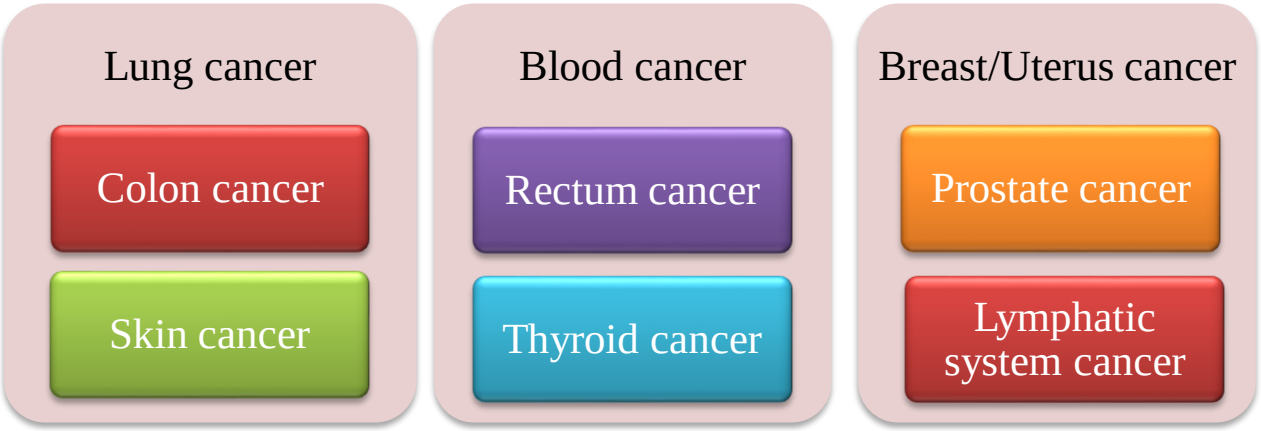

Fig 1: Types of cancer[7]

Lung Cancer

Lung cancer accounts for the highest percentage of cancers in the world (12.3% of all cancers) with approximately 1.2 million cases diagnosed yearly. Tobacco and smoking is currently the leading cause of lung cancer, as between 80%-90% of lung cancers arise in cigarette smokers.[8]A lifetime smoker has a 20-30times increased risk of developing lung cancer as compared to a lifetime non-smoker. Thus, lung cancer is the most preventable of all cancer.[9]

Lung canceralso called lung carcinoma, is a malignant tumour that originates in the tissues of the lungs. Lung cancer is caused by genetic damage to the DNA of cells in the airways, often caused by cigarette smoking or inhaling damaging chemicals. [10]

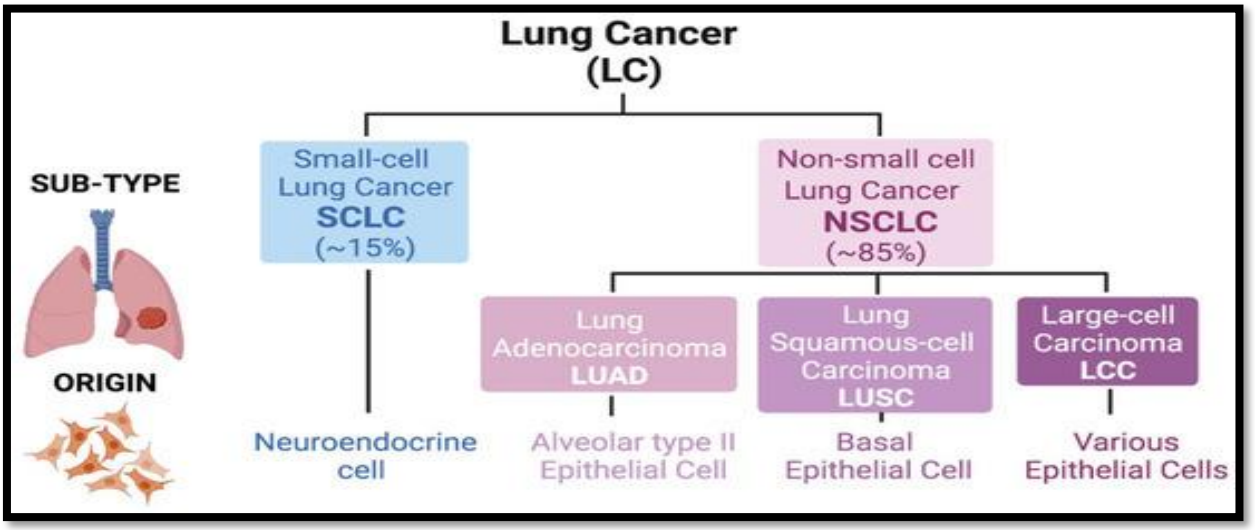

Fig.1: Types of lung cancer [11]

When airway cells are damaged, they can multiply without control, which leads to the growth of a tumor. If it is not treated, tumors spread throughout the lung and make it harder to work properly. Lung tumors eventually spread to other parts of the body.[12] Lung cancer is a very aggressive disease that happens when cells in the lungs start to grow and multiply out of control, making tumors that can make it hard to breathe and may spread to other parts of the body. [9] It usually takes a long time to get worse because harmful substances hurt lung cells. Smoking is the most common cause of lung cancer because the chemicals in tobacco smoke hurt the DNA of lung cells and cause cancer.[13]People who do not smoke can also develop lung cancer due to second-hand smoke, where they inhale smoke from others. Exposure to radon gas, a

naturally occurring radioactive gas that can build up in

Small Cell Lung Cancer

One kind of rapidly expanding cancer that develops in the lung tissues is small cell lung cancer. It comes from neuroendocrine cells and is the most aggressive kind of lung cancer. This cancer's high vascularity contributes to its quick growth.[15] It begins when healthy lung cells undergo mutation or transform into malignant cells. These cells then proliferate and divide uncontrollably, causing cancerous cells to group together in lungs to form tumors. These tumors release cancer cells that are absorbed by the body's lymphatic or circulatory systems.[16]

Smoking and tobacco intake can cause the worsening of the cancer which may also lead to the death of the patients. Inhalation of carcinogens from cigarette or tobacco cause genetic mutations, especially in tumour suppressor genes like TP53 and RB1 which can drive the transformation of healthy lung cells into cancer cells.[12]

Smoking is the leading cause of lung cancer, accounting for 85% of cases. Additional risk factors for lung cancer include second-hand smoke, asbestos, radon, and other environmental factors.[13]The strong association between small cell lung cancer and cigarette smoking has been well documented.[14] Long-term exposure to tobacco smoke introduces carcinogenic substances into the lungs, which can cause genetic mutations and uncontrolled cellular growth. Other risk factors may include exposure to environmental pollutants, occupational carcinogens, and genetic predisposition.[15]

the lungs, is another significant risk factor.[14]

The prognosis for small cell lung cancer is still poor, despite advancements in cancer treatment over the past few decades. Patients who do not receive treatment have a median survival of just a few months.[21] Long-term survival is still uncommon, but it can last up to 8–13 months with treatment. Systemic chemotherapy, immunotherapy, radiation therapy, and palliative care are common treatment options.[22] Recent advancements in targeted therapies and immunotherapy given new hope for better outcomes of the advanced diseases in patients.[23] Clinical trials have demonstrated encouraging outcomes for medications that activate the immune system to identify and fighting against cancer cells. Still, problems like treatment toxicity, drug resistance and relapse continue to make management approaches difficult and burdensome. [14]

Common Risk Factors:

- Smoking: The majority of small cell lung cancer cases are linked to cigarette smoking.
- Asbestos: Occupational exposure to asbestos fibres poses a significant risk.
- Second hand Smoke: Non-smokers exposed to second hand smoke also face increased risks.
- Air Pollution: High levels of air pollution can contribute to lung cancer.
- Occupational Exposures: Jobs involving radon or other hazardous materials increase susceptibility.[16]

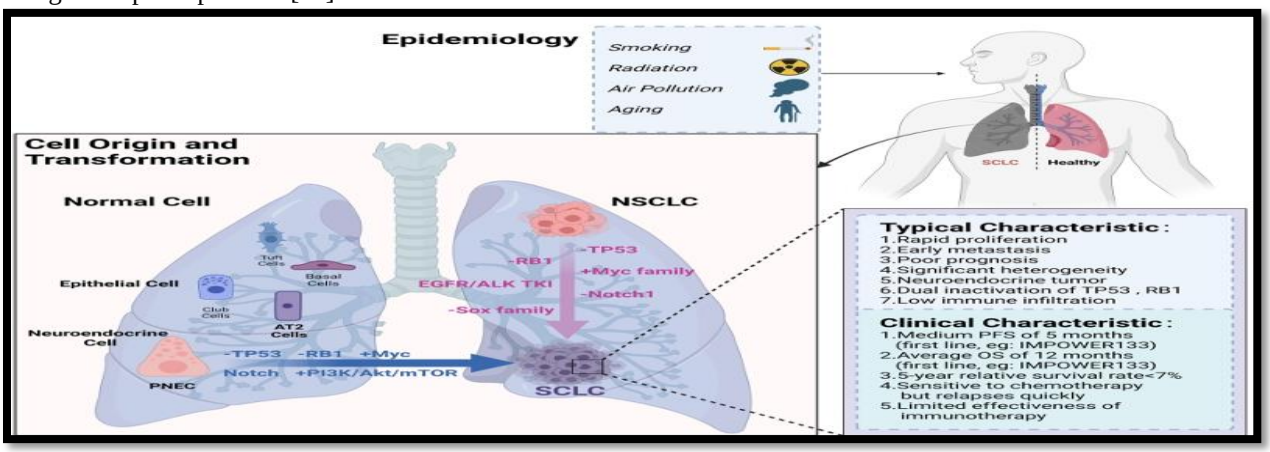

Fig. 2:The epidemiology, cell origin and clinical characteristics of SCLC.[17]

Types of Small Cell Lung Cancer

- Limited Stage SCLC: It is defined as cancer that is confined to one side of the chest (a single hemithorax) and can be safely encompassed within a single, tolerable radiation therapy port. This includes the primary tumor and may involve lymph nodes in the center of the chest (mediastinum) or above

the collarbone (supraclavicular) on the same side as the tumor. Approximately one-third of patients are diagnosed with LS-SCLC.[18]

- Extensive Stage SCLC: The most progressing and aggressive stage of lung cancer is ES-SCLC because it extending beyond LS-SCLC, including malignant pleural, pericardial effusions, contralateral lung involvement, and hematogenous metastases.ES-SCLC remains an incurable disease with a 5-year OS rate of <5%.[19]

Extensive Stage Small Cell Lung Cancer (ES-SCLC)

Extensive-stage small cell lung cancer (ES-SCLC) is an advanced form of Small Cell Lung Cancer, which is a fast-growing type of Lung Cancer that begins in the neuroendocrine cells of the lungs.[19] In this stage, the cancer has already spread beyond the original lung and nearby lymph nodes to other parts of the body such as the liver, brain, bones, adrenal glands or the opposite lung. This cancer grows and spreads quickly, so the many patients are diagnosed only after it has reached to its extensive stage.[20]

This disease is strongly related to long-term cigarette smoking and also exposure to harmful substances like radon or asbestos which also increase the risk. People with ES-SCLC often experience symptoms like persistent cough, chest pain, shortness of breath, tiredness and unexplained weight loss.[21]In some cases, the tumor produces hormone-like substances that can cause conditions such as Syndrome of Inappropriate Antidiuretic Hormone Secretion or Cushing Syndrome.[22]Doctors usually diagnose the disease using imaging tests such as CT scans, PET scans or MRI along with a biopsy to confirm the presence of cancer cells.[23]As the cancer has spread widely, treatment mainly focuses on systemic therapies like chemotherapy and immunotherapy, while radiotherapy may be used to control symptoms or treat brain metastases.[24]

ES-SCLC represents a major therapeutic challenge because of its rapid progression and limited long-term survival outcomes. Although SCLC is initially highly sensitive to chemotherapy and radiotherapy. Most patients eventually develop resistance to treatment, resulting in disease recurrence and progression.[25]The median overall survival for patients with ES-SCLC has ranged between 7 to 12 months and the five-year survival rate remains extremely low, typically below 5%. These poor survival statistics highlight the need for improved therapeutic approaches and a deeper understanding of the biological mechanisms underlying the disease.[26]

Pathophysiology of ES-SCL

Extensive-stage Small Cell Lung Cancer (ES-SCLC) develops through a complex and aggressive biological process that begins at the cellular level in the lungs and rapidly evolves into a widespread systemic disease. It is originates from neuroendocrine cells located in the bronchial epithelium. These cells normally helps to regulate airway function by releasing hormones.[27] In ES-SCLC, they undergo malignant transformation due to prolonged exposure to carcinogens like cigarette smoke. These carcinogens cause repeated DNA damage over the time, leading to the accumulation of genetic mutations that disrupt normal cell regulation. As a result, cells lose their ability to control growth and division which initiate the process of tumor formation.[28]

The inactivation of crucial tumor suppressor genes, such as TP53 and RB1, is a key factor in the development of ES-SCLC. These genes usually act as protective agents, preventing the unregulated division of cells that have sustained damage. Consequently, the loss or mutation of these genes allows cells to bypass critical cell cycle checkpoints, thus promoting rapid and uncontrolled proliferation. [29]

This process culminates in the development of densely packed, small malignant cells characterized by elevated mitotic activity. Furthermore, ES-SCLC cells frequently demonstrate a high tumor mutational load, signifying the presence of numerous genetic alterations, which subsequently contributes to the tumor aggressiveness and adaptability.[30]

As the tumor grows, it develops the ability to invade surrounding tissues and spread throughout the body by bloodstream and lymphatic system through metastasis mechanism. Cancer cells detach from the primary tumor, enters into the circulation and establish secondary tumors in distant organs such as the liver, brain, bones and adrenal glands. The rapid multiplication time of SCLC cells allows metastases to form early, often before the primary tumor is even diagnosed. This shows why many patients already have widespread disease at presentation.[31]

Additional crucial aspect of ES-SCLC is its neuroendocrine nature**,** which enables tumor cells to produce and secrete hormone-like substances which can lead to paraneoplastic syndromes**,** where symptoms are not caused directly by the tumor mass but by these abnormal hormone secretions.[32] For example- patients may develops Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), resulting in low sodium levels or Cushing Syndrome due to excess ACTH production. These systemic effects further complicate the ailment and can remarkably impact patient health.[22]

At the molecular level, ES-SCLC tumors often shows dysregulation of multiple signalling pathways involved in the cell survival and proliferation. It includes MYC amplification, alterations in Notch pathways and PI3K/AKT pathways.[33]

These changes contribute to continuous tumor growth, resistance to programmed cell death (apoptosis) and increased angiogenesis known as the formation of new blood vessels that supply nutrients to the tumor. This blood supply supports rapid tumor expansion and expedites further spread to distant organs.[34]

Despite initially responding well to chemotherapy, ES-SCLC almost always develops **treatment resistance**. This occurs because a small population of cancer cells survives initial therapy and adapts through additional genetic and epigenetic changes. [35]These resistant cells can repopulate the tumor, leading to relapse. Mechanisms of resistance include enhanced DNA repair, drug efflux, and changes in tumor cell phenotype. This makes long-term disease extremely difficult and is a major reason of ES-SCLC has a poor prognosis.[36]

ES-SCLC is a disease that starts silently but progresses rapidly, overwhelming the body's natural defences which begins as microscopic damage in lung cells and evolves into a fast-growing cancer that spreads widely and affects multiple organ systems.[37] Its ability to adapt, resist treatment, and disrupt normal hormonal balance makes it one of the most challenging cancers to manage, highlighting the urgent need for continued research and more effective therapies.[38]

Diagnosis and Treatment

Small Cell Lung Cancer in its extensive stage (ES-SCLC) is a highly malignant neuroendocrine tumor of the lung characterized by rapid multiplication, high growth fraction and early widespread metastasis to organs like brain, liver, bone and adrenal glands. Clinically, patients often present with symptoms including persistent cough, hemoptysis, chest pain, dyspnea, fatigue and significant weight loss. Paraneoplastic syndromes such as syndrome of inappropriate antidiuretic hormone secretion (SIADH) or ectopic ACTH production also associated with ES-SCLC.

Diagnosis

Diagnosis involves a combination of radiological imaging, such as contrast-enhanced CT scans of the chest and abdomen, PET-CT for systemic staging and MRI of the brain due to high risk of intracranial spread. Biopsy is the other diagnosis option like bronchoscopy, endobronchial ultrasound or CT-guided needle aspiration.[39] Microscopically, tumor cells are small, round to spindle-shaped with scant cytoplasm, finely granular chromatin and high mitotic activity. They also express neuroendocrine markers like synaptophysin and chromogranin on immunohistochemistry.[40]

Treatment

The management of ES-SCLC is primarily systemic because of its disseminated nature at diagnosis. First-line treatment consists of platinum-based chemotherapy which include Carboplatin or Cisplatin combined with Etoposide.Immunotherapy includes immune checkpoint inhibitor such as Atezolizumab or Durvalumab, which enhances anti-tumor immune response and has significantly improved overall survival compared to chemotherapy alone.[41]

In case of relapse, second-line therapies include agents like Topotecan and Lurbinectedin. The most recent breakthrough is the development of bispecific T-cell engager therapy, particularly tarlatamab (Imdelltra)**,** which received FDA approval in 2025 for patients whose disease progresses after platinum-based chemotherapy. This drug targets DLL3 on tumor cells and recruits T-cells to destroy cancer and clinical trials have shown it significantly improves survival compared to standard chemotherapy as a new second-line standard of care**.**[42]

Radiotherapy plays a supportive role, particularly for palliation of symptoms such as bone pain or airway obstruction and in some patients, prophylactic cranial irradiation (PCI) may be used to reduce the risk of brain metastases. Comprehensive supportive care

include pain control, nutritional support, psychological counselingand management of treatment related adverse effects which is essential to maintain quality of life.[43]

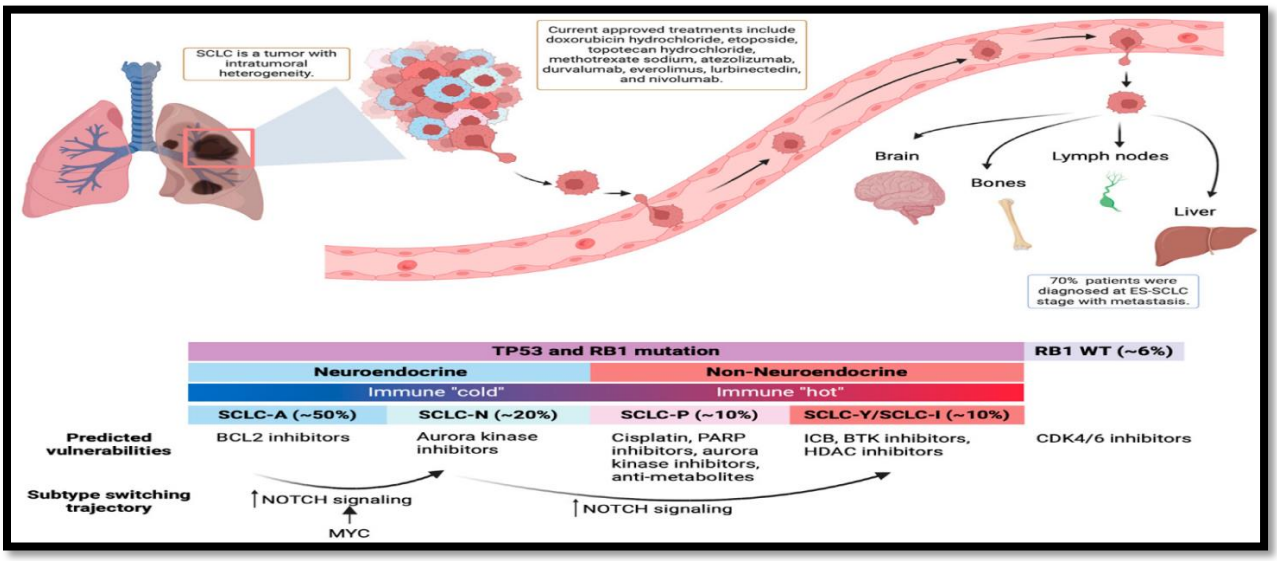

Fig. 3:Treatment of ES-SCLC with the signaling pathways and drugs used for particular type of cancer subtypes.[44]

Conclusion

In conclusion, Small Cell Lung Cancer in its extensive stage (ES-SCLC) represents one of the most aggressive and challenging forms of lung malignancy which is characterized by rapid progression, early metastasis and poor overall prognosis. Despite significant advancements in diagnostic techniques such as imaging and histopathological evaluation, most patients are diagnosed at an advanced stage due to the disease's asymptomatic early course and fast dissemination. The pathophysiology of ES-SCLC, driven by genetic mutations such as TP53 and RB1 inactivation and its neuroendocrine origin, contributes to its highly proliferative and metastatic nature. Current treatment strategies, including platinum-based chemotherapy combined with immunotherapy agents like Atezolizumab and Durvalumab, have improved patient outcomes to some extent; however, relapse and drug resistance remain major obstacles. Emerging therapies, such as Tarlatamab, offer promising new directions by targeting specific molecular pathways and enhancing immune-mediated tumor destruction. Supportive and palliative care also play a crucial role in improving quality of life for patients.Overall, ES-SCLC continues to pose a significant clinical challenge due to its aggressive biology and limited long-term survival. Therefore, ongoing research, early detection strategies, and the development of more effective targeted and immunotherapeutic approaches are essential to improve prognosis and patient outcomes in the future.

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