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A Review on Small-Cell Lung Cancer: Epidemiology, Pathophysiology, Risk Factors, Diagnosis, Clinical Management and Treatment Modalities

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ABSTRACT: Small-cell lung cancer (SCLC) accounts for roughly 15% of all lung malignancies and is distinguished by a high proliferative rate, a proclivity for early metastasis, and a poor prognosis. Exposure to cigarette carcinogens is highly linked to SCLC. Only one-third of individuals have earlier-stage illness that is responsive to possibly curative multimodality treatment at the time of diagnosis. SCLC genomic analysis revealed a high mutation load and widespread chromosomal rearrangements, nearly usually with functional inactivation of the tumour suppressor genes TP53 and RB1. The relative expression of prominent transcriptional regulators has been used to identify subtypes of illness in both human SCLC and murine models, revealing significant intra-tumoural variation. Tumor development, metastasis, and acquired treatment resistance have been linked to aspects of this heterogeneity. Despite the fact that clinical progress in the treatment of SCLC has been notoriously poor, a greater knowledge of the biology of the disease has revealed new vulnerabilities that might be targeted therapeutically. Immune checkpoint blockade, which was recently introduced into the treatment of SCLC patients, has given benefit to patients, with a small fraction of patients experiencing long-term benefits. Strategies to focus tailored therapy to the patients most likely to react and to extend the long-term benefits of successful anti-tumor immunity to a larger number of patients are urgently needed and are now being researched.

KEYWORDS: Adenocarcinoma; Circulating tumour cells (CTCs); Small-cell lung cancer (SCLC); Tumour suppressor genes.

INTRODUCTION

Small-cell lung cancer (SCLC) is a high-grade neuroendocrine carcinoma that mostly affects current or past smokers and has a dismal prognosis [1]. SCLC accounts for around 15% of all lung cancer cases. SCLC patients typically present with respiratory symptoms such as cough, dyspnoea (laboured breathing), or haemoptysis (blood cough), with imaging revealing a centrally located lung mass and frequently bulky thoracic lymph node involvement; two-thirds of patients have distant metastatic disease at the time of diagnosis. The contralateral lung, brain, liver, adrenal glands, and bone are the most common sites of metastasis. The concentration of circulating tumour cells (CTCs) in SCLC is among the highest of any solid tumour, reflecting its strong metastatic proclivity [2]. Despite the fact that multiple biological subtypes of SCLC have been identified based on transcription factor expression profiles, the current therapeutic approach to SCLC therapy is comparable regardless of subtype [3]. Surgery and adjuvant platinum-based chemotherapy may be used in the few patients who show with extremely early-stage illness upon diagnosis, but most patients with early-stage or locally progressed disease are treated with concomitant radiation and platinum-based chemotherapy. Systemic chemotherapy with or without immunotherapy is used to treat patients with metastatic illness. Even in individuals with metastatic illness, SCLC is initially extremely receptive to cytotoxic treatments, with up to 25% of patients with early-stage SCLC achieving long-term disease control with concurrent chemo radiotherapy (CRT) and response rates continuously exceeding 60%. However, these responses are temporary in the great majority of patients, with a median survival time of <2 years for patients with early-stage cancer and ~1 year for individuals with metastatic disease. In this review, we provide an overview of

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current knowledge of SCLC from both a clinical and biological standpoint, with a special focus on how assessments of mice models and human tumours are guiding future therapeutic research approaches in SCLC.

Epidemiology

With an expected 2.1 million new cases and 1.8 million deaths in 2018, lung cancer is the leading cause of cancer death globally [4]. Every year, an estimated 250,000 new cases of SCLC are diagnosed, with at least 200,000 fatalities [5]. Lung cancer is more common in high-income countries, including all histological subtypes, indicating relative cigarette usage levels [4,6]. The particular incidence of SCLC in different countries or continents, on the other hand, is not extensively documented. SCLC is more common in males, as it is with lung cancer in general, although the proportion of cases in women relative to men has increased globally over the last 50 years, mirroring tobacco usage patterns [7]. Incidence of SCLC has decreased in the United States during the last three decades, coinciding with a decrease in the prevalence of cigarette smoking [8]. In the United States, the proportion of elderly SCLC patients (>70 years old) has grown from 23% in 1975 to 44% in 2010 [9]. Despite the fact that African-American men and women smoke more than white Americans, SCLC is less common among African-Americans [10, 11].

Risk factors

SCLC is one of the malignancies with the strongest epidemiological links to tobacco, and its prevalence tends to lag behind that of smoking by roughly 30 years [12]. SCLC incidence peaked in males in 1986 and women in 1991 in the United States, and has been slowly declining since then. Only 2% of SCLC cases occur in never-smokers (defined as fewer than 100 cigarettes smoked in their lifetime) [13]. There are several studies that show a relationship between air pollution [14] and radon [15] exposure and SCLC in never-smokers, although the evidence for both is weak. Inherited genetic variables are likely to play a minimal influence in the development of SCLC susceptibility [16]. Genetic diversity may play a role in the risk of nicotine addiction [17] and, as a result, SCLC risk may be influenced indirectly. Some instances of SCLC in never-smokers emerge by histological transition of EGFR-driven or ALK-driven lung adenocarcinoma to SCLC [18].In smokers, chronic obstructive pulmonary disease (COPD) is a prevalent comorbidity and an independent risk factor for SCLC [12]. Between 1995 - 2012, patients with SCLC increased mainly who had comorbidities, according to a Dutch registry research [19]. Comorbidities increased with age, and the risk of having comorbidities increased more for women than for males. In patients with limited-stage illness, multi-morbidity was linked to a slight increase in the probability of mortality, regardless of therapy. After adjusting for age, sex, stage, and diagnostic modality, the prevalence of comorbidity was linked to worse 8-year survival rates in patients with SCLC in a French registry research. For Charlson comorbidity index grades 1, 2 and ≥ 3, the hazard ratios were 1.6 (95 % CI 1.1–2.3), 1.7 (95 %CI 1.1–2.7), and 2.7 (95 % CI 1.7–4.4) [20].In comparison to other common solid tumours, SCLC has a very high death rate. Although the 5-year survival rate was modestly improving in a US Surveillance, Epidemiology, and End Results (SEER) registry data study, the median survival for the 1983–2012 period was just 7 months [21]. Clinical trial data from the last decade suggests that results are improving; however individuals with comorbidities are notably excluded from these trials due to performance status and other factors. SCLC outcomes do not appear to be improved by current CT screening guidelines, which have been shown to lower overall lung cancer mortality [22,23].

Pathophysiology

SCLC tumour mutational analysis reveals a distinct smoking signature, indicating that tobacco carcinogens are to blame for the development of SCLC [24]. The great majority of SCLC patients had simultaneous inactivation of two tumour suppressors, p53 and RB (encoded by TP53 and RB1, respectively). This simultaneous inactivation of tumour suppressors differs from the major oncogenic drivers of many other solid tumours, including non-small-cell lung malignancies (NSCLC), where activating oncogenic mutations appear to be required for carcinogenesis. SCLC carcinogenesis is thought to be aided by changes in the lung stroma and immune microenvironment [12]. However, it is unclear how these tumor-intrinsic and tumor-extrinsic variables influence the cell type from which SCLC arises, as well as how these tumours develop, spread, and react to therapy.

Key genetic lesions underlying SCLC

The loss of p53 and RB1 occurs often in SCLC [25,26], as has been recognised for decades. Amplification of MYC family genes (MYC, MYCL, and MYCN) in a subgroup of SCLC tumours was documented in other early investigations [27–29]. These findings were supported by DNA and RNA sequencing studies of larger cohorts of primary tumours, as well as patient-derived and CTC-

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derived xenograft models [24,30–33]. Loss-of-function events in RB family members p107 and p130 (encoded by RBL1 and RBL2, respectively) [34–36], the tumour suppressor PTEN [37,38], NOTCH receptors [24,39,40], and the chromatin regulator CREBBP [41] are among the few that have been functionally verified in animal models or cell culture experiments. Amplification of FGFR1 (encoding fibroblast growth factor receptor 1) [45] and GNAS (encoding the α-subunit of the heterotrimeric G protein G_s) [46] occurs in addition to recurrent amplification of MYC family genes [42–44].In 8% of SCLC tumours, the histone methyltransferase KMT2D (also known as MLL) is mutationally inactivated [47]. Importantly, original tumours and patient-derived xenograft models frequently correlate to early phases of SCLC development, which might lead to a bias in identifying genetic drivers. However, other than a possible involvement for WNT signalling in chemoresistant SCLC [48], genomic study of more advanced tumours has not yet uncovered novel drivers.The lack of clear mutationally defined subgroups of SCLC has not been detected using genomic profiling; however this might be related to the small number of tumour samples examined. Although the incidence of oncogenic drivers is expected to be higher in the uncommon never-smokers with SCLC than in tobacco users with SCLC [49], no consistent mutational differences have been established based on ethnicity or smoking status. A growing number of reports have described the histological transformation of lung adenocarcinoma to an aggressive neuroendocrine phenotype resembling SCLC, which is associated with acquired resistance to inhibitors of EGFR or other tyrosine kinase receptors [50–52], but tumour sample numbers are too small to draw firm conclusions about specific genetic or epigenetic alterations beyond the ubiquitous loss of p53 and RB in this transition.The scarcity of material for histological diagnosis and subsequent study has been a long challenge in the SCLC sector. The capacity to separate CTCs from the blood of SCLC patients can help to compensate for the absence of tumour material [53]. However, clinical trials including the collection of tumour material are still needed to uncover major genetic drivers of SCLC and speed up both clinical and fundamental research.Aside from human tissue research, genetically altered mice models have shown to be an essential pre-clinical platform for identifying and characterizing the molecular and cellular pathways of SCLC genesis, development, metastasis, and treatment response. In mice, genetic inactivation of both p53 and RB is required for the onset of SCLC [54], and mouse tumours acquire genomic changes that are comparable to those reported in human tumours [24,37]. The histopathology study of these mice's tumours reveals striking parallels to the breadth of histological traits found in human tumours [55]. Many of the molecular and cellular pathways of SCLC development outlined below have been found using these animal models, according to a recent study [56].

Molecular pathways affected in SCLC

RB is a primary inhibitor of S phase entrance, whereas p53 is a crucial component of several cell cycle checkpoints, causing cell cycle arrest or initiating apoptosis in response to diverse cellular stressors, such as aberrant replication. Loss of p107 or p130, amplification of MYC family members, changes in the PTEN pathway, and elevated BCL-2 expression all have been linked to SCLC cell growth, proliferation, and survival [57–59].The loss of p53 and RB causes the G1–S cell cycle checkpoint to be disabled, resulting in a greater dependence on succeeding cell cycle checkpoints to maintain genome integrity and proper chromosomal segregation. As a result, inhibiting G2–M transition kinases such ATR, WEE1, and CHK1 enhances mitotic catastrophe in SCLC cells, and these kinases are being investigated as therapeutic targets [44, 60–65]. Similarly, SCLC's deregulated cell cycle progression and consequent DNA damage may make it sensitive to a variety of DNA repair pathway inhibitors [66–68]. Activation of the PI3K–AKT–mTOR pathway has been linked to SCLC proliferation and apoptosis resistance [69, 70].A number of the changes discovered in SCLC cells have an impact on stem cell biology, cell fate choices, and lineage plasticity. Increased lineage plasticity and neuroendocrine differentiation in TP53-deficient and RB1-deficient prostate cancer [73,74] are two examples of how both p53 and RB are directly implicated in the control of these processes [71,72]. High amounts of the stem cell transcription factor SOX2, which are produced in response to p53 and RB loss [73–75] or as a result of genomic amplification [31], may also contribute to lineage flexibility in SCLC cells. In SCLC, mutations in chromatin modifiers are common; indicating that changes in epigenetic control may play a role in cell destiny [24, 47, 76, 77].The activation of stem and progenitor pathways in SCLC may allow intra-tumoural plasticity, for example, by promoting the loss of neuroendocrine characteristics in a subpopulation of SCLC cells [39]. Heterogeneity is common in SCLC tumours and may be a key mechanism by which they elude treatment [78,79]. Furthermore, heterogeneity rises in response to treatment. One reason might be that the diverse molecular and cellular fates selected by SCLC create reservoirs of cells with innate resistance to therapy, allowing acquired resistance mechanisms to arise over time as a result of further genetic or epigenetic modifications. The discovery of techniques to limit SCLC tumour plasticity may help to prevent the

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onset of treatment resistance.Changes in lineage plasticity and cell destiny regulators may impact the capacity of SCLC tumours to form from various cell types (including lung adenocarcinoma cells) in addition to being implicated in SCLC evolution and response to treatment [50]. Although it has long been considered that SCLC begins in neuroendocrine lung epithelial cells, evidence from mice models suggests that other lung epithelial cells, in addition to a fraction of neuroendocrine cells [80], might be the source of the disease [56,81–83]. The origin cell's epigenetic memory may have a significant impact on tumour growth, metastasis and therapeutic response.On average, there appears to be less genetic heterogeneity in SCLC tumours than in NSCLC tumours [24]. Although new genetic drivers may be selected for during the process of metastasis, the current findings are consistent with a model in which SCLC tumours have already acquired a set of genetic alterations that allow for rapid growth and rely more on epigenetic mechanisms to generate heterogeneity and respond to their microenvironment.

Cellular pathways affected in SCLC

Despite the fact that SCLC tumours are highly metastatic, little is known about how genetic and transcriptional alterations in SCLC cells impact cell adherence and migration. It is probable that SCLC cells' migration capacity is inextricably linked to neuroendocrine cells' strong migratory characteristics throughout lung development [84]. The extracellular matrix proteins laminin and fibronectin, as well as adhesion molecules like integrins, have been linked to survival and therapeutic resistance [85]. Similarly, high levels of CXCR4, a chemokine receptor for stromal cell-derived factor 1 (SDF1; also known as CXCL12), boost SCLC cell migration and survival [86–88]. Surprisingly, α3β1 integrin-mediated adhesion enhances the formation of axon-like protrusions on SCLC cells [89], suggesting that cell migration may be aided by processes similar to those seen in the migration of neuronal progenitors during brain development [90]. Although the epithelial-to-mesenchymal transition has been linked to treatment resistance in SCLC [77,91,92], it has yet to be investigated as a driver of cell migration. The interaction between adhesion, migration, survival, and proliferation may play a role in SCLC cells' high metastatic potential.SCLC cells can communicate with their milieu in a variety of ways, including autocrine, paracrine, and endocrine. Neuropeptides generated by SCLC cells have been shown in several studies to increase tumour cell survival and proliferation via autocrine and paracrine loops [93–96]. SCLC cell growth can be aided by autocrine KIT, Hedgehog, and IGF1 signalling [97–99], while paracrine FGF signalling between neuroendocrine and non-neuroendocrine SCLC cells may boost survival and metastasis [100]. The occurrence of endocrine paraneoplastic syndromes in SCLC patients [101,102] suggests that SCLC cells communicate with other cells in the body across great distances, although it is unknown whether these systemic effects play a role in SCLC development.Because SCLC cells proliferate at such a high pace, it is possible that they are just dependent on the metabolic pathways necessary for cell reproduction. Drugs utilised in SCLC patients, such as DNA cross-linkers (such as cisplatin), topoisomerase inhibitors (such as etoposide or topotecan), or γ-radiation, target DNA synthesis, replication, and repair directly or indirectly. The glycolytic and lipid production routes have been investigated as possible metabolic vulnerabilities in SCLC [103–105]. Because of the recurring mutations in mTOR signalling pathway components [24,106], investigations of amino acid metabolism in SCLC cells are warranted, and one research found that arginine plays a critical role in MYC-high SCLC tumours [107]. Nonetheless, research on SCLC cell metabolism is just getting started.

Drivers and trajectories of metastasis

SCLC metastases are seldom removed in people but insights into the biology of SCLC metastasis have come from both the research of CTCs and the development of mice models. Patients with SCLC have extraordinarily large numbers of CTCs, offering a unique opportunity to examine probable causes of metastatic seeding, including genetic abnormalities, expression variations and heterogeneity [2,32,53,108–110]. Although lymph node metastases are also common in people with SCLC [111] and in mice models of SCLC [42,83], the frequency of CTCs in SCLC implies that the circulation is a primary route of metastatic transmission. Adhesion between CTCs in these tiny clusters may be a crucial element of cell survival during metastasis [2]. Small clusters of malignant cells have been identified in both blood and lymphatic arteries in individuals with SCLC.SCLC tumours that form in the lungs of genetically modified mice frequently metastasis to the pleural space, lymph nodes, and distant organs, including the liver, much as they do in humans [54]. One major exception is the absence of brain metastasis in SCLC animal models, which might be due to biological differences between human and mouse tumours or mice dying quickly from their initial tumours and liver metastases. The transcription factor NFIB was discovered as a significant predictor of SCLC metastasis in mice models after investigation of primary tumours and metastases [112–114]. In human SCLC metastases, NFIB levels are also higher than in original tumours

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[112,113]. The stimulation of gene expression programmes linked to cell adhesion, cell migration, and neural development is one mechanism driving NFIB's pro-metastatic involvement in SCLC [90, 112]. Other than NFIB, the mechanisms behind SCLC metastatic potential are unknown [83,115]. However, variables involved with neuronal differentiation and migration have been linked to SCLC metastatic potential.

Immune Evasion

SCLC cells have a high tumour mutation load and are expected to elicit significant T cell responses as a result. Indeed, individuals with SCLC who have paraneoplastic neurological syndromes have more immune activity and have a better prognosis than those who do not have these syndromes [116]. Immunotherapies that increase the activity of T cells against cancer cells, such as CTLA4 blockage, PD1 blockade, or PDL1 blockade, has shown to be favourable in SCLC patients [117,118]. On the other hand, T cell checkpoint blocking only works in about 15% of SCLC patients [119,120]. Multiple reasons, including the poor expression of major histocompatibility complex (MHC) class I molecules on the surface of SCLC cells, might explain the limited efficiency of T cell-based immunotherapies against SCLC [121–124]. The presence of immune cells with suppressive qualities in the SCLC tumour microenvironment, such as regulatory T cells, may aid immune evasion [125,126]. Other strategies include neuropeptides released by SCLC cells suppressing antigen-presenting cells [127]. It is still unclear if immune cells and SCLC cells interact similarly in human tumours and genetically manipulated animal models. It is worth noting that mouse tumours have a low mutation burden, but human SCLC is one of the most mutated malignancies [24, 37], which might have a big impact on T cell responses. The stimulation of macrophages [128] and the generation of chimeric antigen receptor-expressing T cells that target SCLC specifically [129] should assist to overcome some of T cells' current lack of effectiveness against SCLC.

An emerging molecular classification

While the mutational landscape of SCLC tumours does not appear to identify subtypes, the expression of certain transcription factors provides a preliminary foundation for distinguishing physiologically distinct SCLC subtypes. High levels of ASCL1 (SCLC-A subtype), NEUROD1 (SCLC-N), POU2F3 (SCLC-P), or YAP1 (SCLC-Y) characterize four primary subtypes of SCLC [130]. SCLC-A has since been divided into two clusters (SCLC-A and SCLC-A2) that differ in their expression of HES1 [131], as well as an uncommon variant with enhanced expression of the transcription factor ATOH1 [79]. These subtypes appear to reflect differential MYC family member expression, with greater MYCL expression linked with SCLC-A and increased MYC expression happening in the other subtypes, among other distinctions. Aurora kinase inhibitors may be preferentially efficacious in MYC-high SCLC, according to data from both rodent models and clinical studies [44,132,133]. Different degrees of neuroendocrine differentiation and changes in metabolism distinguish the transcription programmes of these four subtypes. This newly developed molecular categorization also serves as a basis for further subtype refinement [131]. Single-cell investigations, on the other hand, are expected to aid in defining how intra-tumoural heterogeneity is linked to existing and maybe additional subtypes [109, 110]. A key feature of future research will be to track how SCLC tumours of different subtypes change with time and therapy, similar to how lung adenocarcinoma evolves into SCLC. According to data from mouse SCLC cell lines; there may be a developmental hierarchy among subtypes, with SCLC-A developing into SCLC-N, then SCLC-Y [134]. Note that current mouse models only model the SCLC-A and SCLC-N subtypes [130], and the development of new models combining various genetic alterations and different putative cell-of-origin types [56] will be critical for modelling all subtypes, potentially assisting in the definition of new subtypes and the investigation of intra-tumoural and inter-tumoural heterogeneity in SCLC. The identification of molecular subtypes of SCLC, as well as the relationship between these molecular subtypes and cellular programmes (such as "stem cell," "mesenchymal," or "neuronal"), may aid in the development of therapies targeted to subsets of patients who are most likely to benefit from a particular therapeutic approach. To battle the flexibility of SCLC cells and the heterogeneity of SCLC tumours, this tailored strategy necessitate the development of a variety of new treatment techniques, which would most likely have to be coupled. Blocking transitions between various states will be a significant part of such therapeutic treatments, which might be accomplished by targeting epigenetic regulators.

Diagnosis, screening and prevention

SCLC is a malignant epithelial tumour with a high grade. The tumor's distinctive light microscopic characteristics with haematoxylin and eosin staining are used to confirm the diagnosis. Other diagnoses can be ruled out using immunohistochemistry. Only two

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subtypes are recognised by the current WHO classification: SCLC and combined SCLC [135]. Non-small-cell carcinoma, which can be of any non-small-cell histological subtype, is included in Combined SCLC. Cytology is a strong technique that can be more conclusive than tiny biopsies, which sometimes contain crush artefacts in SCLC.

Clinical Manifestations

The mainly central position of the initial tumour in the major airways, as well as the sometimes substantial extrapulmonary metastatic dissemination at presentation is distinguishing clinical features of SCLC. Because of the fast tumour development and broad metastases, most patients with SCLC are symptomatic at the time of diagnosis, with symptoms lasting fewer than three months on average. Involvement of the bulky mediastinum is frequent. Cough, wheezing, dyspnoea, haemoptysis, superior vena cava compression leading in upper body oedema and flushing, oesophageal compression with dysphagia, and recurrent laryngeal nerve compression with left vocal cord paralysis are all indications of intrathoracic local growth. Distant spread is linked to fatigue, anorexia, weight loss, and neurological symptoms. Metastasis can occur in the brain, liver, adrenal glands, bone, and bone marrow.SCLC has been linked to a variety of paraneoplastic diseases [102,136]. Lambert–Eaton syndrome, encephalomyelitis, and sensory neuropathy syndromes are common SCLC paraneoplasticendocrinopathies caused by autoantibodies; paraneoplastic neurologic disorders induced by autoantibodies include Lambert–Eaton syndrome, encephalomyelitis, and sensory neuropathy syndromes. Dermatomyositis, hyperglycemia, hypoglycemia, hypercalcaemia, and gynecomastia are all rare symptoms. Immune checkpoint blockade, which increases cellular (T cell-mediated) immune responses, did not appear to exacerbate paraneoplastic manifestations in individuals with SCLC [137–139].

Diagnostic work-up

Because of the aggressive nature of SCLC, a diagnostic and staging work-up should be completed as soon as feasible when the patient presents. This evaluation involves imaging to determine the degree of illness, blood tests such as cell counts, liver and kidney function, and lactate dehydrogenase, and electrocardiography to ensure safety prior to cytotoxic drug delivery [136]. Because of the tumor's central placement, bronchoscopy with or without endobronchial ultrasonography is commonly used to acquire biopsies; other options include mediastinoscopy, transthoracic biopsies, or thoracoscopy. A biopsy of a distal metastatic location may be a better alternative depending on accessibility. Only histological investigation with cytology [140] can confirm the diagnosis. In patients with SCLC, a greater CTC count is a negative prognostic factor [2, 141], although it is rarely employed in practice outside of clinical trials. The use of CTCs and circulating cell-free DNA in the assessment of tumour features, such as intratumoural heterogeneity, is currently in the experimental stage [142–144]. The radiological findings in SCLC are comparable to those in other lung malignancies, with tumours being bigger, more centrally situated, and more progressed at presentation [145,146]. Bulky lymph nodes in the mediastinum are prevalent. Radiological evidence of metastatic dissemination, such as pleural and cardiac effusions, is common. Rarely, isolated peripheral nodules without lymph node involvement (approximately 5% of SCLC patients) occur and may be amenable to surgery.

Staging

The tumor–node–metastasis (TNM) classification [147] is preferred to the Veterans Administration Lung Study Group (VALSG) previous staging system, which distinguished limited-stage disease (tumour confined to one hemi-thorax and one radiation port; no malignant pleural or pericardial effusion) from extensive-stage disease (disease not meeting criteria for limited stage) [148]. TNM staging allows for greater anatomic distinction in outcome assessment, prognostic information, and more exact lymph node staging [140,149,150]. The VALSG staging method, for example, makes no distinction between individuals who have early-stage SCLC (T1–T2, N0–N1, M0) and those who have locally progressed illness (any T, N2–N3, M0). The TNM categorization is therefore useful in determining the best treatment options in clinical trials. SCLC has a consistently worse prognosis than NSCLC, stage for stage [147]. Brain metastases are prevalent in SCLC, with around 10% of patients presenting with brain metastases at the time of diagnosis and another 40–50% acquiring brain metastases later. The majority of patients with brain metastases are symptomatic, while MRI detects metastases in 15% of neurologically asymptomatic SCLC patients with no indication of brain involvement on CT [151]. In low-income nations, access to maximally accurate staging techniques is a major barrier. The TNM staging algorithm [147] is strongly recommended for clinicians and cancer registrars. Despite this, the VALSG staging approach is still frequently

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utilised in both the design and presentation of clinical trials, since it successfully differentiates patients treated solely with CRT (limited-stage illness) from those treated with systemic chemotherapy or chemo-immunotherapy (extensive-stage disease).

Pathology

SCLC is divided into two categories by the WHO pathological classification: (pure) SCLC (almost 80% of cases) and mixed SCLC (almost 20% of cases) [135]. Small tumour cells with a round to fusiform shape, sparse cytoplasm, finely granular nuclear chromatin, and missing or inconspicuous nucleoli are key histopathological diagnostic criteria. Mitotic rate is normally high, with an average of 60 and a median of 80 mitoses per mm^2 and >10 mitoses per mm^2. The number of apoptotic figures is high, and necrosis is frequently widespread. Because the cells are close together, nuclear moulding is common. Tumor cells that are densely packed have a sheet-like appearance and lack architectural characteristics. Rosettes (rose-shaped groupings of cells) and nests (circular clusters of cells separated by stroma), trabeculae (ribbons), and peripheral palisading are occasionally seen (parallel arrangement of nuclei at the periphery of nests). Surgical specimens may have more neuroendocrine traits than bronchial biopsy samples [152]. There are a lot of crush artefacts. Large or enormous tumour cells may be present, but they must account for less than 10% of the overall cell population to be diagnosed as pure SCLC [152].Large-cell carcinoma or large-cell neuroendocrine carcinoma (LCNEC) are the most prevalent NSCLC histological subtypes in combined SCLC, accounting for 4–16 % of all SCLC tumours; combined tumours with other NSCLC subtypes account for just 1–3% of all SCLC tumours. Large-cell carcinoma or LCNEC subtypes must account for 10% of the tumour area for a diagnosis of combined SCLC due to histological similarities with SCLC; other histological subtypes have no such criterion. Combined SCLC is more commonly detected in surgical samples than in tiny biopsy samples, presumably because the latter has more crush artefact and fewer cells [152,153]. Patients with mixed SCLC have comparable clinical presentations, chemotherapeutic responses, and survival rates as patients with pure SCLC, while the proportion of peripheral and resectable tumours is greater in combination SCLC [154]. Combined SCLC is uncommon in the SCLC-A and SCLC-N disease subtypes [155]. Analysis for EGFR mutation or ALK rearrangement should be considered in SCLC paired with adenocarcinoma or in never smoker. Following treatment, 13–45 % of pure SCLC tumours display morphological alterations, such as increased cell sizes or mixed histologies, indicating induced lineage plasticity in the setting of acquired chemoresistance [156,157].

- **Immunohistochemistry**

In principle, light microscopy-based histopathological investigation is used to diagnose SCLC, but in fact, immunohistochemistry is frequently used to distinguish SCLC from other diagnoses. Chromogranin, synaptophysin, and CD56 (also known as NCAM) are three commonly utilised neuroendocrine markers; CD56 is the most sensitive (positive in 90% of SCLC) but least specific of the three markers [158]. In the two most frequent subtypes of SCLC, SCLC-A and SCLC-N, a novel neuroendocrine marker, INSM1, is typically positive [159,160].

- **Cytology**

Cytological preparations can be helpful in diagnosing biopsies that are tiny, crushed, or necrotic [145]. Because of reciprocal deformation of squeezed nuclei, cytological smears frequently show solitary tumour cells or loose masses with nuclear moulding. Tumour cell chromatin is hyperchromatic; if well maintained it is finely or coarsely granulated and uniformly dispersed, giving it a distinctive "salt and pepper" appearance. The cytoplasm is small and nucleoli are missing or inconspicuous, resulting in a high nucleus to cytoplasm ratio.

Differential Diagnoses

Other neuroendocrine lung tumours, NSCLC, and, in particular, basaloid carcinoma, extrapulmonary small-cell tumours, and lymphoma are the primary differential diagnosis in SCLC patients. Other neuroendocrine lung tumours (typical and atypical carcinoid, and LCNEC) show neuroendocrine markers and cytokeratins that are similar to SCLC. Carcinoid tumours, both typical and atypical, differ from SCLC in tumour cell shape and mitotic rate, which is very high in SCLC but low in carcinoids (less than 10 mitoses per 2 mm^2). Ki67 nuclear staining shows that the proliferation rate in SCLC is always >50%, frequently reaching 80–100%, whereas it is only 30% in pulmonary carcinoids [161]. Carcinoid tumour cells have more cytoplasm than SCLC tumour cells, and necrosis is generally widespread in SCLC tumours but absent or limited in carcinoid tumours. SCLC is more difficult to distinguish from LCNEC, although it may be done using a combination of morphological criteria in addition to tumour cell size (>3 lymphocyte diameters in LCNEC). LCNEC tumour cells contain more cytoplasm, a polygonal form with a defined cell boundary,

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vesicular nuclear chromatin, and often visible nucleoli when compared to SCLC tumour cells [145].Basaloid carcinoma, a squamous cell carcinoma subtype, has the same tiny cell size as SCLC and can be confused for SCLC in small or crushed samples [162]. Because this marker is invariably negative in SCLC, positive staining for p40 can be utilised to differentiate basaloid carcinoma from SCLC [163]. SCLC is negative for napsin A, an adenocarcinoma marker [164]. SCLC tumours typically show positive staining with the wide-spectrum cytokeratin AE1/AE3 antibody cocktail but are always negative for the CK34βE12 antibody [165], which recognises the high-molecular-weight cytokeratins CK1, CK5, CK10, and CK14; lymphomas are negative for cytokeratins and express leukocyte common antigen (also known as CD45) [145]. Metastatic Merkel cell carcinoma, which tends to be positive for CK20 but negative for TTF1 and CK7 [166], is a rare factor in the differential diagnosis. Ewing sarcoma (with EWSR1 rearrangement) and other small round-cell sarcomas with rearrangements other than EWSR1 may be considered; compared to SCLC, these tumours have more dyscohesive cells, a lower mitotic rate, cytokeratin expression that is negative or very focal, and they stain for CD99 (also known as MIC2) [167–169]. In the event of a question, appropriate fluorescence in situ hybridization (FISH) methods should be used. SMARCA4-deficient thoracic tumours that are small and undifferentiated are known as epithelial sarcomatoid tumours [170].

Screening and prevention

Low-dose CT screening has discovered newly diagnosed SCLC cases in people at risk for lung cancer. The National Lung Screening Trial (NLST) randomised nearly 53,000 people who were at risk for lung cancer (based on age and smoking history) to yearly screening for three years with either a low-dose CT scan or a chest X-ray, and found SCLC tumours in 133 of them [22]. In contrast to NSCLC screening studies, where CT screening resulted in a significant change to earlier stage disease detection at diagnosis, there was no such movement in disease stage at diagnosis for SCLC: Stage I A–B tumours accounted for 10% of identified tumours, stage II A–B for 6%, stage III A–B for 29%, and stage IV with metastatic cancer for 54%; these percentages were identical with CT and chest X-ray screening [22]. Following assessments of the NLST and other comparable trials, it was discovered that CT screening did not identify SCLC at an earlier stage and consequently has no effect on survival in SCLC patients [23, 171–173]. The NELSON screening study enrolled almost 15,000 people at risk of lung cancer and found that yearly low-dose CT screening reduced lung cancer mortality overall, but no data analyses specific to SCLC have been published [174]. Despite the fact that several protein biomarkers for SCLC may be found in patient blood [175], no early intervention approach has been developed. There is currently no early screening method for SCLC that has been proven to be successful.As previously stated, smoking is significantly linked to SCLC, with 98 % occurring in current or past smokers [13]. Smoking cessation and prevention are the most effective strategies for reducing the societal impact of SCLC, as quitting smoking reduces not only the risk of developing SCLC but also the risk of death for patients diagnosed with limited-stage disease (affecting only one side of the chest and contained within a single radiation port) by nearly half [176].

Management

The initial strategy to SCLC therapy differs significantly depending on the stage. Treatment aims for non-metastatic SCLC include attaining long-term thoracic disease control and lowering the likelihood of metastatic spread. With mixed modality therapy, five-year survival rates of 25–30% can be attained. Surgery and radiation are two local therapeutic options for thoracic disease management. Chemotherapy has the ability to improve the local effectiveness of radiation while also treating micro metastatic illness. In this case, the usual chemotherapy treatment is cisplatin–etoposide, which hasn't altered in three decades. This regimen has the benefit of being able to administer the entire dosage in patients receiving concurrent CRT and having a well-established toxicity profile. Carbaplatin–etoposide can be used in patients who are not candidates for cisplatin [177]. Other chemotherapeutic medications, including irinotecan or paclitaxel, have showed action in these patients but not superiority [178]. Immune checkpoint inhibitors are being investigated as concurrent primary or adjuvant treatments in early-stage NSCLC [179] and metastatic SCLC [137,138] due to improved results with immunotherapy, although they are still considered experimental. In most patients with non-metastatic SCLC who respond to initial therapy, prophylactic cranial irradiation (PCI) is also part of conventional practice since it minimizes the likelihood of brain metastases and increases survival [3, 180].

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Early-stage SCLC

Early-stage SCLC (T1–T2N0–N1M0) affects only a tiny percentage of individuals with limited-stage SCLC [181]. Due to a dearth of randomized controlled trials comparing surgical and non-surgical procedures in the era of contemporary staging and therapies, the care of these individuals is contentious. These patients have at least three local treatment options: surgery, fractionated radiotherapy (which divides the overall dosage of radiation into smaller doses), and stereotactic radiotherapy. The role of PCI in these individuals is not as well understood as it is in patients with locally advanced SCLC.

- **Surgery**

Only two phase III studies have been published, one in the 1970s and the other in the 1990s [182,183]. Although currently available randomized controlled trial data do not indicate a role for surgical resection in the therapy of SCLC, a comprehensive review concluded in 2017 that this result is of limited significance due to a paucity of current data and the low quality of available evidence [184]. Inconsistencies in national and international treatment guidelines regarding the role of surgery in the management of SCLC [185] have resulted from this confusion. As a result, both physicians and patients find it difficult to choose between surgical and non-surgical treatments. Patients with clinical stage I or II (cT1–T2N0) illness are usually treated with primary surgical resection [140,186]. A microscopically margin-negative resection (R0 resection) is the goal of surgical therapy [187]. Patients with a full pathologic R0 resection for pT1–T2N0M0 SCLC have a 5-year survival rate of about 50%, according to population-based data studies [188]. Adjuvant chemotherapy should be administered after surgical resection, and adjuvant thoracic radiation should be avoided unless an incomplete resection (R1–R2) was done or histology revealed unexpected mediastinal nodal involvement (N2) [189].

- **Radiation**

Because the TNM classification was not used to grade patients in previous clinical studies of CRT, the information on fractionated radiation in early-stage SCLC is sparse. The CONVERT study found that concurrent CRT provides results equivalent to surgery in individuals with TNM stage I–II SCLC (approximately 15% of the patients enrolled) with minimal rates of acute and late toxicity [190]. Small retrospective studies with promising results on the function of stereotactic ablative radiation for early-stage SCLC have led to its inclusion as a therapeutic option in recommendations for patients with peripheral T1–T2N0M0 illness [191,192].

Locally advanced SCLC

The mediastinal and hilar nodes are involved in the majority of patients with non-metastatic, locally progressed SCLC (any T, N2–N3, M0). In most cases, surgery is not an option for these people. The role of radiation with concurrent chemotherapy in the treatment of locally advanced SCLC is well recognised [196]. Patients with a performance status of 0–1 (indicating they are at least ambulatory and can perform light or sedentary labour) should receive twice-daily thoracic radiation (45 Gy in 3 weeks) with concomitant cisplatin–etoposide [197,198]. Once-daily radiation is a viable option if twice-daily radiotherapy is not possible for patient-specific or practical reasons [197]. Only 42% of European centresutilise twice-daily radiation, according to a 2019 survey [199]. This is mostly owing to logistical considerations. Patients with a performance status of 0–1 after treatment with concurrent CRT are projected to have a 5-year survival rate of 30% in the era of contemporary staging and radiotherapy (that is, 3D conformal radiotherapy or intensity-modulated RT, without elective nodal irradiation) [197]. With modern treatment planning, severe treatment-related toxicity has been reduced: in the CONVERT study, which randomly assigned patients to once-daily or twice-daily radiotherapy, only 20% of patients receiving either treatment developed severe oesophagitis, compared to >30% in earlier trials using 2D radiotherapy techniques [197].Evidence from randomized controlled trials and meta-analyses suggests that radiation should be started as soon as possible during CRT, ideally during the first or second round of chemotherapy [197,198, 200–203]. The dosage to the organs at risk may not allow for early thoracic radiation delivery in situations with bulky disease at presentation. In such circumstances, radiation can be postponed until the third round of chemotherapy has begun, at which point the disease volume is expected to have decreased [204]. Sequential CRT rather than contemporaneous CRT is another alternative, especially in frailer or older (≥75 years old) individuals [205]. Treatment of the post-chemotherapy primary tumour volume and the pre-chemotherapy nodal volume is the standard radiation technique in the sequential context [206].In patients with non-metastatic SCLC, PCI reduces the incidence of symptomatic brain metastases while also improving overall survival [180,207]. Patients with a performance status of 0–1 are currently offered PCI if they respond to first CRT treatment [3]. Patients with a performance status of 2 (ambulatory, capable of self-care but unable to carry out any work activities; up to and about >50 % of waking hours) after

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CRT, patients over 70 years of age, and those with pre-existing neurological conditions such as stroke or epilepsy have less evidence supporting PCI. A joint decision-making process should be fostered in such patients [208].

Metastatic disease

For more than three decades, a platinum drug (cisplatin or carboplatin) in combination with etoposide has been the standard of care for newly diagnosed metastatic SCLC [1]. In a Japanese population, a phase III clinical trial found that cisplatin–irinotecan was superior than cisplatin–etoposide [209], but two following randomised studies in the United States failed to support this finding [210,211]. Adding an immune checkpoint inhibitor to first-line treatment in patients with newly diagnosed metastatic SCLC has been shown to have statistically significant advantages in multiple randomised phase III studies [137–139]. Adding one of two anti-PDL1 monoclonal antibodies (atezolizumab or durvalumab) to a standard platinum–etoposide backbone and continuing immunotherapy as maintenance enhanced progression-free survival and overall survival [137,138]. In the same setting, pembrolizumab, an anti-PD1 antibody, had a similar effect, but only statistically significant for progression-free survival [139]. The benefits are less obvious in the middle (2-month extension of median survival) than at the tail of the survival curve in all of these studies; taken together, these studies imply that immune checkpoint inhibition leads to an approximate doubling of 2-year survival, from 11% to 22%. These findings suggest that while the majority of SCLC patients do not benefit with immunotherapy, there is a subgroup that does. PDL1 expression does not appear to be a correlate of immunotherapy benefit in SCLC, unlike in other solid tumours [139]. The usefulness of tumour mutation burden as a predictive biomarker of SCLC response to immunotherapy is debatable, as the Checkmate-032 study found a link but the IMPOWER133 blood-based study found no link [137,212]. The area of active research is defining tumour and host features linked to immunotherapy response.

After a long period of no new SCLC medicines, the FDA has granted fast approval to three new drugs in the last three years. Until 2020, topotecan, a topoisomerase I inhibitor, was the only second-line treatment option for recurrent metastatic SCLC. Lurbinectedin, an alkylating drug that binds to the minor groove of DNA and inhibits transcription, received accelerated approval for second-line treatment based on a 35 % in a single-arm phase II study of 105 patients [213]. The anti-PD1 monoclonal antibodies nivolumab and pembrolizumab were given fast authorisation for third-line use [119,120], while their relevance in patients who have progressed on first-line immune checkpoint inhibitors is unclear. Many other cytotoxic agents, including the nivolumab–ipilimumab combination, paclitaxel, docetaxel, irinotecan, temozolomide, and oral etoposide, have clinical activity in SCLC and are included as options in treatment guidelines for recurrent SCLC despite not being approved by regulatory authorities for the specific indication [3]. Another option is to give a platinum doublet to patients who have had a response for at least 3 months following first-line treatment.Traditionally, radiotherapy has been used to relieve symptoms in patients with advanced cancer, especially those who have had poor responses to chemotherapy. The brain is the most prevalent location of distant failure in patients with advanced SCLC, with 40–50% of patients acquiring brain metastases after palliative treatment is completed. Although a European phase III research revealed a survival benefit [214], the usefulness of PCI in individuals with metastatic illness is debatable. However, a more recent Japanese phase III research indicated that PCI did not provide a benefit for patients with metastatic SCLC who were monitored using MRI [215]. Clinical trials are under underway to resolve this debate [216]. Leptomeningeal metastasis treatment is still a big unmet need.Given that up to 75% of patients with advanced SCLC have persistent intrathoracic disease following chemotherapy and further intrathoracic disease progression, consolidation thoracic radiation is a viable option. Although there was no statistical difference in 1-year survival in a European trial that randomly allocated patients to consolidative thoracic radiation or best supportive care, a post hoc analysis revealed that radiotherapy improved 2-year survival with a low risk of toxicity [217]. Patients with remaining intrathoracic illness benefited the most from this treatment. The integration of thoracic radiation, PCI, and immunotherapy in the metastatic situation is a significant unresolved question.

Follow-up

Patients with SCLC have a high risk of relapse, with 75% of patients with locally progressed cancer and more than 90% of patients with metastatic disease relapsing within two years of treatment [137,197]. Periodic CT scanning is indicated to detect recurrence as soon as possible and, if necessary, offers salvage treatment. However, there is a lack of evidence to back up the frequency of imaging and its impact on survival. In patients who have not had PCI, a brain MRI is advised as part of their follow-up [215]. Another reason for routine imaging of SCLC patients is the increased risk of developing second malignancies in the lungs and other organs, which

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are usually caused by tobacco use [218,219]. The management of the various comorbidities typically associated with SCLC (including cardiac and respiratory comorbidities generally caused by smoking) should also be included in the follow-up of patients with SCLC, particularly those with non-metastatic illness [19,220]. Treatment-related side effects, such as pulmonary fibrosis or cardiac problems, may require specialised intervention [221]. Patients who are treated by a multidisciplinary team that includes non-oncology specialists are more likely to have better symptom control, a higher quality of life, and maybe better results.Patients should be actively encouraged to cease smoking at the time of diagnosis and during follow-up. Indeed, smoking following a diagnosis of SCLC is linked to an increased risk of secondary tumours, as well as cardiovascular, pulmonary, and cerebrovascular illness, all of which lead to decreased survival [176,222].

Quality of life

Personalized treatment is at the heart of modern oncology, and it should take into account the risk-to-benefit ratio of each patient's treatment. Because the majority of patients with SCLC have a poor prognosis, objectives of treatment, and supporting care, open and honest discussions about prognosis, goals of care, and supportive care should take place early in the management of patients. All patients should be addressed and handled by a multidisciplinary team, including expert nurses and supportive-care specialists. When discussing treatment, patients should be fully informed on the treatment's short- and long-term side effects, as well as their impact on quality of life. This information is especially essential for individuals with metastatic disease who have a short life expectancy and for whom the risk of toxicity should not outweigh the treatment's clinical benefit. Because SCLC is an unusually chemoresponsive disease at diagnosis, patients with low performance status due to the disease may notice a significant improvement after starting chemotherapy. Improvements in survival rates in patients with non-metastatic SCLC over the last 20 years have led to a greater focus on reducing the long-term toxicity of curative-intent treatments like CRT and PCI. The importance of recognising and reducing the effect of treatment-related toxicities has been highlighted by the few patients with metastatic SCLC who respond remarkably well to immunotherapy. The improved results, particularly for patients with non-metastatic SCLC, have increased physician and patient concern about the potential of neurotoxicity associated with PCI [223]. Patients with cerebral shrinkage and white matter abnormalities on brain imaging have been documented to suffer memory loss, intellectual deficiency, dementia, and ataxia. A multitude of factors, including underlying comorbidities caused by smoking, paraneoplastic syndromes, underlying anxiety and depression, chemotherapy, and SCLC itself, have been shown to impact neurocognition. This is confirmed by research that shows impairment in cognitive tests in SCLC patients even before PCI [207,224]. The objective of ongoing clinical trials, such as those examining the effectiveness of hippocampus-sparing PCI and comparing PCI to MRI monitoring [216], is to minimise neurotoxicity.

Outlook

The construction and study of representative genetically altered mice models of SCLC yielded many novel insights into SCLC biology, which were complemented and strengthened by parallel investigations of SCLC cell lines, patient-derived in vivo models, and primary human tumours [225]. Both transcriptome [77] and proteomic [46] analyses of mechanisms of in vivo acquired treatment resistance in SCLC have uncovered additional potential tumor-specific vulnerabilities. The increased knowledge of important transcriptional drivers of SCLC phenotypes, which defines subtypes of illness with different dependencies, may aid therapeutic clinical research by focusing on patient populations that are more likely to react to certain targeted treatments [130]. Improvements in imaging and sophisticated radiation administration have boosted the survival rates of patients with localised illness while lowering the short-term and long-term adverse effects [197]. Immunotherapy's inclusion in conventional treatment for many patients with metastatic SCLC has ultimately resulted in improved overall survival for this group of patients who had a particularly bad prognosis [137,138]. Despite these achievements, SCLC remains a condition that is mostly fatal. There are several gaps in our knowledge of the disease, which contribute to the limited impact of existing medications on patient survival.Especially as the etiologic agent in oncogenesis is remarkably evident, the social burden of SCLC might be avoided with good prophylaxis. SCLC is one of the illnesses that have been closely linked to cigarette carcinogen exposure [12]. It is impossible to overstate the importance of global and multidimensional public health advocacy and governmental regulation efforts to minimise smoking start and increase smoking cessation. Effective screening for SCLC in its early stages is a serious and unmet requirement. Blood-based detection with high sensitivity utilising mutational, proteomic, or multiparameter techniques is a hot topic of research. One possible strategy,

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according to preclinical investigations, is to use mass spectrometry to identify neuroendocrine markers [226]. The majority of SCLC patients die from metastatic illness. As previously stated, yearly CT screening in a high-risk group fails to detect early-stage SCLC; regardless of whether patients are screened or not, the majority of patients are diagnosed with stage IV illness [22]. This finding might point to a biological distinction between limited-stage SCLCs, which are typically diagnosed with a big main mass with bulky adenopathy, and extensive-stage SCLCs, which are frequently diagnosed with widespread metastases. There is a scarcity of evidence on the drivers of haematogenous metastasis in human SCLC, except from the function of NFIB in metastasis in certain but not all SCLC models [83,112]. In SCLC, studies have revealed significant intertumoural and intratumoural heterogeneity. We are barely scratching the surface of how disease biology is influenced by this variability. Separate subtypes of SCLC might represent different cells of origin in the lung epithelium and various routes of oncogenesis, according to the discovery of a discrete subtype of SCLC mediated by the transcription factor POU2F3 [83,227]. We are only just starting to figure out how variable subtype assignments are, and whether tumour development across subtypes is due to lineage plasticity or differential selection among pre-existing subclones [134]. Multiple recurrent mutations impacting epigenetic regulatory mechanisms have been identified in SCLC [24, 40, 41, 77]; nevertheless, it is uncertain how these epigenetic pathways decide or drive the change between transcriptional states. Despite the existence of predicted subtype-specific vulnerabilities [130], the amount to which distinct dominant subtypes impact clinical prognosis, treatment responsiveness, and disease progression patterns has yet to be determined. Intratumoural heterogeneity, which includes a mix of interacting neuroendocrine and non-neuroendocrine subpopulations, has been linked to the propensity for metastatic spread in mice models [39, 228], but has received less attention in human tumours. New single-cell profiling tools, including as single-cell transcriptional profiling, proteomic profiling, and spatial multicolor imaging, are well suited to begin investigating some of these difficulties. The introduction of chemo-immunotherapy as a new standard of care for the first-line treatment of metastatic illness [137, 138] is both a significant hallmark of progress and disappointment. Despite SCLC tumours having a severely altered genome, the overall benefit in survival by adding immune checkpoint blockade is low compared to that reported in many other solid tumours. These findings are both a proof of principle — that cytotoxic T cells can recognize SCLC, resulting in long-term benefit — and a challenge: why is this benefit seen in such a small percentage of patients with metastatic SCLC, and what can be done to activate effective immune responses in the nearly 80% of patients who will die within two years of diagnosis? Clinical research is now focusing on alternative immune activation pathways, such as blocking alternative immune checkpoints, using bispecific T cell engagers or natural killer cell activators, and evaluating DNA damage response inhibitors or epigenetically targeted agents as strategies to induce immune responsiveness in SCLC [229]. Early-stage and locally advanced SCLC have similar obstacles in terms of increasing survival. Multiple studies are in development or in ongoing to examine the function of PD1–PDL1 checkpoint inhibition in patients treated with CRT, building on the results in treating metastatic illness. Combining immunotherapy with radiotherapy has a good rationale: radiation impacts the tumour microenvironment by releasing tumour antigens, inducing the cGAS–STING pathway, up regulating MHC class I expression, stimulating type I interferons, and promoting $CD8^+$ T cell infiltration [230–232]. Patients with limited-stage SCLC are also being tested for novel medicines that target DNA damage responses (for example, PARP inhibitors) or epigenetic regulators (for example, LSD1 inhibitors). This environment is suitable for the discovery and testing of biomarkers of residual illness, as 25–30% of patients treated with mixed modality therapy remain alive and free of progression after 5 years, while the majority of patients are destined to acquire disease progression within 18 months [197]. It would be fascinating to learn whether sensitive methods for detecting circulating tumour DNA in blood and, possibly, in cerebrospinal fluid could be used to distinguish between patients who would benefit from additional treatment, such as PCI or additional systemic therapies, and those who would be cured by thoracic CRT alone.Multiple innovative therapy methods have been found as a result of the breakthroughs made in understanding the genetics and molecular processes that drive SCLC during the last decade. Laboratory research in SCLC has increased rapidly, facilitated in large part to an increase in the quantity and diversity of representative preclinical models. There are still many gaps in our understanding of SCLC, and clinical progress is lagging behind that of NSCLCs. Clinical research is now pursuing a number of innovative treatment targets. In the coming decade, we expect that continuing to employ new insights from laboratory investigations to educate and concentrate clinical trials will result in clinically substantial advances for SCLC patients.

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CONCLUSIONS

Although early results employing cytokine and vaccination treatments were greeted with modest success, the development of immunotherapies as a therapy for SCLC has taken several years. The most significant developments in SCLC treatment in decades have only lately been made possible by the discovery and use of checkpoint inhibitors. These discoveries have led to a new standard of care and resurgence in the study of immunotherapy for this condition. Efforts are being made now and in the future to investigate the interactions between immunotherapies, small-molecule drugs, and chemotherapy, as well as the use of biomarkers to choose the best immunotherapies.

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