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REVIEW

Combined small-cell lung carcinoma

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Abstract: Currently, studies assessing combined small-cell lung carcinoma (C-SCLC) are relatively scarce and limited. Indeed the clinicopathological features, treatment, and prognosis of patients with C-SCLC have not been fully determined. The incidence of C-SCLC ranges from 5%–28% in different studies, which is related to the specimen types used. The clinical features of C-SCLC are characterized by the higher proportion of peripheral locations, earlier stage, and more opportunity to experience surgery. Surgery is more important for earlier stage C-SCLC. There have been no recent changes in the chemotherapy of C-SCLC, which is recommended by the treatment guidelines for SCLC, neither showing survival benefit from the 3-agent regimen. Meanwhile, the efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) in EGFR-mutated C-SCLC patients remains inconclusive. This review focuses on clinical and pathologic features, prognostic factors, and optimized treatment model in C-SCLC.

Keywords: C-SCLC, clinical, pathologic, molecular features, treatment, prognosis

Introduction

Combined small-cell lung carcinoma (C-SCLC) is defined by the World Health Organization (WHO) as small-cell carcinoma (SCLC) combined with additional components that consist of any of the histological types of non-small-cell lung carcinoma (NSCLC); usually adenocarcinoma (ADC), squamous-cell carcinoma (SCC), large-cell carcinoma (LCC), large-cell neuroendocrine carcinoma (LCNEC), or less commonly spindle-cell carcinoma or giant cell carcinoma.[1] When ADC, SCC or sarcomatoid carcinoma are combined with SCLC, C-SCLC is diagnosed irrespective of cell amounts. However, at least 10% LCC (or LCNEC) is required for C-SCLC diagnosis.[2] The 1999 WHO classification of lung tumor acknowledged 2 SCLC types, including pure and combined subsets;[3] C-SCLC belonged to a subset of SCLC. With recent advances in diagnostic techniques, C-SCLC incidence currently has shown an increasing trend. However, reports assessing C-SCLC are still scarce. C-SCLC contains a variety of NSCLC components, resulting in significant differences between it and pure SCLC in terms of biological and clinical features, as well as molecular and pathologic characteristics. Treatment of C-SCLC is based on the National Comprehensive Cancer Network (NCCN) guidelines for SCLC (2017 version 3). Due to C-SCLC comprising some NSCLC components, there should be different from pure SCLC. Therefore, C-SCLC should not be completely equivalent to pure SCLC.

Definition and history of C-SCLC

In the 1981 revision of the WHO classification, SCLC was subdivided into 3 categories, ie, oat cell, intermediate cell, and combined cell types. Combined subtypes were described as SCLC mixed with areas of differentiated SCC or ADC, other than LCC.[4]

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In 1988, the International Association for the Study of Lung Cancer (IASLC) groups classified SCLC into pure small cell, non-pure small cell (SC)/large cell (LC), and combined small cell types. However, subsequent findings suggested the prognosis of patients with non-pure SC/LC carcinoma was not as poor as described in the original literature. As such, WHO/IASLC retained the C-SCLC type and deleted non-pure SC/LC carcinoma in 1999; hence, the initial definition of C-SCLC dates back to 1999.[5] Furthermore, the WHO consistently modified the latter classification by dichotomizing SCLC into pure and combined types in 2004. More recently (in 2015), the WHO consistently considered C-SCLC to be a subset of SCLC, both of which were neuroendocrine tumors.

Histogenesis of C-SCLC

Combined tumors raise critical questions regarding the pathogenetic mechanism of each component and the association between the entities at hand. The exact mechanisms and histogenesis of C-SCLC remain unclear, which attracts increasing attention from scientists. Wagner et al[6] first assessed 7 C-SCLC cases for genotypic and immunophenotypic associations of individual components in the lesions, determining whether NSCLC constituents displayed features specific to SCLC. In this study, several biomarkers were utilized, including synaptophysin, CD56, chromogranin, bcl-2, thyroid transcription factor-1 (TTF-1), cytokeratin 7, and PAX-5. Clonal relationship between individual constituents was evaluated by analyzing loss of heterozygosity (LOH) for loci frequently missing in SCLC (chromosome 22q13), NSCLC (chromosome 17q), or both SCLC and NSCLC (chromosomes 3p and 17p). This study suggested the SCLC and NSCLC constituents of such tumors have comparable immunophenotypic properties, with neuroendocrine differentiation, indicating that a common clonal precursor with closer relationship with SCLC than NSCLC exists. Thus, that 22q13 is frequently deleted in C-SCLC reflects the immunophenotypic resemblance of individual lesion constituents, further indicating C-SCLCs are closer to SCLC than NSCLC. C-SCLC constituents have a close relationship, although they show apparent morphological differences. Biologically, morphologically distinct constituents could reflect divergent differentiation patterns from the same cancer stem cell. Furthermore, whether the divergent molecular properties of individual C-SCLC constituents dictate the morphological disparity observed was assessed. Meder et al[7] proposed SCLC might have an NSCLC associated secondary origin via inactivation of Notch mutations, ASCL1 (Achaete-scute family BHLH transcription factor 1) expression, and bi-allelic deletion of TP53 and RB1. Consistently, Ito et al[8] suggested elevated ASCL1 levels in NSCLC result in co-occurrence of a SCLC constituent. Hassan et al[9] recently reported histone deacetylation close to the Notch 1 promoter downregulates Notch 1 in SCLC; meanwhile, restoring Notch 1 expression promotes co-appearance of epithelial-like areas in SCLC, providing a possible mechanism underlying C-SCLC histogenesis. Therefore, epigenetic modifications, in particular histone acetylation, play critical roles in C-SCLC histogenesis.

Incidence of C-SCLC

The incidence of C-SCLC ranges from 5% to 28% in different studies, and is related to the type of specimens used.[10–12] The diagnosis frequency of combined histology is higher in surgical resection specimens compared with small biopsy or cytology samples, eg bronchial biopsy and needle aspiration. Babakoohi et al[10] identified 22 (5%) cases of C-SCLC in 428 consecutive SCLC patients. Among them, 12 specimens originated from bronchial biopsy or needle aspiration, with only 10 from surgical tissues. Only considering 23 SCLC patients who have underwent surgery, 10 patients were found with C-SCLC, indicating an incidence of C-SCLC as high as 45%. The most frequently encountered pathologic type was small-cell/LCC (n = 16), followed by small-cell/SCC (n = 3), small-cell/non-specified NSCLC (n = 2), and small-cell/ADC (n = 1). In contrast, Nicholson et al[2] reported a high incidence of C-SCLC (28%) in 100 consecutive resected SCLC cases. In the latter study, combination with LCC was the most common type (n = 16), followed by combination with ADC (n = 9) and SCC (n = 3). The results were similar between Eastern and Western countries, as Zhang et al[12] described 97 (30.1%) of 322 consecutive resected SCLC cases with C-SCLC. Indeed, C-SCLC incidence may be still underestimated, especially in patients without surgery. Luo et al[11] retrospectively analyzed 80 patients with pathologically confirmed C-SCLC, including 46 cases who had undergone surgery and diagnosed from surgical tissue specimens. Among the 46 patients, 21 (45.7%) failed to be diagnosed with C-SCLC from preoperative pathological or cytological examinations, including 13, 5, and 3 cases from bronchial biopsy, sputum or bronchial brushing cytology, and percutaneous transthoracic needle aspiration biopsy, respectively. The overlooked C-SCLC cases may be because of incomplete diagnostic data obtained with limited cytology samples or small biopsies.

Clinical and pathological characteristics of C-SCLC

Compared to pure SCLC, C-SCLC has unique characteristics, although there are no differences in patient's age, gender, or smoking history. The median age of C-SCLC patients is 59–64 years;[10,11] the majority of C-SCLC patients are male, at a proportion ranging from 43%–82.5%.[12,13] This gender imbalance might be closely associated with smoking since almost all C-SCLC patients have a history of heavy smoking. In agreement, Nicholson et al[2] reported that among 43 C-SCLC cases, 41 had a history of smoking (25–160 packs/year) with only 2 nonsmokers. Moreover, Luo et al[14] reported smokers are clearly more represented in the C-SCLS group, with a verified smoking history in 71 of the 88 C-SCLS cases assessed (more than 400 packs/year). Consistently, Luo et al[11] also revealed 62 patients (77.5%) with smoking history among 80 C-SCLC patients.

There are large differences in C-SCLC locations. In previously published studies, most authors proposed that C-SCLC develops predominantly in central sites (59.1%–86.4%). Indeed, Luo et al[14] found imaging features of central mass in 86.4% cases, including enlarged lymphoid nodes in the mediastinum (77.3%). The main clinical symptoms of C-SCLC are cough, dyspnoea, and hemoptysis. Men et al[15] reported that in 92 of 114 (80.7%) C-SCLC patients, the tumor occurred in the central areas. It is currently admitted that SCLC mostly occurs in the lobe or bronchial segment, with only about 25% of SCLC located in the peripheral parts. However, Mangum et al[16] reported 56% of C-SCLC in peripheral regions, a rate higher than the incidence of about 14% for pure SCLC. Collectively, compared with pure SCLC, C-SCLCs are more likely to occur in peripheral areas and to be accompanied by malignant pleural effusion, relative to pure SCLC. As such, we should consider the possibility of C-SCLC when peripheral SCLC is diagnosed by needle aspiration biopsy or cytology, as well as SCLC cells detected in pleural effusion.

With regard to tumor stage, approximately 40% of SCLCs are diagnosed at limited stage (limited disease [LD]) because of elevated rate of distant metastasis. In contrast, most C-SCLCs are found in LD. Consistently, LD occurs in more than 70% of C-SCLCs; indeed, Men et al[15] reported LD in 73% of 114 C-SCLC cases. Based on TNM staging, less than 5% of SCLC cases are stage I–II,[17] a rate that increases to 29% for C-SCLC in the same report. Meanwhile, Babakoohi et al[10] reported that C-SCLC has a much higher incidence (32%) in early stages (stages I and II) than pure SCLC (5%; 19 of 406 patients). In addition, the latter authors indicated a much higher resection rate for C-SCLC (45% of cases) than pure SCLC (3% of cases). Based on TNM staging, 29% of C-SCLCs were found to be stage I–II, a rate that decreases to 10% in SCLC cases.[18] Luo et al[11] demonstrated that more LD than extensive stage (extensive disease [ED]) (2.3:1; Table 1) are found in C-SCLC cases. Patients with stages I, II, III, and IV were found in 8 (10.0%), 13 (16.3%), 37 (46.3%), and 22 (27.5%) cases, respectively. This marked difference in disease stage between C-SCLC and pure SCLC might be explained as follows. First, most of the above cases had confirmed pathological diagnosis only postoperatively. Generally, cases eligible for surgical treatment showed a comparatively higher rate of early disease stage. Second, C-SCLC is not similar to pure SCLC in terms of clinical characteristics, with pure SCLC showing a higher frequency of distant metastasis.

Biomarkers and molecular features of C-SCLC

Mangum et al [16] reported that 9 (2%) of 429 SCLC patients treated in Vanderbilt University in 1977–1983 displayed a combined subtype of SCLC, with reduced amounts of lactate

Table 1 The differences in the clinical features, treatment methods and prognostic factors for C-SCLC compared with pure SCLC

	Pure SCLC	C-SCLC
Clinical features		
Location	Overwhelming majority central sites	About half were peripheral, especially pleural effusion
Stage	About 40% limited stage	About 70% limited stage
	About 5% I–II stage	About 30% I–II stage
Treatment		
Surgery	Little benefit	More benefit
Chemotherapy	Sensitive	Lower sensitive
Radiotherapy	Sensitive	Lower sensitive
EGFR-TKI	Less effective	Potential effective
Prognostic factors		Receive surgery, limited disease extent, good PS, right lung location, central site, combination with adenocarcinoma or spindle cell carcinoma, low NLR and normal CRP levels, and reduced RABEX-5 expression

Abbreviations: SCLC, small-cell carcinoma; C-SCLC, combined small-cell lung carcinoma; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; PS, performance status; NLR, neutrophile-lymphocyte ratio; CRP, C-reactive protein.

dehydrogenase (LDH) (301 versus 341 IU/L, $P = 0.0002$) at diagnosis. LDH levels in C-SCLC cases were between 215 and 605 IU/L (median, 301 IU/L; normal, <250 IU/L); meanwhile, they ranged from 210 to 10,960 IU/L (median, 341 IU/L) in SCLC patients. The underlying mechanisms remain unclear.

It is widely admitted that carcinoembryonic antigen (CEA) is an important biomarker of lung ADC. Serum CEA levels are different between pure SCLC and SCLC combined with ADC. In a previous study, 41 SCLC patients (35 with pure SCLC and 6 with C-SCLC) were reviewed after surgical resection between 2000 and 2014 in Zhejiang Cancer Hospital. Preoperative serum CEA levels were collected, and their association with SCLC type assessed. Interestingly, serum CEA levels > 6 ng/mL were found more frequently in C-SCLC patients compared with the pure SCLC group ($P = 0.031$). Therefore, preoperative serum CEA levels > 6 ng/mL could constitute a predictive diagnostic biomarker of SCLC combined with ADC.[19]

Epidermal growth factor receptor (EGFR) mutations are present in NSCLC and related to tumor response to EGFR tyrosine kinase inhibitors (TKIs), indicating that EGFR constitutes a potential biomarker. However, such mutations are rarely found in SCLC, and combined SCLC/ADC in patients with a history of light smoking may potentially harbor EGFR mutations. Previous studies reported that EGFR mutations occur in less than 5% of pure SCLC cases, while a rate reaching 15%–20% can be found in C-SCLC.[20–22] In our previous study, 2/40 SCLC patients had mutations in exon 19 of EGFR, as assessed by the xTAG technology (SurExam, Guangzhou, China). A 19-Del in EGFR was found in a woman with no history of smoking, whose pathological type was mixed SCLC/ADC; the second was a man with a history of smoking, who had combined SCLC and SCC.[21] EGFR mutations were detected in 5 (4%) SCLC cases in a Japanese study, and they were mostly light smokers with histologically combined subtype; the authors proposed that SCLCs harboring EGFR mutations are more likely to be combined with ADC relative to the entire SCLC patient pool. In an effort to confirm EGFR mutations in both the SCLC and ADC constituents, microdissected specimens were employed; this was the first study reporting a patient with combined SCLC and ADC with EGFR mutated in both constituents.[23] Shiao in Taiwan reported that of 76 SCLC samples, 2 (2.6%) had EGFR mutations (exon 19 deletions).[24] Routinely, SCLC samples are not assessed for EGFR mutations unless ADC is also detected. However, other points of view have been proposed. A recent review reported 27 patients with de novo SCLC harboring EGFR mutations, ruling out a potential involvement of small cell transformation in resistance to TKIs; 10 cases (37%) were C-SCLC, mixed with ADC (9 cases) and SCC (1 case).[25] EGFR mutations are scarce in SCLCs, and likely more frequent in C-SCLC, especially combined with ADC, compared with pure SCLC. Further assessment is required for improved understanding of the clinical implications of EGFR mutations in SCLC and C-SCLC.

Treatment of C-SCLC

Optimized treatment models for C-SCLC so far remain inconclusive, yet they more or less differ for NSCLC and SCLC: surgery is mainly applied in NSCLC, while the majority of SCLC cases are instead administered radiation and chemotherapeutics. Routinely, C-SCLC is treated based on SCLC guidelines, with multimodality treatment (surgery, radiotherapy and chemotherapy) often employed.

Surgical treatment may be applied in stage IA, IB, IIA, IIB, and IIIA NSCLC cases; among SCLC patients, only those classified as T1-2N0M0 are eligible for surgical treatment according to NCCN guidelines. Studies confirmed that use of surgery, and particularly lobectomy, yields optimal local control and results in a higher survival rate in patients with early stage SCLC.[26,27] However, the role of surgery in the early stage of C-SCLC remains largely unknown. Hage et al[28] evaluated 26 cases with combined and pure SCLC after surgery; interestingly, stage I C-SCLC cases showed a cumulative 5-year survival rate of 31% postoperatively, while stage II and III cases had no survival at this time point. Therefore, surgery might confer long-term disease-free survival (DFS) or even be curative in stage I C-SCLC. Babakoohi et al[10] identified 22 cases with C-SCLC, and compared them with 406 pure SCLC cases assessed simultaneously; the C-SCLC group was more commonly treated surgically compared with pure SCLC cases (45% versus 3%; $P < 0.0001$). Meanwhile, overall survival (OS) after surgery was 2.5-fold lower in SCLC cases compared with C-SCLC patients. Men et al[15] reported a 5-year OS in C-SCLC post-surgery of 48.9% in the LD group, a rate markedly elevated compared with that of the non-surgery group (36.6%) and much improved relative to previously reported ones. Therefore, surgery is more significant in C-SCLC than SCLC, especially in the LD group. It is widely admitted that surgery is critical not only to C-SCLC diagnosis, but also improves treatment outcomes.

SCLC is mostly treated by chemotherapeutics, which may be also important in C-SCLC. We retrospectively assessed the clinical characteristics of 7 C-SCLC cases after surgery in Zhejiang Cancer Hospital from 2007 to 2010. One patient received no chemotherapy, and showed reduced survival

compared with other stage IIIA patients administered chemotherapeutics. This suggests that chemotherapy is significant for C-SCLC, and correlated with survival time.[21] Nine (2%) of 429 SCLC cases treated in Vanderbilt University from 1977 to 1983 had combined SCLC. Initially, all 429 patients underwent chemotherapy, and response rates were similar between the combined- and other subtypes of SCLC.[16] Men et al[15] reported that although nearly 84% C-SCLC patients (112) received chemotherapy, 5-year OS in C-SCLC cases after chemotherapy was 37.7%, which was close to that of individuals who did not undergo chemotherapy (35.4%), with no significant difference between the 2 groups. These findings equally indicated the relatively reduced C-SCLC sensitivity to chemotherapeutics; an objective response rate (ORR) of approximately 50% was reported, likely because C-SCLCs contain an NSCLC constituent, while a relatively lower sensitivity to traditional chemotherapeutic regimens is observed in SCLC. However, the optimal chemotherapeutic regimen for C-SCLC remains undefined. Additional individualized chemotherapeutic regimens taking into account SCLC and NSCLC constituents are required. A retrospective study[29] was performed to compare treatment efficacy between the NIP (navelbine + ifosfamide + cisplatin) and EP (etoposide + cisplatin) regimens, as first-line treatments of stage III–IV C-SCLC. A total of 167 eligible patients were enrolled and divided into NIP (n = 76) and EP (n = 91) regimen groups. ORRs in the NIP (30.0%) and EP (38.5%) groups showed no statistically significant difference (P = 0.236). Median progression-free survival (PFS) was slightly prolonged in the EP group compared with the NIP group (6.5 versus 6.0 months, P = 0.163). Median OS and 1-year survival were 10.4 months and 36.3% in the NIP group, while 10.8 months and 49.0% were obtained in individuals administered EP, respectively. This suggested that the EP regimen has better survival benefits compared with the NIP regimen, but statistical significance was not reached. Therefore, the NIP regimen might be inferior to the EP regimen in C-CSLC, which should be also treated with EP as standard regimen. Another retrospective study[30] compared chemotherapeutic regimens based on 3 (taxol + carboplatin/cisplatin + etoposide) and 2 (carboplatin/cisplatin + etoposide) in C-SCLC with 19 patients received the 3-drug regimen and 43 the 2-drug regimen. ORRs in the 3- and 2-drug groups showed a marked difference (90% versus 53%, P = 0.033). In addition, administration of these 3 drugs resulted in non-significantly higher median PFS in comparison with the 2-drug regimen (10.5 versus 8.9 months, P = 0.484). Median OS in both groups were comparable (24.0 versus 17.5 months, P = 0.457). Grade IV bone marrow depression and treatment discontinuation associated with severe side effects were starkly more frequent in the 3-drug regimen compared with the 2-drug regimen (26.3% versus 7.0%, P = 0.036; 31.6% versus 4.7%, P = 0.004, respectively). These findings showed the 2-drug regimen has a similar survival but lower toxicity in comparison with the 3-drug counterpart, and should be routinely used for C-SCLC; the 3-component regimen did not improve efficacy.

Studies assessing the significance of radiotherapy in C-SCLC are virtually absent. Most clinicians consider C-SCLC is more resistant not only to chemotherapy but also thoracic radiotherapy, compared with pure SCLC. Indeed, whether radiotherapy improves OS in C-SCLC (as in pure SCLC) remains unclear.

EGFR-TKIs are broadly employed in NSCLC with EGFR mutations, but no randomized clinical trial evaluating these drugs for C-SCLC treatment has been reported. Small case series suggest that some may help treat C-SCLC and SCLC. A Japanese SCLC patient with deleted exon-19 in EGFR responded to gefitinib.[31] In addition, an American SCLC case with no history of smoking and mutated EGFR responded to erlotinib and gefitinib.[32] Another study[20] reported a woman with stage IV ADC and no history of smoking who was administered carboplatin and paclitaxel; tumor recurrence was observed in lymph nodes of the neck after biopsy. Next, L858R mutation was detected, and the patient was administered gefitinib. Partial response (PR) was achieved but the tumor recurred, and was surgically resected; histological examination revealed combined SCLC and ADC; EGFR was mutated in both ADC in the lymph node and the recurrent SCLC. Another study[33] reported a female SCLC patient (70 years) with no history of smoking. Biopsy indicated combined SCLC and ADC; EGFR L861Q mutation was found in both tumor constituents. Due to the advanced stage, first-line treatment with cisplatin and irinotecan was started, achieving PR. Seven months later, enlargement of the primary tumor occurred, and only ADC with the L861Q mutation was detected (biopsy). Erlotinib was administered, but multiple brain metastases and enlarged mediastinal lymph nodes subsequently occurred. Whole-brain radiotherapy was carried out, and endobronchial ultrasonography-guided transbronchial biopsy from revealed reverse transformation to SCLC with the L861Q mutation. In this patient, administration of 2-cycle amrubicin resulted in PR, and tumor shrinkage lasted for 8 months. Therefore, EGFR-TKIs could also be used in C-CSLC with EGFR mutations; however, it is difficult to accurately evaluate the efficacy of EGFR-TKIs because they are rarely assessed. In general, the efficacy of EGFR-TKIs in C-SCLC or SCLC is inferior to that in NSCLC.

Prognosis

Despite the increasing incidence of C-SCLC, few factors to predict prognosis of C-SCLC patients are available. Babakoohi et al[10] showed that OS is markedly elevated in C-SCLC in comparison with pure SCLC (15 versus 10.8 months; $P = 0.035$). However, OS was similar between C-SCLC and pure SCLC patients not surgically treated ($P = 0.64$). This indicates that C-SCLC patients, who benefit from more opportunities for surgery, have a better prognosis compared with pure SCLC cases. Wang et al[34] analyzed 613 SCLC, including 499 pure SCLC patients and 114 C-SCLC cases, and OS was comparable between the 2 groups ($P = 0.995$). Multivariable analysis showed that OS was influenced by the disease extent (HR = 3.406, $P < 0.001$), American Eastern Oncology Group (ECOG) performance status (PS) (HR = 2.001, $P = 0.012$), and neutrophile-lymphocyte ratio (NLR) (HR = 1.704, $P = 0.030$) in C-SCLC. A total of 44 C-SCLC cases administered radical surgery in Tianjin Medical University Cancer Institute and Hospital in 2006–2008 were assessed.[35] Median OS of C-SCLC cases was 20 months, for DFS of 14.5 months; in comparison with male cases, females showed prolonged DFS, and OS was influenced by tumor location and the pathological types of morphological components ($P < 0.05$). OS in SCLC combined with LC carcinoma was lower than that of either SCLC combined with ADC or spindle-cell carcinoma. OS in C-SCLC located in right lung was longer than that of left lung, and in central tumors compared with peripheral ones. Cox multivariate analysis demonstrated tumor location and pathomorphological classification of combined constituents are independent prognostic factors for OS. Shao and Cai[36,37] equally found that the disease extent, PS, and neuron-specific enolase levels independently predict prognosis. They revealed that elevated pretreatment NLR (≥4.15) and serum C-reactive protein (CRP) amounts predict poor long-term prognosis in C-SCLC. NLR was shown to be significantly associated with disease stage ($P = 0.033$) and recurrence ($P = 0.014$); meanwhile, OS and PFS were markedly reduced in patients with elevated NLR amounts. Median OS was markedly prolonged in patients with normal CRP levels compared with those showing elevated CRP (22.0 versus 11.5 months, $P < 0.001$). The above clinical trials were focused on clinical characteristics predicting recurrence and prognosis. However, novel molecular and specific markers with promising predictive values are required for prognosis improvement. Zhang et al[38] assessed the significance of RABEX-5 in C-SCLC, since numerous reports have demonstrated that it plays oncogenic roles in malignancies. They found that high RABEX-5 content is associated with poor prognosis in NSCLC. Meanwhile, high RABEX-5 protein amounts were found to be associated with clinical stage and tumor recurrence. Median OS and DFS were markedly reduced in patients with elevated RABEX-5 levels in comparison with those lowly expressing this protein (OS: 12.0 versus 21.7 months, $P = 0.014$; DFS, 6.7 versus 11.8 months, $P = 0.005$). Taken together, patients with clinical characteristics such as surgical treatment, limited disease extent, good PS, right lung location, central site, combination with ADC or spindle cell carcinoma, low NLR and normal CRP levels, and reduced RABEX-5 expression, may have a better prognosis.

Conclusion

C-SCLC currently accounts for approximately 5%–10% of all SCLC cases, probably reaching as high as 25%–45% in patients diagnosed after surgical resection. Since C-SCLC is in a relatively early stage at diagnosis, more opportunities for surgery are available. OS was similar between C-SCLC and pure SCLC, however, C-SCLC cases have a better prognosis compared with individuals with the pure small-cell type, benefiting from surgery. Therefore, surgery plays a more important role in the comprehensive treatment of C-SCLC. C-SCLCs are relatively less sensitive to chemotherapy (ORR of approximately 50%), likely because they contain the NSCLC constituent. C-SCLC should be considered when peripheral SCLC is diagnosed or in case of SCLC resistance to chemotherapy. EGFR-TKIs have only been used in very few C-SCLC cases with EGFR mutations, and it is difficult to accurately evaluate their efficacy because of data sparsity.

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Disclosure

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References

1. Travis WD. The 2015 WHO classification of lung tumors. *Pathologe*. 2014;35(Suppl 2):188.
2. Nicholson SA, Beasley MB, Brambilla E, et al. Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens. *Am J Surg Pathol*. 2002;26(9):1184–1197.
3. Beasley MB, Brambilla E, Travis WD. The 2004 World Health Organization classification of lung tumors. *Semin Roentgenol*. 2005;40(2):90–97.

4. Sobin LH. The World Health Organization's histological classification of lung tumors: a comparison of the first and second editions. *Cancer Detect Prev*. 1982;5(4):391–406.
5. Wagenaar SS. New WHO-classification of lung and pleural tumors. *Ned Tijdschr Geneeskd*. 1999;143(19):984–990.
6. Wagner PL, Kitabayashi N, Chen YT, Saqi A. Combined small cell lung carcinomas: genotypic and immunophenotypic analysis of the separate morphologic components. *Am J Clin Pathol*. 2009;131(3):376–382.
7. Meder L, Konig K, Ozretic L, et al. NOTCH, ASCL1, p53 and RB alterations define an alternative pathway driving neuroendocrine and small cell lung carcinomas. *Int J Cancer*. 2016;138(4):927–938.
8. Ito T, Kudoh S, Ichimura T, Fujino K, Hassan WA, Udaka N. Small cell lung cancer, an epithelial to mesenchymal transition (EMT)-like cancer: significance of inactive Notch signaling and expression of achaete-scute complex homologue 1. *Hum Cell*. 2017;30(1):1–10.
9. Hassan WA, Takebayashi SI, Abdalla MOA, et al. Correlation between histone acetylation and expression of Notch1 in human lung carcinoma and its possible role in combined small-cell lung carcinoma. *Lab Invest*. 2017;97(8):913–921.
10. Babakoohi S, Fu P, Yang M, Linden PA, Dowlati A. Combined SCLC clinical and pathologic characteristics. *Clin Lung Cancer*. 2013;14(2):113–119.
11. Luo Y, Hui Z, Yang L, Li J. Clinical analysis of 80 patients with combined small-cell lung cancer. *Zhongguo Fei Ai Za Zhi*. 2015;18(3):161–166.
12. Zhang C, Yang H, Zhao H, Lang B, Yu X, Xiao P, Zhang X. Clinical outcomes of surgically resected combined small cell lung cancer: a two-institutional experience. *J Thorac Dis*. 2017;9(1):151–158.
13. Wallace AS, Arya M, Frazier SR, Westgate S, Wang Z, Doll D. Combined small-cell lung carcinoma: an institutional experience. *Thorac Cancer*. 2014;5(1):57–62.
14. Luo J, Ni J, Zheng H, et al. Clinical analysis of 88 cases with combined small cell carcinoma. *Tumor*. 2009;29(2):156–159. Chinese.
15. Men Y, Hui Z, Liang J, et al. Further understanding of an uncommon disease of combined small cell lung cancer: clinical features and prognostic factors of 114 cases. *Chin J Cancer Res*. 2016;28(5):486–494.
16. Mangum MD, Greco FA, Hainsworth JD, Hande KR, Johnson DH. Combined small-cell and non-small-cell lung cancer. *J Clin Oncol*. 1989;7(5):607–612.
17. Kalemkerian GP, Schneider BJ. Advances in small cell lung cancer. *Hematol Oncol Clin North Am*. 2017;31(1):143–156.
18. Brock MV, Hooker CM, Syphard JE, et al. Surgical resection of limited disease small cell lung cancer in the new era of platinum chemotherapy: its time has come. *J Thorac Cardiovasc Surg*. 2005;129(1):64–72.
19. Lei L, Chen Q, Wang Z, et al. Usefulness of carcinoembryonic antigen in the diagnosis of small cell lung cancer combined with adenocarcinoma. *Adv Clin Exp Med*. 2017;26(7):1091–1094.
20. Tatematsu A, Shimizu J, Murakami Y, et al. Epidermal growth factor receptor mutations in small cell lung cancer. *Clin Cancer Res*. 2008;14(19):6092–6096.
21. Lu HY, Mao WM, Cheng QY, et al. Mutation status of epidermal growth factor receptor and clinical features of patients with combined small cell lung cancer who received surgical treatment. *Oncol Lett*. 2012;3(6):1288–1292.
22. Lu HY, Sun WY, Chen B, et al. Epidermal growth factor receptor mutations in small cell lung cancer patients who received surgical resection in China. *Neoplasma*. 2012;59(1):100–104.
23. Fukui T, Tsuta K, Furuta K, et al. Epidermal growth factor receptor mutation status and clinicopathological features of combined small cell carcinoma with adenocarcinoma of the lung. *Cancer Sci*. 2007;98(11):1714–1719.
24. Shiao TH, Chang YL, Yu CJ, et al. Epidermal growth factor receptor mutations in small cell lung cancer: a brief report. *J Thorac Oncol*. 2011;6(1):195–198.
25. Siegele BJ, Shilo K, Chao BH, et al. Epidermal growth factor receptor (EGFR) mutations in small cell lung cancers: two cases and a review of the literature. *Lung Cancer*. 2016;95:65–72.
26. Schreiber D, Rineer J, Weedon J, et al. Survival outcomes with the use of surgery in limited-stage small cell lung cancer: should its role be re-evaluated? *Cancer*. 2010;116(5):1350–1357.
27. Varlotto JM, Recht A, Flickinger JC, Medford-Davis LN, Dyer AM, DeCamp MM. Lobectomy leads to optimal survival in early-stage small cell lung cancer: a retrospective analysis. *J Thorac Cardiovasc Surg*. 2011;142(3):538–546.
28. Hage R, Elbers JR, Brutel de la Riviere A, van den Bosch JM. Surgery for combined type small cell lung carcinoma. *Thorax*. 1998;53(6):450–453.
29. Luo J, Wu FY, Li AW, Zheng D, Liu JM. Comparison of vinorelbine, ifosfamide and cisplatin (NIP) and etoposide and cisplatin (EP) for treatment of advanced combined small cell lung cancer (cSCLC) patients: a retrospective study. *Asian Pac J Cancer Prev*. 2012;13(9):4703–4706.
30. Li YY, Zhou C, Yang DX, Wang J, Liu ZJ, Wang XY, Li K. Paclitaxel-etoposide-carboplatin/cisplatin versus etoposide-carboplatin/cisplatin as first-line treatment for combined small-cell lung cancer: a retrospective analysis of 62 cases. *Cancer Biol Med*. 2015;12(2):117–125.
31. Okamoto I, Araki J, Suto R, Shimada M, Nakagawa K, Fukuoka M. EGFR mutation in gefitinib-responsive small-cell lung cancer. *Ann Oncol*. 2006;17(6):1028–1029.
32. Zakowski MF, Ladanyi M, Kris MG. EGFR mutations in small-cell lung cancers in patients who have never smoked. *N Engl J Med*. 2006;355(2):213–215.
33. Takagi Y, Nakahara Y, Hosomi Y, Hishima T. Small-cell lung cancer with a rare epidermal growth factor receptor gene mutation showing "wax-and-wane" transformation. *BMC Cancer*. 2013;13:529.
34. Wang X, Jiang R, Li K. Prognostic significance of pretreatment laboratory parameters in combined small-cell lung cancer. *Cell Biochem Biophys*. 2014;69(3):633–640.
35. Lv X, Sun LN, Zhan ZL, Sun BC, Wang CL. Clinicopathological characteristics and prognosis of combined small cell lung cancer. *Chin J Clin Oncol*. 2011;38(13):769–772, 777. Chinese.
36. Shao N, Cai Q. High pretreatment neutrophil-lymphocyte ratio predicts recurrence and poor prognosis for combined small cell lung cancer. *Clin Transl Oncol*. 2015;17(10):772–778.
37. Shao N, Cai Q. High pretreatment serum C-reactive protein level predicts a poor prognosis for combined small-cell lung cancer. *Tumour Biol*. 2015;36(11):8465–8470.
38. Zhang F, Zhang M, Hu G, Cai Q, Xu T. Elevated RABEX-5 protein expression predicts poor prognosis in combined small cell lung cancer. *Tumour Biol*. 2015;36(11):8287–8293.