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Efficacy of addition immune checkpoint inhibitors to chemotherapy as first-line treatment for small cell lung cancer patients with liver or brain metastases: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Differential organ-specific tumor response to immune checkpoint inhibitors (ICIs) has been reported in multiple solid tumors. We aim at investigating the efficacy differences of ICIs combined with chemotherapy (CT) *vs.* CT alone as first-line treatment for extensive-stage small-cell lung cancer (ES-SCLC).

MATERIALS AND METHODS: We searched PubMed, Embase, Medline, and China National Knowledge Infrastructure databases to identify relevant trials comparing ICIs combined with CT *vs.* CT alone in ES-SCLC patients with brain or liver metastases. The primary outcome was overall survival (OS). The secondary outcomes included progression-free survival (PFS). The pooled hazard ratio (HR) was analyzed using the fixed or random effects model, according to heterogeneity among included trials.

RESULTS: We identified 5 randomized controlled trials of 8 studies that involved a total of 1,401 patients, 310 with brain metastases and 1,091 with liver metastases. The quality of included trials was high. The pooled results showed that ICIs combined with CT significantly improved OS of ES-SCLC with liver metastases (HR 0.88, 95%CI: 0.78-1.00, *p*=0.049), and a tendency to improve PFS (HR 0.86, 95%CI: 0.68-1.07, *p*=0.17). For patients with brain metastases, no survival benefit could be obtained from combination therapy of ICIs with CT in terms of PFS (HR 0.91, 95%CI: 0.63-1.32, *p*=0.62) and OS (HR 1.12, 95%CI: 0.88-1.43, *p*=0.36). No publication bias was detected.

CONCLUSIONS: The addition of ICIs to CT significantly improves OS in ES-SCLC patients with liver metastases compared with CT alone. No survival benefit could be obtained from ICIs and CT combination therapy for ES-SCLC with brain metastases.

Key Words:
Small-cell lung cancer, Extensive stage, Liver metastasis, Brain metastasis, Meta-analysis.

Introduction

Small cell lung cancer (SCLC), accounting for approximately 10-15% of all lung cancers, is characterized by rapid growth and early development of metastases[1]. As a result, most SCLC patients presented with advanced disease and distant metastases at the time of diagnosis[2]. Although SCLC accounts for a minority of lung cancers, the prognosis of SCLC patients remains dismal with a 5-year overall survival rate of less than 10%, including patients with both limited stage and extensive stage disease[3]. According to the staging system of the Veterans Administration Lung Study Group (VALSG), SCLC could be classified as limited-stage (LS) disease (tumor confined to one hemi-thorax and one radiation port; no malignant pleural or pericardial effusion) and extensive-stage (ES) disease (not meeting criteria for LS)[4]. Systematic treatment options for SCLC patients have not changed during the past three decades. For patients with limited-stage small-cell lung cancer (LS-SCLC), concurrent chemoradiotherapy with platinum-etoposide remained

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to be the standardized treatment. For patients with extensive-stage small-cell lung cancer (ES-SCLC), chemotherapy with platinum-etoposide is the most often used treatment strategy[5]. Although up to 80% of ES-SCLC initially responds to first-line chemotherapy exceptionally well, all patients would eventually recur later on. Once relapse, the median survival is around six months and few live beyond one year[6]. Therefore, there is an urgent need for innovative and effective first-line treatment for ES-SCLC.

Previous studies[7,8] have indicated that SCLC is a heterogeneous disease with a high tumor mutational burden (TMB) likely resulting from chronic tobacco exposure. In addition, SCLC is frequently associated with autoimmune paraneoplastic syndromes, such as hypercalcaemia, Cushing syndrome, myasthenia gravis[9]. Both of them suggest that SCLC might potentially be a good candidate for treatment with immune checkpoint inhibitors (ICIs). In the past decade, several prospective randomized trials have investigated the blockade of the cytotoxic T-lymphocyte-associated protein 4 and PD-L1 (CTLA-4/PD-L1) axis in addition to standard chemotherapy or as maintenance therapy, but the results are controversial. Subsequently, three meta-analyses demonstrated that ICI combined with chemotherapy as first-line treatment can significantly improve the OS and progression-free survival (PFS) of ES-SCLC patients ($p<0.05$)[10-13]. Based on these results, the U.S. Food and Drug Administration (FDA) approved atezolizumab and durvalumab for use in combination with platinum-etoposide for the first-line treatment of adult patients with ES-SCLC[14]. Although addition of ICIs to front line chemotherapy followed by maintenance now offers new hope for these patients, identifying the population who can benefit from immunotherapy is still a challenge. Indeed, subgroups analysis of phase 3 trials indicates that the clinical benefits obtained from ICIs in ES-SCLC with baseline brain or liver metastases were controversial. Therefore, we conducted this meta-analysis to comprehensively investigate whether ES-SCLC with brain or liver metastases could benefit from combination therapy of ICIs with platinum-etoposide chemotherapy.

Materials and Methods

Data Source

We searched PubMed, Embase, Medline, and China National Knowledge Infrastructure databases to identify the potentially relevant trials. The following keywords including immunotherapy therapy, immune checkpoint inhibitors, extensive-stage small-cell lung cancer, extensive-disease small-cell lung cancer, pembrolizumab, atezolizumab, ipilimumab, nivolumab, durvalumab, first line, randomized controlled trials were used. In addition, we also read recent meta-analyses to identify relevant trials investigating immunotherapy in SCLC patients. We only included the most complete and recent studies for analysis in order to avoid duplication. All results were input into Endnote X8 reference software (Thomson-Reuters, Stamford, CT, USA) for duplication exclusion and further reference management.

Study Selection

All included trials met the following criteria: (1) prospective trials involved extensive-stage SCLC patients; (2) prospective trials investigating efficacy difference between chemotherapy alone and immunotherapy combined with chemotherapy; and (3) survival outcomes of ES-SCLC patients with brain or liver metastases could be available.

Data Extraction

The following information including first author's name, publication year, phase of trial, number of patients presented with brain metastases, number of patients presented with liver metastases, treatment regimen, median age, and treatment line were independently extracted by two investigators, and any discrepancy between the reviewers was resolved by consensus.

Outcome Measures

We perform the present meta-analysis by using Comprehensive Meta Analysis software (Version 2.0). The survival outcome was pooled and reported as hazard ratio (HR). The primary outcome of interest was OS and secondary outcomes PFS in ES-SCLC patients receiving ICIs and chemotherapy. Between-study heterogeneity was estimated using the χ^2-based Q statistic[15]. Heterogeneity was considered statistically significant when $p_{\text{heterogeneity}} < 0.1$. The Begg and Egger tests were used to evaluate the presence of publication bias[16,17]. A statistical test with a p-value lower than 0.05 was considered significant. The Cochrane Risk of Bias Tool was used to estimate the quality of randomized controlled trials (RCTs)[18]. The Jadad scale was based on the reporting of the studies' methods and results to assess the study quality[19].

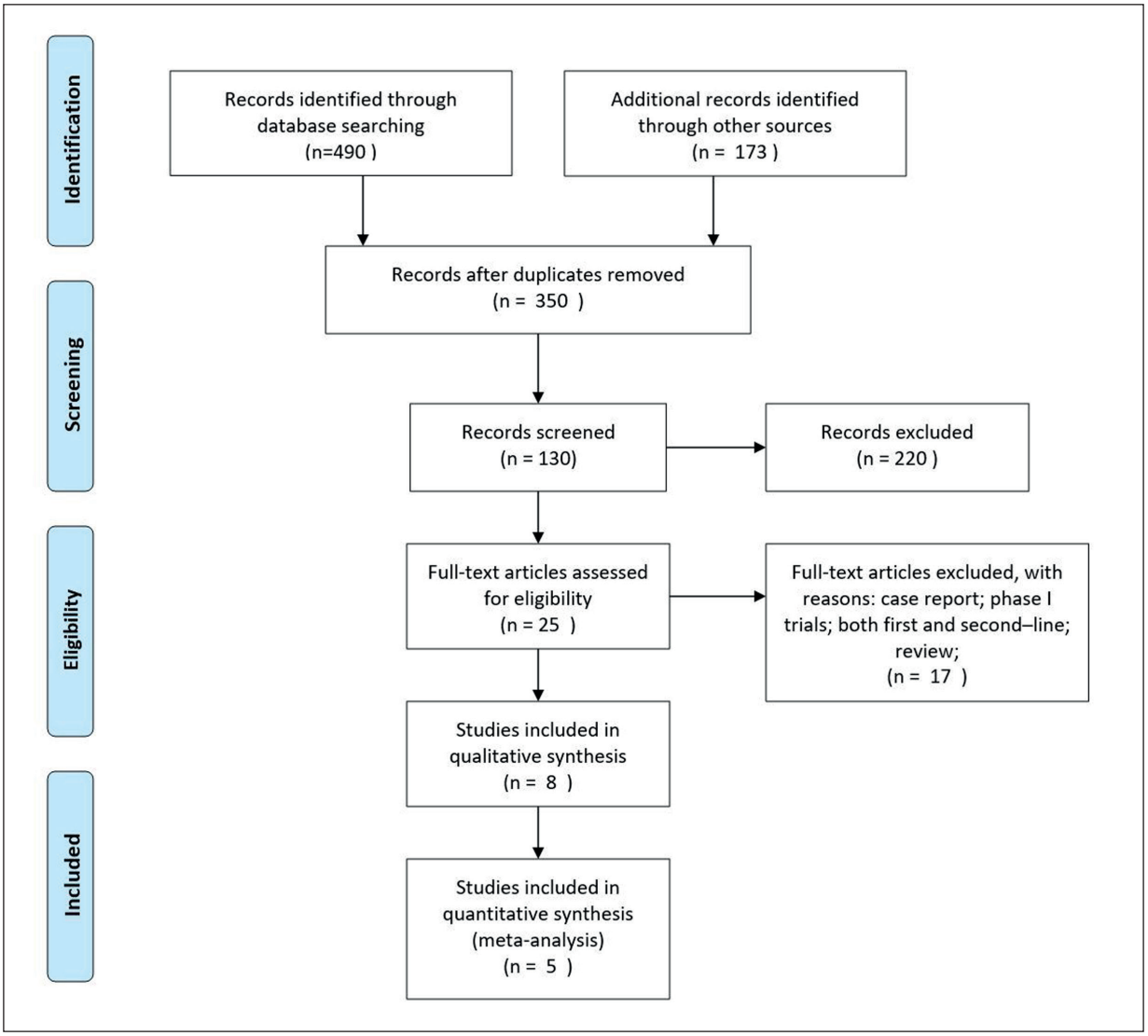

Figure 1. PRISMA flow diagram.

Results

Eligible Studies and Characteristics

We performed the systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[20]. Our initial search yielded 1,250 potentially relevant reports. After excluding review articles, phase I studies, case reports, meta-analyses, and observation studies, a total of 5 prospective randomized controlled clinical trials were included. After reviewing of included trials, 2 included trials were undated analyses of previously published trials. Finally, 8 studies of 5 randomized trials were included[21-27]. Figure 1 shows the process of selection.

The main characteristics of included studies are summarized in Table I. Briefly, 1,401 patients from 5 studies were included, 310 with brain metastases and 1,091 with liver metastases. All the included studies were subgroup analyses of multicenter, randomized, phase III trials, published between 2016 and 2021. All of the included ES-SCLC patients received ICIs combined with chemotherapy as first-line treatment. Of them, only CheckMate-451 investigate maintenance therapy with ICIs in ES-SCLC[21], and other 4 trials assess the efficacy of addition ICIs to standard chemotherapy, followed by maintenance therapy.

Quality of Included Studies

In general, most of the included studies provided adequate outcome ascertainment, enrolled a

Table I. Baseline characteristics of included trials.

Author/year	Trial name	Study population	No. of baseline liver metastases	No. of baseline brain metastases	Intervention	Treatment line	Primary endpoint	Jadad score
Horn et al[26] / Liu et al[22]	IMpower 133	Extensive-stage SCLC	149	35	Atezolizumab+EP	First-line	OS and PFS	5
					EP			
Reck et al[27]	NA	Extensive-stage SCLC	NA	100	Ipilimumab+EP	First-line	OS	7
					Placebo+EP			
Paz-Ares et al[25] / Goldman et al[23]	CASPIAN	Extensive-stage SCLC	108	28	Durvaluzumab +EP	First-line	OS	5
			117	38	Durvaluzumab +tremeli-zumab+ EP			
			104	27	EP			
Rudin et al[24]	KEYNOTE-604	Extensive stage SCLC	187	55	Pembolizumab+EP	First-line	OS	7
					Placebo +EP			
Owonikoko et al[21]	Checkmate-451	Extensive stage SCLC	110	38	CT followed by Nivolumab +ipilimumab	First-line	OS	7
			106	46	CT followed by Nivolumab	First-line	OS	
			106	32	EP followed by Placebo			

Abbreviation: SCLC, small-cell lung cancer; EP, etoposide plus platinum; CT, chemotherapy; OS, overall survival; PFS, progression-free survival.

representative sample of patients, and had an acceptable length of follow-up. As a result, methodological quality of these studies was fair (Figure 2). We also used Jadad scale to evaluate the quality of each included study. 3 of the 5 randomized controlled trials were double-blind placebo-controlled trials, thus had a Jadad's score of 7. Other 3 trials were an open-label controlled trial, thus had a Jadad's score of 5.

Effect of Icis on Patients with Brain Metastases

A total of 4 trials reported OS data with 310 patients to analyze the efficacy of combination ICIs with chemotherapy on patients with brain metastasis. The pooled hazard ratio for OS demonstrated that addition of ICIs to chemotherapy in ES-SCLC patients did not improve OS giving HR 1.12 (95%CI: 0.88-1.43, p=0.36, Figure 3A), in comparison with chemotherapy alone. There was significant heterogeneity between trials (I^2=23%, p=0.27), and the pooled HR for OS was performed by using fixed-effects model. A total of 3 trials reported PFS data of ES-SCLC with brain metastasis. Similarly, no survival benefit of PFS could be obtained from ICIs combination therapy with HR of 0.91 (95%CI: 0.63-1.32, p=0.62, Figure 3B) by using fixed-effects model.

Effect of Icis on Patients with Liver Metastases

4 studies were included for the analysis of OS of 1,091 ES-SCLC patients with liver metastases, and the pooled results indicated that patients treated with combination of ICIs and chemotherapy had significantly longer OS than chemotherapy group (HR, 0.88; 95%CI, 0.78-1.00; p=0.049, Figure 4A), with no significant heterogeneity among included trials (I^2=0%; p=0.51). Thus, the pooled analysis was performed by using fixed-effects model. Only KEYNOT-604[24] and IMpower 133[22,26] reported outcomes of ES-SCLC with liver metastasis, and the pooled results demonstrated that the addition of ICIs to chemotherapy had a tendency to improve PFS when compared to chemotherapy alone (HR 0.86, 95%CI: 0.68-1.07, p=0.17, Figure 4B).

Publication Bias

Visual inspection of the Begg funnel plots was symmetry, indicating absence of significant publication bias (Figure 5). Further tests suggested no statistically significant publication bias was detected in OS for patients with brain metastases (Begg's test, p=0.62; Egger's test, p=0.37) and OS for patients with liver metastases (Begg's test, p=0.85; Egger's test, p=0.40).

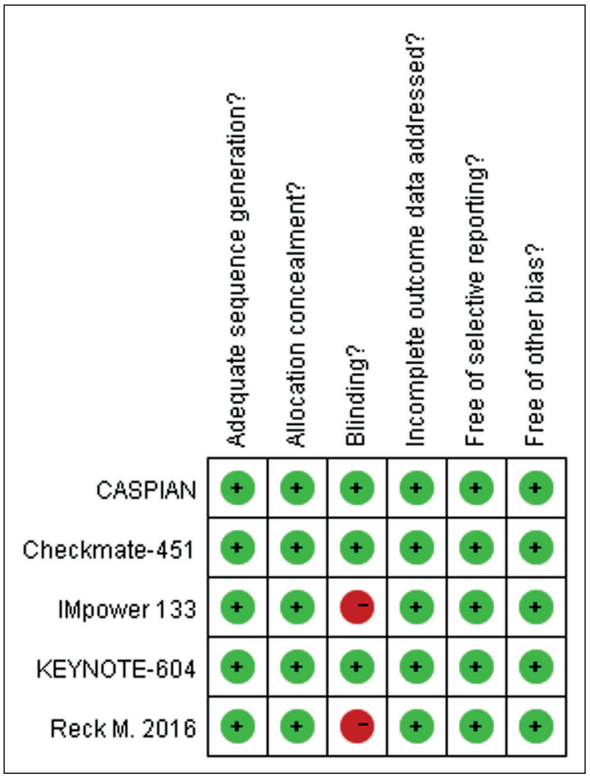

Figure 2. Selected methodologic al quality indicator.

Discussion

During the past decade, the management of ES-SCLC has been significantly changed with the introduction of immune checkpoint inhibitors. Due to survival benefits obtained from combination therapy, addition of ICIs to front line chemotherapy followed by maintenance has been the standard of care for treatment-native ES-SCLC. However, the differential tumor microenvironments of various organs may potentially influence the therapeutic effect of ICIs. Indeed, differential organ-specific tumor response to immune checkpoint inhibitors (ICIs) has been reported in multiple solid tumors, including renal cell carcinoma[28], non-small-cell lung cancer[29,30] and liver cancer[31]. In Liu et al[22] study on 75 advanced hepatocellular carcinomas (HCC), the authors found that hepatic tumors of HCC may be less responsive to ICIs than extrahepatic lesions, and lung metastases responded most favorably to ICIs. Similarly, mixed

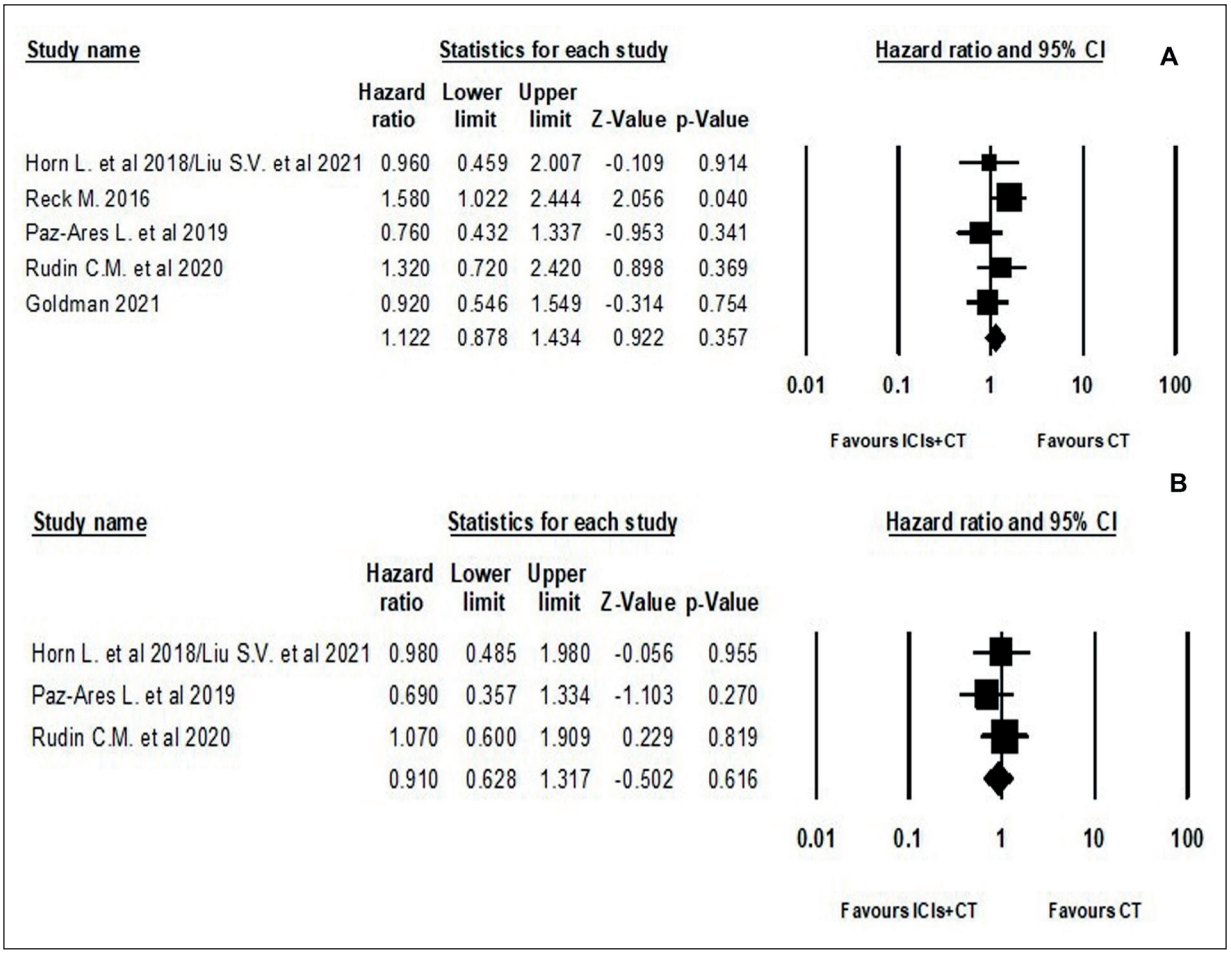

Figure 3. Fixed-effect Model of hazard ratio (95%CI) of PFS and OS in ES-SCLC with BM metastasis treated ICIs with CT versus CT alone.

responses to ICIs are also observed in NSCLC. However, to our best knowledge, there is no specific meta-analysis to comprehensively investigate the immune response to ICIs in ES-SCLC with different metastases.

In the present study, a total of 1,401 patients, with 310 presented with brain metastases, from 5 randomized controlled trials have been included for analysis. As we all known, brain metastases are normally considered as a frequent metastatic site of SCLC with unfavorable prognosis; it has been reported[32] that approximately 10% of SCLC patients presented with BM at diagnosis and it rises to more than 50% after 2-year survival. As a result, if no progression is observed after completion of chemoradiotherapy for limited-stage SCLC, prophylactic cranial irradiation (PCI) is recommended for the prevention of brain metastases[33].

Recently, two meta-analyses also demonstrated that PCI significantly improved overall survival [Hazard ratio (HR) = 0.57; 95% confidence interval (CI): 0.47, 0.69; $p<0.001$] and brain metastasis [Risk ratio (RR) = 0.47, 95%CI: 0.33, 0.69; $p<0.01$] for ES-SCLC[34,35]. In the present study, our pooled result showed that no survival benefit could be obtained from combination therapy of ICIs with CT in terms of PFS (HR 0.91, 95%CI: 0.63-1.32, $p=0.62$) and OS (HR 1.12, 95%CI: 0.88-1.43, $p=0.36$) for ES-SCLC with brain metastasis. One possible explanation for this finding is that the prognosis of ES-SCLC with brain metastasis is dismal, and only patients with asymptomatic or treated and stable off steroids and anticonvulsants for at least 1 month before study entry were included in the randomized controlled trials. However, brain radiotherapy is the mainstream therapy for patients with brain metastases. Radiotherapy is a promising immunological adjuvant and a complex modifier of the tumor microenvironment[36]. Several studies[37,38]

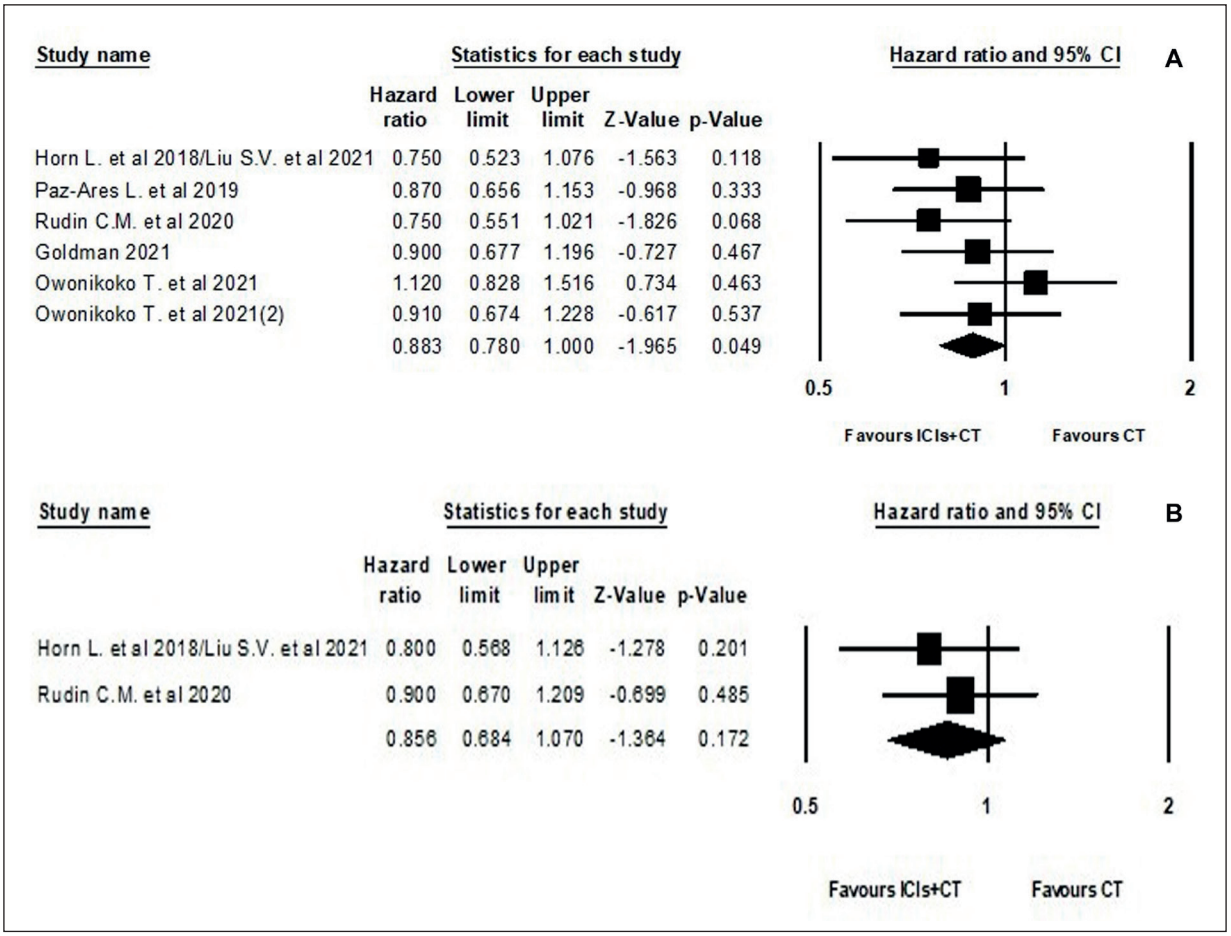

Figure 4. Fixed-effect Model of hazard ratio (95%CI) of PFS and OS in ES-SCLC with liver metastasis treated ICIs with CT versus CT alone.

have suggested that the immune system has an important role in the therapeutic effects of radiation, promoting tumor cell death in the radiation field. As a result, it has been hypothesized that the combination of brain RT and ICIs would generate a synergistic effect. Further studies are still needed to investigate the combination of brain RT and ICIs with chemotherapy in ES-SCLC with brain metastases.

Liver metastases is the second most common extra-thoracic metastatic organs, accounting for 24.7%[39]. Conventional treatment of liver metastases consists of systematic and palliative therapy. Although several studies have demonstrated liver metastases as an independent poor prognostic factor of immunotherapy for NSCLC, the impact of site of involvement on survival of ES-SCLC remains unknown[40]. In the present study, a total of 1,091 ES-SCLC with liver metastases were included for analysis. The pooled results showed that ICIs combined with CT significantly improved OS of ES-SCLC with liver metastases (HR 0.88, 95%CI: 0.78-1.00, p=0.049), and a tendency to improve PFS (HR 0.86, 95%CI: 0.68-1.07, p=0.17). Based on our findings, the addition of ICIs to front line chemotherapy followed by maintenance is recommended for ES-SCLC with liver metastasis due to its survival benefit.

Limitations

Several limitations in this meta-analysis need to be acknowledged. First, the number of trials included in this meta-analysis is relatively small, although the quality of included trials is high. Secondly, our study is a pooled analysis of subgroup analysis of published studies, thus the statistical power is limited. As a result, the conclusion is preliminary and should be cautiously interpreted. However, in the present study, we firstly observe a survival benefit from ICIs combination for ES-SCLC with liver metastases.

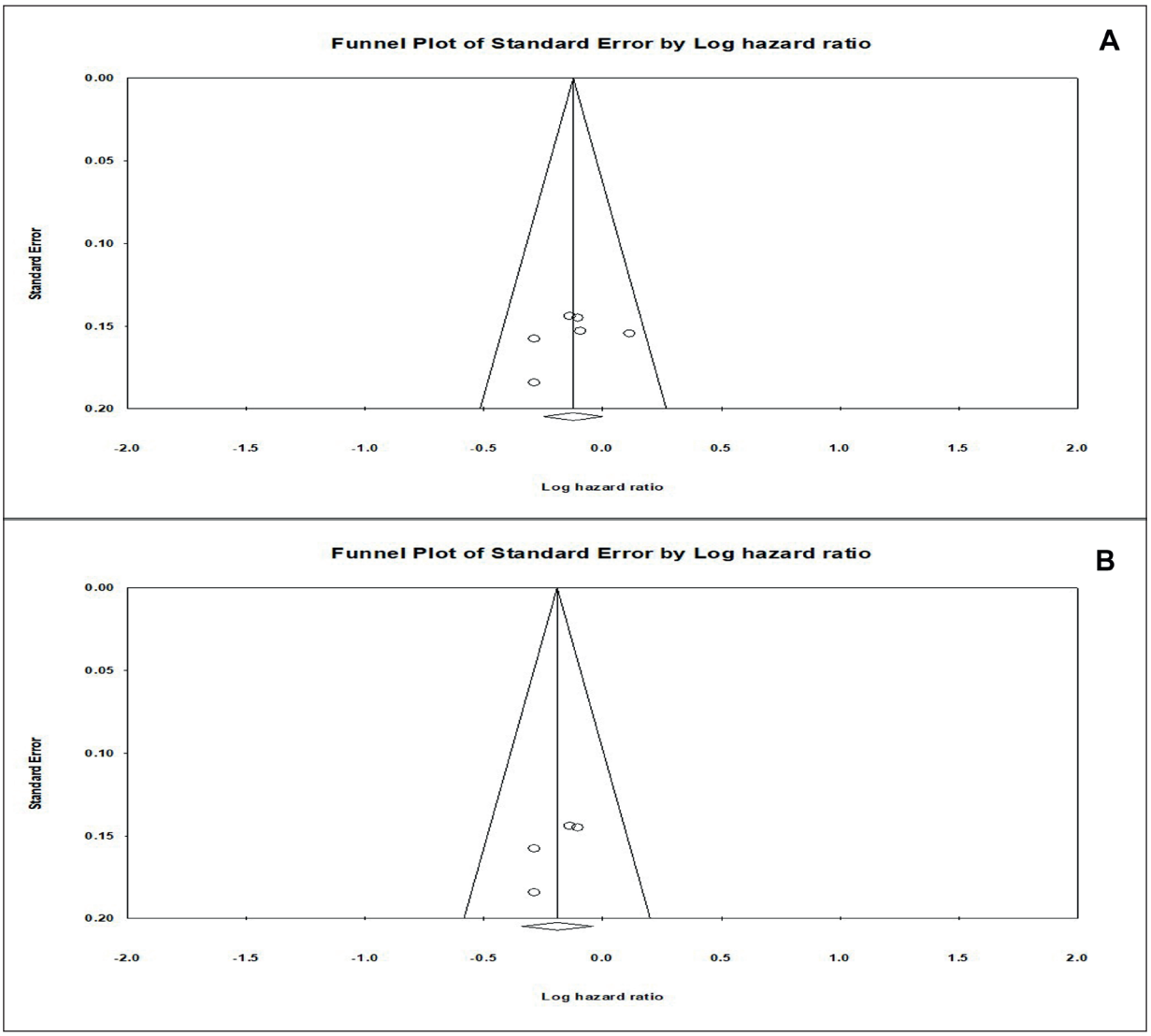

Figure 5. Publication bias of OS for ES-SCLC with BM or liver metastasis.

Conclusions

In conclusion, the present study suggests that addition of ICIs to chemotherapy can significantly prolong OS in ES-SCLC patients with liver metastases and a tendency to improve PFS in those patients, while no survival benefit could be obtained from combination therapy in ES-SCLC with brain metastasis in terms of OS and PFS. Therefore, this study still indicates combination of ICIs with chemotherapy are effective treatment options for ES-SCLC patients with liver metastasis. Further strategies are still recommended to investigate synergistic effect of radiotherapy and immune checkpoint inhibitors in ES-SCLC with brain metastases.

Acknowledgements

Not applicable.

Authors' Contributions

Chunrong Chen conducted data extraction, quality appraisal, data synthesis and analysis, and drafted the manuscript. WXQ and C.C. designed the protocol, performed the search, data extraction, quality appraisal, data synthesis and interpretation, and drafted the manuscript. T.L, W.X.Q., C.C. and T.X. contributed to writing and editing the manuscript. C.C. determined the scope of the review and contributed to protocol design and writing and editing the manuscript. W.X.Q. and T.X. had full access to the data, takes responsibility for data integrity, and is the guarantor of the review. All authors read and approved the final manuscript.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

Not applicable.

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Conflict of Interest

The authors declare that they have no competing interests.

References

1) Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, Spitznagel EL, Piccirillo J. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006; 24: 4539-4544.
2) Wong SK, Iams WT. Front Line Applications and Future Directions of Immunotherapy in Small-Cell Lung Cancer. Cancers 2021; 13: 506.
3) Ortega-Franco A, Ackermann C, Paz-Ares L, Califano R. First-line immune checkpoint inhibitors for extensive stage small-cell lung cancer: clinical developments and future directions. ESMO open 2021; 6: 100003.
4) Kozower BD, Larner JM, Detterbeck FC, Jones DR. Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143: e369S-e399S.
5) Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143: e400S-e419S.
6) von Pawel J, Schiller JH, Shepherd FA, Fields SZ, Kleisbauer JP, Chrysson NG, Stewart DJ, Clark PI, Palmer MC, Depierre A, Carmichael J, Krebs JB, Ross G, Lane SR, Gralla R. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999; 17: 658-667.
7) Rudin CM, Durinck S, Stawiski EW, Poirier JT, Modrusan Z, Shames DS, Bergbower EA, Guan Y, Shin J, Guillory J, Rivers CS, Foo CK, Bhatt D, Stinson J, Gnad F, Haverty PM, Gentleman R, Chaudhuri S, Janakiraman V, Jaiswal BS, Parikh C, Yuan W, Zhang Z, Koeppen H, Wu TD, Stern HM, Yauch RL, Huffman KE, Paskulin DD, Illei PB, Varella-Garcia M, Gazdar AF, de Sauvage FJ, Bourgon R, Minna JD, Brock MV, Seshagiri S. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. Nat Genet 2012; 44: 1111-1116.
8) George J, Lim JS, Jang SJ, Cun Y, Ozretic L, Kong G, Leenders F, Lu X, Fernandez-Cuesta L, Bosco G, Müller C, Dahmen I, Jahchan NS, Park KS, Yang D, Karnezis AN, Vaka D, Torres A, Wang MS, Korbel JO, Menon R, Chun SM, Kim D, Wilkerson M, Hayes N, Engelmann D, Pützer B, Bos M, Michels S, Vlasic I, Seidel D, Pinther B, Schaub P, Becker C, Altmüller J, Yokota J, Kohno T, Iwakawa R, Tsuta K, Noguchi M, Muley T, Hoffmann H, Schnabel PA, Petersen I, Chen Y, Soltermann A, Tischler V, Choi CM, Kim YH, Massion PP, Zou Y, Jovanovic D, Kontic M, Wright GM, Russell PA, Solomon B, Koch I, Lindner M, Muscarella LA, la Torre A, Field JK, Jakopovic M, Knezevic J, Castaños-Vélez E, Roz L, Pastorino U, Brustugun OT, Lund-Iversen M, Thunnissen E, Köhler J, Schuler M, Botling J, Sandelin M, Sanchez-Cespedes M, Salvesen HB, Achter V, Lang U, Bogus M, Schneider PM, Zander T, Ansén S, Hallek M, Wolf J, Vingron M, Yatabe Y, Travis WD, Nürnberg P, Reinhardt C, Perner S, Heukamp L, Büttner R, Haas SA, Brambilla E, Peifer M, Sage J, Thomas RK. Comprehensive genomic profiles of small cell lung cancer. Nature 2015; 524: 47-53.
9) Sabari JK, Lok BH, Laird JH, Poirier JT, Rudin CM. Unravelling the biology of SCLC: implications for therapy. Nat Rev Clin Oncol 2017; 14: 549-561.
10) Zhang S, Li S, Cheng Y. Efficacy and safety of PD-1/PD-L1 inhibitor plus chemotherapy versus chemotherapy alone as first-line treatment for extensive-stage small cell lung cancer: A systematic review and meta-analysis. Thorac Cancer 2020; 11: 3536-3546.
11) Arriola E, Gonzalez-Cao M, Domine M, De Castro J, Cobo M, Bernabe R, Navarro A, Sullivan I, Trigo JM, Mosquera J, Crama L, Isla D. Addition of Immune Checkpoint Inhibitors to Chemotherapy vs Chemotherapy Alone as First-Line Treatment in Extensive-Stage Small-Cell Lung Carcinoma: A Systematic Review and Meta-Analysis. Oncol Ther 2022; 10: 167-184.
12) Abunasser AAA, Xue J, Balawi EJA, Zhu Y. Combination of the EP and Anti-PD-1 Pathway or Anti-CTLA-4 for the Phase III Trial of Small-Cell Lung Cancer: A Meta-Analysis. J Oncol 2021; 2021: 6662344.
13) Facchinetti F, Di Maio M, Tiseo M. Adding PD-1/PD-L1 Inhibitors to Chemotherapy for the First-Line Treatment of Extensive Stage Small Cell Lung Cancer (SCLC): A Meta-Analysis of Randomized Trials. Cancers 2020; 12: 2645.

14) Mathieu L, Shah S, Pai-Scherf L, Larkins E, Vallejo J, Li X, Rodriguez L, Mishra-Kalyani P, Goldberg KB, Kluetz PG, Theoret MR, Beaver JA, Pazdur R, Singh H. FDA Approval Summary: Atezolizumab and Durvalumab in Combination with Platinum-Based Chemotherapy in Extensive Stage Small Cell Lung Cancer. Oncologist 2021; 26: 433-438.
15) Zintzaras E, Ioannidis JP. Heterogeneity testing in meta-analysis of genome searches. Genet Epidemiol 2005; 28: 123-137.
16) Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985; 27: 335-371.
17) Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088-1101.
18) Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.
19) Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998; 352: 609-613.
20) Moher D LA, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.
21) Owonikoko TK, Park K, Govindan R, Ready N, Reck M, Peters S, Dakhil SR, Navarro A, Rodriguez-Cid J, Schenker M, Lee JS, Gutierrez V, Percent I, Morgensztern D, Barrios CH, Greillier L, Baka S, Patel M, Lin WH, Selvaggi G, Baudelet C, Baden J, Pandya D, Doshi P, Kim HR. Nivolumab and Ipilimumab as Maintenance Therapy in Extensive-Disease Small-Cell Lung Cancer: CheckMate 451. J Clin Oncol 2021; 39: 1349-1359.
22) Liu SV, Reck M, Mansfield AS, Mok T, Scherpereel A, Reinmuth N, Garassino MC, De Castro Carpeno J, Califano R, Nishio M, Orlandi F, Alatorre-Alexander J, Leal T, Cheng Y, Lee JS, Lam S, McCleland M, Deng Y, Phan S, Horn L. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133). J Clin Oncol 2021; 39: 619-630.
23) Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, Hochmair MJ, Ozguroglu M, Ji JH. Garassino MC, Voitko O, Poltoratskiy A, Ponce S, Verderame F, Havel L, Bondarenko I, Każarnowicz A, Losonczy G, Conev NV, Armstrong J, Byrne N, Thiyagarajah P, Jiang H, Paz-Ares L; CASPIAN investigators. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2021; 22: 51-65.
24) Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csoszi T, Cheema PK, Rodriguez-Abreu D, Wollner M, Yang JC. Mazieres J, Orlandi FJ, Luft A, Gümüş M, Kato T, Kalemkerian GP, Luo Y, Ebiana V, Pietanza MC, Kim HR; KEYNOTE-604 Investigators. Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study. J Clin Oncol 2020; 38: 2369-2379.
25) Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, Hochmair MJ, Ozguroglu M, Ji JH. Voitko O, Poltoratskiy A, Ponce S, Verderame F, Havel L, Bondarenko I, Kazarnowicz A, Losonczy G, Conev NV, Armstrong J, Byrne N, Shire N, Jiang H, Goldman JW, CASPIAN investigators. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019; 394: 1929-1939.
26) Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, Huemer F, Losonczy G, Johnson ML, Nishio M. Reck M, Mok T, Lam S, Shames DS, Liu J, Ding B, Lopez-Chavez A, Kabbinavar F, Lin W, Sandler A, Liu SV, IMpower133 Study Group. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018; 379: 2220-2229.
27) Reck M, Luft A, Szczesna A, Havel L, Kim SW, Akerley W, Pietanza MC, Wu YL, Zielinski C, Thomas M. Felip E, Gold K, Horn L, Aerts J, Nakagawa K, Lorigan P, Pieters A, Kong Sanchez T, Fairchild J, Spigel D. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol 2016; 34: 3740-3748.
28) Koelzer VH, Rothschild SI, Zihler D, Wicki A, Willi B, Willi N, Voegeli M, Cathomas G, Zippelius A, Mertz KD. Systemic inflammation in a melanoma patient treated with immune checkpoint inhibitors-an autopsy study. J Immunother Cancer 2016; 4: 13.
29) Yang K, Li J, Bai C, Sun Z, Zhao L. Efficacy of Immune Checkpoint Inhibitors in Non-small-cell Lung Cancer Patients With Different Metastatic Sites: A Systematic Review and Meta-Analysis. Front Oncol 2020; 10: 1098.
30) Schmid S, Diem S, Li Q, Krapf M, Flatz L, Leschka S, Desbiolles L, Klingbiel D, Jochum W, Früh M. Organ-specific response to nivolumab in patients with non-small cell lung cancer (NSCLC). Cancer immunol Immunother 2018; 67: 1825-1832.
31) Lu LC, Hsu C, Shao YY, Chao Y, Yen CJ, Shih IL, Hung YP, Chang CJ, Shen YC, Guo JC. Liu TH, Hsu CH, Cheng AL. Differential Organ-Specific Tumor Response to Immune Checkpoint Inhibitors in Hepatocellular Carcinoma. Liver cancer 2019; 8: 480-490.
32) Nakahara Y, Sasaki J, Fukui T, Otani S, Igawa S, Hayakawa K, Masuda N. The role of prophylactic cranial irradiation for patients with small-cell lung cancer. Jpn J Clin Oncol 2018; 48: 26-30.
33) Tomassen ML, Pomp J, van der Stap J, van Lindert ASR, Peters M, Belderbos JSA, De Ruysscher

DKM, Lin SH, Verhoeff JJC, van Rossum PSN. The overall survival impact of prophylactic cranial irradiation in limited-stage small-cell lung cancer: A systematic review and meta-analysis. Clin Transl Radiat Oncol 2022; 33: 145-152.
34) Wen P, Wang TF, Li M, Yu Y, Zhou YL, Wu CL. Meta-analysis of prophylactic cranial irradiation or not in treatment of extensive-stage small-cell lung cancer: The dilemma remains. Cancer Radiother 2020; 24: 44-52.
35) Ge W, Xu H, Yan Y, Cao D. The effects of prophylactic cranial irradiation versus control on survival of patients with extensive-stage small-cell lung cancer: a meta-analysis of 14 trials. Radiat Oncol 2018; 13: 155.
36) Chajon E, Castelli J, Marsiglia H, De Crevoisier R. The synergistic effect of radiotherapy and immunotherapy: A promising but not simple partnership. Crit Rev Oncol Hematol 2017; 111: 124-132.
37) Brooks ED, Chang JY. Time to abandon single-site irradiation for inducing abscopal effects. Nat Rev Clin Oncol 2019; 16: 123-135.
38) Onderdonk BE, Chmura SJ. The Yin and Yang of Cytoreductive SBRT in Oligometastases and Beyond. Front Oncol 2019; 9: 706.
39) Ni J, Zhang X, Wang H, Si X, Xu Y, Zhao J, Chen M, Zhang L, Wang M. Clinical characteristics and prognostic model for extensive-stage small cell lung cancer: A retrospective study over an 8-year period. Thorac Cancer 2022; 13: 539-448.
40) Tas F, Aydiner A, Topuz E, Camlica H, Saip P, Eralp Y. Factors influencing the distribution of metastases and survival in extensive disease small cell lung cancer. Acta Oncol 1999; 38: 1011-1015.