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Role of radiotherapy on long-term outcomes of patients with small cell lung cancer under different metastasis patterns

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Abstract

Objective Assessing the role of radiotherapy on the long-term outcomes in patients with small cell lung cancer (SCLC).

Methods A total of 6819 patients with SCLC diagnosed histologically from 2011 to 2020 were collected from the Surveillance, Epidemiology, and End Results database. The importance of radiation on overall survival (OS) and cancer-specific survival (CSS) was assessed by a random forest algorithm. The association of radiation with OS and CSS was evaluated by COX regression and subgroup analysis. The survival difference between radiation and non-radiation groups was analyzed by the Kaplan-Meier (KM) method. The conditional survival (CS) and competing risk analyses were performed to evaluate the influence of radiation on CSS.

Results Among all variables, the importance of tumor metastasis to OS and CSS ranked first. COX regression analysis indicated independent association (all $P < 0.05$) of radiation with OS and CSS in patients with metastasis in the liver, lymphatic, and other sites (not found in bone and brain). KM showed better OS and CSS in the radiation group (vs. non-radiation) in the 3 types of metastases (all $P < 0.05$). Among 5 metastasis patterns, liver metastasis (LM) was identified as the key pattern to OS and CSS. We found that LM patients with chemotherapy, female, and stage IV can significantly benefit from radiotherapy. However, radiation cannot decrease the incidence of cancer-specific death in male LM patients.

Conclusions This study determined the importance of radiotherapy on the long-term outcomes of patients. In particular, male LM patients may not benefit from radiotherapy.

Keywords Small cell lung cancer, Radiation, Metastasis, SEER

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Introduction

Lung cancer is a major public health problem in the world, containing non-small cell lung cancer and small cell lung cancer (SCLC) types. SCLC is a poorly differentiated epithelial cell tumor of neuroendocrine origin, and accounts for 14% of all lung cancer case [1]. There are approximately 250,000 new cases of SCLC diagnosed each year and more than 80% of SCLC patients deaths [2]. The 2-year survival rate of SCLC patients was about 46%, and the prognosis for SCLC patients remains poor [3]. This tumor presents exceptionally high proliferative rate, strong tendency for early widespread metastasis and acquired chemoresistance [4], leading to it as one of the most intractable diseases in clinical practice.

Among SCLC patients, 70% of patients belong to the subtypes of extensive-stage small-cell lung cancer (ES-SCLC) [5]. Unfortunately, most of patients with ES-SCLC have distant organ metastasis, and the 2-year survival rate of patients with distant metastasis was 7% [6]. Previous studies have found that the common metastatic organs of SCLC include bone, brain, liver [7, 8], especially liver metastasis shows high frequency in advanced SCLC. Meng et al. made a retrospective study on 541 patients and found that the prognosis of single organ metastasis in patients with SCLC was better than that of multiple organ metastasis; in addition, the prognosis in singe brain metastasis was relatively better, and it was worst in the patients with liver metastasis [9]. The harm of liver metastasis on the prognosis in SCLC was also demonstrated, as only liver metastasis showed significant independent effect on survival time among different metastases [10]. It followed that metastasis pattern and number of metastatic sites should not be ignored when considering the prognosis in SCLC.

In the treatment of SCLC, it is sensitive to chemotherapy and radiotherapy. It has been found that radiotherapy can significantly improve the prognosis of patients with SCLC [11]. In the ES-SCLC, the 1-year overall survival (OS) was not different between patients with or without consolidative thoracic radiotherapy; but 2-year OS and 6-months progression-free survival (PFS) was significantly higher in patients who received radiotherapy [12]. However, radiotherapy seemed to result in higher PFS in patients with 0–2 distant metastases, but had no effect in patients with two or more distant metastases [13]. Shang et al., also detailly revealed that radiotherapy can improve the prognosis of ES-SCLC with distant metastasis only for patients with one metastatic site [14]. These knowledges highlighted the importance of metastasis sites number on the prognostic effect of radiotherapy in ES-SCLC. Currently, there is a lack of systematic and in-depth research on the specific impact of radiotherapy on the prognosis of patients with SCLC accompanied by metastases in different locations, and there are still many unknown areas.

In this study, we first explored the importance of metastasis on the prognosis of patients with SCLC based on the SEER database. Then we identified the harmfulness of different metastasis on the survival time. Finally, we assessed the potential benefit of radiotherapy on the long-term prognosis of patients with different metastatic site. This study may bring theoretical and practical significance to enriching the clinical treatment strategies for SCLC, optimizing radiotherapy regimens, and improving patient prognosis.

Methods

Data source and patient selection

The data of patients with SCLC were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. Inclusion criteria: year of diagnosis 2011–2020; diagnosed with SCLC (ICD-O-3 code: 8041/3, 8042/3, 8043/3, 8044/3, 8045/3) within the lung (ICD O-3 codes: C34.1, C34.2, C34.3, C34.8, C34.9); type of reporting source was non-autopsy and non-death certificate. A total of 48,838 patients were selected. Exclusion criteria: age less than 20 years old ($N=3$); had multiple cancers ($N=1311$); unknown race ($N=83$); unknown marital status ($N=2199$); radiation recommended, unknown if performed ($N=453$); missing specific cause death classification ($N=320$); survival time was 0 ($N=7353$); the primary site was not clear ($N=6800$); unknown clinical stage ($N=21786$); unknown T stage ($N=770$); unknown N stage ($N=138$); missing information from diagnosis to treatment ($N=802$). Finally, 6819 patients were enrolled in this study.

Variables extraction

We collected the data of age, gender, household income, race, primary site, laterality, American Joint Committee on Cancer (AJCC) 8th stages (T stage, N stage, M stage, clinical stage), months from diagnosis to treatment, scope of regional lymph nodes, radiation record, chemotherapy record, liver metastasis, bone metastasis, brain metastasis, lymphatic metastasis, metastasis at other sites, survival months, vital status recode, and cause-specific death classification. According to the vital status recode and cause-specific death classification, the overall survival (OS) and cancer-specific survival (CSS) can be determined. In addition, the tumor size, tumor extension, and lymph nodes were also extracted. However, almost no one recorded the values of these 3 variables. Therefore, these 3 variables were not considered in this study.

Statistical analysis

The statistical analyses were performed with SPSS (version 23.0) and the R software (version 3.5.0). In this study,

all the variables were defined as categorical variables, and their distribution differences between the 2 groups were analyzed by χ^2 test. The importance of clinical features to OS and CSS was ranked by a machine learning-based random forest algorithm. The association between radiation and OS/CSS was analyzed by COX regression analysis. The Kaplan-Meier method and log-rank test were used to analyze the difference of OS and CSS between radiation and non-radiation groups. The conditional survival (CS) analysis was conducted to compare the OS and CS among patients receiving radiation. CS refers to the probability of a patient who has survived for X years surviving for another Y years, calculated as CS (Y) = S(X + Y)/S(X). This study mainly focused on the half a year CS at the baseline of survived for 1 month, namely CS (7 months) = S(6 month + 1 month)/S(1 month). Considering the other death causes than this cancer, we also performed a competing risk model to explore the influence of radiation on cancer-specific death. The interested event was the dead attributable to this cancer; the competitive event was the dead attributable to causes other than this cancer. Two-sided $P < 0.05$ was considered a significant difference.

Results

Baseline characteristics

This study included 6819 patients with SCLC, of whom 3274 patients were male and 3545 patients were female. The baseline characteristics of all patients were presented in Table 1 by stratifying them by OS and CSS status. The results showed that the distributions of the primary site and laterality were not different between the 2 groups regarding OS and CSS status, respectively (all $P > 0.05$). The remaining variables showed differences between alive and dead groups regarding OS and CSS (all $P < 0.05$).

Further, the importance of significant features ($P < 0.05$) within Table 1 to OS and CSS were ranked using a random forest algorithm. As the definition of the clinical stage was based on the T, N, and M stages, therefore we only considered the clinical stage in importance ranking analysis. The result showed that the importance of tumor metastasis to OS and CSS all ranked first (Fig. 1A and B).

Association between radiation and long-term outcomes of patients with different metastasis sites

The above results have indicated the importance of tumor metastasis on the long-term outcomes of patients, we then explored the metastasis condition of different sites. Among 6819 patients with SCLC, 335 patients only showed bone metastasis; 412 patients only showed brain metastasis; 365 patients showed liver metastasis; 96 patients showed lymphatic metastasis; and 340 patients showed metastasis at other sites. Each type of metastasis did not include other metastasis types.

The baseline data of patients with different metastasis sites stratified by OS and CSS status was presented in Table 2. The results showed that the distributions of bone metastasis, brain metastasis, liver metastasis, and metastasis at other sites were different between the 2 groups stratified by OS and CSS status (all $P < 0.001$). The lymphatic metastasis showed no difference between the 2 groups in terms of OS.

Next, we explored the association between radiation and OS/CSS among patients under different metastasis patterns by COX regression analysis (Table 3). The results showed that radiation was significantly associated with OS and CSS in patients with liver metastasis, lymphatic metastasis, and metastasis at other sites both in the crude model and adjusted model (all $P < 0.05$). In these 3 metastasis types, radiation was an independent factor of OSS and CSS. However, their association was not observed in patients with bone metastasis and brain metastasis.

We also compared the survival difference (OS/CSS) of patients with or without radiation under 3 metastasis types. The Kaplan-Meier analysis showed that compared with patients without radiation, patients receiving radiation had better OS and CSS no matter which types of metastases (Fig. 2A and B, all $P < 0.05$).

In addition, the importance of SCLC metastasis patterns to OS and CSS was also evaluated. The results showed that liver metastasis ranked first commonly involved in the OS and CSS (Fig. 3A and B).

According to the above analyses, liver metastasis was regarded as the most important metastasis pattern for OS and CSS. Therefore, this study subsequently conducted subgroup analysis only regarding SCLC patients with liver metastasis.

Association between radiation and long-term outcomes of patients with liver metastasis

The association between radiation and long-term outcomes of patients with liver metastasis was then analyzed by subgroup analysis. In this study, the subgroup was classified based on clinical indicators related to disease prognosis (age, gender, and clinical stage) and treatment-related indicators (chemotherapy and treatment delay time). The subgroup analysis (Table 4) showed that the independent association between radiation and 2 types of long-term outcomes was significant regardless of age and treatment delay time (all adjusted $P < 0.05$). Their association was also observed in patients receiving chemotherapy ($P = 0.001$ for OS; $P < 0.001$ for CSS). Maybe that's because the sample size was small ($N = 13$), and their association was insignificant in patients without chemotherapy. All the patients with liver metastasis showed a clinical stage IV, and our analysis showed a significant association of radiation with OS ($P = 0.003$) and CSS ($P = 0.001$) among these patients. In addition, the

Table 1 The baseline data of all patients with SCLC stratified by OS and CSS status

		OS			CSS		*P*
		Alive (*N* = 2803)	**Dead (*N* = 4016)**	**P**	**Alive (*N* = 3179)**	**Dead (*N* = 3640)**	
Age	< 50 years	80(2.854)	80(1.992)	< 0.001	85(2.674)	75(2.060)	0.018
	50–59 years	470(16.768)	625(15.563)		523(16.452)	572(15.714)	
	60–69 years	1122(40.029)	1500(37.351)		1252(39.383)	1370(37.637)	
	70–79 years	915(32.644)	1392(34.661)		1055(33.187)	1252(34.396)	
	> 80 years	216(7.706)	419(10.433)		264(8.304)	371(10.192)	
Gender	male	1237(44.131)	2037(50.722)	< 0.001	1424(44.794)	1850(50.824)	< 0.001
	female	1566(55.869)	1979(49.278)		1755(55.206)	1790(49.176)	
Household income	< $60,000	878(31.324)	1380(34.363)	0.009	1014(31.897)	1244(34.176)	0.046
	≥ $60,000	1925(68.676)	2636(65.637)		2165(68.103)	2396(65.824)	
Race	American Indian	23(0.821)	42(1.046)	0.017	25(0.786)	40(1.099)	0.023
	Asian	124(4.424)	125(3.113)		133(4.184)	116(3.187)	
	Black	258(9.204)	342(8.516)		299(9.405)	301(8.269)	
	White	2398(85.551)	3507(87.326)		2722(85.624)	3183(87.445)	
Treatment delay	no	1134(40.457)	1872(46.614)	< 0.001	1290(40.579)	1716(47.143)	< 0.001
	yes	1669(59.543)	2144(53.386)		1889(59.421)	1924(52.857)	
Radiation	no	862(30.753)	1767(43.999)	< 0.001	1014(31.897)	1615(44.368)	< 0.001
	yes	1941(69.247)	2249(56.001)		2165(68.103)	2025(55.632)	
Primary site	upper lobe	1826(65.144)	2555(63.621)	0.642	2068(65.052)	2313(63.544)	0.364
	middle lobe	141(5.030)	211(5.254)		152(4.781)	200(5.495)	
	lower lobe	776(27.685)	1159(28.860)		894(28.122)	1041(28.599)	
	overlapping lesion	60(2.141)	91(2.266)		65(2.045)	86(2.363)	
Laterality	left	2790(99.750)	4002(99.800)	0.660	3166(99.779)	3626(99.780)	0.997
	right	7(0.250)	8(0.200)		7(0.221)	8(0.220)	
T stage	T1	896(31.966)	796(19.821)	< 0.001	1000(31.456)	692(19.011)	< 0.001
	T2	576(20.549)	850(21.165)		654(20.573)	772(21.209)	
	T3	473(16.875)	781(19.447)		554(17.427)	700(19.231)	
	T4	858(30.610)	1589(39.567)		971(30.544)	1476(40.549)	
N stage	N0	678(24.188)	570(14.193)	< 0.001	757(23.813)	491(13.489)	< 0.001
	N1	342(12.201)	354(8.815)		384(12.079)	312(8.571)	
	N2	1198(42.740)	2015(50.174)		1376(43.284)	1837(50.467)	
	N3	585(20.870)	1077(26.818)		662(20.824)	1000(27.473)	
M stage	M0	1682(60.007)	1255(31.250)	< 0.001	1870(58.824)	1067(29.313)	< 0.001
	M1	1121(39.993)	2761(68.750)		1309(41.176)	2573(70.687)	
Clinical stage	early	652(23.261)	300(7.470)	< 0.001	718(22.586)	234(6.429)	< 0.001
	advanced	2151(76.739)	3716(92.530)		2461(77.414)	3406(93.571)	
Scope of regional lymph nodes	none	1601(85.798)	2668(96.737)	< 0.001	1851(86.901)	2418(96.953)	< 0.001
	1–3 removed	45(2.412)	25(0.906)		49(2.300)	21(0.842)	
	≥ 4 removed	220(11.790)	65(2.357)		230(10.798)	55(2.205)	
Chemotherapy	no	196(6.993)	549(13.670)	< 0.001	242(7.612)	503(13.819)	< 0.001
	yes	2607(93.007)	3467(86.330)		2937(92.388)	3137(86.181)	
Tumor metastasis	no	1712(61.077)	1303(32.445)	< 0.001	1904(59.893)	1111(30.522)	< 0.001
	yes	1091(38.923)	2713(67.555)		1275(40.107)	2529(69.478)	

Note: treatment delay was defined as months from diagnosis to treatment greater than 1 month; early clinical stage (I + II); advanced clinical stage (III + IV); OS, overall survival; CSS, cancer-specific survival

association between radiation and 2 types of long-term outcomes was also found in female patients ($P = 0.018$ for OS; $P < 0.004$ for CSS).

Further, we conducted the conditional survival (CS) analysis regarding subgroup patients with chemotherapy, gender of female, and clinical stage IV. The results (Fig. 4A) showed that although the overall CSS rate decreased from 87.5% (5 months) to 25% (25 months) among all subgroups, the CS rate increased from 50% (lowest spot) to 75% (23 months). These results suggested the favorable survivability of patients receiving radiation after experiencing the natural selection effect.

However, it should be noted that radiation was associated with OS ($P = 0.047$) rather than CSS ($P = 0.076$) in

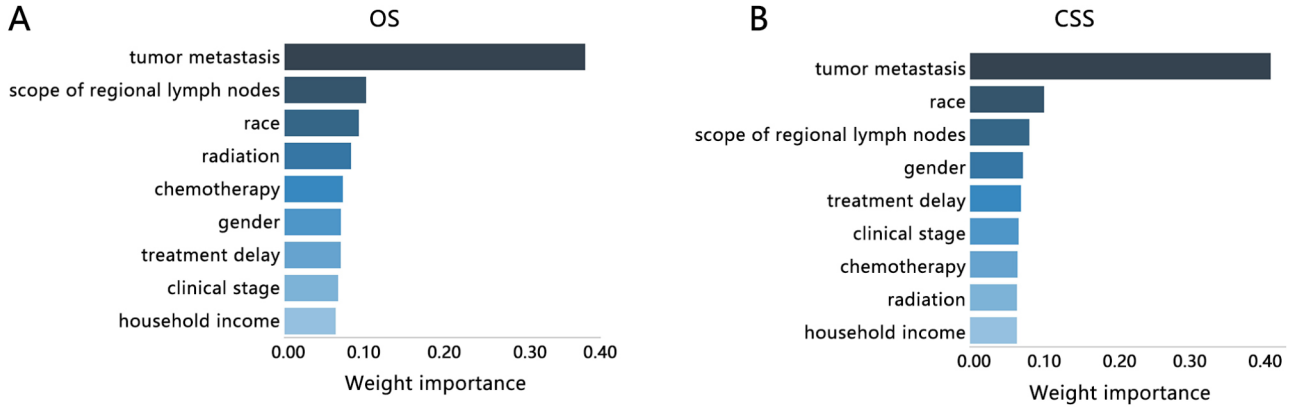

Fig. 1 The feature's importance ranking using a random forest algorithm to (**A**) OS and (**B**) CSS. OS, overall survival; CSS, cancer-specific survival

Table 2 The baseline data of patients with different metastasis sites stratified by OS and CSS status

		OS			CSS		
		Alive (*N* = 2803)	**Dead (*N* = 4016)**	**P**	**Alive (*N* = 3179)**	**Dead (*N* = 3640)**	**P**
Bone metastasis	no	1712(94.066)	1303(85.163)	< 0.001	1904(93.932)	1111(83.976)	< 0.001
	yes	108(5.934)	227(14.837)		123(6.068)	212(16.024)	
Brain metastasis	no	1712(92.291)	1303(82.888)	< 0.001	1904(92.114)	1111(81.691)	< 0.001
	yes	143(7.709)	269(17.112)		163(7.886)	249(18.309)	
Liver metastasis	no	1712(94.743)	1303(82.835)	< 0.001	1904(94.304)	1111(81.631)	< 0.001
	yes	95(5.257)	270(17.165)		115(5.696)	250(18.369)	
Lymphatic metastasis	no	1712(97.328)	1303(96.376)	0.128	1904(97.391)	1111(96.107)	0.045
	yes	47(2.672)	49(3.624)		51(2.609)	45(3.893)	
Metastasis at other sites	no	1712(92.993)	1303(86.063)	< 0.001	1904(92.742)	1111(85.330)	< 0.001
	yes	129(7.007)	211(13.937)		149(7.258)	191(14.670)	

Notes: Each type of metastasis was unique and did not include other metastasis types. OS, overall survival; CSS, cancer-specific survival

Table 3 Association between radiation and OS/CSS among patients with different metastasis types

	Crude model			**Adjusted model**		
	HR	**95%CI**	**P**	**HR**	**95%CI**	**P**
Outcome = OS						
Bone metastasis	0.896	[0.690,1.165]	0.413	0.892	[0.686,1.159]	0.392
Brain metastasis	0.750	[0.542,1.037]	0.081	0.789	[0.570,1.092]	0.153
Liver metastasis	0.618	[0.454,0.841]	0.002	0.622	[0.454,0.852]	0.003
Lymphatic metastasis	0.482	[0.269,0.862]	0.014	0.478	[0.266,0.858]	0.013
Metastasis at other sites	0.611	[0.462,0.809]	0.001	0.623	[0.470,0.825]	0.001
Outcome = CSS						
Bone metastasis	0.911	[0.695,1.194]	0.499	0.904	[0.689,1.186]	0.465
Brain metastasis	0.788	[0.559,1.110]	0.173	0.827	[0.586,1.167]	0.279
Liver metastasis	0.580	[0.418,0.804]	0.001	0.580	[0.416,0.809]	0.001
Lymphatic metastasis	0.470	[0.256,0.865]	0.015	0.465	[0.253,0.858]	0.014
Metastasis at other sites	0.634	[0.473,0.850]	0.002	0.642	[0.479,0.861]	0.003

Crude model: no variable was adjusted. Adjusted model: age, gender, race, income, and clinical stage were adjusted. OS, overall survival; CSS, cancer-specific survival

male patients with liver metastasis (Table 4). We speculated that male patients with liver metastasis may not benefit from radiation. We performed a competing risk analysis (that considered the death causes other than this cancer) to explore the influence of radiation on CSS. The results (Fig. 4B) showed that radiation only decreased the cumulative incidence of cancer-specific death both in female patients with liver metastasis (Interested event: $P = 0.001$) and whole female patients (Interested event: $P < 0.001$). However, radiation also decreased the cumulative incidence of cancer-specific death in whole male patients (Interested event: $P < 0.001$). However, among the subgroup of male patients with liver metastasis, radiation did not decrease the cumulative incidence of

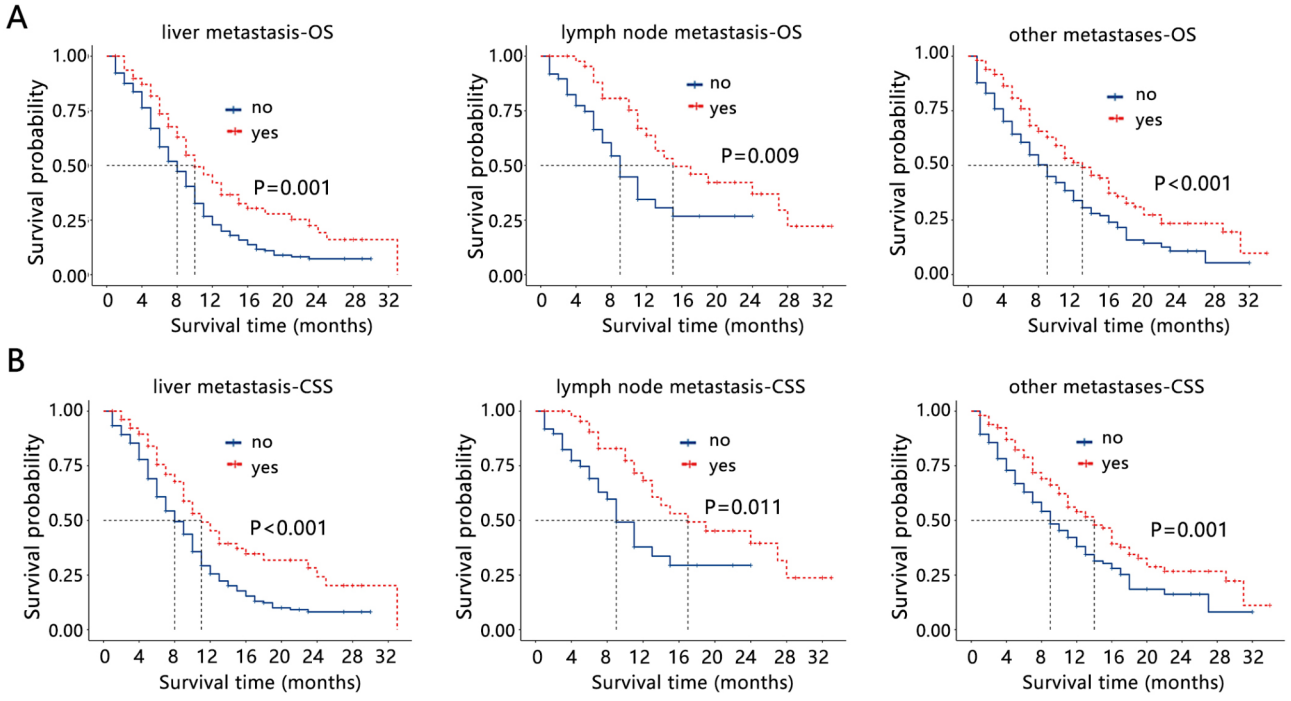

Fig. 2 The survival time assessment of patients under different metastasis types regarding the outcomes of (**A**) OS and (**B**) DSS. The survival time of patients was analyzed by Kaplan-Meier method and the survival difference between patients with or without radiation treatment was compared by log-rank test. OS, overall survival; CSS, cancer-specific survival

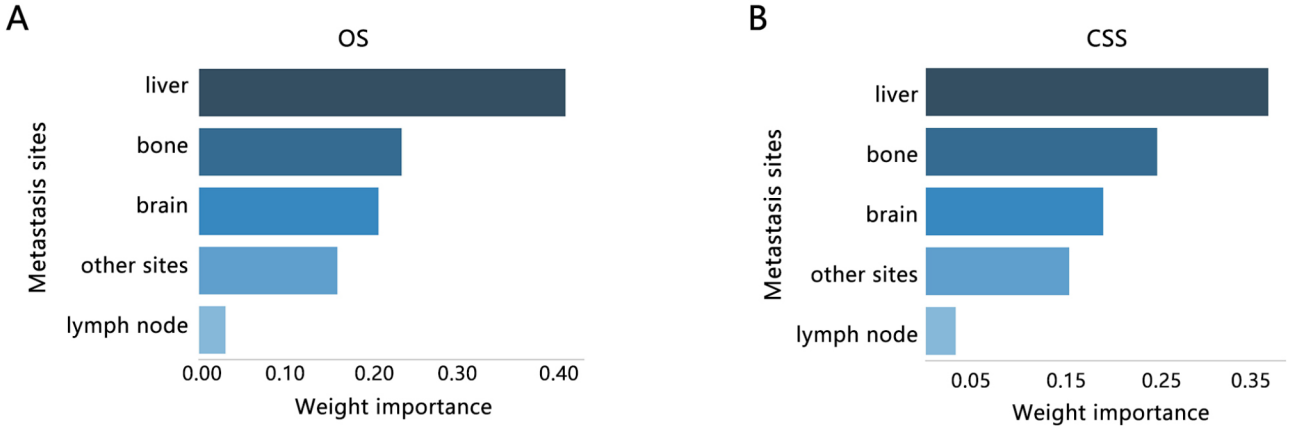

Fig. 3 The importance of different SCLC metastasis patterns to (**A**) OS and (**B**) CSS using random forest algorithm. OS, overall survival; CSS, cancer-specific survival

cancer-specific death (Interested event: $P = 0.227$). These results suggested that the subgroup of male patients with liver metastasis cannot benefit from radiation.

Discussion

SCLC is the pathological type of lung cancer with the highest degree of malignancy and the easiest metastasis. This study found that radiation was independently associated with OS and CSS in SCLC patients with liver metastases, lymphatic metastases, and metastases to other sites. In all 3 metastasis types, OS and CSS were better in the radiation group (compared to the non-radiation group). In addition, liver metastasis was the key pattern affecting OS and CSS. Patients with chemotherapy, gender of women, and in stage IV can significantly benefit from radiation.

Tumor metastasis is the process by which malignant tumor cells travel from the primary site to other sites via lymphatic channels, blood vessels, or body cavities to continue to grow [15]. In this study, we found that 22.7% of patients with SCLC had metastasis, with a bone metastasis rate of 4.9%, brain metastasis rate of 6%, liver

Table 4 Association between radiation and long-term outcomes of subgroup patients with liver metastasis

		OS			CSS		
		HR	95%CI	P	HR	95%CI	P
Age	≤ 60 years	0.452	[0.223,0.917]	0.028	0.442	[0.210,0.931]	0.032
	> 60 years	0.652	[0.457,0.930]	0.018	0.612	[0.421,0.890]	0.010
Gender	male	0.627	[0.396,0.993]	0.047	0.649	[0.402,1.047]	0.076
	female	0.594	[0.386,0.916]	0.018	0.500	[0.312,0.799]	0.004
Chemotherapy	no	0.837	[0.257,2.722]	0.767	0.604	[0.146,2.495]	0.486
	yes	0.559	[0.401,0.778]	0.001	0.523	[0.368,0.743]	< 0.001
Treatment delay time	no	0.569	[0.342,0.946]	0.03	0.558	[0.327,0.953]	0.033
	yes	0.654	[0.435,0.982]	0.041	0.599	[0.389,0.924]	0.020
Clinical stage IV		0.622	[0.455,0.851]	0.003	0.580	[0.417,0.808]	0.001

All the analyses were adjusted for age, gender, race, income, and clinical stage. Note: The patients with liver metastasis all belonged to clinical stage IV. OS, overall survival; CSS, cancer-specific survival

metastasis rate of 5.4%, and lymph metastasis rate of 5.0%. Based on the SEER database, Li et al. found that the metastasis rates of SCLC in bone, brain, liver, and lung were 12.5%, 14.3%, 24.3%, and 7.9% [16]. Another study, which included 10,347 SCLC patients, found that multi-organ metastases accounted for 32.9%, followed by liver metastases in 19.0%, bone metastases in 10.0%, and brain metastases in 12.1% of cases [17]. We suspected that the lower metastasis rate in this study may be related to the inclusion and exclusion criteria of the study. In this study, it was found that bone metastasis, brain metastasis, liver metastasis, and metastasis at other sites were related to the long-term prognosis of SCLC patients. China scholars have studied patients with extensive SCLC and found that among different organ metastases, patients with liver metastasis or bone metastasis have poor OS and PFS [18].

Regarding to the prognostic effect of radiation in the treatment of metastatic SCLC, the current researches have not yet reached a unified conclusion. Many studies have found that radiation does not affect the prognosis of patients with liver/brain metastasis [19]. Qie and other researchers studied the role of radiation in ES-SCLC patients and found that radiation could not change the survival rate of patients with brain metastases and liver metastases [20]. However, our study found that radiation was significantly associated with OS and CSS in SCLC patients with liver metastasis, lymphatic metastasis, and metastasis at other sites, but their association was not found in patients with brain metastasis and bone metastasis. Our study suggested that the effect of radiation on the prognosis of ES-SCLC may be related to the metastasis patterns. Another study found that chest radiation can improve the survival rate of patients with oligometastases not involving the liver/brain ES-SCLC, but it was not beneficial to patients with brain/liver/multimetastatic ES-SCLC [21]. China scholars also found that in ES-SCLC patients, thoracic radiation provides significant overall survived benefits in patients with oligmetastases ES-SCLC without liver metastasis [22]. Radiation was also found as a protective factor for prognosis in SCLC patients with bone metastasis [23, 24]. These knowledges suggest that when radiotherapy is given to a patient, we should comprehensively evaluate the metastatic sites to make a more accurate assessment of the patient's prognosis. We also found that radiotherapy cannot reduce the incidence of cancer-specific death in male SCLC patients with liver metastasis. Male was identified as a risk factor for the prognosis of patients with liver metastasis SCLC [25], and these gender-related prognosis difference may be related to the lifestyle.

In addition, we found that liver metastasis ranked first involved in the OS and CSS, highlighting the importance of liver function on the prognosis in SCLC. Liver is the largest detoxification and metabolic organ in the human body. When SCLC metastasizes to the liver, tumor cells will grow and proliferate in the liver, and related cancer cachexia can exert metabolic, inflammatory, and molecular impact on the liver [26], thus destroying the normal tissue structure and cellular functions of the liver. The intake and utilization of nutrients can be affected and the anti-tumor ability is further reduced, thus leading to the disease aggravation.

This study has some limitations. First, the SEER database contains little basic information about patients and does not include specific treatment plans of patients, types of gene mutations of lung cancer patients, etc. Secondly, the number of patients with metastasis in this study is relatively small, and large data samples are still needed for verification. In addition, the data in the SEER database only provides an indicator of whether radiotherapy was administered and does not record information on the radiotherapy method, dosage, or irradiation area. This information is closely related to the effectiveness of radiotherapy and its impact on prognosis, which may affect the analyzed findings.

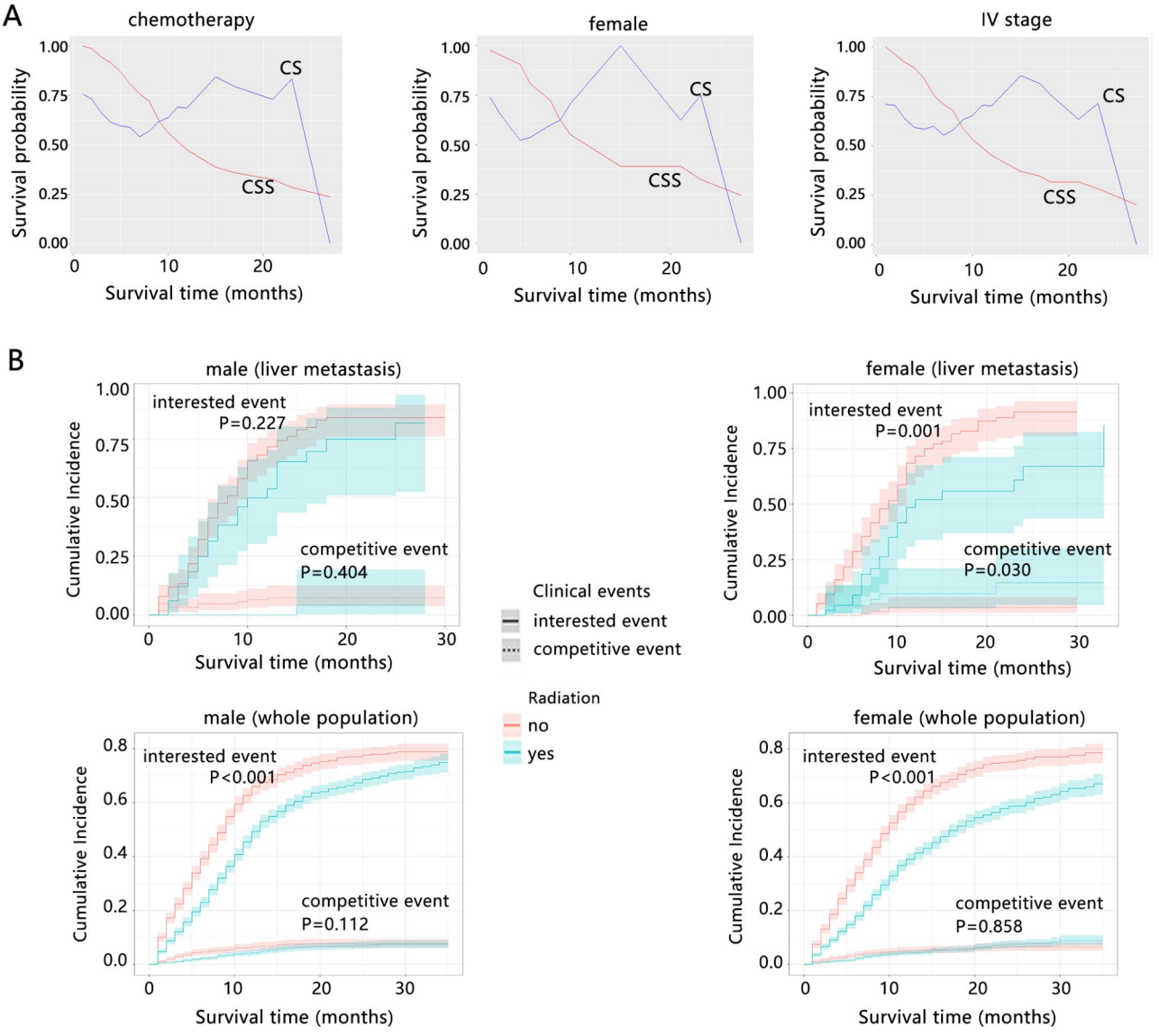

Fig. 4 The influence of radiation on the patient's prognosis. (**A**) The comparison of cancer-specific survival (CSS) with cancer-specific conditional survival (CS) of subgroup patients receiving radiation using conditional survival (CS) analysis. CS refers to the probability of a patient who has survived for X years surviving for another Y years, calculated as CS (Y) = S(X + Y)/S(X). (**B**) The influence of radiation on cancer-specific death using a competing risk model among subgroup populations. Gray's test was used to identify any statistical differences between radiation and non- radiation due to competing risk events. Interested event: dead (attributable to this cancer); Competitive event: Dead (attributable to causes other than this cancer)

Conclusions

Radiation was independently associated with OS and CSS in patients with SCLC liver metastasis, lymphatic metastasis, and metastasis at other sites. The radiation group had better OS and CSS compared with the non-radiation group in these 3 metastasis patterns. Among all metastasis patterns, liver metastasis was the key pattern. In particular, male patients with SCLC liver metastasis may not benefit from radiation.

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Author contributions
HD contributed to the conception and design. HD and WW contributed to the collection and assembly of data. HD and WW analyzed and interpreted the data. All authors wrote and approved the final manuscript.

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Data availability
Data will be made available on request.

Declarations

Ethics approval and consent to participate
The Ethics Committee of People's Hospital of Haining deemed that this research is based on open-source data, so the need for ethics approval was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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