Original Article

Surgical resection of primary tumors improves survival in patients with lung metastases: a population-based SEER analysis

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Background: The lung is a common site for cancer metastasis. Some cancer patients would develop lung metastases throughout the course of their illness. However, choosing surgical resection of the primary tumor (SRPT) or palliative treatment in patients with lung metastases remains controversial.

Methods: Lung metastatic patients diagnosed from 2010 to 2016 were selected from the Surveillance, Epidemiology, and End Results (SEER) database. Selected patients were divided into two subgroups (surgery and non-surgery). Further, all the 58 tumor types were classified into 13 subtypes. The clinical and demographic features were examined by the Fisher's exact test, chi-squared test, or z-test. Overall survival (OS) was analyzed using the Kaplan-Meier (K-M) estimator and a log-rank test for each primary tumor type. Multivariable survival analyses of OS were performed using the Cox proportional hazards model.

Results: Among the 118,088 patients selected for study, 18,688 (15.83%) patients had undergone surgery. The analyses demonstrated that there was a significant association between SRPT and better OS in patients with lung metastases. The median survival time increased from 4.0 months in the non-surgery group to 19.0 months in the surgery group. Multivariate Cox regression analyses further validated that patients who underwent SRPT had an improved OS.

Conclusions: The current study demonstrated that patients with lung metastases can benefit from SRPT. SRPT should be considered in patients with lung metastases. Properly designed prospective randomized clinical trials would be required to further verify the conclusion.

Keywords: Primary tumor; lung metastasis; surgical resection of the primary tumor (SRPT); survival; Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Distant metastases are the main cause of death in cancer patients, and are mostly found in the brain, liver, lungs, kidneys, and lymph nodes (1). The mechanism of distant metastasis is unclear. For cancer patients who exhibit no obvious symptoms, the tumors are difficult to be detected at earlier stage using present methods. Hence, for many patients, tumors were already in their advanced stages or had metastasized to other sites at the point of diagnosis, which further complicated the treatments. Many tumors are prone to distant metastases. For example, in osteosarcoma (2) and early-stage breast cancer (3), 13% and 20–30% of patients experienced distant metastases respectively. The lung is one of the most common metastatic sites for cancer metastasis, which accounts for 30–50% of all metastasis-related cases. Although distant lung metastases could occur in most types of cancer, they are most common in cancers involving melanoma, breast, colorectal, thyroid, head and

neck and renal cell cancer (4). However, compared to other types of distant metastases, lung metastasized tumors have relatively lower growth rate and better overall survival (OS) (5). Therefore, treatment options for lung metastases could be different to that of metastases at other sites.

Although multiple treatment options, including locoregional and/or lung surgery, chemotherapy, immunotherapy and radiotherapy, could be used for lung metastatic cancer, the potential curative treatment approach would be comprehensive treatment for lung metastatic tumors. However, patients with lung metastasized tumors, which are already in advanced stages, are not recommended by the clinical guidelines to remove the primary tumors. Surgical resection of the primary tumor (SRPT) treated patients could have a 30–40% 5-year survival rate. Furthermore, previous studies revealed that SRPT resulted in better OS in several types of metastatic cancer, such as pancreatic cancer (6), gastroenteropancreatic neuroendocrine neoplasms (7), colorectal cancer (8), prostate cancer (9,10), and Ewing's sarcoma (11). Nevertheless, none of these studies revealed a survival difference between lung metastases and other sites of metastases, as all these studies have relatively small sample size.

Given that the lungs are the predominant metastatic sites, it will be vital to understand how SRPT would affect the OS of patients with lung metastases. In the present study, we took advantage of the SEER database, which has a relatively large sample size, to assess whether SRPT should be considered for lung metastatic patients. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2459/rc).

Highlight box

Key findings

- The current study demonstrated that patients with lung metastases can benefit from SRPT.

What is known and what is new?

- SRPT resulted in better OS in several types of metastatic cancer.
- SRPT should be considered for lung metastatic patients.

What is the implication, and what should change now?

- In addition to radiotherapy and systemic chemotherapy, SRPT should also be seriously considered for lung metastatic patients. It is appreciated that the conclusion here will be validated and surgical inclusion criteria could be further clarified through well-designed, prospective, and randomized clinical trials.

Methods

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The data on cancer in the Surveillance, Epidemiology, and End Results (SEER) database is continually reported in every state of the United States and retrieved with no need for informed patient consent.

Patient cohort

Eligible patients and their related information were obtained from the SEER database by employing a specific software (SEER*Stat, version 8.3.5, National Center Institute, USA). The SEER database recorded various clinical information including tumor characteristics, demographics, cancer incidence and prevalence, treatments and mortality. The SEER database has been widely used for clinical cancer studies. Patients diagnosed between 2010 and 2016 were included. The exclusion criteria were as following: (I) patients diagnosed before 2010 or after 2016, (II) diagnosed at autopsy or via death certificate, (III) patients with no clear lung metastasis information or surgery information. Detailed patient selection procedures are displayed in *Figure 1*.

Data collection

For each patient, the following clinical data were obtained: primary tumor type, age at diagnosis, gender, marital status, insurance status, income level, laterality, tumor grade, tumor stage, lymph node stage, metastasis sites (bone, brain, or liver), OS, and surgery status (yes or no). OS was used as the major endpoint outcome in the study. OS was defined as the duration from diagnosis to death due to any causes. Selected patients were classified into two subgroups (surgery and non-surgery). Additionally, 58 types of cancer identified from the SEER database were further divided into 13 cancer subtypes based on the primary tumor sites, including the oral cavity and pharynx, bones and joints, digestive, respiratory, soft tissue and skin, urinary, endocrine, male genital, female genital, blood, nervous, lymphatic, and the remaining systems.

Statistical analyses

Depending on different variables, differences in the clinical

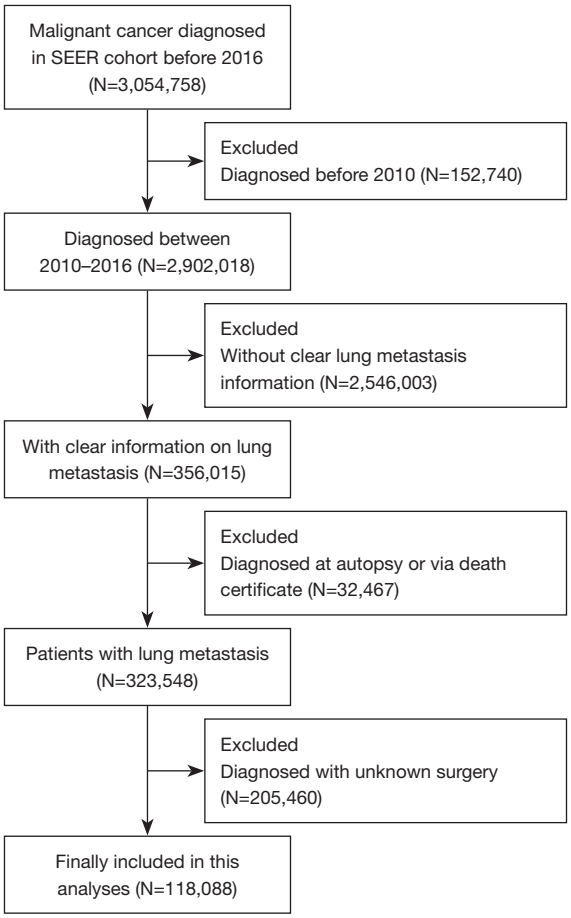

Figure 1 The flow-chart for the subject selection in the present study. SEER, Surveillance, Epidemiology, and End Results.

and demographic features between surgery and non-surgery groups were analyzed by the Fisher's exact test, chi-squared test, or z-test. For each type of cancer, OS was evaluated by the Kaplan-Meier (K-M) estimator or a log-rank test. OS was further estimated by K-M curves. In addition, survival analyses were also performed for the 13 cancer subtypes. Median survival times and the associated 95% confidence intervals (CIs) were calculated by the K-M method. Multivariable survival analyses of OS were performed utilizing the Cox proportional hazards model. The loss to follow-up or follow-up interruption at the end of the observation was treated as a censoring event. Moreover, we applied a subgroup analysis to test the robustness of our results. For the above analyses, the following software was used: SPSS Statistics 22.0 software (IBM, NY, USA) for the chi-square test, z-test, K-M curves, log-rank test, and Cox regression analysis; GraphPad Prism 8.3 software (GraphPad, CA, USA) was used to generate the histograms; Comprehensive Meta-Analysis (CMA) Software 2.0 (Biostat, NJ, USA) was employed for the forest plotting. A two-tailed P value smaller than 0.05 was recognized as statistically significant.

Results

Patient and tumor characteristics

Detailed demographic and clinical parameters of the patients were summarized in *Table 1*; 118,088 selected patients with lung metastases were collected from the SEER database, of whom 18,688 (15.83%) had undergone surgery and 99,400 (84.17%) had not (*Figure 1*). The median age at diagnosis was 68.0 years; 77.85% and 94.18% of patients were white and insured, respectively. Selected patients in the non-surgery group were older than those in the surgery group (median age: 69.0 *vs.* 62.0 years, P<0.001). Younger age was also associated with improved OS from univariate and multivariable Cox proportional hazard regression analyses (*Table 2*). There was a larger proportion (41.37% *vs.* 28.98%) of patients with N0 stage cancer in the surgery group. Patients undergoing surgery were at lower T and N stage, but with higher grade. Univariate and multivariable Cox proportional hazard regression analyses showed that patients with lower N stage had a better OS (*Table 2*). Patients with cancer of the urinary (21.62%) and the female genital systems (12.92%) had higher ratio of SRPT. Moreover, the ratio of patients who underwent SRPT increased through the years from 2010 to 2016. This suggests that SRPT might be a mainstream treatment option for patients with lung metastasis in the future (*Figure 2*). Additionally, the survival rates in the surgery and non-surgery groups were 38.86% (n=7,263) and 16.19% (n=16,090), respectively.

Survival analyses

Of the 118,088 patients, 94,735 (80.22%) were deceased by the end of follow-up. The median survival time was 19.0 months (95% CI: 18.45–19.55 months) and 4.0 months (95% CI: 3.94–4.06 months) for the surgery and non-surgery groups, respectively (P<0.001) (*Table 3*). After adjustment for parameters including age, gender, marital status, insurance status, income level, laterality, tumor grade, tumor stage, lymph node stage, metastasis sites (bone, brain, or liver), OS, and surgery status (yes or

Table 1 Demographic and clinical characteristics for lung metastases patients of non-surgery and surgery

Subject characteristics	Total, n (%)	Non-surgery, n (%)	Surgery, n (%)	χ^2/Z	P value
All patients	118,088 (100.00)	99,400 (100.00)	18,688(100.00)		
Age, years				71.33	<0.001
≤18	979 (0.83)	305 (0.31)	674 (3.61)		
19–40	4,050 (3.43)	2,281 (2.29)	1,769 (9.47)		
41–64	42,972 (36.39)	34,938 (35.15)	8,024 (42.94)		
≥65	70,097 (59.35)	61,876 (62.25)	8,221 (43.99)		
Sex				86.82	<0.001
Male	60,907 (51.58)	51,713 (50.03)	9,194 (49.20)		
Female	57,181 (48.42)	47,687 (49.97)	9,494 (50.80)		
Race				72.25	<0.001
White	91,927 (77.85)	77,172 (77.64)	14,775 (79.06)		
Black	15,385 (13.03)	13,198 (13.28)	2,187 (11.70)		
Others*	10,482 (8.88)	8,812 (8.87)	1,670 (8.94)		
Unknown	274 (0.23)	218 (0.22)	56 (0.30)		
Marital status				1,295.19	<0.001
Married	56,233 (47.62)	46,897 (47.18)	9,336 (49.96)		
Unmarried	56,431 (47.79)	47,874 (48.16)	8,557 (45.79)		
Unknown	5,424 (4.59)	4,629 (4.66)	795 (4.25)		
Insurance				66.20	<0.001
Insured	111,218 (94.18)	93,521 (94.09)	17,697 (94.70)		
Uninsured	4,568 (3.87)	3,841 (3.86)	727 (3.89)		
Unknown	2,302 (1.95)	2,038 (2.05)	264 (1.41)		
Income				3.04	0.002
<6,000	28,325 (23.99)	24,090 (24.24)	4,235 (22.66)		
6,000–7,000	35,641 (30.18)	29,830 (30.01)	5,811 (31.10)		
7,000–8,000	16,864 (14.28)	14,103 (14.19)	2,761 (14.77)		
>8,000	37,255 (31.55)	31,375 (31.56)	5,880 (31.47)		
Laterality				1,951.55	<0.001
Right	35,852 (30.36)	31,169 (31.36)	4,683 (25.06)		
Left	29,051 (24.60)	24,577 (24.72)	4,474 (23.94)		
Bilateral	3,687 (3.12)	3,062 (3.08)	625 (3.34)		
Unknown	49,498 (41.92)	40,592 (40.84)	8,906 (47.66)		
Grade				97.84	<0.001
I	3,291 (2.79)	2,571 (2.59)	720 (3.85)		
II	16,654 (14.10)	12,368 (12.44)	4,286 (22.94)		
III	24,478 (20.73)	19,297 (19.41)	5,181 (27.73)		
IV	6,212 (5.26)	2,885 (2.91)	3,327 (17.80)		
Unknown	67,450 (57.12)	62,277 (62.65)	5,173 (27.68)		

Table 1 (*continued*)

Table 1 (*continued*)

Subject characteristics	Total, n (%)	Non-surgery, n (%)	Surgery, n (%)	χ^2/Z	P value
T stage				68.69	<0.001
T1	11,166 (9.46)	9,022 (9.08)	2,144 (11.47)		
T2	16,070 (13.61)	12,732 (12.81)	3,338 (17.86)		
T3	28,352 (24.01)	21,531 (21.66)	6,821 (36.50)		
T4	35,547 (30.10)	31,058 (31.25)	4,489 (24.02)		
Unknown	26,953 (22.82)	25,057 (25.21)	1,896 (10.15)		
N stage				63.24	<0.001
N0	36,542 (30.94)	28,810 (28.98)	7,732 (41.37)		
N1	24,467 (20.72)	19,316 (19.43)	5,151 (27.56)		
N2	25,395 (21.51)	22,318 (22.45)	3,077 (16.47)		
N3	13,226 (11.20)	12,429 (12.50)	797 (4.26)		
Unknown	18,458 (15.63)	16,527 (16.63)	1,931 (10.33)		
Bone MET				3,186.79	<0.001
None	81,588 (69.09)	66,229 (66.63)	15,359 (82.19)		
Yes	32,925 (27.88)	29,940 (30.12)	2,985 (15.97)		
Unknown	3,575 (3.03)	3,231 (3.25)	344 (1.84)		
Brain MET				2,184.96	<0.001
None	99,823 (84.53)	82,478 (81.98)	17,345 (92.81)		
Yes	13,934 (17.80)	13,005 (13.08)	929 (4.97)		
Unknown	4,331 (3.67)	3,917 (3.94)	414 (2.22)		
Liver MET				1,168.42	<0.001
None	76,782 (65.02)	63,119 (63.50)	13,663 (73.11)		
Yes	37,991 (32.17)	33,269 (33.47)	4,722 (25.27)		
Unknown	3,315 (2.81)	3,012 (3.03)	303 (1.62)		
Cancer system					
Oral cavity and pharynx	1,690 (1.43)	1,440 (1.45)	250 (1.34)		
Digestive system	31,829 (26.95)	27,171 (27.34)	4,658 (24.93)		
Respiratory system	47,679 (40.38)	45,156 (45.43)	1,523 (8.15)		
Bones and joints	626 (0.53)	318 (0.32)	308 (1.65)		
Soft tissue including heart	1,800 (1.52)	1,154 (1.16)	646 (3.46)		
Skin excluding basal squamous	2,777 (2.35)	2,039 (2.05)	738 (3.95)		
Breast	7,777 (6.59)	6,090 (6.13)	1,687 (9.03)		
Female genital system	6,478 (5.49)	4,064 (4.09)	2,414 (12.92)		
Male genital system	3,710 (3.14)	2,330 (2.34)	1,380 (7.38)		
Urinary system	10,652 (9.02)	6,611 (6.65)	4,041 (21.62)		
Eye and orbit	39 (0.03)	20 (0.02)	19 (0.10)		
Brain and other nervous system	63 (0.05)	30 (0.03)	33 (0.18)		

Table 1 (*continued*)

Table 1 (*continued*)

Subject characteristics	Total, n (%)	Non-surgery, n (%)	Surgery, n (%)	χ^2/Z	P value
Endocrine system	1,768 (1.50)	947 (0.95)	821 (4.39)		
Lymphoma	571 (0.48)	498 (0.50)	73 (0.39)		
Myeloma	59 (0.05)	50 (0.05)	9 (0.05)		
Leukemia	111 (0.09)	93 (0.09)	18 (0.10)		
Mesothelioma	456 (0.39)	298 (0.30)	58 (0.31)		
Kaposi sarcoma	18 (0.02)	16 (0.02)	2 (0.01)		
Miscellaneous	85 (0.07)	75 (0.08)	10 (0.05)		
Overall survival				8,038.88	<0.001
Survival	23,353 (19.78)	16,090 (16.19)	7,263 (38.86)		
Death	94,735 (80.22)	83,310 (83.81)	11,425 (61.14)		

*, American Indian/Alaska Native, Asian or Pacific Islander. MET, metastases.

Table 2 Univariate and multivariate survival analyses of overall survival in patients who underwent surgery

Subject characteristics	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, years				
≤18	Reference		Reference	
19–40	1.822 (1.539–2.157)	<0.001	1.781 (1.500–2.116)	<0.001
41–64	3.505 (3.005–4.088)	<0.001	2.877 (2.453–3.374)	<0.001
≥65	4.826 (4.139–5.627)	<0.001	3.835 (3.269–4.499)	<0.001
Sex				
Male	Reference		Reference	
Female	0.935 (0.901–0.970)	<0.001	0.876 (0.843–0.909)	<0.001
Race				
White	Reference		Reference	
Black	1.133 (1.072–1.197)	<0.001	1.214 (1.148–1.284)	<0.001
Others*	0.903 (0.845–0.966)	0.003	0.910 (0.851–0.973)	0.006
Unknown	NA		NA	
Grade				
I	Reference		Reference	
II	1.364 (1.221–1.524)	<0.001	1.331 (1.190–1.488)	<0.001
III	1.788 (1.603–1.994)	<0.001	2.004 (1.796–2.237)	<0.001
IV	2.255 (2.017–2.521)	<0.001	2.962 (2.646–3.315)	<0.001
Unknown	NA		NA	

Table 2 (*continued*)

Table 2 (*continued*)

Subject characteristics	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
T stage				
T1	Reference		Reference	
T2	1.256 (1.167–1.353)	<0.001	1.195 (1.109–1.288)	<0.001
T3	1.256 (1.176–1.343)	<0.001	1.104 (1.031–1.182)	0.005
T4	1.818 (1.697–1.947)	<0.001	1.462 (1.361–1.570)	<0.001
Unknown	NA		NA	
N stage				
N0	Reference		Reference	
N1	1.066 (1.019–1.115)	0.006	1.087 (1.037–1.139)	<0.001
N2	1.356 (1.288–1.428)	<0.001	1.333 (1.261–1.409)	<0.001
N3	0.994 (0.903–1.095)	0.904	1.139 (1.032–1.257)	0.01
Unknown	NA		NA	
Bone MET				
None	Reference		Reference	
Yes	1.494 (1.425–1.566)	<0.001	1.305 (1.242–1.371)	<0.001
Unknown	NA		NA	
Brain MET				
None	Reference		Reference	
Yes	1.729 (1.602–1.867)	<0.001	1.826 (1.684–1.980)	<0.001
Unknown	NA		NA	
Liver MET				
None	Reference		Reference	
Yes	1.679 (1.613–1.748)	<0.001	1.716 (1.643–1.792)	<0.001
Unknown	NA		NA	
Radiotherapy				
No	Reference		Reference	
Yes	0.865 (0.827–0.905)	<0.001	0.853 (0.813–0.895)	<0.001
Unknown	NA		NA	
Chemotherapy				
No	Reference		Reference	
Yes	0.587 (0.566–0.610)	<0.001	0.592 (0.569–0.616)	<0.001

*, American Indian/Alaska Native, Asian or Pacific Islander. OR, odds ratio; CI, confidence interval; NA, not available; MET, metastases.

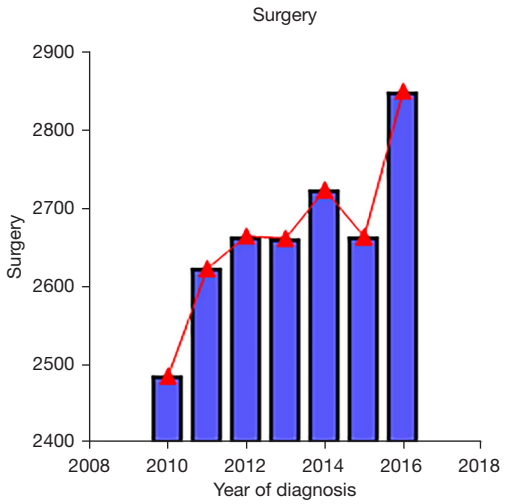

Figure 2 Variation of surgery quantity with time.

no), the multivariate Cox regression analysis indicated that recipients of SRPT were significantly related to a better OS [hazard ratio (HR) =0.49; 95% CI: 0.48–0.51, P<0.001] (*Table 3*).

Of the 58 types of cancer, subjects who underwent SRPT had improved OS to varying degrees compared to those who did not. Moreover, the 58 types of cancer were divided into 13 subtypes and subjects with SRPT were associated with improved OS (*Table 3*). Among the patients whose primary tumors were in the oral cavity and pharynx system, median survival time was 16.00 months (95% CI: 12.68–19.32 months) and 7.00 months (95% CI: 6.42–7.58 months) for the surgery and non-surgery groups, respectively (P<0.001). Similarly, the median survival time of patients in the surgery group was significantly longer than that of those in the non-surgery group in cancer of the digestive system (17.00 months, 95% CI: 16.16–17.84 months *vs.* 3.00 months, 95% CI: 2.92–3.08 months; P<0.001), bones and joints (29.00 months, 95% CI: 23.00–35.00 months *vs.* 10.00 months, 95% CI: 8.02–11.98 months; P<0.001), soft tissue and skin (13.00 months, 95% CI: 11.85–14.15 months *vs.* 5.00 months, 95% CI: 4.68–5.32 months; P<0.001), female genital (24.00 months, 95% CI: 22.69–25.31 months *vs.* 9.00 months, 95% CI: 8.53–9.47 months; P<0.001), urinary (13.00 months, 95% CI: 12.30–13.70 months *vs.* 5.00 months, 95% CI: 4.77–5.23 months; P<0.001), endocrine (53.00 months, 95% CI: 43.22–63.78 months *vs.* 4.00 months, 95% CI: 3.27–4.73 months; P<0.001), lymphatic (32.00 months, 95% CI: 11.82–52.19 months *vs.* 15.00 months, 95% CI: 11.50–18.50 months; P=0.01), blood (27.00 months, 95% CI: 14.08–39.92 months *vs.* 6.00 months, 95% CI: 3.43–8.57 months; P<0.001), and the remaining miscellaneous systems (23.00 months, 95% CI: 1.12–44.88 months *vs.* 6.00 months, 95% CI: 1.89–10.11; P=0.041). However, a log-rank test revealed no difference of survival time between surgery and non-surgery groups in the nervous system (P=0.146). The K-M OS curves for the surgery and non-surgery groups were shown in *Figure 3*. At each time point, the survival time of patients in the surgery group was longer than that of those in the non-surgery group.

Patients who underwent SRPT exhibited a significant improvement in rate of survival, a finding observed across diverse synchronous metastases patterns (*Table 4*). In lung metastasis only, the median survival times of the surgery and non-surgery groups, were 15.00 months (95% CI: 14.56–15.44 months) and 5.00 months (95% CI: 4.90–5.11 months) (P<0.001), respectively. In lung metastasis combined with liver metastasis, the median survival times of the surgery and non-surgery groups, were 10.00 months (95% CI: 9.46–10.55 months) and 2.00 months (95% CI: 1.91–2.09 months) (P<0.001), respectively. In lung metastases combined with bone metastases, the median survival times were 10.00 months (95% CI: 9.26–10.74 months) and 4.00 months (95% CI: 3.86–4.14 months) for the surgery and non-surgery groups, respectively (P<0.001). Similarly, the median survival time of patients in the surgery group was significantly longer than that of patients in the non-surgery group in lung metastases combined with brain metastases [respectively, 8.00 months (95% CI: 6.98–9.02 months) and 3.00 months (95% CI: 2.82–3.18 months); P<0.001] (*Table 4*). Furthermore, most of the subjects had received primary tumour resection as the first treatment. No radiation and/or cancer-directed surgery accounted for 93.1%. Radiation prior to surgery accounted for 6.0%. Radiation after to surgery accounted for 0.7%. The sum of intraoperative radiation, intraoperative rad with other rad before/after and sequence unknown, but both were given accounted for 0.1% (*Figure 4*). Patients who underwent SRPT and chemotherapy or radiotherapy experienced a significant survival improvement. In chemotherapy, the median survival times were 24.00 months (95% CI: 23.29–24.71 months) and 9.00 months (95% CI: 8.87–9.13 months) for the surgery and non-surgery groups, respectively (P<0.001). In radiotherapy, the median survival times were 20.00 months (95% CI: 18.71–21.29 months) and 6.00 months (95% CI: 5.87–6.13 months) for the surgery

Table 3 The median survival time and multivariable Cox regression for analyzing the overall survival of lung metastases of non-surgery and surgery

Cancer system	Cancer site	Non-surgery (months), median (95% CI)	Surgery (months), median (95% CI)	Log Rank	P value	HR (95% CI)	P
–	All patients	4.00 (3.94–4.06)	19.00 (18.45–19.55)	8792.07	<0.001	0.49 (0.48–0.51)	<0.001
Oral cavity and pharynx system	Lip	1.00 (0.37–1.63)	5.00	2.46	0.117	0.00 (0.00–0.01)	0.013
	Tongue	7.00 (5.28–8.72)	11.00 (6.17–1.83)	7.46	0.006	0.54 (0.37–0.80)	0.002
	Salivary gland	8.00 (5.42–10.56)	23.00 (16.93–29.07)	27.19	<0.001	0.38 (0.26–0.56)	<0.001
	Floor of mouth	5.00 (2.94–7.06)	20.00 (4.90–35.11)	8.12	0.004	0.28 (0.11–0.71)	0.007
	Gum and other mouth	5.00 (3.47–6.53)	8.00 (4.06–11.94)	3.72	0.054	0.60 (0.36–1.00)	0.051
	Larynx	6.00 (5.07–6.93)	12.00 (8.86–15.14)	11.61	0.001	0.55 (0.39–0.80)	0.001
	Nasopharynx	13.00 (8.67–17.33)	20.00	2.60	0.107	0.64 (0.25–1.64)	0.411
	Tonsil	9.00 (7.50–10.51)	17.00 (1.35–32.65)	4.03	0.045	0.64 (0.36–1.13)	0.122
	Oropharynx	5.00 (2.99–7.01)	6.00 (0.00–12.20)	1.21	0.271	0.65 (0.30–1.40)	0.272
	Hypopharynx	6.00 (4.23–7.77)	16.00 (3.60–28.40)	4.59	0.032	0.50 (0.26–0.96)	0.037
	Other oral cavity and pharynx	3.00 (1.24–4.76)	12.00 (0.00–25.72)	0.73	0.391	1.23 (0.35–4.29)	0.742
	Nose, nasal cavity and middle ear	7.00 (0.78–13.22)	14.00 (8.91–19.09)	2.37	0.124	0.65 (0.31–1.34)	0.241
	Subtotal	7.00 (6.42–7.58)	16.00 (12.68–19.32)	74.99	<0.001	0.50 (0.43–0.58)	<0.001
Digestive system	Esophagus	4.00 (3.72–4.29)	10.00 (6.63–13.37)	14.60	<0.001	0.56 (0.40–0.79)	0.001
	Stomach	3.00 (2.72–3.28)	6.00 (4.22–7.78)	13.36	<0.001	0.62 (0.50–0.77)	<0.001
	Small intestine	5.00 (3.36–6.64)	12.00 (7.36–16.64)	10.02	0.002	0.74 (0.55–1.01)	0.059
	Colon cancer	4.00 (3.66–4.34)	15.00 (13.94–16.06)	739.75	<0.001	0.58 (0.55–0.62)	<0.001
	Rectum and rectosigmoid junction	11.00 (10.27–11.73)	26.00 (23.04–28.07)	294.04	<0.001	0.55 (0.50–0.60)	<0.001
	Anus, anal canal and anorectum	9.00 (6.80–11.20)	10.00 (5.51–14.49)	0.17	0.68	1.01 (0.69–1.48)	0.970
	Liver and intrahepatic bile duct	2.00 (1.90–2.11)	20.00 (11.33–28.67)	178.43	<0.001	0.29 (0.22–0.37)	<0.001
	Gallbladder cancer	3.00 (2.46–3.54)	6.00 (3.67–8.33)	4.89	0.027	0.74 (0.53–1.05)	0.095
	Other biliary	2.00 (1.65–2.36)	11.00 (4.56–17.44)	14.46	<0.001	0.58 (0.35–0.99)	0.045
	Pancreas	2.00 (1.89–2.12)	12.00 (8.45–15.55)	79.77	<0.001	0.41 (0.33–0.52)	<0.001
	Retroperitoneum	5.00 (2.52–7.48)	18.00 (11.09–24.92)	7.96	0.005	0.68 (0.44–1.05)	0.078
	Peritoneum, omentum and mesentery	7.00 (3.69–10.31)	29.00 (25.32–32.68)	26.19	<0.001	0.53 (0.36–0.79)	0.002
	Other digestive organs	2.00 (1.77–2.23)	6.00 (0.16–11.84)	2.62	0.015	1.06 (0.50–2.23)	0.876
	Subtotal	3.00 (2.92–3.08)	17.00 (16.16–17.84)	2653.93	<0.001	0.47 (0.46–0.49)	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Cancer system	Cancer site	Non-surgery (months), median (95% CI)	Surgery (months), median (95% CI)	Log Rank	P value	HR (95% CI)	P
Respiratory system	Lung and bronchus	4.00 (3.91–4.09)	16.00 (14.19–17.81)	752.60	<0.001	0.42 (0.40–0.45)	<0.001
	Pleura	0.00	3.00	0.14	0.702		0.08
	Trachea, mediastinum and other respiratory organs	7.00 (4.35–9.66)	17.00 (8.57–25.43)	16.66	<0.001	0.42 (0.25–0.71)	0.001
	Subtotal	4.00 (3.91–4.09)	16.00 (14.23–17.77)	777.86	<0.001	0.42 (0.40–0.45)	<0.001
Bones and joints system	Bones and joints	10.00 (8.02–11.98)	29.00 (23.00–35.00)	59.78	<0.001	0.62 (0.49–0.79)	<0.001
Soft tissue and skin system	Melanoma of the skin	5.00 (4.61–5.39)	11.00 (9.60–12.40)	72.16	<0.001	0.70 (0.63–0.78)	<0.001
	Soft tissue including heart	5.00 (4.35–5.65)	16.00 (13.73–18.27)	181.85	<0.001	0.50 (0.44–0.57)	<0.001
	Other non-epithlia skin	6.00 (2.75–9.25)	9.00 (6.31–11.69)	0.98	0.323	0.62 (0.35–1.09)	0.097
	Mesothelioma	4.00 (3.09–4.91)	9.00 (5.99–12.01)	9.21	0.002	0.72 (0.52–1.00)	0.050
	Eye and orbit	4.00 (1.70–6.30)	37.00 (4.26–69.74)	6.32	0.012	0.80 (0.15–4.28)	0.791
	Kaposi sarcoma			0.28	0.597	0.00	0.599
	Subtotal	5.00 (4.68–5.32)	13.00 (11.85–14.15)	269.51	<0.001	0.59 (0.54–0.63)	<0.001
Female genital system	Cervix uteri	6.00 (5.34–6.66)	12.00 (10.09–13.91)	16.94	<0.001	0.63 (0.48–0.82)	0.001
	Breast cancer	15.00 (14.11–15.89)	29.00 (26.71–31.29)	216.38	<0.001	0.71 (0.66–0.76)	<0.001
	Corpus and uterus, NOS	3.00 (2.61–3.39)	14.00 (12.60–15.40)	341.18	<0.001	0.50 (0.45–0.56)	<0.001
	Ovary	3.00 (2.53–3.47)	30.00 (27.68–32.32)	607.92	<0.001	0.37 (0.32–0.43)	<0.001
	Vagina	5.00 (2.92–7.08)	18.00 (2.81–33.19)	2.15	0.143	0.68 (0.32–1.44)	0.316
	Vulva	3.00 (1.90–4.11)	6.00 (2.73–9.27)	4.80	0.029	0.48 (0.30–0.75)	0.001
	Other female genital organs	16.00 (7.05–24.95)	47.00 (32.50–61.50)	14.17	<0.001	1.09 (0.69–1.74)	0.708
	Subtotal	9.00 (8.53–9.47)	24.00 (22.69–25.31)	675.06	<0.001	0.69 (0.66–0.73)	<0.001
Male genital system	Penis	2.00 (0.21–3.79)	7.00 (5.24–8.76)	2.05	0.152	0.51 (0.20–1.34)	0.170
	Testis	8.00 (4.25–11.75)	0.00	181.87	<0.001	0.33 (0.24–0.47)	<0.001
	Subtotal	7.00 (3.31–10.69)		204.66	<0.001	0.37 (0.27–0.51)	<0.001
Urinary system	Prostate	12.00 (10.99–13.01)	18.00 (14.19–21.81)	11.36	0.001	0.84 (0.70–1.00)	0.054
	Urinary	2.00 (1.63–2.37)	5.00 (4.46–5.54)	54.33	<0.001	0.83 (0.74–0.93)	0.001
	Kidney and renal pelvis	4.00 (3.82–4.18)	19.00 (17.47–20.54)	1597.74	<0.001	0.40 (0.37–0.43)	<0.001
	Ureter	4.00 (2.63–5.37)	7.00 (5.18–8.82)	4.27	0.039	0.90 (0.47–1.70)	0.740
	Other urinary organs	2.00 (0.95–3.05)	9.00 (7.13–10.88)	2.69	0.101	0.76 (0.44–1.31)	0.318
	Subtotal	5.00 (4.77–5.23)	13.00 (12.30–13.70)	837.30	<0.001	0.69 (0.66–0.73)	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Cancer system	Cancer site	Non-surgery (months), median (95% CI)	Surgery (months), median (95% CI)	Log Rank	P value	HR (95% CI)	P
Nervous system	Cranial nerves other nervous system	1.00	46.00 (0.00–106.01)	1.10	0.294	0.00 (0.00–0.001)	0.474
	Brain	6.00 (0.00–15.79)	7.00 (2.85–11.15)	0.08	0.766	0.54 (0.20–1.48)	0.230
	Subtotal	5.00 (0.00–11.09)	10.00 (0.00–20.76)	2.11	0.146	0.33 (0.15–0.76)	0.009
Endocrine system	Other endocrine including thymus	9.00 (6.27–11.74)	48.00 (40.69–55.31)	59.12	<0.001	0.31 (0.23–0.42)	<0.001
	Thyroid	2.00 (1.49–2.51)	59.00 (41.39–70.61)	412.80	<0.001	0.28 (0.23–0.33)	<0.001
	Subtotal	4.00 (3.27–4.73)	53.00 (43.22–63.78)	409.71	<0.001	0.26 (0.22–0.30)	<0.001
Lymphatic system	Non-Hodgkin lymphoma	12.00 (8.52–15.48)	32.00 (23.88–40.13)	5.97	0.015	0.55 (0.35–0.87)	0.010
	Hodgkin lymphoma			1.43	0.232	1.72 (0.00–2.86)	0.964
	Subtotal	15.00 (11.50–18.50)	32.00 (11.82–52.19)	6.64	0.01	0.52 (0.33–0.82)	0.004
Blood system	Leukemia	6.00 (2.83–9.17)	42.00 (20.61–63.39)	15.75	<0.001	0.31 (0.15–0.66)	0.002
	Myeloma	6.00 (1.61–10.39)	7.00 (0.76–13.24)	0.41	0.522	0.46 (0.12–1.78)	0.262
	Subtotal	6.00 (3.43–8.57)	27.00 (14.08–39.92)	15.58	<0.001	0.42 (0.23–0.77)	0.005
Other system	Miscellaneous	6.00 (1.89–10.11)	23.00 (1.12–44.88)	4.20	0.041	0.49 (0.20–1.17)	0.107

Adjustment factors: adjusted for Ages at diagnosis, Sex, Marriage, Insurance, Race, Income, Grade, T stage, N stage, Radiation, Chemotherapy, Bone metastases, Brain metastases, Liver metastases. CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified.

and non-surgery groups, respectively (P<0.001). Patients who underwent chemotherapy or radiotherapy were also associated with improved OS from multivariable Cox proportional hazard regression analyses (*Table 2*).

Multivariate Cox analyses in 13 subgroups displayed similar results. The HRs and 95% CIs for the surgery and non-surgery groups in each type of cancer were summarized in the forest plots (*Figure 5*). After adjustment for confounding factors, we found that SRPT improved OS among patients with cancer in the oral cavity and pharynx (HR =0.50; 95% CI: 0.43–0.58; P<0.001), digestive (HR =0.47; 95% CI: 0.46–0.49; P<0.001), bones and joints (HR =0.62; 95% CI: 0.49–0.79; P<0.001), female genital (HR =0.69; 95% CI: 0.66–0.73; P<0.001), soft tissue and skin (HR =0.59; 95% CI: 0.54–0.63; P<0.001), male genital (HR =0.37; 95% CI: 0.27–0.51; P<0.001), urinary (HR =0.69; 95% CI: 0.66–0.73; P<0.001), endocrine (HR =0.26; 95% CI: 0.22–0.30; P<0.001), nervous (HR =0.33; 95% CI: 0.15–0.76; P=0.009), lymphatic (HR =0.52; 95% CI: 0.33–0.82; P=0.004), and blood systems (HR =0.42; 95% CI: 0.23–0.77; P=0.005) (*Table 3*). Furthermore, we performed HR meta-analysis by using the random-effects model (*Figure 5*) and showed that SRPT was an independent prognostic factor corresponding to better OS (HR =0.34; 95% CI: 0.33–0.36; P<0.001).

Discussion

For decades, there is no effective therapy modality for patients with lung metastases. With the advancement of science and technology, new treatment methods, including systemic chemotherapy, radiotherapy, targeted therapy, immunotherapy and combination therapy, have emerged; however, their applicability and effectiveness are still limited. The curative treatment is still considered to be the complete removal of primary and metastatic tumors, and whether SRPT improves survival or not is still controversial. Thus, it is worth the in-depth investigation.

The results of the study demonstrated that there is a significant association between SRPT and better OS in patients with lung metastases based on the SEER dataset. The median survival time increased from 4.0 months in the non-surgery group to 19.0 months in the surgery group. Multivariate Cox regression analysis also validated that patients who received SRPT had a better OS. Thus, SRPT

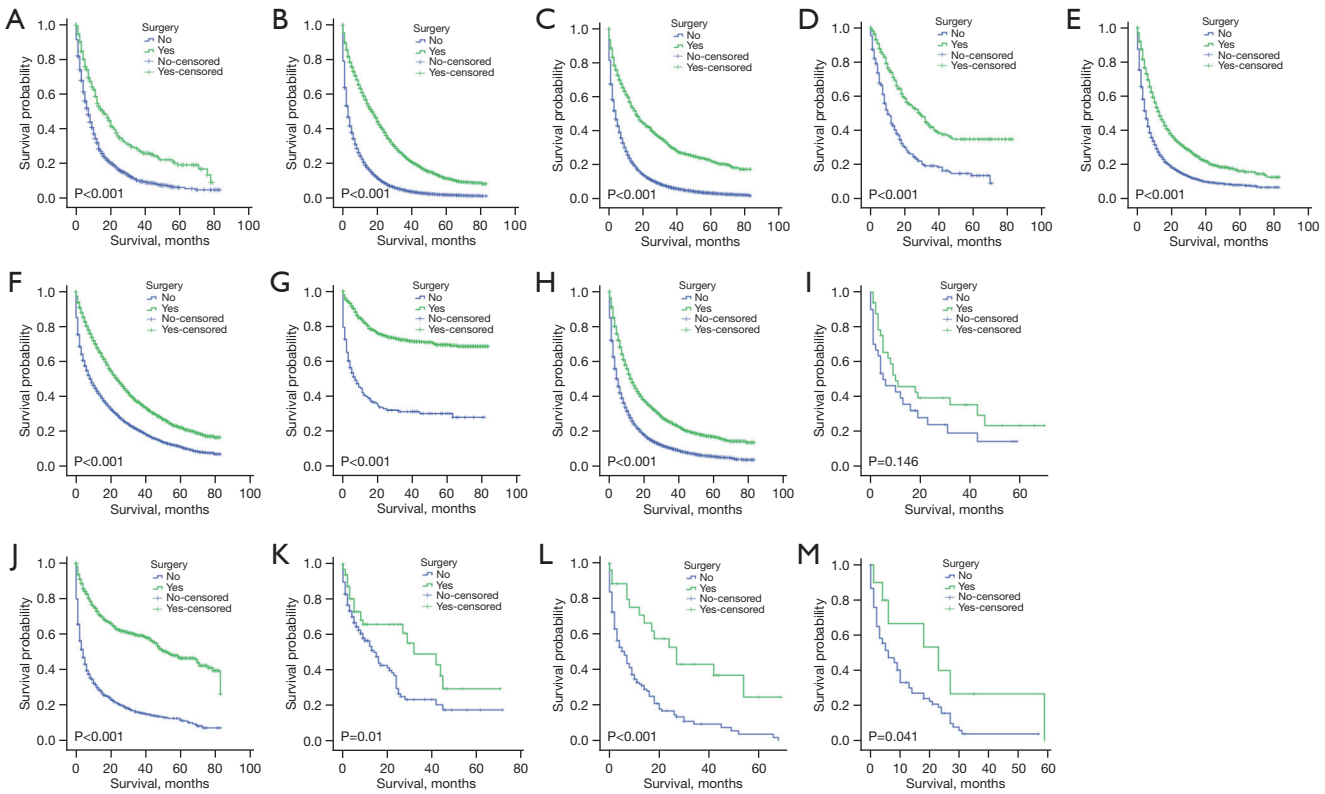

Figure 3 Kaplan-Meier analyses for survival in different cancer system surgery or non-surgery. Overall survival: (A) patients with oral cavity and pharynx system: surgery *vs.* non-surgery; (B) patients with digestive system: surgery *vs.* non-surgery; (C) patients with respiratory system: surgery *vs.* non-surgery; (D) patients with bones and joints system: surgery *vs.* non-surgery; (E) patients with soft tissue and skin system: surgery *vs.* non-surgery; (F) patients with female genital system: surgery *vs.* non-surgery; (G) patients with male genital system: surgery *vs.* non-surgery; (H) patients with urinary system: surgery *vs.* non-surgery; (I) patients with nervous system: surgery *vs.* non-surgery; (J) patients with endocrine system: surgery *vs.* non-surgery; (K) patients with lymphatic system: surgery *vs.* non-surgery; (L) patients with blood system: surgery *vs.* non-surgery; (M) patients with other system: surgery *vs.* non-surgery.

Table 4 Survival analysis of different metastatic organs and treatment modalities

Parameter	Non-surgery (months), median (95% CI)	Surgery (months), median (95% CI)	Log Rank	P value
Only lung metastasis	5.00 (4.90–5.11)	15.00 (14.56–15.44)	3,834.12	<0.001
Lung + liver metastasis	2.00 (1.91–2.09)	10.00 (9.46–10.55)	1,548.96	<0.001
Lung + bone metastasis	4.00 (3.86–4.14)	10.00 (9.26–10.74)	442.61	<0.001
Lung + brain metastasis	3.00 (2.82–3.18)	8.00 (6.98–9.02)	125.80	<0.001
Chemotherapy				
Yes	9.00 (8.87–9.13)	24.00 (23.29–24.71)	7,849.03	<0.001
No	1.00 (0.97–1.03)	9.00 (8.37–9.63)		
Radiotherapy				
Yes	6.00 (5.87–6.13)	20.00 (18.71–21.29)	8,923.70	<0.001
No	3.00 (2.94–3.06)	18.00 (17.39–18.61)		

CI, confidence interval.

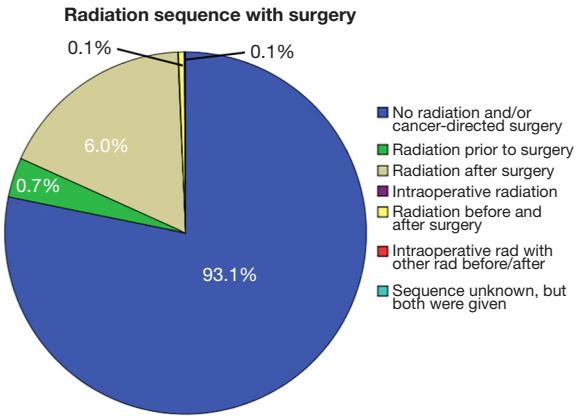

Figure 4 Radiation sequence with surgery.

can be an alternative treatment strategy for cancer patients with lung metastases. The current study is believed to be the largest retrospective study that focused on evaluating the benefits of SRPT in patients with metastatic lung cancer.

In the subgroup analyses, we found that SRPT was beneficial for not only the general cancer patients but also the patients in each cancer subgroups. For primary tumors originated from the oral cavity and pharynx systems, the results suggested that SRPT could improve OS, which is consistent with previous reports. Harris *et al.* and Pan *et al.* suggested that compared to non-surgical patients, those who received SRPT showed a clear survival advantage with distant metastasis in laryngeal carcinoma (12,13). Tumors in the digestive system might cause bleeding, perforation, obstruction and malnutrition. SRPT can lower the risk of severe tumor-related complications and improve patients' quality of life. Therefore, SRPT was recommended for patients with stage IV gastric cancer (14-16) and colorectal cancer (17,18). Additionally, Wang *et al.* also found that cancer patients with pancreas metastases who underwent SRPT had improved OS (19). Thus, the conclusion is also aligned with findings from previous studies.

The results of the study also showed that SRPT is associated with improved survival in surgery group with cancer in the bone and joint system. Likewise, several studies have found that SRPT improved OS of chondrosarcoma (20), osteosarcoma (21), and Ewing's sarcoma in the bone system (11) with lung metastases. Melanoma is a type of skin cancer with increasing incidence and high malignancy (22). Melanoma patients with distant metastases usually have a worse prognosis regarding 5-year survival rates (<16%) and median survival time (<1 year) (23). The results of the study suggested that SRPT improved median survival time and OS for melanoma patients with lung metastases. A phase-2 clinical trial by Sosman *et al.* concluded that for certain selected patients, SRPT provided a promising treatment option that can improve OS of the patients (24). For breast cancer, the current study indicated that patients who received SRPT had improved OS. Some recent studies have also shown that SRPT in metastatic breast cancer was related to better OS (25,26). Moreover, SRPT has been shown to be effective in patients diagnosed with metastatic prostate (9), ovarian (27), and renal cell cancer (28). In addition, the current study also demonstrated that SRPT improved OS in other lung metastatic patients, which had not been reported previously.

The conclusions from the present study are consistent with that of the previous studies. We noticed that patients with metastatic lung cancer who received SRPT had improved OS. However, the underlying mechanisms are unclear. The possible mechanisms could be as following: (I) SRPT may reduce the number of blood circulating tumor cells which prevents micrometastases from becoming macrometastases (29,30) and eliminates the "seeding source" to blocking cancer progression (31); (II) SRPT may alleviate tumor burden to the body (32); (III) SRPT may associate with the recovery of the immune system by reversing systemic inflammation (33,34). In addition, SRPT can reduce severe tumor-related complications, and thus lead to better survival outcomes. The ratio of patients that had undergone SRPT was increasing from 2010 to 2016 except for 2015. This indicated that more and more lung metastasis patients tend to choose SRPT as a treatment option. With the advancement systemic therapies, surgical techniques and imaging techniques, distant metastases at earlier stages would be more capable of being detected. Further, neoadjuvant therapy provides another opportunity for clinicians to perform SRPT on these patients (35). In addition, the development of imaging techniques can help the clinicians to visualize the tumor borders and blood supply more clearly and thus help in developing surgical protocols that could remove tumors more safely and thoroughly.

Although the current study is supported by detailed analysis, it has limitations in several ways. Firstly, considering that the study design was based solely on the SEER database, it could not avoid the potential inherent subject selection bias. Secondly, the SEER database lacks information for factors such as disease burden, surgical

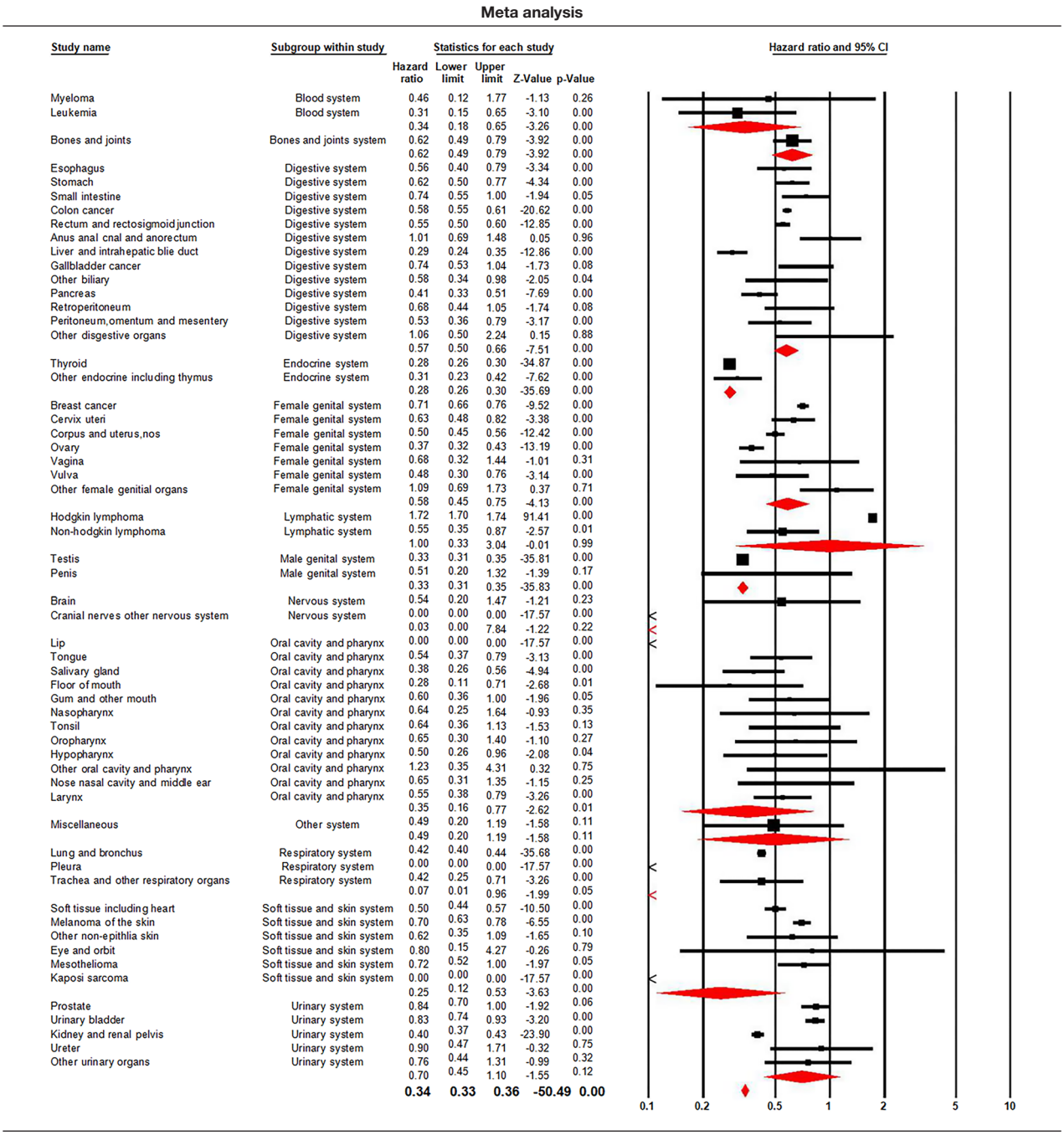

Figure 5 Forest plot. CI, confidence interval.

margin status, preoperative status, smoking status, alcohol intake and other detailed factors (e.g., the presence of comorbidities and complications). How these factors would affect OS is unknown, which may influence the surgical decisions. It was not known for the reasons why the patients underwent SRPT. Thirdly, some factors were not described in detail in the SEER database. For example, types of surgery, whether palliative or radical surgery, open operation or minimally invasive surgery, were unknown. Chemicals and their doses used for chemotherapy or

the radiation strategies used were also unknown. These unrecorded factors might affect the outcomes of survival analyses. Fourthly, apart from lung metastases, it is possible to combine data for metastases at other sites, which might have an impact on OS of patients. Finally, the SEER database does not provide computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), B-ultrasound and other imaging data, which has a certain impact on the evaluation of whether to perform surgical treatment and the prognosis. Despite the aforementioned limitations, this population-based study included a large number of lung metastasis patients and showed significant correlations with rigorous analyses, and thus should be very convincing and conclusive.

Conclusions

The results of the study showed that SRPT is effective for patients with lung metastases. However, at present, the criteria for suitability of undergoing surgery are unknown. Therefore, it is appreciated that the conclusion here will be validated and surgical inclusion criteria could be further clarified through well-designed, prospective, and randomized clinical trials. Finally, in addition to radiotherapy and systemic chemotherapy, SRPT should also be seriously considered for lung metastatic patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2459/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2459/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The data on cancer in the SEER database is continually reported in every state of the United States and retrieved with no need for informed patient consent.

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