Original Article

Treatment outcomes of surgery and chemotherapy for pulmonary metastases from non-lung cancers: a propensity score-matched analysis

Kun Gao, Xianben Liu, Wenqun Xing, Haibo Sun, Shilei Liu, Peng Li, Peinan Chen, Yan Zheng

Department of Thoracic Surgery, The Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital, Zhengzhou, China

Contributions: (I) Conception and design: H Sun, P Li, Y Zheng; (II) Administrative support: X Liu, W Xing; (III) Provision of study materials or patients: H Sun, S Liu, P Chen; (IV) Collection and assembly of data: K Gao, Y Zheng; (V) Data analysis and interpretation: K Gao, Y Zheng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yan Zheng, MD, PhD. Department of Thoracic Surgery, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China. Email: zlyysunnyzheng@zzu.edu.cn.

Background: The optimal treatment for pulmonary metastases has not been determined, and the survival benefit of surgical resection in selected patients remains controversial. The purpose of this retrospective study was to explore whether surgery can prolong survival in patients with pulmonary metastases compared with chemotherapy, and to analyze the factors that may affect the long-term survival of patients with pulmonary metastases.

Methods: We retrospectively analyzed the medical records of patients with pulmonary metastases from June 2012 to June 2019. Propensity score matching (PSM) was used to balance factors that might affect survival between the two groups. The data were analyzed by Kaplan-Meier survival analysis and Cox proportional hazards models to compare the survival of the surgery group and the chemotherapy group.

Results: A total of 202 patients with pulmonary metastases were enrolled in the study, with 43 patients in the surgery group and 43 in the chemotherapy group after screening and PSM. After PSM, patients in the surgery group had better survival than those in the chemotherapy group, with 5-year overall survival (OS) rates of 75.1% and 48.0%, respectively (P=0.017). Univariate analysis of the two groups of patients found that the treatment method, the number of metastases, and the total diameter of metastases were prognostic factors, but multivariate analysis did not find independent prognostic factors. In the surgical group, univariate analysis found that disease-free interval (DFI), the number of metastases, surgical methods, resection scope and surgical route were prognostic factors, and multivariate analysis showed that only DFI was an independent prognostic factor. In the chemotherapy group, DFI and the response of metastases to chemotherapy were found to be prognostic factors in univariate analysis, but no independent prognostic factors were found in multivariate analysis.

Conclusions: Surgery does not provide a significant survival advantage. For patients undergoing surgery, longer DFI predicts better survival.

Keywords: Pulmonary metastases; surgery; chemotherapy; survival; prognosis

Submitted Sep 26, 2022. Accepted for publication Jan 12, 2023. Published online Feb 13, 2023.
doi: 10.21037/tcr-22-2286
View this article at: https://dx.doi.org/10.21037/tcr-22-2286

Introduction

Cancer mortality in the United States declined from 1991 to 2017, with an overall decline of 29%, according to the American Cancer Society (1). However, tumor metastasis is a common cause of death. Davidson *et al.* reported that 25–30% of patients with malignant tumors had pulmonary metastases at autopsy (2). A retrospective analysis of 5,206 patients with pulmonary metastases from 18 healthcare facilities in the United States, Canada, and Europe, namely, the International Registry of Lung Metastases (IRLM), provides evidence that metastasectomy appeared to be associated with better survival (3). Since then, a large number of retrospective studies have reported and confirmed the benefits of surgical treatment in patients with pulmonary metastases (4). While surgical treatment seems to be associated with better survival, there are some things we should know. First of all, lung metastasis progresses slowly, and it is difficult to judge the survival benefit brought by pulmonary metastasectomy (PM) for this inert biological behavior. Second, PM needs to meet demanding surgical indications. It has been reported that for patients with primary colorectal cancer (CRC), only 4.1% of synchronous lung metastases and 14.8% of metachronous lung metastases can be treated with PM (5). It can be seen that the patients who underwent surgery were highly selected to exclude those with a poor prognosis. Finally, for selected patients, surgery is a recognized standard of practice, and the evidence of improving overall survival (OS) is mostly retrospective studies. It has been reported that we should not be assumed with the benefits brought by surgery and ignore the importance of randomized clinical trial (RCT) (6,7), which shows that it is urgent for us to use RCT to verify and find the best treatment method for lung metastases.

Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC), a randomized controlled trial funded by Cancer Research UK in 2010 (8), is the first and currently only prospective randomized controlled trial of pulmonary metastases in the world. During the implementation of PulMiCC, clinicians (rather than patients) were unwilling to randomly select patients according to the previous concept, which led to the early end of the study due to poor recruitment and deterioration of the situation (9). Yang *et al.* believe that RCT faces great challenges, and further and larger retrospective studies may be helpful (10).

Therefore, we retrospectively analyzed and studied patients with pulmonary metastases who received surgery and chemotherapy as the main treatment in our hospital in recent years and adjusted the background characteristics of the two groups of patients by propensity score-matched (PSM) analysis. Then, we analyzed the effects of surgery and chemotherapy on disease prognosis in the matched cohort. The aim of this study is to provide a basis for clinical treatment decisions and prospective clinical trial planning of pulmonary metastases. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2286/rc).

Highlight box

Key findings

- For selected patients with pulmonary metastases, surgical treatment did not significantly improve survival compared with chemotherapy.

What is known and what is new?

- The survival of patients with pulmonary metastases treated surgically was generally better than that of patients treated with chemotherapy.
- In patients in the surgery and chemotherapy groups, we analyzed survival after propensity score matching (PSM) matching of disease characteristics that affected survival. Finally, after PSM, the number and total diameter of lung metastases in the chemotherapy group were still significantly larger than those in the surgery group. However, on the premise that the surgery group had good prognostic disease characteristics, a multivariate analysis of the prognosis of the two groups did not support the treatment method (surgery *vs.* chemotherapy) as an independent prognostic factor.

What is the implication, and what should change now?

- We need to rethink the rationality of surgical treatment of lung metastases, emphasizing the importance and urgency of large-scale randomized clinical trial.

Methods

Patients

In this study, the clinical data of patients with pulmonary metastases diagnosed in our hospital from June 2012 to June 2019 were collected from the first page of medical records. Patient demographic information, course of treatment, tumor characteristics, and radiological images were obtained from the hospital's electronic medical record system. The following factors were assessed: age, sex, disease-free interval (DFI), smoking history, pathological types of primary lesions, complete resection, number of metastases,

total diameter of metastases, adjuvant treatment plan of pulmonary metastases, the surgical method, resection range, lymph node management, lymph node pathology, specimen pathology, R0 resection, and chemotherapeutic efficacy.

To minimize the inherent bias of the retrospective study, the cases in this study needed to meet the following requirements: (I) pathology, radiology, history, and disease features supporting pulmonary metastases; (II) the diagnosis of the primary lesion was clear; (III) the primary lesion was a solid tumor. In addition, we excluded the following conditions: (I) the primary lesion recurred before treatment for lung metastases; (II) primary tumor without surgical treatment; (III) the primary tumor was lung cancer; (IV) the treatment process was not detailed; (V) in addition to surgery and chemotherapy, other treatment options were the mainstay of lung metastases; and (VI) nonneoplastic causes of death.

Outcome definition and follow-up

OS was defined as the time between the date of surgery or chemotherapy for pulmonary metastases and the date of death or last follow-up. DFI was defined as the time between the date of surgery for the primary tumor and the first sign of metastasis to distant organs (lungs, liver, brain, etc.). Adjuvant therapy was defined as the treatment of pulmonary metastases in addition to surgery and chemotherapy, such as targeted drugs, radiation therapy, and immunotherapy. Combination therapy was defined as the application of two or more adjuvant therapies. Complete resection was defined as the surgeon's empirical opinion that all metastases could be resected with a margin of at least 1 cm, regardless of the number of metastases, by radiographic evaluation of lung metastases prior to surgery or chemotherapy. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 was used to evaluate the efficacy of chemotherapy groups. Complete response (CR) was defined as the disappearance of all metastases, and the short diameter of all pathological lymph nodes must be reduced to less than 10 mm. Partial response (PR) was defined as a reduction of at least 30% in the sum of lung metastases from baseline. Progressive disease (PD) was defined as a minimum of the sum of the diameters of all lung metastases measured throughout the course of treatment, with a relative increase of at least 20%, and the absolute increase in diameters must be greater than 5mm (baseline was used as a reference if baseline measurements were minimal; the presence of one or more new lesions is also considered PD). Stable disease (SD) was defined as lung metastases that did not decrease to the level of PR and did not increase to the level of PD. Patient survival data were mainly obtained from telephone follow-up and previous medical records, and a few results were obtained from direct patient inquiries. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Henan Cancer Hospital (No. 2015051) and individual consent for this retrospective analysis was waived.

Statistical analysis

All data were statistically analyzed using IBM SPSS Statistics 26.0. The Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables were used to compare the baseline characteristics of patients in the surgery and chemotherapy groups. Factors including PSM were as follows: age, sex, DFI, smoking history, pathological types of primary lesions, complete resection, and adjuvant treatment plan. During the matching process, a caliper was defined as 0.15 of the standard deviation of the propensity score logit, and no replacement was made during the matching process. OS was estimated using the Kaplan-Meier method. Differences in survival were assessed using log-rank tests. Kaplan-Meier method was used for univariate analysis and Cox proportional hazards regression model was used for multivariate analysis. All tests were bilateral with a significance level of 0.05.

Results

Patient demographics

After preliminary screening, we enrolled a total of 122 patients who met the requirements, and 86 patients were used for further analysis after PSM. A flow diagram of the study is shown in *Figure 1*. In the chemotherapy group, there were 3 patients with concurrent liver metastases and 1 patient with concurrent brain metastases. After PSM, the patients in both groups had simple lung metastases. Before PSM, there were 1 and 7 cases of synchronous pulmonary metastases in the surgery group and chemotherapy group, respectively. After PSM, there were 1 and 3 cases of synchronous pulmonary metastases in the surgery group and chemotherapy group, respectively. Patients diagnosed with pulmonary metastases during treatment of the primary

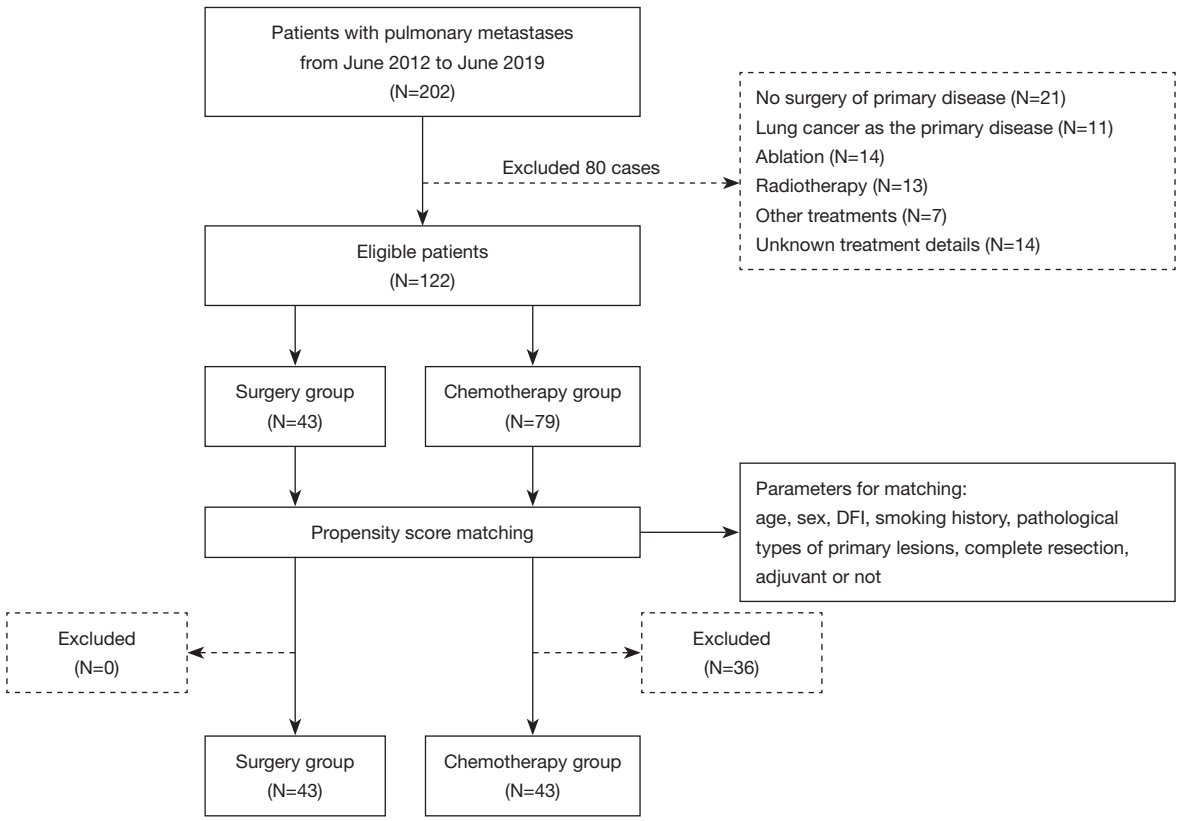

Figure 1 Flow diagram for the study. Other treatments: immunotherapy, targeted therapy, Chinese medicine therapy. DFI, disease-free interval; N, number.

lesion and regular reviews accounted for 85% (73/86), and only 15% (13/86) of the patients had symptoms such as cough, expectoration, or chest pain. Compared with the chemotherapy group, patients in the surgery group had a longer DFI, fewer pulmonary metastases, and a shorter total diameter. The baseline characteristics of patients with pulmonary metastases are shown in *Table 1*. Pathological types of primary lesions in the surgery group and chemotherapy group were shown in Table S1 and Table S2.

Treatment and follow-up

The maximum number of metastases in the surgery group was six, all of which were located in the upper lobe of the right lung and were removed completely by open surgery and lobectomy. Only one patient had pulmonary metastases on both sides of the lung with a total diameter of 12 mm, and the lesions on both sides were removed by video-assisted thoracic surgery (VATS) without serious postoperative complications. Lymph node dissection was performed in 28% (12/43) of patients, and lymph node sampling was performed in 21% (9/43) of patients. All patients in the surgery group were confirmed to achieve R0 resection, and no positive lymph nodes were found by postoperative pathology. There were no perioperative deaths. The details of metastasis resection are shown in *Table 2*. In the chemotherapy group, most of the patients received platinum-based chemotherapy, and the specific chemotherapy regimen and chemotherapy period were determined according to the primary disease.

The final follow-up date was March 2021, and 8% (10/122) of patients were lost to follow-up. The median follow-up time after diagnosis of pulmonary metastases was 44 months, and the numbers of deaths in the surgery group and chemotherapy group were 13/43 (30%) and 47/79 (59%), respectively.

Survival data for patients

The survival of the surgery group was significantly better

Table 1 Baseline characteristics of patients with pulmonary metastases

Characteristic	Primary cohort			Matching cohort		
	Surgery	Chemotherapy	P value	Surgery	Chemotherapy	P value
N	43	79		43	43	
Age, years [median]	53 [41–58]	54 [39–60]	0.891†	53 [41–58]	51 [38–59]	0.688†
Sex, female	20 [47]	44 [56]	0.332	20 [47]	22 [51]	0.666
DFI, months [median]	24 [13–36]	21 [7–44]	0.459†	24 [13–36]	20 [6–27]	0.083†
Smoking, yes	11 [26]	15 [19]	0.396	11 [26]	7 [13]	0.289
Pathology for primary lesion			0.096			0.239
Cancer	31 [72]	63 [80]		31 [72]	33 [77]	
Sarcoma	12 [28]	12 [15]		12 [28]	8 [19]	
Germ cell tumor	0	4 [5]		0	2 [4]	
Completely removed	43 [100]	54 [83]	0.003‡*	43 [100]	43 [100]	
No. of metastases			<0.001*			<0.001*
Single	36 [84]	7 [9]		36 [84]	6 [14]	
2–3	6 [14]	22 [28]		6 [14]	16 [37]	
>3	1 [2]	50 [63]		1 [2]	21 [49]	
Adjuvant therapy			0.240‡			0.848‡
No	24 [56]	28 [35]		24 [56]	20 [46]	
Targeted therapy	1 [2]	6 [8]		1 [2]	1 [2]	
Radiotherapy	3 [7]	12 [15]		3 [7]	5 [12]	
Combination therapy	8 [19]	18 [23]		8 [19]	11 [26]	
Else	7 [16]	15 [19]		7 [16]	6 [14]	
Adjuvant or not			0.030*			0.388
No	24 [56]	28 [35]		24 [56]	20 [46]	
Yes	19 [44]	51 [65]		19 [44]	23 [54]	
Diameter, mm§ [median]	20 [14–30]	45 [30–74]	<0.001†*	20 [14–30]	40 [27–78]	<0.001†*

The median is followed by the interquartile range; data are expressed as n [%] unless otherwise specified. †, Mann-Whitney U test; ‡, Fisher's exact test; §, sum of the diameter for metastatic lesions; *, P<0.05. N, number; DFI, disease-free interval.

Table 2 Details of patients with pulmonary metastases who underwent surgery

Items	Subgroups (n, %)
Methods of diagnosis	CT (30, 70%), CT + PETCT (12, 28%), CT + pathology (1, 2%)
Distribution	Left (16, 37%), right (25, 58%), bilateral (2, 5%)
Treating strategy	Surgery alone (24, 56%), surgery + adjuvant therapy (19, 44%)
Surgical route	Open (14, 33%), VATS (29, 67%)
Resection scope	Wedge (26, 61%), lobectomy (16, 37%), total pneumonectomy (1, 2%)
Lymph node management	Untouched (22, 51%), sampling (9, 21%), dissection (12, 28%)

n, number; CT, computed tomography; PETCT, positron emission tomography/computed tomography; VATS, video-assisted thoracic surgery.

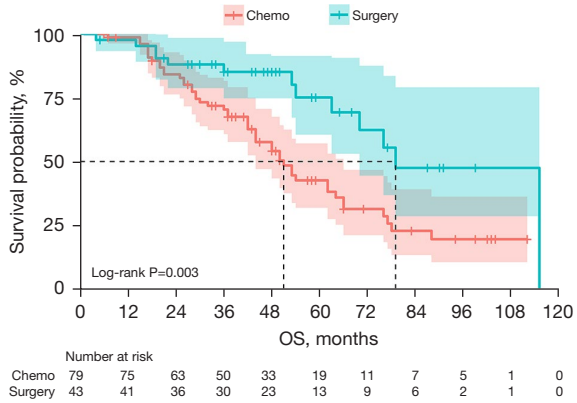

Figure 2 Survival curves of patients with pulmonary metastases in the surgery and chemotherapy groups (before PSM). Chemo, chemotherapy; PSM, propensity score matching; OS, overall survival.

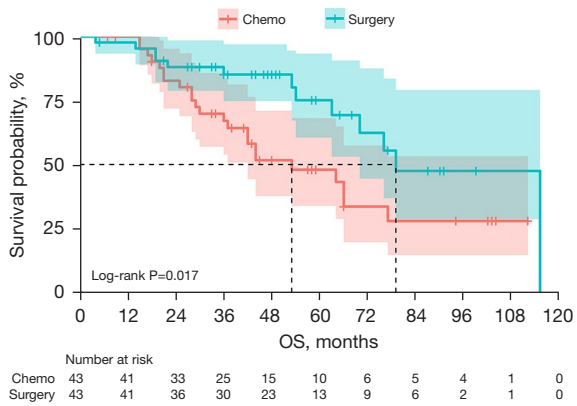

Figure 3 Survival curves of patients with pulmonary metastases in the surgery and chemotherapy groups (after PSM). Chemo, chemotherapy; PSM, propensity score matching; OS, overall survival.

Table 3 Cox multivariate prognostic analysis of patients in surgery group

Characteristic	P	HR	95% CI
DFI	0.004*	24.014	2.804–205.704
No. of metastases	0.092	3.295	0.825–13.162
Surgical route	0.130	3.447	0.694–17.113
Resection scope	0.301	3.526	0.323–38.496
Lymph node management	0.820	0.796	0.112–5.653

*, P<0.05. DFI, disease-free interval; HR, hazard ratio; CI, confidence interval.

than that of the chemotherapy group before matching (*Figure 2*) (P<0.05), and the result was still the same after matching (*Figure 3*) (P<0.05). After matching, the 3-year OS rates of the surgery and chemotherapy groups were 85.1% and 67.1%, respectively, the 5-year OS rates were 75.1% and 48.0%, and the median OS were 79 months (95% CI: 61.99–96.02 months) and 53 months (95% CI: 28.31–77.69 months), respectively. Before matching, the 3- and 5-year OS rates of the chemotherapy group were 70.4% and 42.7%, respectively, and the median OS was 51 months (95% CI: 42.50–59.50 months).

Prognostic analysis of patients

In the two groups, univariate prognostic analysis showed that the following factors significantly affected the survival of patients: number of lung metastases, total diameter of lung metastases, and treatment method. Cox multivariate analysis of the above three prognostic factors did not find independent prognostic factors. The results of univariate analysis were shown in Table S3, and the survival curve was shown in Figure S1.

In the surgery group, univariate prognostic analysis showed that the following factors predicted better survival: longer DFI (≥24 months), number of lung metastases (single), VATS, wedge resection, and untreated lymph nodes. Cox multivariate analysis of the above factors showed that only longer DFI (≥24 months) was an independent prognostic factor, as shown in *Table 3*. Univariate results were shown in Table S4, and survival curves were shown in Figure S2.

In the chemotherapy group, univariate prognostic analysis showed that the following factors influenced survival: DFI and chemotherapy response. Univariate results were shown in Table S5, and the survival curve were shown in Figure S3. Cox multivariate analysis of these factors did not find independent prognostic factors.

Discussion

The treatment of pulmonary metastases is a very controversial issue, and treatment methods include surgery, chemotherapy, radiotherapy, ablation therapy, targeted therapy, immunotherapy, and combination therapy. The main treatment methods are surgery and chemotherapy. Treatment of this condition began to make great strides in

the 1970s with the introduction of chemotherapy. However, since IRLM has reported the advantages of surgery in selected patients with pulmonary metastases, surgery has been increasingly recognized and implemented in clinical practice. Between 2000 and 2011, despite all the advances in the systematic treatment of pulmonary metastases, the proportion of surgeries increased substantially (11). The results show that surgical treatment of pulmonary metastases has been recognized by doctors and patients. However, what is universally accepted in the clinic is not necessarily true. It would be wrong to try to compare patients in the surgery and chemotherapy groups, as they are in different stages of the disease. It is difficult to determine how much of the favorable prognosis is due to selective bias and how much is due to surgical treatment. RCTs could answer this question, but they are so difficult to conduct that only one RCT on pulmonary metastases has been conducted thus far.

In March 2010, PulMiCC, a randomized controlled trial funded by Cancer Research UK, began recruiting patients with pulmonary metastases after CRC surgery (8). After 10 years, the results of the trial showed that the control group had better survival than the expectation of "close to zero" 5-year survival, with estimated 5-year survival rates of 36.4% in the resection group and 29.6% in the control group (12). As the world's first randomized clinical study, the results are surprising and not only upend the concept of treatment but also make us rethink whether we should continue to pursue aggressive surgery. A limitation of the PulMiCC trial was poor and worsening recruitment (9). It is difficult to carry out RCT in the clinic, and even Yang *et al.* believe that only a large retrospective study after PMS can answer this question (10). However, lung metastases resection is widely performed in Western countries and in large cities such as Beijing, Shanghai, and Guangzhou in China, which makes matching difficult. However, as there is no international RCT guideline for the treatment of lung metastases, the treatment in our hospital has always tended to be conservative. A large number of patients with low-risk factors did not undergo surgery. Therefore, patients with low risk factors (surgery *vs.* chemotherapy) can be well matched, which lays the foundation for the answer to this question.

IRLM analysis of 5,206 patients with postoperative lung metastases showed that there was no significant difference in survival between patients with primary cancer and sarcoma (3). Considering the small number of cases in this study, patients were divided into cancer, sarcoma and germ cell tumor according to primary pathological type.

In our study, the survival of the surgery group was significantly better than that of the chemotherapy group before and after PSM, which was consistent with most studies (13-17). After PSM, the 5-year OS rates of the surgery and chemotherapy groups were 75.1% and 48.0%, respectively, and the median OS rates were 79 months (95% CI: 61.99–96.02 months) and 53 months (95% CI: 28.31–77.69 months), respectively. The 5-year survival rates reported by Zhao *et al.* (75.5% and 47.8%, respectively) in the surgical and non-surgical groups with pulmonary metastases of nasopharyngeal carcinoma were similar to ours (13). Univariate prognostic analysis showed that the number of lung metastases, the total diameter of lung metastases and the treatment method affected the survival of patients. Cox multivariate analysis found no independent prognostic factors. An analysis of the CRC simple lung metastases population based on the National Cancer Institute in the United States SEER database showed that resection of lung metastases had no significant effect on OS compared with non-surgical treatment (HR =0.86, 95% CI: 0.65–1.14, P=0.280) (18), this is consistent with our prognostic analysis. The results of multifactorial analysis again cast doubt on the usefulness of surgery.

In the surgical group, we preferred minimally invasive surgery; 61% (26/43) of patients underwent wedge resection, and 67% (29/43) of patients underwent VATS. The treatments were similar to those in some other studies. A Dutch analysis of surgical methods for pulmonary metastases from 2012 to 2017 found that 74% of patients underwent minimally invasive procedures such as VATS and robot-assisted thoracic surgery (RATS), and 70.7% underwent wedge resection (19), the incidence of which was slightly higher than in our study. Another study, based on data from the European Society of Thoracic Surgeons database, found that the rate of VATS procedures for patients with pulmonary metastases increased from 15% in 2007 to 58% in 2018 (20).

In the surgical group, we also found better survival in three subgroups: VATS, wedge resection, and untouched lymph nodes (P<0.05). Further analysis revealed that the number and total diameter of metastases in the three subgroups were smaller than those in the other corresponding subgroup, and there was a significant difference in the total diameter of metastases between wedge resection and lobectomy (P<0.05). One study showed that the number and size of metastases significantly influenced prognosis (21). Therefore, we believe that better

survival may be associated with a lower tumor load and not with differences in surgical treatment. In our study, open surgery did not improve survival compared with VATS, suggesting that high-resolution CT and adequate preoperative preparation could compensate for missed metastases due to the inability to touch the lungs with the hand in VATS. This is consistent with one study (22). In addition, one of the characteristics of metastatic tumors is that they are prone to recurrence. As long as R0 resection can be guaranteed, wedge resection is a better choice than lobectomy, which can preserve more lung tissue and provide sufficient lung tissue for re-resection after recurrence. In our study, a patient with left total pneumonectomy had a survival of only 4 months, suggesting the importance of preserving adequate lung tissue.

Whether it is necessary to deal with lymph nodes during surgery is also controversial, and the Society of Thoracic Surgeons expert consensus recommended routine lymph node dissection to predict patient survival and guide postoperative treatment (23). In our study, 49% (21/43) of the patients were treated with lymph nodes. Postoperative pathology indicated that there was no positive lymph node metastasis, while the patients without lymph node treatment had a better survival, which may be due to the choice of the patients by the surgeon. Further studies are needed to determine whether lymph node dissection is beneficial for survival.

In the surgery group, 49% patients had DFI <24 months, 3-year and 5-year OS were 79.3% and 52.8%, and 51% patients had DFI ≥24 months, 3-year and 5-year OS were 90.9% and 81.8%, respectively ($P<0.05$). Both univariate and multivariate analyses suggested that DFI was a prognostic factor. In some studies, although the primary lesion and DFI were inconsistent, the results of univariate or multivariate analysis suggested that longer DFI predicted better survival (24-26). However, there is also a study that does not support this view (27). The reason for the difference between the studies may be the different pathological types of the primary lesions, and another important reason is the different definitions of DFI. In this study, DFI was defined as the time between the date of primary tumor surgery and the first sign of metastasis in distant organs (lung, liver, brain, etc.), which can better evaluate disease progression. However, many studies define DFI as the time between the date of primary tumor surgery and the first sign of lung metastases or the date of resection of lung metastases. Unless otherwise specified, such a definition extends the DFI relative to the true transfer time. Because it is uncertain whether extrapulmonary metastases have occurred before lung metastases. For example, liver metastases are most frequently found in CRC, followed by lung metastases. In addition, when suspicious pulmonary nodules are found during the follow-up period after the treatment of the primary tumor, it is generally recommended to regularly review CT monitoring, and perform surgical treatment when there is significant progress. Therefore, PM may not be performed until months or even years after the first detection. In our study, 2 patients were diagnosed with pulmonary nodules at the time of primary diagnosis, and pulmonary nodules were found to be progressive after 19 and 2 months of follow-up, respectively, and were confirmed as pulmonary metastatic tumor by postoperative pathology. Therefore, our definition of DFI can more accurately reflect the real progress of the disease.

In the chemotherapy group, univariate analysis found that DFI and the response of metastases to chemotherapy were prognostic factors. Patients with DFI <20 months had better prognosis compared with DFI ≥20 months, and patients with PR had better prognosis than those with PD. However, multivariate analysis found no independent prognostic factors. We consider this to be related to the following two aspects: (I) differences in primary lesions lead to different responses to chemotherapy; and (II) regular postoperative review of the primary lesion in patients with short DFI can timely detect the traces of lung metastases, while the statistical results of DFI in patients with long DFI are not accurate due to irregular postoperative review. Li *et al.* showed that the assessment of the first response to first-line chemotherapy for CRC was an independent factor in predicting OS, and there was a significant difference in survival among patients with PR, SD and PD (28). This is similar to our results and suggests that timely evaluation is needed after chemotherapy and that timely adjustments of treatment should be made if there is no response to chemotherapy.

Although our study excluded obviously unresectable patients from the chemotherapy group and balanced the factors that might affect survival between the two groups by PSM, the limitations of our retrospective study cannot be ignored. First, as a retrospective study, this study cannot avoid selective bias. Secondly, the sample size of this study is small. Finally, after PSM, the number and total diameter of lung metastases in the chemotherapy group were still significantly larger than those in the surgery group. However, on the premise that the surgery group

had good prognostic disease characteristics, a multivariate analysis of the prognosis of the two groups did not support the treatment method (surgery *vs.* chemotherapy) as an independent prognostic factor. This suggests that we need to rethink the rationality of surgical treatment of lung metastases, emphasizing the importance and urgency of large-scale RCT.

Conclusions

For selected patients with pulmonary metastases, surgery does not provide a significant survival advantage. For patients treated with surgery, a longer DFI predicted better survival.

Acknowledgments

Funding: This work was supported by National Natural Science Foundation of China (NSFC) (grant No. 82002521); Natural Science Foundation of Henan Province (grant No. 202300410389); Henan Anti-Cancer Association Youth Talent Project (grant No. 2019HYTP018, 2019); Wu Jieping Medical Foundation (CN) (grant No. 320.6750.2020-15-1); Henan Province Health Science and Technology Innovation Outstanding Young Talents Training Project (No. YXKC2021029); Henan Province Medical Science and Technology Key Projects Co-constructed by the Ministry of health (Thoracic Surgery-3202730).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2286/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2286/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2286/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 study was approved by the Medical Ethics Committee of Henan Cancer Hospital (No. 2015051) and individual consent for this retrospective analysis was waived.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
2. Davidson RS, Nwogu CE, Brentjens MJ, et al. The surgical management of pulmonary metastasis: current concepts. Surg Oncol 2001;10:35-42.
3. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 1997;113:37-49.
4. Dudek W, Schreiner W, Haj Khalaf M, et al. Surgery for Pulmonary Metastases: Long-Term Survival in 281 Patients. Thorac Cardiovasc Surg 2021;69:660-5.
5. Mitry E, Guiu B, Cosconea S, et al. Epidemiology, management and prognosis of colorectal cancer with lung metastases: a 30-year population-based study. Gut 2010;59:1383-8.
6. Fiorentino F, Hunt I, Teoh K, et al. Pulmonary metastasectomy in colorectal cancer: a systematic review and quantitative synthesis. J R Soc Med 2010;103:60-6.
7. Treasure T, Milošević M, Fiorentino F, et al. Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness? Thorax 2014;69:946-9.
8. Treasure T, Fallowfield L, Lees B. Pulmonary metastasectomy in colorectal cancer: the PulMiCC trial. J Thorac Oncol 2010;5:S203-6.
9. Treasure T, Farewell V, Macbeth F, et al. Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer (PulMiCC): a multicentre randomised clinical trial. Trials 2019;20:718.
10. Yang YH, Park SY, Kim HE, et al. Effects of mediastinal lymph node dissection in colorectal cancer-related pulmonary metastasectomy. Thorac Cancer

2021;12:3248-54.
11. Bartlett EK, Simmons KD, Wachtel H, et al. The rise in metastasectomy across cancer types over the past decade. Cancer 2015;121:747-57.
12. Milosevic M, Edwards J, Tsang D, et al. Pulmonary Metastasectomy in Colorectal Cancer: updated analysis of 93 randomized patients - control survival is much better than previously assumed. Colorectal Dis 2020;22:1314-24.
13. Zhao ZR, Liu DH, Wang YZ, et al. Pulmonary Metastasectomy in Patients with Lung Metastases from Nasopharyngeal Carcinoma. Ann Surg Oncol 2021;28:4542-50.
14. Lardinois I, Dequanter D, Lechien JR, et al. Survival and treatment outcome of head and neck cancer patients with pulmonary oligometastases. Clin Otolaryngol 2021;46:311-7.
15. Miyamaru S, Murakami D, Nishimoto K, et al. Treatment Outcomes of Pulmonary Metastases from Head and Neck Squamous Cell Carcinoma. Acta Med Okayama 2021;75:31-7.
16. Kawamoto T, Hara H, Morishita M, et al. Prognostic influence of the treatment approach for pulmonary metastasis in patients with soft tissue sarcoma. Clin Exp Metastasis 2020;37:509-17.
17. Song Z, Ye T, Ma L, et al. Surgical Outcomes of Isolated Malignant Pulmonary Nodules in Patients with a History of Breast Cancer. Ann Surg Oncol 2017;24:3748-53.
18. Siebenhüner AR, Güller U, Warschkow R. Population-based SEER analysis of survival in colorectal cancer patients with or without resection of lung and liver metastases. BMC Cancer 2020;20:246.
19. van Dorp M, Beck N, Steup WH, et al. Surgical treatment of pulmonary metastases in the Netherlands: data from the Dutch Lung Cancer Audit for Surgery. Eur J Cardiothorac Surg 2020;58:768-74.
20. Gonzalez M, Brunelli A, Szanto Z, et al. Report from the European Society of Thoracic Surgeons database 2019: current surgical practice and perioperative outcomes of pulmonary metastasectomy. Eur J Cardiothorac Surg 2021;59:996-1003.
21. Religioni J, Orłowski T. Surgical treatment of metastatic diseases to the lung. Kardiochir Torakochirurgia Pol 2020;17:52-60.
22. Perentes JY, Krueger T, Lovis A, et al. Thoracoscopic resection of pulmonary metastasis: current practice and results. Crit Rev Oncol Hematol 2015;95:105-13.
23. Handy JR, Bremner RM, Crocenzi TS, et al. Expert Consensus Document on Pulmonary Metastasectomy. Ann Thorac Surg 2019;107:631-49.
24. Su X, Ma G, Zhang X, et al. Surgical approach and outcomes for treatment of pulmonary metastases. Ann Thorac Med 2013;8:160-4.
25. Kobayashi N, Kohno T, Haruta S, et al. Pulmonary metastasectomy secondary to esophageal carcinoma: long-term survival and prognostic factors. Ann Surg Oncol 2014;21 Suppl 3:S365-9.
26. Gonzalez M, Poncet A, Combescure C, et al. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol 2013;20:572-9.
27. Cheung FP, Alam NZ, Wright GM. The Past, Present and Future of Pulmonary Metastasectomy: A Review Article. Ann Thorac Cardiovasc Surg 2019;25:129-41.
28. Li WH, Peng JJ, Xiang JQ, et al. Oncological outcome of unresectable lung metastases without extrapulmonary metastases in colorectal cancer. World J Gastroenterol 2010;16:3318-24.

Cite this article as: Gao K, Liu X, Xing W, Sun H, Liu S, Li P, Chen P, Zheng Y. Treatment outcomes of surgery and chemotherapy for pulmonary metastases from non-lung cancers: a propensity score-matched analysis. Transl Cancer Res 2023;12(3):585-594. doi: 10.21037/tcr-22-2286

Supplementary

Table S1 Pathological types of primary tumors in the surgery group

The surgery group	Before/after PSM (N=43), n (%)
Colorectal cancer	16 (37.2)
Soft tissue sarcoma	10 (23.3)
Osteosarcoma	2 (4.7)
Renal cell carcinoma	4 (9.3)
Cervical squamous carcinoma	3 (7.0)
Breast cancer	2 (4.7)
Hepatocellular carcinoma	2 (4.7)
Cervical adenocarcinoma	1 (2.3)
Adenosquamous carcinoma of the cervix	1 (2.3)
Head and neck squamous cell carcinoma	1 (2.3)
Gastric carcinoma	1 (2.3)

PSM, propensity score matching; N/n, number.

Table S2 Pathological types of primary tumors in the chemotherapy group

The chemotherapy group	Before PSM (N=79), n (%)	After PSM (N=43), n (%)
Colorectal cancer	25 (31.6)	14 (32.6)
Breast cancer	22 (27.8)	9 (20.9)
Soft tissue sarcoma	9 (11.4)	6 (14.0)
Osteosarcoma	3 (3.8)	2 (4.7)
Esophageal squamous cell carcinoma	4 (5.1)	3 (7.0)
Germ cell tumor	4 (5.1)	2 (4.7)
Cervical squamous carcinoma	3 (3.8)	3 (7.0)
Cervical adenocarcinoma	3 (3.8)	2 (4.7)
Adenoid cystic carcinoma	2 (2.5)	0
Gastric carcinoma	1 (1.3)	1 (2.3)
Pancreatic cancer	1 (1.3)	1 (2.3)
Hepatocellular carcinoma	1 (1.3)	0
Ovarian carcinoma	1 (1.3)	0

PSM, propensity score matching; N/n, number.

Table S3 Univariate analysis of the prognosis of patients in the two groups after PSM

Characteristic	N [%]	OS, %		P
		3 years	5 years	
Age, years				0.716
≤52	43 [50]	79.6	65.5	
>52	43 [50]	72.8	57.8	
Sex				0.219
Male	44 [51]	80.7	72.4	
Female	42 [49]	71.3	50.1	
DFI, months				0.808
<21	42 [49]	82.3	59.3	
≥21	44 [51]	70.4	63.5	
Smoking				0.313
Yes	18 [21]	79.4	63.6	
No	68 [79]	75.2	57.4	
Pathology for primary lesion				0.455
Cancer	64 [75]	79.8	62.3	
Sarcoma	20 [23]	62.9	55.9	
Germ cell tumor	2 [2]	–	–	
No. of metastases				0.015*
Single (=1)	42 [49]	86.9	78.1	
Multiple (≥2)	44 [51]	65.7	47.7	
Adjuvant therapy				0.188
No	44 [51]	80.3	72.3	
Yes	42 [49]	72.6	52.1	
Diameter, mm[§]				0.014*
≤30	52 [60]	87.3	69.7	
>30	34 [40]	58.8	48.2	
Treatment method				0.017*
Surgery	43 [50]	85.1	75.1	
Chemotherapy	43 [50]	67.1	48.0	

*, P<0.05; [§], sum of the diameter for metastatic lesions. PSM, propensity score matching; N, number; OS, overall survival; DFI, disease-free interval.

https://dx.doi.org/10.21037/tcr-22-2286

Table S4 Univariate analysis of the prognosis of patients in the surgery group after PSM

Characteristic	N [%]	OS, %		P
		3 years	5 years	
Age, years				0.165
≤53	22 [51]	85.3	64.0	
>53	21 [49]	85.7	71.4	
Sex				0.143
Male	23 [53]	86.2	75.5	
Female	20 [47]	84.1	60.1	
DFI, months				0.005*
<24	21 [49]	79.3	52.8	
≥24	22 [51]	90.9	81.8	
Smoking				0.935
Yes	11 [26]	77.9	51.9	
No	32 [74]	87.1	72.6	
Pathology for primary lesion				0.153
Cancer	31 [72]	93.2	85.4	
Sarcoma	12 [28]	65.6	52.5	
No. of metastases				0.038*
Single (=1)	36 [84]	90.6	84.1	
Multiple (≥2)	7 [16]	57.1	38.1	
Adjuvant therapy				0.925
No	24 [56]	87.1	77.4	
Yes	19 [44]	83.2	72.8	
Diameter, mm[§]				0.141
≤20	24 [56]	95.2	86.6	
>20	19 [44]	73.7	61.4	
Surgical route				0.014*
Open	14 [33]	61.9	44.2	
VATS	29 [67]	96.4	82.7	
Resection scope				0.027*
Wedge	26 [60]	90.9	77.9	
Lobectomy	17 [40]	62.3	51.9	
Lymph node management				0.037*
Untouched	22 [51]	95.5	86.8	
Sampling and dissection	21 [49]	72.9	60.8	

[§], sum of the diameter for metastatic lesions; *, P<0.05. PSM, propensity score matching; N, number; OS, overall survival; DFI, disease-free interval; VATS, video-assisted thoracic surgery.

Table S5 Univariate analysis of the prognosis of patients in the chemotherapy group after PSM

Characteristic	N [%]	OS, %		P
		3 years	5 years	
Age, years				0.272
≤51	22 [51]	68.8	61.2	
>51	21 [49]	65.4	36.0	
Sex				0.701
Male	21 [49]	74.1	56.0	
Female	22 [51]	60.1	40.6	
DFI, months				0.026*
<20	21 [49]	84.7	65.9	
≥20	22 [51]	49.9	33.3	
Smoking				0.289
Yes	7 [16]	80.0	40.0	
No	36 [84]	64.7	43.4	
Pathology for primary lesion				0.415
Cancer	33 [76]	67.5	42.1	
Sarcoma	8 [19]	57.1	38.1	
Germ cell tumor	2 [5]	–	–	
No. of metastases				0.636
Single (=1)	6 [14]	66.7	44.4	
Multiple (≥2)	37 [86]	67.3	49.3	
Adjuvant therapy				0.128
No	20 [47]	72.2	65.0	
Yes	23 [53]	63.6	34.3	
Diameter, mm[§]				0.512
≤40	22 [51]	73.7	43.8	
>40	21 [49]	60.0	49.5	
Response of chemotherapy				0.024*
PR	16 [43]	72.0	54.9	
SD	15 [41]	84.6	65.3	
PD	6 [16]	33.3	16.7	

[§], sum of the diameter for metastatic lesions; *, P<0.05. PSM, propensity score matching; N, number; OS, overall survival; DFI, disease-free interval; PR, partial response; SD, stable disease; PD, progressive disease.

https://dx.doi.org/10.21037/tcr-22-2286

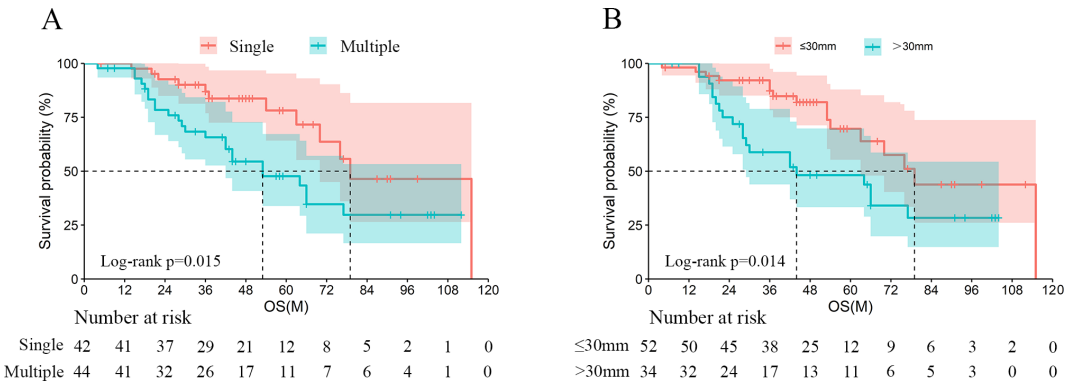

Figure S1 Survival curve of univariate prognostic analysis in the two groups after PSM. (A) Survival curve for the number of metastases (single *vs.* multiple); (B) survival curve of pulmonary metastases diameter (≤30 *vs.* >30 mm). PSM, propensity score matching; OS, overall survival; M, month.

https://dx.doi.org/10.21037/tcr-22-2286

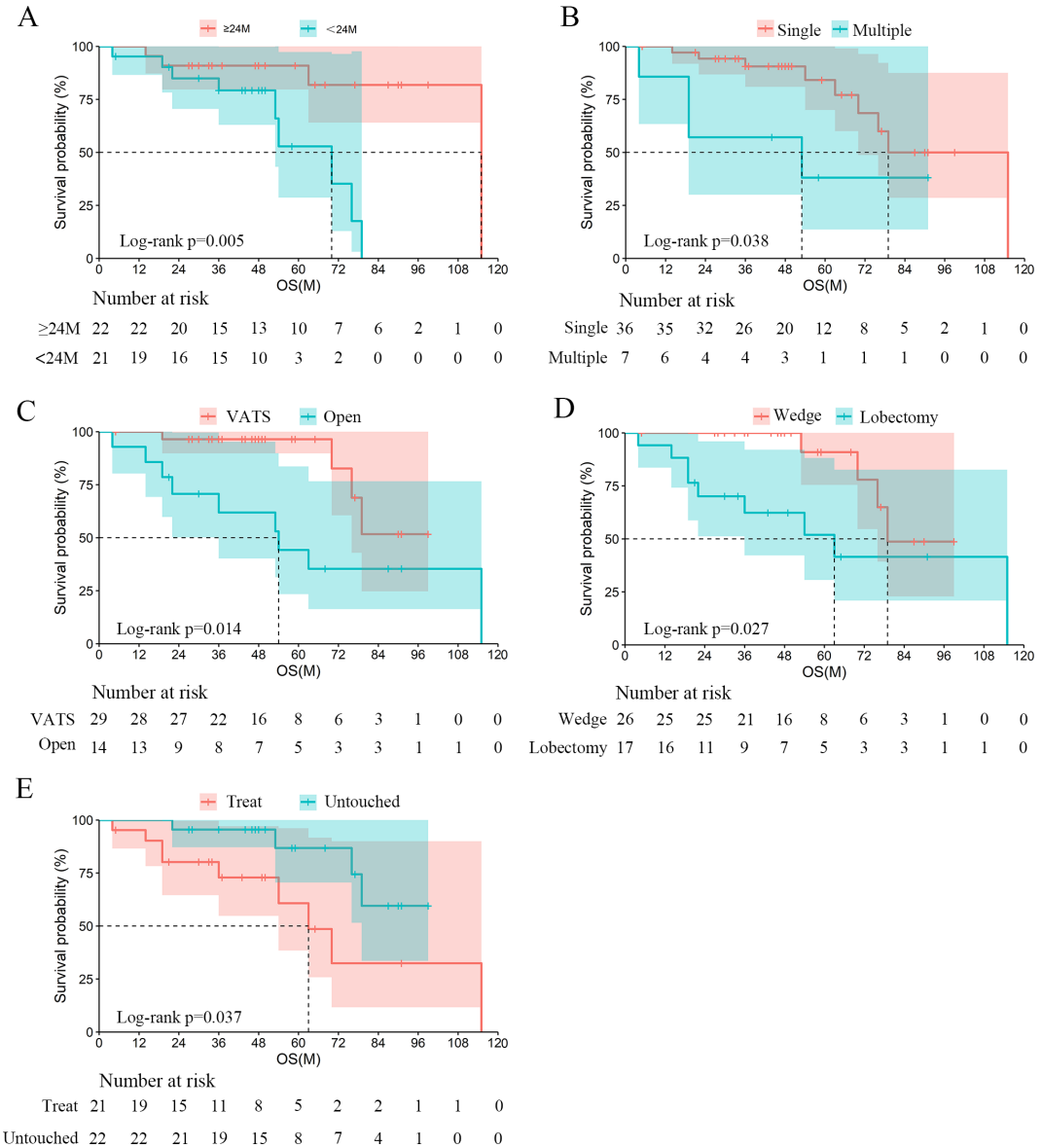

Figure S2 Survival curve of univariate prognostic analysis in surgery group after PSM. (A) Survival curve of DFI (≥24 *vs.* <24 M); (B) survival curve for the number of metastases (single *vs.* multiple); (C) survival curve of surgical route (VATS *vs.* open); (D) survival curve of resection scope (wedge *vs.* lobectomy); (E) survival curve of lymph node management (treat *vs.* untouched). OS, overall survival; M, month; PSM, propensity score matching; DFI, disease-free interval; VATS, video-assisted thoracic surgery.

https://dx.doi.org/10.21037/tcr-22-2286

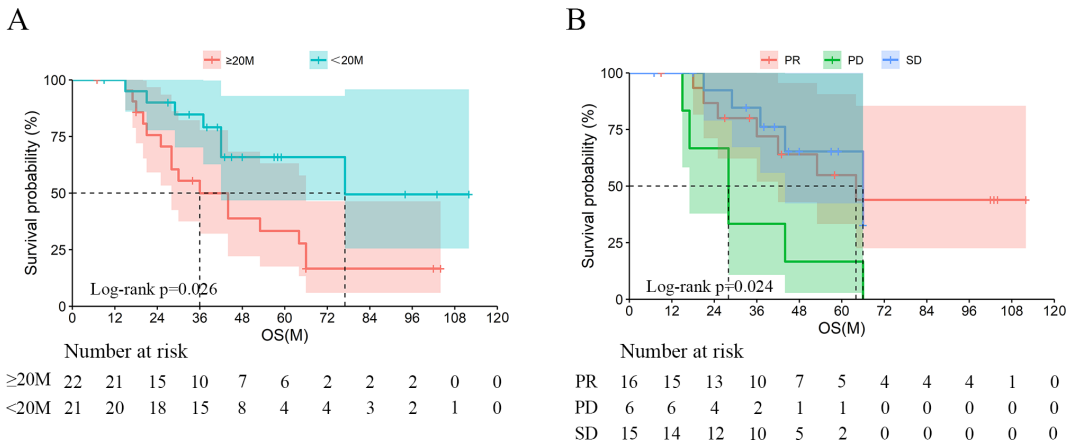

Figure S3 Survival curve of univariate prognostic analysis in the chemotherapy group after PSM. (A) Survival curve of DFI (≥20 *vs.* <20 M); (B) survival curve of response to chemotherapy (PR *vs.* PD *vs.* SD). OS, overall survival; M, month; PSM, propensity score matching; DFI, disease-free interval; PR, partial response; PD, progressive disease; SD, stable disease.

https://dx.doi.org/10.21037/tcr-22-2286