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ORIGINAL RESEARCH

Non-Small Cell Lung Cancer with Malignant Pleural Effusion May Require Primary Tumor Radiotherapy in Addition to Drug Treatment

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Purpose: The impact of primary tumour radiotherapy on the prognosis for non-small-cell lung cancer (NSCLC) with controlled malignant pleural effusion (MPE-C) (MPE-C-NSCLC) is unclear. This study aimed to analyze the efficacy and safety of primary tumor radiotherapy in patients with MPE-C-NSCLC.

Patients and Methods: A total of 186 patients with MPE-C-NSCLC were enrolled and divided into two groups. The patients in the D group were treated with only drugs. Those in the RD group were treated with drugs plus primary tumour radiotherapy. The Kaplan-Meier method was used for survival analysis, and the Log rank test was used for between-group analysis and univariate prognostic analysis. The Cox proportional hazards model was used to perform multivariate analyses to assess the impacts of factors on survival. Propensity score matching (PSM) was matched based on clinical characteristics, systematic drug treatment and drug response to further adjust for confounding factors.

Results: The overall survival (OS) rates at 1, 2, and 3 years for the RD group and D group were 54.4%, 26.8%, and 13.3% and 31.1%, 11.5%, and 4.4%, respectively; the corresponding MSTs were 14 months and 8 months, respectively (χ^2=15.915, $p<0.001$). There was a significant difference in survival by PSM ($p=0.027$).Before PSM, multivariate analysis showed that metastasis status (organ≤3 and metastasis≤5), primary tumour radiotherapy, chemotherapy cycles≥4, and drug best response (CR+PR) were independent predictors of prolonged OS. After PSM, primary tumour radiotherapy and drug best response (CR+PR) were independent predictors of prolonged OS were still independent predictors of prolonged OS. There were no grade 4–5 radiation toxicities.

Conclusion: For MPE-C-NSCLC, the response of systemic drug treatment plays a crucial role in survival outcomes, and we also should pay attention to primary tumour radiotherapy in addition to systematic drug treatment.

Keywords: non-small cell lung cancer, controlled malignant pleural effusion, radiotherapy, overall survival, prognosis

Background

Lung cancer remains the most common cancer in the world, with approximately 1.8 million new patients diagnosed yearly, and 86% of diagnosed patients have non-small cell lung cancer (NSCLC).[1] Approximately 40% of patients with lung cancer develop pleural effusions (PE) during their disease, and approximately 50% of PE are malignant pleural effusion (MPE),[2] which is associated with a poor prognosis (mean survival time (MST) ≤ 4 months)[3,4] and reduced quality of life.[5,6] Currently, the National Comprehensive Cancer Network (NCCN) guidelines and other groups still recommend that treatment for NSCLC with MPE (MPE-NSCLC) be mainly aimed at improving patient quality of life, such as thoracic puncture and drainage, thoracic catheter drainage, pleurodesis and intrathoracic chemotherapy.[7]

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The results of previous systemic chemotherapy studies showed that patients with simple MPE and intrapulmonary metastasis had better overall survival (OS) than those with other extrapulmonary metastases, and two types of metastases were defined as M1a in the seventh edition of the Union for International Cancer Control (UICC) staging system.[8] In addition, the American Joint Committee on Cancer (AJCC)/UICC eighth edition guidelines reported that M1a and M1b had similar MSTs of 11.5 months and 11.4 months, respectively.[9] Therefore, MPE-NSCLC should be actively treated.

In the context of systemic therapy, such as chemotherapy, EGFR-TKIs or immunotherapy, three-dimensional radiotherapy (3D-CRT) administered to the primary tumour improves the survival of patients with advanced NSCLC, and these outcomes have been gradually recognized.[10–15] However, all of the above studies excluded patients with MPE-NSCLC. Furthermore, there are few reports on three-dimensional radiotherapy for MPE-NSCLC, mainly used as palliative treatment, such as half-chest irradiation.[16,17] Therefore, there is no evidence regarding whether three-dimensional radiotherapy administered to the primary tumour can benefit the survival of MPE-NSCLC patients.

The primary tumour and its related clinical manifestations were found to be independent influencing factors of a poor prognosis in stage IIIB/IV NSCLC patients receiving first-line chemotherapy, according to the Higginson study.[18] An uncontrolled primary tumour accounted for more than 90% of the treatment failure factors after chemotherapy combined with stereotactic body radiation therapy (SBRT) administered to oligometastases in a study of advanced NSCLC.[19] The failure rate of the primary tumour was more than 80% after EGFR-TKI treatment,[20] and primary tumour radiotherapy significantly prolonged OS and progression-free survival (PFS) according to the results of a meta-analysis.[21] The above results provided the basis for this retrospective analysis. If MPE was controlled by drug treatment for NSCLC, primary tumour radiotherapy might be an option. This retrospective study investigated survival outcomes and prognosis of MPE-C-NSCLC combined with primary tumour radiotherapy and provide evidence for further prospective clinical trials in patients with MPE-C-NSCLC.

Materials and Methods

Patients

A retrospective study was conducted on patients with stage IV NSCLC who had MPE within two months of diagnosis from April 2007 to January 2019 at our hospital.The retrospective analysis includes only patients who met the following criteria: (1) newly histologically or cytologically confirmed MPE-NSCLC; (2) no previous thoracic radiotherapy or surgery; (3) no previous malignancy or other concomitant malignant diseases; (4) a Karnofsky performance status (KPS) score ≥70%;and (5) MPE was controlled by drug treatment (one week after intrathoracic infusion chemotherapy, thoracic ultrasound demonstrated that MPE was stable or less).Pathology was divided into two main types: squamous cell lung cancer (SCC) and Non-SCC (NSCC). NSCC included adenocarcinoma, large cell and NOS-NSCLC. Drug treatment included intrathoracic infusion chemotherapy, systemic drug chemotherapy+intrathoracic chemotherapy and EGFR-TKIs + intrathoracic chemotherapy. In this study, 186 patients were enrolled and divided into two groups (Figure 1). The D group (n=61) included patients who were given only drug treatment (without radiotherapy or with a radiation dose<36Gy/20f).[11,22] The RD group (n=125) included patients who were treated with primary tumour radiotherapy (dose≥36Gy/20f) in addition to drug treatment. A total of 32 pairs were successfully matched by propensity score matching (PSM).

Drug Treatment

1. Drug treatment: Intrathoracic infusion chemotherapy and systematic drug treatment were administered for most patients.A small number of patients were treated with only intrathoracic infusion chemotherapy.
2. Intrathoracic chemotherapy: (a) An indwelling pleural catheter was placed, and (b) cisplatin (DDP; 80–100 mg/m^2, every 21–28 days) was instilled via the catheter until controlled MPE (MPE-C) was achieved.
3. Systematic drug treatment: (a) Chemotherapy: Platinum-based doublet chemotherapy was performed for most patients. During intrathoracic infusion of DDP, another chemotherapeutic drug was given intravenously. After MPE-C was achieved, both drugs were given intravenously. (b) EGFR-TKIs: For EGFR+disease, gefitinib, erlotinib or icotinib was administered; for ALK/ROS+ disease, crizotinib was administered. There were 161

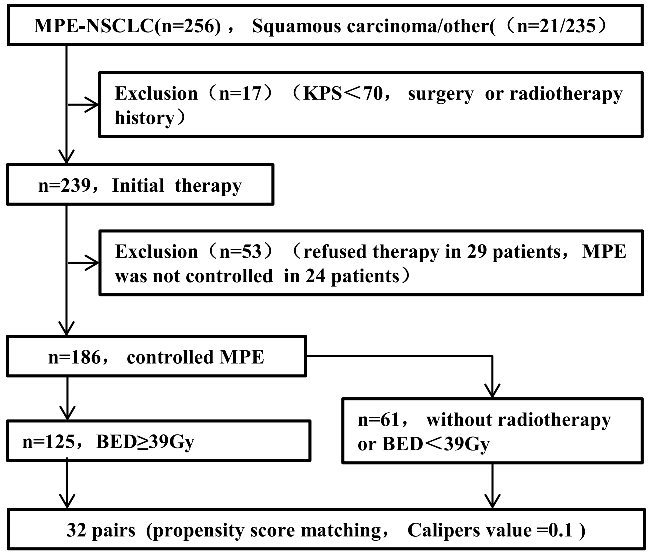

Figure 1 Flow diagram of eligible patients.
Abbreviations: MPE-NSCLC, non-small cell lung cancer with malignant pleural effusion; KPS, Karnofsky performance status; MPE, malignant pleural effusion; BED, biological effective dose.

cases of chemotherapy (1–3 cycles in 43 patients and 4–6 cycles in 118 patients). 55 patients were treated with EGFR-TKIs (first-line treatment in 21 patients). Systemic chemotherapy was mainly drug treatment for some reasons. Up to now, driver gene and programmed cell death protein 1/ ligand 1 (PD1/PDL-1) testing were not covered by health insurance. EGFR-TKIs and anti-PD1/PDL-1 were covered by health insurance in October 2017 and December 2019, respectively.

Primary Tumour Radiotherapy

Radiotherapy Timing

Primary tumour radiotherapy can be performed after MPE-C is achieved (MPE was monitored by thoracic ultrasound once every week).

Radiotherapy Management

During radiotherapy, MPE was monitored by thoracic ultrasound once every week. Radiotherapy continued according to the original radiotherapy plan, while MPE did not change. If MPE changed, computed tomography (CT) was performed, and CT images were combined with adjusting the radiotherapy plan.

Radiotherapy

Three-dimensional radiotherapy/intensity-modulated radiotherapy (3-DCRT/IMRT) was performed. The radiotherapy plan was created using the Pinnacle treatment planning system. Gross tumour volume (GTV) included the primary thoracic tumour plus any enlarged (>1 cm on short axis) mediastinal lymph nodes. Clinical target volume (CTV) was defined as the GTV plus a 0.6-cm margin; planning target volume (PTV) was defined as the CTV plus another margin of 0.5 to 1.0 cm.

The plans were evaluated as 100% of the prescription dose line, including 100% of the GTV and 90% of the prescription dose, including 98% of the PTV. The percentage of total lung volume receiving ≥20 Gy (V_{20}) was kept to ≤32%, the maximum point dose to the spinal cord was ≤50 Gy, the mean oesophageal dose was ≤35 Gy, and the mean heart dose was ≤30 Gy for all individual treatment plans. Patients received late-course accelerated hyper-fractionated radiotherapy (LCAHRT)[23–27] to the primary tumour. The first course of radiotherapy was given in 1.8Gy fractions, 5 days per week, to deliver a total dose of 36 Gy; LCAHRT was then delivered in twice-daily fractions of 1.35 Gy each, separated by 6 to 8 hours per day.

Study Endpoints

The primary endpoints were overall survival (OS) and objective response (ORR), and the secondary endpoints were acute radiation toxicities, including radiation pneumonitis (RP), oesophagitis, hematologic toxicity and gastrointestinal toxicity. OS was defined as the time from the date of drug treatment to the last follow-up date or death from any cause. The objective response rate (ORR) by the primary tumour was defined as a complete response (CR) or partial response (PR), and a nonresponse (NR) by the primary tumour was defined as no change (NC) or progressive disease (PD) according to WHO criteria. Systemic drug treatment toxicities and radiation toxicities were scored during treatment according to CTCAE 3.0 criteria.

Statistical Analysis

Statistical analysis was performed using SPSS software(version 23.0). Dichotomous variables were presented as counts and were analysed using Pearson's chi-square test or Fisher exact test. Propensity score matching (PSM) was used for the PSM process with 1:1 nearest neighbor matching (match tolerance=0.1). The Kaplan-Meier method was used for survival analysis, and the Log rank test was used for between-group analysis and univariate prognostic analysis. Variables with P values less than or equal to 0.1 from the univariate prognosis analysis were incorporated into the Cox regression model for multivariate prognosis analysis. All statistical tests were 2-sided, and P values <0.05 were considered statistically significant.

Results

Patient Characteristics

From April 2007 to January 2019, a total of 186 patients were statistically analysed. The ratio of males to females was 1.38, the median age was 56 years (26–86 years), and the median KPS was 80. The T and N stages were as follows: 47 cases $T_{1–2}$, 139$T_{3–4}$, 68 $N_{0–2}$ and 118 N_3. The most common site of metastatic disease at the diagnosis was the bone (43.0% of patients), 54 (29.0%) patients had lung metastasis, and 54 (29.0%) patients had metastasis in the brain. All patients received intrathoracic infusion chemotherapy (median number=1 cycle, range 1–4 cycles). The drug treatment in the D group (n=61) was simple intrathoracic infusion chemotherapy in 3 patients and intrathoracic infusion chemotherapy plus systemic drug treatment in 58 patients (systemic chemotherapy in 43 patients, first-line EGFR-TKIs in 15 patients and second-line EGFR-TKIs in 8 patients). The drug treatment in the RD group (n=125) was simple intrathoracic infusion chemotherapy in 1 patient and intrathoracic infusion chemotherapy plus systemic drug treatment in 124 patients (systemic chemotherapy in 118 patients, first-line EGFR-TKIs in 6 patients and second-line EGFR-TKIs in 25 patients). The median radiation dose was 63 Gy (36–71.1 Gy). There were significantly different between groups in age and chemotherapy cycles. No other significant difference was observed between the groups (Table 1). Patients were matched on the basis of sex, age, pathology, KPS, T status, N status, MPE alone, metastasis status, liver metastasis, chemotherapy cycles, EGFR-TKIs, and drug best response with 1:1 nearest neighbor matching and the D group as the reference group. A total of 32 pairs were successfully matched. All clinical factors were comparable after matching (Table 1).

Primary Endpoints

Efficacy

The ORR of the primary tumor in the RD group and D group of the first-line treatment was 62.3% and 42.6%, respectively (χ^2 =5.389, P=0.025); corresponding the best OR rates of the primary tumor in all treatments were 68.9% and 53.2%, respectively (χ^2 =3.634, P=0.073).

Overall Survival (OS) in All Patients

The last follow-up time was July 2021, with a median follow-up period of 12 months (range of 3–75 months). At the time of the last follow-up, 10 patients were still alive. The median OS time for all patients was 12.0 months (95% CI 10.2–13.8), and the OS rates were 46.8% at 1 year, 21.8% at 2 years, and 10.4% at 3 years.

Table 1 Patient Characteristics

Characteristic		All (n=186)	Overall Cohort			After PSM		
			D Group (n=61)	RD Group (n=125)	*P* value	D Group (n=32)	RD Group (n=32)	*P* value
Sex	Male	108	38	70	0.433	21	23	0.788
	Female	78	23	55		11	9	
Age (years)	≤65	148	43	105	0.035	24	23	>0.999
	>65	38	18	20		8	9	
Pathology	SCC	13	5	8	0.761	4	4	>0.999
	NSCC	173	56	117		28	28	
KPS	90	49	13	36	0.294	6	9	0.556
	70–80	137	48	89		26	23	
T status	T1–2	47	15	32	>0.999	7	8	>0.999
	T3–4	139	46	93		25	24	
N status	N0–2	68	21	47	0.747	12	14	0.799
	N3	118	40	78		20	18	
MPE only	Yes	48	14	34	0.595	8	9	>0.999
	No	138	47	91		24	23	
Other metastasis								
Bone	Yes	80	26	54	>0.999	13	16	0.616
	No	106	35	71		19	16	
Brain	Yes	54	19	35	0.731	13	10	0.603
	No	132	42	90		19	22	
Lung	Yes	54	21	33	0.303	12	10	0.793
	No	132	40	92		20	22	
Liver	Yes	15	6	9	0.572	4	2	0.672
	No	171	55	116		28	30	
Adrenal	Yes	16	5	11	>0.999	4	2	0.672
	No	170	56	114		28	30	
Other	Yes	27	11	16	0.378	4	3	>0.999
	No	159	50	109		28	29	
Metastasis status	Yes	99	28	71	0.210	14	15	>0.999
Organ≤3and metastasis≤5	No	87	33	54		18	17	
Chemotherapy cycles	1–3	43	13	38	<0.001	22	17	0.128
	≥4	118	30	80		10	15	
EGFR-TKIs	Yes	55	23	32	0.123	8	7	>0.999
	No	131	38	93		24	25	
Drug response(OR)* in first line	Yes	87	20	67	0.171	8	7	>0.999
	No	82	27	55		24	25	
Drug best response(OR)*	Yes	102	25	77	0.293	13	10	0.603
	No	67	22	45		19	22	
EGFR/ALK/ROS	Positive	56	25	45	0.684	16	17	0.674
	Negative	36	11	29		6	3	
EGFR/ALK/ROS	No test	75	25	50		8	10	

Abbreviations: PSM, propensity score matching; SCC, Squamous cell lung cancer; NSCC, adenocarcinoma (n=161), large cell (n=6) and NOS-NSCLC(n=7); KPS, Karnofsky performance status; drug response*, the response of the systematic drug treatment could not be confirmed in 13 patients and simple intrathoracic infusion chemotherapy in 4 patients.

OS Analysis Between Groups

The OS rates at 1, 2, and 3 years for the RD group and D group were 54.4%, 26.8%, and 13.3% and 31.1%, 11.5%, and 4.4%, respectively; the corresponding MSTs were 14 months and 8 months, respectively (χ^2=15.915, p <0.001) (Figure 2).After PSM, the OS rates at 1, 2 and 3 years for the RD group and D group were 43.8%, 25.0%, and 17.9% and 28.1%, 9.4%, and 6.3%, respectively; the corresponding MSTs were 12 months and 7 months, respectively (χ^2=4.871; p=0.027) (Figure 3). The stratified

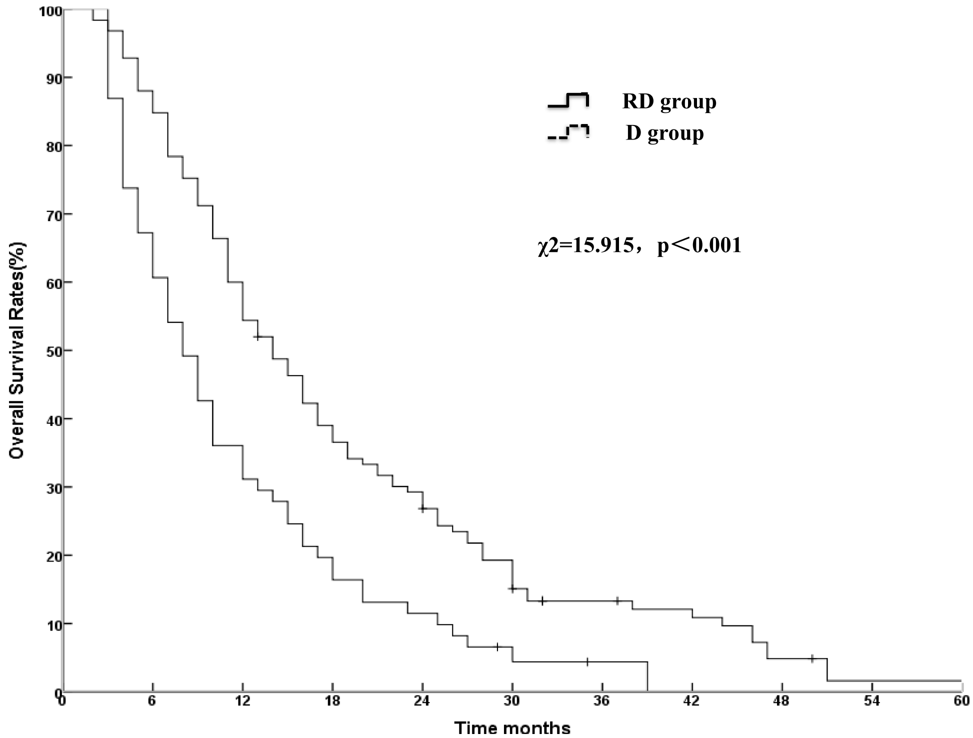

Figure 2 Overall survival for D and RD group.

Abbreviations: D group, patients treated with only drug treatment; RD group, patients treated with primary tumour radiotherapy in addition to drug treatment.

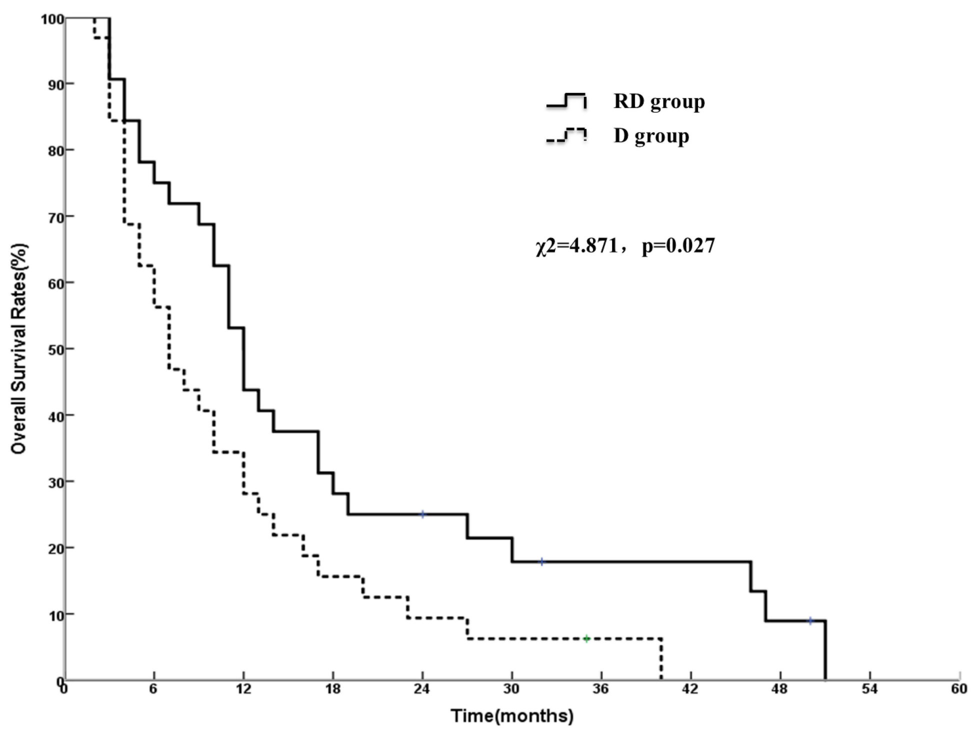

Figure 3 Overall survival for patients by the PSM.

Abbreviations: D group, patients treated with only drug treatment; RD group, patients treated with primary tumour radiotherapy in addition to drug treatment; PSM, propensity score matching.

analysis showed three statuses. The first status was that radiotherapy could not improve OS for patients with age > 65 years or liver metastasis. The second status was that radiotherapy may improve OS for patients with KPS = 90 or MPE alone. The third status was that radiotherapy significantly improved OS for patients with conditions as follows: age≤ 65 years; KPS 70–80; MPE with other metastasis; no liver metastasis; regardless of gender, pathology T status, N status, metastatic status, chemotherapy cycles, EGFR-TKIs, and drug best response (Table 2).

Factors Associated with OS

Before PSM

Univariate variables with P<0.10 were analysed by multivariate analysis. The results showed that metastasis status (organ≤3 and metastasis≤5), primary tumour radiotherapy, chemotherapy cycles≥4, and drug best response (CR+PR) were independent predictors of prolonged OS. EGFR-TKIs were marginally correlated with better OS. However, OS was not significantly associated with sex, age, pathology, KPS, T status, N status, MPE alone, and liver metastasis (Table 3).

After PSM

Multivariate analysis showed that primary tumour radiotherapy and drug best response (CR+PR) were independent predictors of prolonged OS (Table 3).

Secondary Endpoints

Toxicity

Grade 3 to 4 white blood cells, neutrophils, and gastrointestinal toxicity of the RD group was significantly higher than those of the D group. However, grade 3–4 haemoglobin and platelet toxicities were not significantly different between the

Table 2 Stratified Analyses

Items		D Group					RD Group					Value	
		n	OS Rates(y)%			MST	n	OS Rates(y)%			MST	χ^2	P
			1	2	3			1	2	3			
Sex	Male	38	28.9	13.2	7.0	7	70	48.6	23.6	12.4	12	6.104	0.013
	Female	23	34.8	8.7	0	10	55	61.8	30.9	14.5	17	10.714	0.001
Age (years)	≤65	43	34.9	11.6	2.3	10	105	58.1	31.0	14.9	16	13.954	<0.001
	>65	18	22.2	11.1	0	5	20	35.0	5.0	0	11	0.994	0.319
Pathology	SCC	5	0	0	0	4	8	37.5	28.1	18.0	7	4.220	0.040
	NSCC	56	33.9	12.5	4.8	9	117	55.6	26.1	12.9	14	12.430	<0.001
KPS	<90	48	25.0	8.3	4.2	7	89	49.4	22.5	10.1	12	11.990	0.001
	≥90	13	53.8	23.1	0	13	36	66.7	37.8	21.6	17	2.970	0.085
T status	T1–2	15	40.0	13.3	6.7	10	32	75.0	31.3	21.4	18	6.535	0.011
	T3–4	46	28.3	10.9	3.3	7	93	47.3	25.3	10.4	12	9.702	0.002
N status	N0–2	21	38.1	19.0	9.5	10	47	66.0	27.7	23.0	16	5.786	0.016
	N3	40	27.5	7.5	2.5	8	78	47.4	26.4	7.9	12	9.676	0.002
MPE only	Yes	14	42.9	21.4	10.7	10	34	73.5	36.9	12.3	18	2.863	0.091
	No	47	27.7	8.5	2.1	8	91	47.3	23.1	13.8	12	12.025	0.001
Metastasis status	Yes	28	42.9	21.4	9.5	10	71	66.2	36.0	16.5	19	5.489	0.019
Organ≤3 and metastasis≤5	No	33	21.2	3.0	0	7	54	38.9	14.8	9.3	12	7.471	0.006
Liver metastases	No	55	32.7	12.7	4.8	9	116	56.9	28.9	14.3	15	15.353	<0.001
	Yes	6	16.7	0	0	7	9	22.2	0	0	10	0.088	0.767
Chemotherapy cycles	<4	33	18.2	6.1	3.0	6	44	36.4	13.6	5.5	11	5.372	0.020
	≥4	10	40.0	10.0	0	7	74	63.5	32.4	16.2	16	5.137	0.023
EGFR-TKIs	No	38	15.8	2.6	0	6	93	45.2	17.2	9.2	12	24.008	<0.001
	Yes	23	56.5	30.4	11.6	16	32	81.3	55.3	25.3	25	5.709	0.017
Drug best response (OR)	Yes	25	56.0	24.0	10.7	16	77	71.4	41.0	21.0	19	3.898	0.048
	No	22	9.1	0	0	5	45	28.9	4.4	0	10	9.628	0.002

Abbreviations: PSM, propensity score matching; MST, mean survival time (months); SC, squamous carcinoma; KPS, Karnofsky performance status.

Table 3 Multivariate Analysis of Prognostic Factors for Overall Survival

	Variable	HR	95% CI		P value
			Lower	Upper	
Before PSM	Metastasis organ≤3 and metastasis≤5 (yes vs no)	0.670	0.467	0.963	0.030
	EGFR-TKIs (yes vs no)	0.643	0.401	1.032	0.067
	Primary tumour radiotherapy (yes vs no)	0.633	0.410	0.976	0.039
	Chemotherapy cycles≥4 (yes vs no)	0.633	0.439	0.915	0.015
	Drug best response(CR+PR vs SD+PD)	0.423	0.281	0.638	<0.001
After PSM	Primary tumour radiotherapy (yes vs no)	0.479	0.281	0.816	0.007
	Drug best response(CR+PR vs SD+PD)	0.231	0.119	0.447	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 4 Toxicity Comparison

Toxicity	Grade	D Group (%)	RD Group (%)	P
Gastrointestinal	0–2	57 (93.4)	102 (81.6)	0.044
	3–4	4 (6.6)	23 (18.4)	
White blood cells	0–2	52 (85.2)	61 (48.8)	<0.001
	3–4	9 (14.8)	64 (51.2)	
Neutrophils	0–2	54 (88.5)	76 (60.8)	<0.001
	3–4	7 (11.5)	49(39.2)	
Haemoglobin	0–2	55 (90.2)	107 (85.6)	0.488
	3–4	6 (9.8)	18 (14.4)	
Thrombocytopenia	0–2	56 (91.1)	105 (84.0)	0.173
	3–4	5 (8.9)	20(16.0)	
Radiation oesophagitis	5	0 (0.0)	0 (0.0)	
	3–4	0 (0.0)	13 (10.4)	
Radiation pneumonitis	5	0 (0.0)	0 (0.0)	
	3–4	0 (0.0)	8 (6.4)	

two groups (Table 4). Grade 3 radiation oesophagitis and pneumonitis were observed in 10.4% and 6.4% of patients. There were no grade 4–5 radiation toxicities.

Discussion

The clinical characteristics included a male-to-female ratio of 1.36, age of high incidence ≤ 70 years, mainly adenocarcinoma pathological type, distant metastasis, and $T_{3–4}$ and N_3 for 73.7% and 63.4% of patients, respectively, which were similar to the characteristics in reports on advanced NSCLC without MPE.[14,28] The MST of the D group was 8 months, which was similar to the MST of 5–7 months for MPE-NSCLC treated with cisplatin and other drugs, pleurodesis, thoracoscopic and surgical treatment, EGFR-TKIs, bevacizumab combined with chemotherapy, or immunotherapy in the context of high expression of PD-L1.[7,16,29–33] Our study showed that the OR rates of the primary tumor in the RD group of the first-line treatment were significantly better than that in the D group (χ^2 =5.389, P=0.025). The best OR rates of the primary tumor in the RD group of all treatments were marginally better than those in the D group (χ^2 =3.634, P=0.073). $T_{3–4}$ and $N_{2–3}$ were the majority of MPE-NSCLC cases in our study. Radiotherapy administered to the primary tumour, and metastatic lymph nodes in the drainage area significantly improved the ORR of the primary tumour. However, whether a higher ORR rate for the primary tumour will translate into a survival benefit is still unknown.

Higginson et al analysed stage III/IV NSCLC patients who received only systemic chemotherapy and found that the state of the primary tumour (large central tumour, pulmonary symptoms, and bronchial or vascular compression) was associated with poor OS.[18] The results indicated that active control of the primary tumour played an important role in the survival of advanced NSCLC patients.[18] Nearly 50% of patients with advanced NSCLC have a poor prognosis because of an uncontrolled primary tumour.[34] In recent years, numerous studies have shown that radiotherapy plus drug treatment of primary advanced NSCLC tumours without MPE can reduce the local failure rate to 30% and significantly prolong OS.[10–15] For MPE-C-NSCLC, few studies have reported whether primary tumour radiotherapy affects OS. Our study found that the OS rates of the RD group were significantly higher than those of the D group, and the MST of the RD group was twice as long as that of the D group. These results suggest that primary tumour radiotherapy improves OS. However, this was a retrospective study, with some unaccounted confounders, selection bias and recall bias. PSM may simulate a randomised controlled trial (RCT) because it can reduce this bias and be used to balance covariates between the two groups.[35–37] Thirty-two pairs were successfully matched through PSM. The OS outcome still showed a similar significant difference between the two groups (Figure 3). The survival outcome was consistent with that of advanced NSCLC without MPE treated with primary tumour radiotherapy, as reported in the previous studies.[11–13,28,38–40]

Stratified analyses of 186 patients showed that primary tumour radiotherapy significantly improved OS under the following conditions: age≤ 65 years; KPS 70–80; MPE with other metastasis; no liver metastasis; regardless of gender, pathology T status, N status, metastatic status, chemotherapy cycles, EGFR-TKIs, and drug best response (Table 2). EGFR-TKIs are an important drug treatment for MPE-NSCLC due to the pathological type, mainly adenocarcinoma with a high EGFR mutation rate.[2,41,42] Wu et al reported that the MST of MPE-NSCLC treated with EGFR-TKIs at initial diagnosis was 16.3 months,[30] which was similar to that found in our study (MST of 16 months). The stratified analysis showed that the MST of the RD group and D group were 25 and 16 months, respectively, in the EGFR-TKIs subgroup and the difference between the groups was statistically significant (P=0.017). The longer survival of the RD group might be due to a reduction in local failure, which was 82% for advanced NSCLC treated with only EGFR-TKIs.[20] The above results suggest that primary tumour radiotherapy plays an important role in survival outcomes for MPE-C-NSCLC, especially in patients meeting the conditions of the third status.

Before or after PSM, multivariate analysis showed that primary tumour radiotherapy and drug treatment were independent predictors of prolonged OS. Our result also showed that drug best response (CR+PR) was an independent predictor of prolonged OS. Our study suggested that the treatment mode of MPE-C-NSCLC should not be limited to a single treatment but rather be a comprehensive treatment mode. OS benefits were derived from the synergistic combination of radiotherapy and systemic drug treatment based on MPE-C.

It is accepted that primary tumour radiotherapy in addition to drug treatment for NSCLC increases toxicity compared with drug treatment alone. There were no significant differences in grade 3–4 haemoglobin and platelet toxicities between the two groups. Grade 3–4 gastrointestinal tract, leukocyte and neutrophil toxicities were significantly increased in the RD group, similar to the concurrent chemoradiotherapy toxicity observed in locally advanced NSCLC.[43,44] Grade 3 radiation oesophagitis and pneumonitis were observed in 10.4% and 6.4% of patients, respectively, which were similar to the concurrent chemoradiotherapy toxicities observed in advanced NSCLC without MPE.[13,39,45] The results suggested that the radiation toxicities observed were acceptable for MPE-C-NSCLC.

We acknowledge several limitations to the current study. First, the sample size was small. Second, this was a single-institution study. Survival data for patients treated at other institutions might differ. Third, drug treatment regimens were not uniform and included several drugs. Fourth, we assessed certain clinical factors and their impacts on prognosis. There were likely other factors that were not evaluated in this analysis. Finally, this was a retrospective study with some unaccounted confounders, selection bias and recall bias. Although PSM and multivariate regression analysis were used to reduce these biases, some unaccounted confounders could still have existed between the two groups because of the retrospective nature of this study. PSM can simulate but not replace an RCT. Therefore, randomized studies are needed to confirm the conclusions of this study.

Conclusions

For MPE-C-NSCLC, our results showed that primary tumour radiotherapy and drug best response (CR+PR) were independent predictors of a prolonged OS with no grade 4–5 radiation toxicities. Therefore, we should pay more attention to primary tumour radiotherapy in addition to drug treatment based on MPE-C, which warrants the performance of a prospective RCT, and such a trial will be conducted in the near future.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors (Lu Bing, Email: lbgymaaaa@163.com), without undue reservation.

Ethics Statement

All procedures were in accordance with the ethical standards of the Helsinki Declaration issued in 1975 and later amendments.The studies involving human participants were reviewed and approved by the Ethics Committee of Affiliated Cancer Hospital of Guizhou Medical University.The patients/participants provided written informed consent to participate in this study.

Consent for Publication

The abstract of this paper was presented at the ASTRO's 62nd Annual Conference name "Non-Small Cell Lung Cancer with Malignant Pleural Effusion May Require Primary Tumor Radiotherapy in Addition to Drug Therapy" as a poster presentation with interim findings. The poster's abstract was published in "Poster Abstracts" in Int J Radiat Oncol Biol Phys name "Non-Small Cell Lung Cancer with Malignant Pleural Effusion May Require Primary Tumor Radiotherapy in Addition to Drug Therapy". Publication of this manuscript has been approved by all co-authors. I would like to declare on behalf of my co-authors that the work described is an original report that has not been published previously and is not under consideration for publication elsewhere.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors report no conflicts of interest in this work.

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