Survival and Prognostic Factors of 40 Patients with Pulmonary Oligometastases Treated with Tomotherapy Hypofractionated Radiotherapy

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Research

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Abstract

Background: With continued improvement in radiotherapy technology, hypofractionated radiotherapy has helped achieve good results in the local control and toxicity of pulmonary oligometastases. This study aimed to investigate the efficacy of radiotherapy and the prognostic factors that affect survival in patients with pulmonary oligometastases who undergo helical tomotherapy (TOMO) hypofractionated radiotherapy.

Methods: Ninety pulmonary oligometastases in 40 patients (26 males, 14 females; median age 57 years) were retrospectively investigated and treated with hypofractionated radiotherapy in the Department of Oncology and Radiotherapy of the First Affiliated Hospital of Bengbu Medical College during 2018-2020. Their Karnofsky performance status (KPS) was ≥ 70 points. The primary endpoints were overall survival (OS), local control (LC), and progression-free survival (PFS), and we determine the related influencing factors.

Results: The median gross tumor volume (GTV) and planning target volume (PTV) were 9.7 cm³ (range 1.1–287.0 cm³) and 56.9 cm³ (range 16.3–494.2 cm³), respectively, the median biological effective dose, $\alpha/\beta=10$ (BED10), was 76.8 Gy (range 56–96 Gy), and four-dimensional computed tomography positioning was applied to 52.5% of the patients. All patients completed the treatment plan during a median follow-up of 16.1 months (range 4.9–33.3 months). The 1- and 2-year OS rates were 90.3% and 55.2%, respectively. The 1- and 2-year LC rates were 80.8% and 64.7%, respectively. The 1- and 2-year PFS rates were 47.3% and 28.4%, respectively. Univariate analysis revealed that colorectal primary ($p=0.004$), age >57 years ($p=0.037$), and number of organ metastases ≥ 2 ($p=0.046$) were associated with OS, whereas disease-free interval (DFI) ≤ 17.4 months ($p=0.032$), number of lung metastases ≥ 2 ($p=0.049$), and PTV >56.9 cm³ ($p=0.041$) were associated with LC; and number of metastatic organs ≥ 2 ($p=0.015$) was independently associated with PFS. In multivariate analysis, colorectal cancer ($p=0.010$) and age >57 years ($p=0.009$) were significantly associated with OS. No $>$ grade 3 toxic reaction.

Conclusions: The median OS, LC, and PFS rates of TOMO hypofractionated radiotherapy for pulmonary oligometastases were 24.9, 25.9, and 11.8 months, respectively, showing that good survival rates and low toxicity could still be achieved using the medium dose.

Introduction

With continuous development in diagnosis and treatment methods for malignant tumors, the survival time of patients has increased, with an associated increase in the detection rate of distant metastasis; among these, the lung is the most common site of metastasis of most malignant tumors (1). The concept of oligometastases was first proposed by Hellman et al. in 1995 (2). It refers to a transitional state in which a tumor metastasizes to a limited number of organs before it progresses to multiple distant metastases. Most researchers regard the diagnostic criteria for oligometastases to include not more than five metastases seen during clinical imaging examinations, and metastasis to not more than

three organs. The limited number of metastases provides opportunities for local clinical treatment. Previous studies have shown that combining effective local treatments with systemic therapy could improve the progression-free survival (PFS) and overall survival (OS) of patients with oligometastases (3–5), and some patients could even be cured.

Local diseases are usually treated by surgical resection or local ablation. Studies have shown that the 10- and 15-year OS rates of patients with complete resection of metastases are 26% and 22%, respectively (6), but not all patients are suitable candidates for radical surgical resection. Radiation therapy is an important choice for patients with lesions in an unsuitable position for surgery, a history of lobectomy or pneumonectomy, inoperability, failure of surgery and chemotherapy, other diseases that are not suitable for surgery, and refusal to undergo surgery. Due to the continuous advancement and development of precision radiotherapy technology, the target area during radiotherapy has become more precise, and protection of normal tissues is currently more reliable. Radiotherapy has the same therapeutic effect as that of surgical resection (7–9). This study explored the efficacy of radiotherapy and those prognostic factors that affect survival in patients with pulmonary oligometastatic tumors who undergo helical tomotherapy (TOMO) hypofractionated radiotherapy to provide evidence for clinical decision-making and treatment.

Materials And Methods

Patient selection

This retrospective study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Bengbu Medical College (approval number: 2020KY109). The inclusion criteria were as follows: 1) age $\geq$ 18 years old, regardless of the sex; 2) the primary tumor needed to be diagnosed histopathologically, and the diagnosis of pulmonary oligometastases was made with at least clear imaging evidence or pathological confirmation; 3) no more than three systemic metastatic organs and no more than five lung metastases before radiotherapy; 4) Karnofsky Performance Status (KPS) score of $\geq$ 70 points; 5) Estimated survival time of $\geq$ 3 months; 6) Volunteering to join the study and sign an informed consent form, with good compliance and follow-up. The exclusion criteria were as follows: 1) KPS score of $\leq$ 70 points; 2) more than five lung metastases before radiotherapy; 3) the primary tumor and extrapulmonary metastases were not controlled, and 4) poor lung function.

Treatment schedules

All patients were treated using TOMO, and 21 cases (52.5%) were located using four-dimensional computed tomography (4D-CT). All patients underwent professional breathing exercise training before radiotherapy. The radiation dose that was used depended on the location and size of the tumor and the patient's lung function status; peripheral lung metastases were treated using 45–60 Gy in 8–12 fractions; central lung metastases (within 2 cm from the trachea and main bronchus) received a dose of 40–60 Gy in 10–20 fractions, and the treatment volume covered at least 95% of the planned target volume (Table 1). Gross tumor volume (GTV) was defined as visible lesions on imaging examination, including

CT or positron emission tomography/CT evaluation. Planning target volume (PTV) was determined based on the maximum activity interval of the tumor when the patient was breathing calmly as observed under the simulator, and the GTV was formed by expanding 5–8 mm in the three-dimensional direction. When the tumor was located close to the bronchus, heart, and other important organs, appropriate adjustments for the range of target area and recovery were made after release to not damage the vital organs. The dose division plan was jointly formulated by multiple senior radiation oncologists based on tumor volume, location, and normal tissue dose limits. The biological effective dose, $\alpha/\beta = 10$ (BED10), estimation formula for different segmentation schemes was as follows: $BED = n \cdot d [1 + d / (\alpha/\beta)]$, where n is the number of divisions, d is the fractionated dose, and the ratio of α/β for pulmonary oligometastases was 10 Gy. All patients underwent TOMO system image verification before each treatment to ensure the accuracy of the treatment target area.

Table 1
Dose division characteristics

D (GY)	n (fractions)	Total (Gy)	BED10 (Gy)	Number
3	15–20	45–60	58.5–78.0	11
4	10–15	40–60	56.0–84.0	9
5	9–12	45–60	67.5–90.0	9
6	8–10	48–60	76.8–96.0	11
<i>d</i> : fractionated dose; <i>n</i> : number of divisions; BED10: biological effective dose, $\alpha/\beta = 10$.				

Definition of endpoints

Follow-up was conducted using telephone follow-up, outpatient, and inpatient review, and other methods. The first follow-up was 4–8 weeks after radiotherapy, and then every 3 months until April 30, 2021. OS was computed from the date of the first radiotherapy to the date of death or the date of the last follow-up; local control time (LC) was computed from the date of the first radiotherapy to the progression of the radiotherapy focus, local recurrence was the recurrence within the PTV area, progression-free survival (PFS) was computed from the date of the first radiotherapy to the date of local, regional, or distant recurrence (whichever occurs first); use of CR, PR, SD, and PD evaluate short-term efficacy; mainly observe OS, LC, PFS, and toxicity after treatment. The Radiation Therapy Oncology Group radiotherapy injury grading standard was used to evaluate the grade of adverse reactions (10).

Statistical analysis

In survival analysis, the Kaplan-Meier curve represents the cumulative survival rate of OS, LC, and PFS at 1 and 2-years, and the log-rank test was used for curve comparison. To analyze the influence of potential risk factors on the observation endpoint indicators, univariate and multivariate Cox regression analyses were used at the same time, and factors with $P < 0.1$ were selected in univariate Cox regression analysis

to enter the multivariate Cox regression model analysis ($p < 0.05$). All analyses were performed using IBM SPSS Statistics, version 25.0, software package.

Results

Patient and tumor characteristics

The clinical data of 90 pulmonary oligometastases in 40 patients who received hypofractionated radiotherapy were collected from January 1, 2018, to December 31, 2020, of the First Affiliated Hospital of Bengbu Medical College.

The primary tumors were mainly head and neck tumors in 10 cases, colorectal cancer in 8 cases, soft tissue sarcoma in 6 cases, esophageal cancer in 5 cases, and breast cancer and lung cancer in 3 cases, respectively. All patients received systemic treatment, including chemotherapy, targeted therapy, and immunotherapy, before receiving radiotherapy for pulmonary oligometastases. Two patients underwent surgical resection of lung metastases and γ -knife treatment followed by TOMO hypofractionated radiotherapy. Five patients with lung metastases and recurrent or primary tumors, received radiotherapy simultaneously. Twelve cases (30%) of extrapulmonary metastases included sites such as lymph nodes, bones, liver, and brain, of which 10 cases had one metastatic organ, two cases had three metastasis organs, and one case had two metastatic organs, and the primary tumor and extrapulmonary metastases were well controlled. Overall, 22 patients (55%) received simultaneous systemic therapy, including targeted therapy and chemotherapy. The median BED10 was 76.8 Gy (range, 56–96 Gy). Disease-free interval (DFI) was defined as the interval between the day the primary tumor was controlled and the day when the first metastasis was confirmed. A patient with Ewing's sarcoma of the buttocks was diagnosed with both the primary focus and lung metastasis. Therefore, the DFI was calculated as 0 (Tables 2 and 3).

Table 2

Patient's demographics at the time of hypofractionated radiotherapy

Characteristics	Number	Percentage
Age, years		
≤ 57	21	52.5%
> 57	19	47.5%
Gender		
Male	26	65.0%
Female	14	35.0%
KPS		
Median, range	80	70–90
Primary tumor		
Head and neck tumor	10	25%
Colorectal cancer	8	20%
Soft tissue sarcoma	6	15%
Esophageal cancer	5	12.5%
Breast cancer	3	7.5%
Lung cancer	3	7.5%
Others	5	12.5%
Pathology		
Squamous	17	42.5%
Adenocarcinoma	8	20.0%
Sarcoma	6	15.0%
Others	9	22.5%
Number of organs metastases		
Single	25	62.5%
Multiple	15	37.5%
Synchronized systemic therapy		
Yes	22	55.0%
KPS: Karnofsky Performance Status; DFI: Disease-free interval.		

Characteristics	Number	Percentage
No	18	45.0%
Systemic therapy after radiotherapy		
Yes	34	85.0%
No	6	15.0%
DFI (months)		
≤ 15.8	20	50.0%
> 15.8	20	50.0%
Lung metastasis to radiotherapy (months)		
≤ 4.3	21	52.5%
> 4.3	19	47.5%
KPS: Karnofsky Performance Status; DFI: Disease-free interval.		

Table 3
Tumor and treatment characteristics

Characteristics	Number	Percentage
Number of lung metastases		
1	20	50.0%
2	5	12.5%
3	6	15.0%
4	3	7.5%
5	6	15.0%
GTV (cm ³)		
≤ 9.7	21	52.5%
> 9.7	19	47.5%
PTV (cm ³)		
≤ 56.9	20	50.0%
> 56.9	20	50.0%
BED10 (Gy)		
< 70	8	20.0%
70–85	21	52.5%
> 85	11	27.5%
4D-CT		
Yes	21	52.5%
No	19	47.5%
GTV, gross tumor volume; PTV, planning target volume; BED10, biological effective dose; α/β, 10		

Survival analysis

Within a median follow-up duration of 16.1 months, all patients undergoing hypofractionated radiotherapy completed the treatment plan. Among the 40 patients, CR, PR, SD, and PD rates were 50.0%, 32.5%, 12.5%, and 5.0%, respectively (Fig. 1). The 1- and 2-year OS rates were 90.3% and 55.2%, respectively. The 1- and 2-year LC rates were 80.8% and 64.7%, respectively. The 1- and 2-year PFS rates were 47.3% and 28.4%, respectively. At the last follow-up, 14 patients had died. One patient died of lung infection caused by bone marrow suppression after radiotherapy, and one patient died of radiation pneumonia due to lung re-metastasis after 2 months of secondary radiotherapy. Most patients died from

multiple organ failure caused by extensive bones and brain metastases. A common toxic reaction was radiation pneumonitis; 16 patients (40.0%) developed radiation pneumonitis, of which 10 (25.0%) developed grade 1 radiation pneumonitis and 6 (15.0%) developed grade 2 radiation pneumonitis. Bone marrow suppression was another toxic reaction. Ten patients (25.0%) had bone marrow suppression, of which four (10.0%) had first-degree bone marrow suppression, and six (15.0%) had second-degree bone marrow suppression. No rib pain or rib fracture was found and intercostal neuralgia and other adverse reactions. No grade 3 or 4 toxic reactions were observed.

The univariate Cox regression analysis is shown in Table 4. The 2-year OS rates of patients with primary tumor types of colorectal cancer and non-colorectal cancer were 22.2% and 62.3%, respectively, and the difference was statistically significant ($p = 0.004$, hazard ratio [HR] = 5.865, 95% confidence interval [CI] = 1.76–19.51) (Fig. 2a); the number of organ metastases ≥ 2 and the 2-year OS rates of single patients were 36.3% and 68.5%, respectively, and the difference was statistically significant ($p = 0.046$, HR = 3.15, 95% CI = 1.02–9.76) (Fig. 3a). The 2-year OS rates of patients aged > 57 and ≤ 57 years were 24.4% and 69.8%, respectively, and the difference was statistically significant ($p = 0.037$, HR = 3.35, 95% CI = 1.08–10.41). DFI ≤ 17.4 months ($p = 0.032$, HR = 9.77, 95% CI = 1.21–78.60) (Fig. 2b), number of lung metastases ≥ 2 ($p = 0.049$, HR = 8.08, 95% CI = 1.01–64.68), and PTV ≥ 56.9 cm³ ($p = 0.041$, HR = 8.97, 95% CI = 1.09–73.77) were significantly associated with LC. While the number of systemic metastatic organs ≥ 2 ($p = 0.015$, HR = 2.93, 95% CI = 1.23–6.95) was an independent prognostic factor for PFS (Fig. 3b).

Table 4
Results of univariate Cox proportional analyses

Factors	OS	P	LC	P	PFS	P
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
Age, years						
≤ 57						
> 57	3.35 (1.08–10.41)	0.037	0.50 (0.10–2.47)	0.397	0.74 (0.30–1.81)	0.511
Sex						
Male						
Female	0.97 (0.32–2.99)	0.960	0.60 (0.13–2.92)	0.530	1.24 (0.51–3.00)	0.640
KPS						
≤ 80						
> 80	0.71 (0.23–2.19)	0.554	0.43 (0.11–1.76)	0.240	1.21 (0.51–2.86)	0.661
Primary tumor						
Non-CRC						
CRC	5.865 (1.76–19.51)	0.004	1.97 (0.37–10.38)	0.427	2.29 (0.84–6.23)	0.104
Pathology						
Others						
Squamous	8.85 (1.07–73.36)	0.043	0.79 (0.15–4.06)	0.774	1.28 (0.42–3.84)	0.664
Adenocarcinoma	18.62 (1.93–180.11)	0.012	1.71 (0.24–12.06)	0.592	1.90 (0.52–6.93)	0.329

Hazard ratios and 95% confidence intervals were calculated using a stratified Cox proportional hazards model. P values of less than 0.05 are indicated in italics. OS, overall survival; LC, local control; PFS, progression-free survival; KPS, Karnofsky Performance Status; CRC, colorectal cancer; DFI, disease-free interval; GTV, gross tumor volume; PTV, planning target volume; BED10, biological effective dose; α/β , 10.

Factors	OS		LC		PFS	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Sarcoma	3.30 (0.20–54.81)	0.405	0.78 (0.08–8.16)	0.838	0.65 (0.13–3.36)	0.606
Synchronized systemic therapy						
Yes						
No	0.55 (0.18–1.69)	0.295	0.45 (0.11–1.85)	0.270	1.24 (0.52–2.94)	0.623
Systemic therapy after radiotherapy						
Yes						
No	2.09 (0.57–7.62)	0.266	0.04 (0–106.21)	0.419	0.46 (0.11–2.00)	0.300
DFI (months)						
> 17.4						
≤ 17.4	0.92 (0.30–2.78)	0.880	9.77 (1.21–78.60)	0.032	1.55 (0.65–3.69)	0.327
Lung metastasis to radiotherapy (months)						
≤ 4.3						
> 4.3	1.36 (0.43–4.23)	0.601	4.20 (0.86–20.63)	0.077	1.37 (0.58–3.25)	0.479
Number of organs metastases						
Single						
Multiple	3.15 (1.02–9.76)	0.046	0.997 (0.25–4.04)	0.997	2.93 (1.23–6.95)	0.015
Hazard ratios and 95% confidence intervals were calculated using a stratified Cox proportional hazards model. P values of less than 0.05 are indicated in italics. OS, overall survival; LC, local control; PFS, progression-free survival; KPS, Karnofsky Performance Status; CRC, colorectal cancer; DFI, disease-free interval; GTV, gross tumor volume; PTV, planning target volume; BED10, biological effective dose; α/β, 10.						

Factors	OS		LC		PFS	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Number of lung metastases						
Single						
Multiple	0.62 (0.21–1.88)	0.398	8.08 (1.01–64.68)	0.049	1.66 (0.69–4.02)	0.258
GTV (cm ³)						
≤ 9.7						
> 9.7	1.86 (0.59–5.83)	0.290	1.41 (0.36–5.52)	0.623	1.29 (0.53–3.11)	0.578
PTV (cm ³)						
≤ 56.9						
> 56.9	2.49 (0.76–8.16)	0.131	8.97 (1.09–73.77)	0.041	2.40 (0.96–6.00)	0.061
BED10 (Gy)						
> 76.8						
≤ 76.8	0.39 (0.12–1.31)	0.128	1.03 (0.25–4.33)	0.966	0.82 (0.34–2.01)	0.665
4D-CT						
Yes						
No	0.34 (0.08–1.43)	0.141	1.57 (0.28–8.69)	0.606	1.83 (0.72–4.67)	0.208
Hazard ratios and 95% confidence intervals were calculated using a stratified Cox proportional hazards model. P values of less than 0.05 are indicated in italics. OS, overall survival; LC, local control; PFS, progression-free survival; KPS, Karnofsky Performance Status; CRC, colorectal cancer; DFI, disease-free interval; GTV, gross tumor volume; PTV, planning target volume; BED10, biological effective dose; α/β, 10.						

Multivariate Cox regression analysis

Multivariate Cox regression analysis is reported in Table 5. Colorectal cancer (P = 0.010, HR = 7.32, 95% CI = 1.61–33.37) and age > 57 years (P = 0.009, HR = 6.00, 95% CI = 1.57–22.90) were significant risk factors

for OS. The number of systemic organs metastases ≥ 2 ($p = 0.010$, HR = 3.23, 95% CI = 1.32–7.89) and PTV ≤ 56.9 cm³ ($p = 0.043$, HR = 2.66, 95% CI = 1.03–6.85) were significantly associated with PFS and were significant risk factors for PFS. Multivariate Cox analysis did not identify any obvious influencing factors for LC.

Table 5
Results of multivariable Cox proportional analyses

Factors	OS		PFS	
	HR (95% CI)	P	HR (95% CI)	P
Age, years			-	-
≤ 57				
> 57	6.00 (1.57–22.90)	0.009		
Primary tumor			-	-
Non-CRC				
CRC	7.32 (1.61–33.37)	0.010		
Number of organs metastases				
Single				
Multiple	2.04 (0.55–7.63)	0.288	3.23 (1.32–7.89)	0.010
PTV (cm ³)	-	-		
≤ 56.9				
> 56.9			2.66 (1.03–6.85)	0.043
Hazard ratios and 95% confidence intervals were calculated using a stratified Cox proportional hazards model. P values of less than 0.05 are indicated in italics. OS, overall survival; PFS, progression-free survival; CRC, colorectal cancer; PTV, planning target volume				

Discussion

Tomotherapy is currently the most advanced radiotherapy device. It uses a radiotherapy system that has the same source of treatment (6 MV) as impact-guided CT (3.5 MV). It has high imaging accuracy and automatically corrects positioning errors before radiotherapy, which makes the target area conformability and dose distribution more reasonable. TOMO integrates three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, image-guided radiation therapy, dose-guided radiation therapy, adaptive radiation therapy, and other radiotherapy technologies in one, could be clinically used for a variety of tumors throughout the body, especially for frequently occurring tumors and tumors adjacent to important organs and tissues, which improves the accuracy of the target area while reducing the

occurrence of complications (11, 12). All patients in this study used TOMO to treat lung metastases, and this has a certain research value.

Studies have shown that the survival rate of certain patients with oligometastases can be improved through local treatment, such as surgery, ablation therapy, and radiation therapy (13–17). Yamamoto et al. performed stereotactic body radiotherapy (SBRT) on patients with colorectal cancer and oligometastatic lung tumors. The 3-year LC, OS, and PFS rates were 64.9%, 63.4%, and 34.9%, respectively (18). The RADIOSTEREO-CAMPTO study was a prospective multicenter phase 2 trial that observed SBRT (40–48 Gy/4 times) in the treatment of inoperable colorectal cancer with liver and/or lung oligometastases combined with intravenous irinotecan, in which pulmonary oligometastases were found in 12 patients with tumors. In that study, the 1- and 2-year survival rates without local (distal) progression and OS were 84.2% (38.4%), 67.4% (21.3%), and 97.5% and 75.5%, respectively (19). Ricco et al. reported SBRT treatment in patients with pulmonary oligometastases of different primary tumors, using a dose of 48–54 Gy divided into 3–5 fractions, and the 1-year OS and LC rates were 74.1% and 80.4%, respectively (20). Lardinois et al. retrospectively analyzed 100 patients with head and neck squamous cell carcinoma with lung metastases, and the median OS and recurrence-free survival rates were 21 and 7 months, respectively (21). This study found that the median OS, LC, and PFS rates were 24.9, 25.9, and 11.8 months, respectively, and these were similar to the results of related studies.

In most studies, the risk factors related to OS, LC, and PFS include functional status, lesion diameter, primary tumor type, number of metastases, history of local metastases, and the number of metastatic organs throughout the body. Lardinois et al. found that the survival time of patients with single lung metastasis was significantly prolonged, and the local control rate of the site of metastasis was better than those of patients with multiple lung metastases ($P < 0.001$) (21). Yamamoto et al. reported that functional status PS was an independent prognostic factor for OS (PS 1 vs. PS 0, $p = 0.02$; PS 2–3 vs. PS 0, $p = 0.04$) (22). Chai et al. discussed the therapeutic effects of SBRT on pulmonary metastatic tumors. Univariate analysis showed that age ≥ 63 years, primary colorectal cancer, BED10 < 85.2 Gy, adenocarcinomas, PTV min BED10 < 76.6 Gy, and GTV ≥ 8.8 cc were significantly correlated with local recurrence-free survival (LRFS) (23). This study found that patients who were younger than 57 years of age ($p = 0.037$, HR = 3.35, 95% CI = 1.08–10.41) and those whose metastatic organs were the lungs ($p = 0.046$, HR = 3.15, 95% CI = 1.02–9.76) had a better overall survival time, which is consistent with the findings of previous reports.

Studies have reported the impact of the primary tumor type on the survival rate of patients with pulmonary oligometastases. Takeda et al. found that the primary tumor type was an important factor that affected the survival rate of patients with lung metastases. Comparing patients with colorectal cancer and those with non-colorectal cancer revealed that the 1-year LC rates were 80% and 72%, respectively, the 2-year LC rates were 94% and 94%, respectively, and the 3-year non-local progression rates were 39% and 83%, respectively (24). Wang et al. compared the effects of SBRT treatment on early-stage non-small cell lung cancer and colorectal cancer with less severe metastatic lung cancer. The 1- and 3-year LRFS rates of patients with colorectal cancer were 80.6% and 100%, respectively, and for those

with non-small cell lung cancer, they were 68.6% and 97.2%, respectively (25). However, Duijm et al. in a study of patients with inoperable lung metastases with SBRT, found that the 2-year-, 3-year-, and 5-year OS rates were 63%, 47%, and 30%, respectively, while the 2-year-, 3-year-, and 5-year PFS rates were 36%, 25%, and 16%, respectively. Further analysis found that compared with patients with other histological types, patients whose primary tumor was colorectal cancer had a median OS rate of 39.2 months, and their OS was relatively good ($p = 0.018$, $HR = 0.64$, $95\% \text{ CI} = 0.44\text{--}0.92$) (26). In this study, the median OS of patients with colorectal cancer as the primary tumor was 10.2 months, while the median OS rate of patients with non-colorectal cancer was 29.4 months. The difference was statistically significant at $p < 0.05$, which may be because non-colorectal cancer patients included head and neck tumors and breast cancer patients with good prognosis; however, its relationship with LC and PFS was not found. This was a retrospective study, with certain limitations. Combined with the results of previous studies, the impact of the primary tumor type on the survival of patients with pulmonary oligometastases needs to be determined by a well-designed prospective study. The possible reason was that the older the patient, the more metastatic organs, the worse the physiological function, and the poor tolerance of treatment.

Sharma et al. showed that $BED10 \geq 100 \text{ Gy}$ can improve the OS and LC of patients with tumors (27). Similarly, Kang et al. found that the SBRT dose was correlated with OS (28). Considering that the patient in this study had distant metastasis and the possibility of side effects as well as potential toxic effects, the median BED10 in this study was 76.8 Gy (range, 56–96 Gy), and this was lower than that reported in related studies. However, no relationship was found between radiation dose and survival rate.

Regarding the adverse reaction report, a study by Osti et al. reported that 34.4% of patients had grade 2 fibrosis, 7.4% of patients had grade 3 fibrosis, 1.3% had rib fractures, and one toxic death occurred after treatment (29). Le et al. reported that 19% of patients had pneumothorax, 12.7% had grade 2–3 pneumonia, and three deaths related to side effects occurred after treatment (30). The toxic reactions in this study included radiation pneumonia (10 patients had grade 1 radiation pneumonitis; six patients had grade 2 radiation pneumonitis), bone marrow suppression (four patients had grade 1 bone marrow suppression, six patients had grade 2 bone marrow suppression), Grade 1 radiation dermatitis in two patients had, and seven out of 10 patients had myelosuppression and received systemic simultaneous treatment, and these may be related to the side effects of chemotherapy. There were no grade 3 or 4 toxic reactions, and no toxicity-related deaths.

Conclusions

In conclusion, the median OS, LC, and PFS of TOMO hypofractionated radiotherapy for pulmonary oligometastases tumors were 24.9, 25.9, and 11.8 months, respectively. Good survival and low toxicity could still be achieved with a medium-dose BED10. The type of primary tumor, the number of organ metastases before radiotherapy, and patients' age were significantly associated with the survival rate of patients with pulmonary oligometastases.

Abbreviations

TOMO, tomotherapy

KPS, Karnofsky performance status

OS, overall survival

LC, local control

PFS, progression-free survival

GTV, gross tumor volume

BED10, biological effective dose, $\alpha/\beta = 10$

DFI, disease-free interval

4D-CT, four-dimensional computed tomography

PTV, planning target volume

SBRT, stereotactic body radiotherapy

HR, hazard ratio

CI, confidence interval

LRFS, local recurrence-free survival

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Declarations

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Not applicable.

[Ethics approval and consent to participate]

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The retrospective study has been approved by notification by the local ethics committee. Wherever necessary informed consent from the patients has been obtained.

[Consent for publication]

Consent to publish individual data was obtained from all participants.

[Availability of data and materials]

The datasets supporting the study conclusions are included within this manuscript.

[Authors' contributions]

RC and YZ designed and wrote the manuscript for this research. FC, HX, QW and GW provide the patient plan data, clinical support and manuscript revision. RC, ML and XC involved in analysis and interpretation of data. HJ and QS participated in review for result and manuscript. All authors read and approved the final manuscript.

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There were no conflicts to declar.

Figures

Figure 1

(1a) Dose coverage on an axial CT image in a patient with nasopharyngeal carcinoma, The blue line represents the 60-Gy dose. (1b) CT scan at 4-month follow-up shows a complete response

Figure 2

(2a) Impact of Primary tumor on Overall survival. (2b) Impact of Disease-free interval on Local control rate

Figure 3

(3a) Impact of Number of organs metastases on Overall survival. (3b) Impact of Number of organs metastases on Progression-free survival