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Role of radiotherapy to the primary lesion in metastatic non-small cell lung cancer patients after first-line systemic therapy — a prospective randomized phase II study

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ABSTRACT

Introduction. Radiation therapy for oligometastatic non-small cell lung cancer (NSCLC) showed overall survival (OS) benefit in phase II clinical trials, with stereotactic body radiation therapy (SBRT) being the main modality for distant metastases. This study aimed to assess the benefit of consolidative irradiation of the primary lesion in patients with partial response or stationary disease after first-line therapy, regardless of their metastatic burden.

Material and methods. Stage IV NSCLC patients without progressive disease after initial systemic therapy were randomly assigned to arm 1 (consolidative primary radiotherapy 45Gy/15 fractions followed by standard treatment) or arm 2 (standard treatment). The primary endpoint was progression-free survival (PFS), and the secondary endpoints were OS and toxicity.

Results. Between September 2020 and January 2023, 75 patients were randomized: 37 to the radiotherapy arm and 38 to the control arm. The median follow-up was 13.50 months (4.50–35.93). Median PFS was 15.37 months in the radiotherapy group versus 10.93 months in the control group (univariate HR = 1.99; 95% CI 1.16–3.41; p = 0.012). Median OS was 18.30 months versus 13.73 months, respectively (HR = 1.84; 95% CI 0.98–3.46; p = 0.057). Except for one patient in the radiotherapy group who experienced grade 3 dysphagia, no grade 3 or higher toxicities were noted.

Conclusions. Primary consolidative radiotherapy in metastatic NSCLC after standard systemic treatment added a benefit for patients who had stationary disease or showed partial response to standard systemic treatment.

Keywords: radiotherapy, lung; metastatic, clinical trial, lung irradiation

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Introduction

Metastatic non-small cell lung cancer (NSCLC) accounts for the majority of NSCLC cases at diagnosis, and unfortunately, the prognosis is often poor [1]. Systemic therapy is the main treatment of metastatic NSCLC. Patients with targetable mutations benefit from first-line targeted therapy. However, patients lacking targetable mutations can receive immunotherapy according to their programmed death-ligand 1 (PD-L1) status. Anti-programmed death 1 (PD1)/ /PD-L1 drugs are used either as single agents or added to platinum-based chemotherapy doublet tailored to histological subtype and organ function [2, 3].

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For decades, radiotherapy's role in metastatic tumors was confined to palliative care, utilizing low doses. Recently, evidence supporting the survival benefit of higher-intensity radiotherapy in various metastatic tumors has emerged. This approach involves irradiating either the primary tumor alone or both primary and metastatic sites [4–10].

Aggressive local therapy targeting the primary lesion and all distant metastatic sites in oligometastatic NSCLC has been investigated in phase II clinical trials, demonstrating a survival benefit [11–15]. The term oligometastatic NSCLC, which relates only to the number of distant metastases, may be limited, as varying overall survival (OS) is observed in these patients. Critical prognostic factors also include the location and volume of distant metastases, performance status (PS), and response to initial systemic therapy. Additionally, phase II trials show variations in defining oligometastasis, including differences in cut-off numbers, inclusion of regional nodes, the timing of counting lesions, and baseline or post-systemic treatment [15, 16].

Through examining disease failure patterns in metastatic NSCLC and evaluating retrospective data, it has been observed that the majority of patients progress only at the primary site. These patients constitute nearly half of all cases with disease progression, followed by those with progression at both primary and initial metastatic sites [4]. Regional nodal progression was mostly limited to patients with a history of nodal disease. The role of radical irradiation of the primary lesion alone in metastatic NSCLC remains uncertain, particularly in terms of its potential benefit for patients with varying metastatic burdens and limited tolerance of toxicity. This uncertainty persists as the approach has not been investigated in randomized controlled clinical trials [4].

To bridge this knowledge gap, we conducted a randomized phase II study to examine if patients with metastatic NSCLC who did not experience disease progression following first-line systemic therapy could derive further benefits from consolidative radiation of the primary tumor after systemic therapy.

Material and methods

This prospective phase II clinical trial was conducted in Menoufia University hospitals from September 2020 till January 2023. Patients were eligible if they had pathologically confirmed stage 4 NSCLC, were aged 18 years old or more, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and had completed at least four cycles of platinum-based chemotherapy doublet or three months of targeted therapy, with stable disease or partial response according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Conversely, patients with poor ECOG PS 3–4, prior radiotherapy to the chest, disease progression on first-line systemic therapy, and persistent malignant pleural effusion after initial systemic therapy were excluded. For further assessment of geriatric patients, the geriatric 8 assessment tool (G8) was applied to patients over 65 years old. Patients with scores of 14 or less underwent full geriatric assessment, and frail patients were excluded. Ethics committee approval was obtained from the Menoufia Faculty of Medicine. All participants signed informed consent. The trial was registered at clinicalTrials.gov with ID (NCT04776083).

After first-line systemic therapy, randomization with a simple computer application was done according to medical record numbers. Patients were randomly assigned to arm 1 (consolidative radiotherapy to the primary lung lesion and positive nodes 45Gy/15 fractions followed by standard treatment; maintenance therapy or observation; a test arm) or arm 2 (standard treatment; a control arm). Conventional 3-dimensional conformal radiation therapy (3D CRT) was used for primary irradiation. A dose variation in the planning target volume (PTV) between 95% and 107% was allowed (Fig. 1), and treatment was delivered using the Elekta Synergy linear accelerator (LINAC). The use of intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) was not allowed as per the local policy of the institution: IMRT and VMAT were approved only for radical cases like head and neck cancer or rectal cancer. Palliative radiotherapy for brain or bone metastases was allowed in both arms.

The primary endpoint was progression-free survival (PFS), and the secondary endpoints were OS and toxicity. Manifestations indicating radiotherapy-related toxicity such as cough, pneumonitis, dysphagia, dyspnea, chest wall pain, and dermatitis were assessed at baseline, 3 months, and 9 months from randomization using the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE V.5); they were compared to the control arm.

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY:

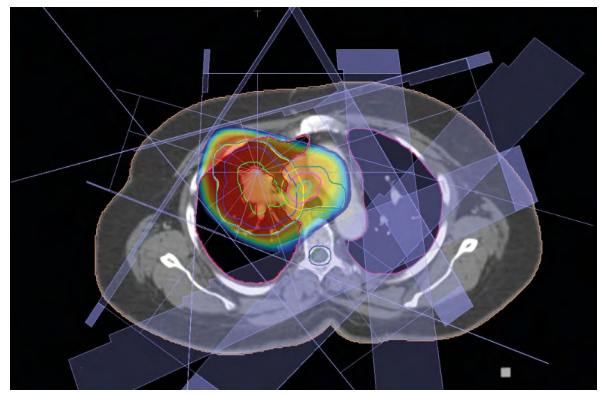

Figure 1. Sample plan for one of the patients in the study

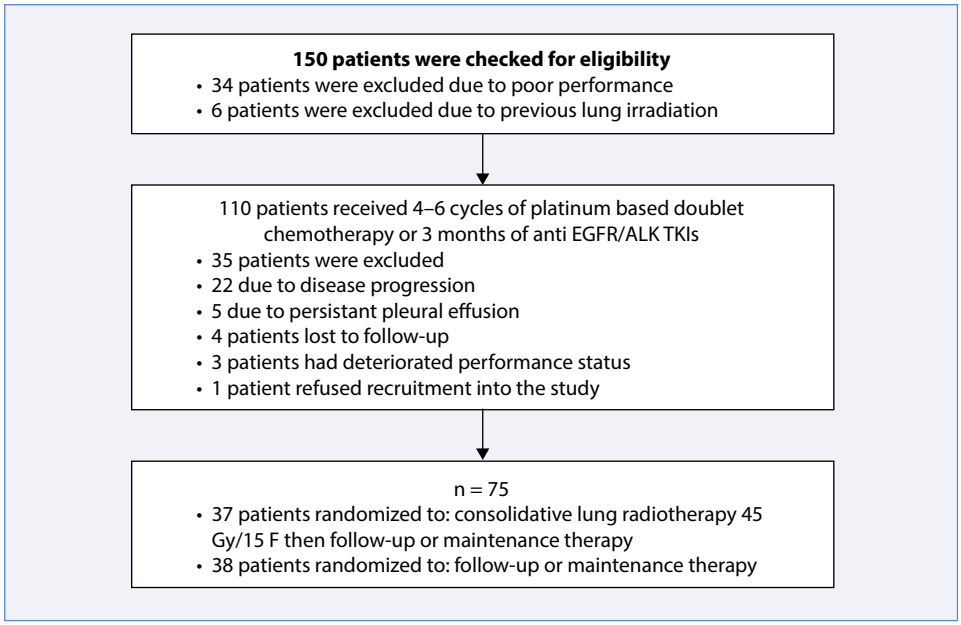

Figure 2. Patient flowchart (CONSORT); TKI — tyrosine kinase inhibitor

IBM Corp). To compare the characteristics of patients in both groups, Pearson's chi-square test, independent sample t-test, Monte Carlo correction test, and Fisher's exact test were utilized.

Progression-free survival was defined as the time from randomization to the date of progression or the date of death, whichever occurred first. Overall survival was defined as the time from the date of randomization to the date of death as a result of any cause. The estimation of survival was performed by the Kaplan-Meier method and was compared by the log-rank test. Univariable analysis for PFS and OS was performed using the Cox proportional hazards regression model. Differences between groups were assessed using the log-rank test. A two-sided p-value < 0.05 was considered statistically significant.

Results

Between September 2020 and January 2023, 75 patients were enrolled in the study: 37 patients in arm 1 and 38 patients in arm 2 (Fig. 2). More than half of the patients in arm 1 were staged by positron emission tomography–computed tomography (PET-CT; 54.1% and 47% in the control arm). Magnetic resonance imaging (MRI) brain for central nervous system (CNS) assessment was done for all patients. A comprehensive comparison between the two arms regarding patient, disease, and treatment characteristics is included in Table 1.

A statistically significant difference was observed in the T category of T.N.M classification (8^{th} edition) with a more locally advanced tumor in arm 1 (p-value = 0.011). Otherwise, there were no statistically significant differences.

At a median follow-up period of 13.50 months (range 4.50–35.93), a statistically significant improvement in PFS was observed, with median PFS of 15.37 months for the consolidative radiotherapy arm *vs.* 10.93 months in the control arm and a univariate hazard ratio of 1.99 [95% confidence interval (CI) 1.16–3.41; p = 0.012]. However, in terms of OS, only a non-statistically significant difference was found, with median OS of 18.30 months in the radiotherapy group *versus* 13.73 months in the control group [hazard ratio (HR) = 1.84; 95% CI 0.98–3.46; p = 0.057; Fig. 3].

Toxicity grades 1 and 2 did not significantly differ between the two arms, except for chest wall pain. Notably, 21% of patients in the radiotherapy arm experienced a deterioration by one grade, whereas no such cases were observed in the control arm (p = 0.005). Only one patient developed grade 3 dysphagia in the radiotherapy group vs. none in the control arm. No treatment-related deaths were observed. On the other hand, fourteen patients (37.8%) in the intervention arm *vs.* five (13.2%) in the control arm had an improvement in cough by one grade at 3 months of follow-up, which was statistically significant (p = 0.033). No other significant differences were found between the studied arms in pneumonitis, dysphagia, dyspnea, and radiation dermatitis at 3 months of follow-up.

At 9 months of follow-up, the radiotherapy arm had a significant improvement in dysphagia, pain, and dyspnea (p = 0.031, 0.004, and 0.013, respectively) compared to the control arm. Four patients (16.7%) in the intervention arm had an improvement in dysphagia

Table 1. Patients, disease, and treatment characteristics in both arms

	Arm		p-value
	Intervention (n = 37)	Control (n = 38)	
Sex			
Male	25 (67.6%)	23 (60.5%)	0.525
Female	12 (32.4%)	15 (39.5%)	
Age [years]			
Mean ± SD	62.1 ± 9.69	58.9 ± 12.4	0.217
Median (Min.–Max.)	63 (34–80)	64 (28–75)	
ECOG PS			
0	7 (18.9%)	13 (34.2%)	0.172
1	24 (64.9%)	23 (60.5%)	
2	6 (16.2%)	2 (5.3%)	
G8 score	(n = 28)	(n = 24)	
Mean ± SD	15.1 ± 0.91	15.5 ± 0.63	0.112
Median (Min.–Max.)	15 (12.5–16)	16 (14.5–16)	
AACI			
Mean ± SD	8.22 ± 1.20	7.79 ± 1.17	0.123
Median (Min.–Max.)	8.0 (6.0–11.0)	8.0 (6.0–10.0)	
Pathology			
Adenocarcinoma	30 (81.1%)	30 (78.9%)	0.797
Squamous	4 (10.8%)	4 (10.5%)	
Sarcomatoid	1 (2.7%)	0 (0.0%)	
NSCLC NOS	2 (5.4%)	4 (10.5%)	
Grade			
Grade II	19 (51.4%)	27 (71.1%)	0.080
Grade III	18 (48.6%)	11 (28.9%)	
***EGFR* status**			
Wild	27 (73.0%)	29 (76.3%)	0.739
Mutant	10 (27.0%)	9 (23.7%)	
***ALK* fusion status**			
Negative	29 (78.4%)	29 (76.3%)	1.000
Positive	1 (2.7%)	2 (5.3%)	
Unknown	7 (18.9%)	7 (18.4%)	
Baseline imaging			
PET-CT	20 (54.1%)	18 (47.4%)	0.563
Conventional CT	17 (45.9%)	20 (52.6%)	
T			
T1	0 (0.0%)	9 (23.7%)	0.011
T2	12 (32.4%)	7 (18.4%)	
T3	9 (24.3%)	8 (21.1%)	
T4	16 (43.2%)	14 (36.8%)	
N			
N0	6 (16.2%)	10 (26.3%)	0.234
N1	3 (8.1%)	6 (15.8%)	
N2	20 (54.1%)	19 (50.0%)	
N3	8 (21.6%)	3 (7.9%)	

→

Table 1 cont. Patients, disease, and treatment characteristics in both arms

	Arm		p-value
	Intervention (n = 37)	Control (n = 38)	
M			
M1a	10 (27.0%)	8 (21.1%)	0.411
M1b	6 (16.2%)	11 (28.9%)	
M1c	21 (56.8%)	19 (50.0%)	
CNS involvement	8 (21.6%)	8 (21.1%)	0.952
Number of brain lesions			
1	4 (50.0%)	3 (37.5%)	0.054
2	3 (37.5%)	0 (0.0%)	
3	0 (0.0%)	4 (50.0%)	
4	1 (12.5%)	1 (12.5%)	
Total number of metastases			
1	8 (21.6%)	17 (44.7%)	0.179
2	4 (10.8%)	2 (5.3%)	
3	3 (8.1%)	3 (7.9%)	
> 3	22 (59.5%)	16 (42.1%)	
First line			
Chemotherapy	26 (70.3%)	27 (71.1%)	1.000
Gefitinib	5 (13.5%)	5 (13.2%)	
Chemotherapy followed by gefitinib	5 (13.5%)	4 (10.5%)	
Chemotherapy followed by crizotinib	1 (2.7%)	1 (2.6%)	
Crizotinib	0 (0.0%)	1 (2.6%)	
Chemotherapy regimen	(n = 33)	(n = 32)	
Gemcitabine carboplatin	29 (87.9%)	28 (87.5%)	1.000
Gemcitabine cisplatin	1 (3.0%)	2 (6.3%)	
Paclitaxel carboplatin	3 (9.1%)	2 (6.3%)	
Number of cycles	(n = 32)	(n = 32)	
4	2 (6.3%)	0 (0.0%)	0.492
6	30 (93.8%)	32 (100.0%)	
Maintenance therapy	(n = 37)	(n = 38)	
No	22 (59.5%)	22 (57.9%)	0.891
Yes	15 (40.5%)	16 (42.1%)	
Maintenance regimen	(n = 15)	(n = 15)	
Gefitinib	10 (66.7%)	9 (56.3%)	1.000
Crizotinib	1 (6.7%)	2 (12.5%)	
Gemcitabine	4 (26.7%)	5 (31.3%)	
Response at randomization			
PR	18 (48.6%)	17 (44.7%)	0.734
SD	19 (51.4%)	21 (55.3%)	
Palliative lung radiotherapy	–	6 (15.8%)	–
Other sites of palliative radiotherapy			
Brain	7 (46.7%)	6 (35.3%)	0.513
Bone	8 (53.3%)	11 (64.7%)	
Second line	10/22 (45.4%)	16/35 (45.7%)	0.799
Chemotherapy	10 (100.0%)	14 (87.5%)	0.536
Alecitinib	0 (0.0%)	2 (12.5%)	

± SD — ± standard deviation; AACI — Age-adjusted Charlson comorbidity index; ALK — anaplastic lymphoma kinase; CNS — central nervous system; CT — computed tomography; ECOG PS — Eastern Cooperative Oncology Group performance status; EGFR — epidermal growth factor receptor; G — geriatric; NOS — not otherwise specified; NSCLC — non-small cell lung cancer; PET — positron emission tomography; PR — partial response; SD — stationary disease

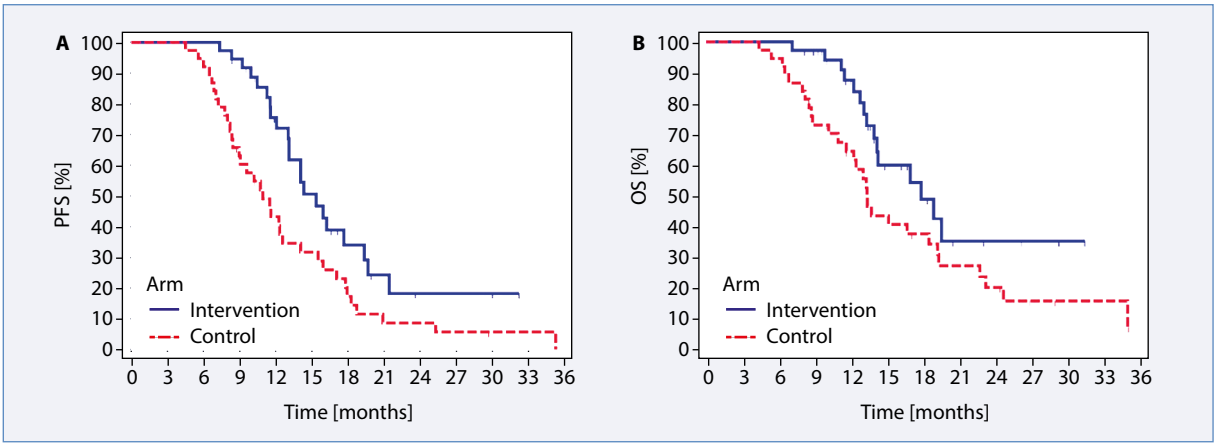

Figure 3. Progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) in patients given local consolidative radiotherapy *vs.* control in metastatic non-small cell lung cancer (NSCLC)

Table 2. Pattern of disease progression in both arms

	Arm		p-value
	Intervention (n = 37)	Control (n = 38)	
Site progression	**(n = 22)**	**(n = 35)**	
Locoregional	4 (18.18%)	19 (54.3%)	0.015*
Distant	10 (45.45%)	12 (34.3%)	
Local and distant	8 (36.36%)	4 (11.4%)	

*Statistically significant at $p \leq 0.05$

by one grade, while in the control arm, three patients (20%) suffered a deterioration by grade. Eight patients (33.3%) in the intervention arm had an improvement in chest wall pain by one grade; however, five patients (33.3%) in the control arm suffered a deterioration by one grade. Four patients (16.7%) in the intervention arm had an improvement in one grade of dyspnea, while in the control arm, seven patients (46.7%) suffered a deterioration by one grade.

In terms of disease progression patterns, a statistically significant difference was observed between the two arms. The consolidative radiotherapy arm exhibited a lower incidence of locoregional disease progression ($p = 0.015$), as detailed in Table 2.

Discussion

This study offers a unique perspective as the only prospective randomized study evaluating the benefits of consolidative irradiation for the primary lesion without extending radical irradiation to distant lesions in metastatic NSCLC patients. This is achievable after gaining a response from first-line systemic therapy, regardless of the metastatic burden.

Three prospective phase II randomized trials in metastatic NSCLC were carried out by Gomez et al. [17], Iyengar et al. [18], and Palma et al. [19] as part of the SABR COMET trial. Furthermore, multiple phase III randomized controlled trials are currently ongoing [20, 21]. All of these studies involved irradiating the primary tumor in addition to radical irradiation of all distant lesions. The number of distant metastases treated with SBRT was limited to three; therefore, it is unknown if radical irradiation of more lesions will be safe or not. The ongoing SABR-COMET-10 trial (NCT03721341) tries to expand this number to 10 lesions [22].

In Authors of this article study, radiotherapy managed to reduce the local progression rate from 54.3% to 18.18%. This was reflected in PFS with an absolute benefit of about 4.44 months (15.37 months in the radiotherapy arm and 10.93 months in the control arm). Similarly, consolidative radiotherapy resulted in a 6-month improvement in PFS in a study by Iyengar et al. [18] and a 10-month improvement in PFS in a study by Gomez et al. [18]. Although these numbers are higher than those observed in our study, other studies had a different trial design. Both trials included patients with exclusively oligometastatic disease, and irradiation was offered to the primary tumor as well as the metastatic sites [17, 19].

Again, PFS was doubled with radiotherapy delivered to all tumor sites in the SABR-COMET trial. However, the study included a heterogeneous group of patients, mainly with breast and colon cancers. Lung cancer represented only 18% of the included patients [19].

In terms of overall survival, the addition of consolidation radiotherapy resulted in 5 months of improvement, but that was not statistically significant (p-value = 0.054). However, this trial was not designed to detect OS benefits. Moreover, the OS data are still immature and require longer follow-up. Conversely, two prospective trials found OS benefits in long-term follow-up. At a median follow-up of 38.8 months, radiotherapy was found to prolong median overall survival from 7 months to 41.2 months (p-value = 0.017) [17]. Even at a longer follow-up of eight years, radiotherapy was found to increase overall survival from 13.6% to 27.2% after irradiation of all tumor sites. However, it is worth reporting that this longer follow-up duration was feasible as the study included patients with prostate and breast cancer who already have better prognoses than lung cancer patients [23].

Cough, dyspnea, and pain were significantly improved in the radiotherapy arm (p-value = 0.033). This is an observation that is explained by the palliative role of radiotherapy. About 20% of NSCLC patients are expected to receive palliative radiotherapy during their treatment course. Additionally, higher doses of radiation offer better symptom control. An additional advantage of using higher radiotherapy doses is the reduced need for re-irradiation [24]. Effective symptom control and minimizing treatment toxicity are essential for enhancing the quality of life in NSCLC patients.

Consolidative radiotherapy did not result in added toxicity in this study. Chest wall pain was the only low-grade toxicity that increased in the radiotherapy arm. In terms of high-grade toxicity, no treatment-related deaths were observed, and only one patient developed grade 3 dysphasia due to radiotherapy-induced mucositis. In contrast to our results, Gomez et al. [17] reported that 20% of patients in the local consolidative therapy group experienced grade 3 adverse events. In addition, one patient may have experienced SBRT-related pneumothorax due to a rib fracture. Furthermore, in the SABR-COMET trial, the rate of treatment-related deaths was higher in the radiotherapy arm (4.5%). Similarly, toxicities higher than grade 2 were significantly increased by about 20% (p-value = 0.03) [17, 19]. The acceptable toxicity profile in our study, compared to other studies, is probably related to the optimal choice of dose and fractionation schedule balancing tolerability and efficacy.

However, this study's findings are constrained by the small sample size. To confirm these results, a phase III study is necessary. The exclusive use of 3D CRT radiotherapy techniques may be dose-limiting. Improved outcomes could be achieved with modern techniques such as IMRT and VMAT. Additionally, the dose selected in this study could be increased with these advanced techniques, allowing for avoiding organs at risk more easily.

Moreover, it is impossible to identify which subgroups defined by various clinical or molecular criteria would benefit more from this strategy. Subsequent studies are required to examine this query while taking into consideration the most recent systemic treatment for metastatic NSCLC patients, which may involve immunotherapy or third-generation TKIs based on the presence of oncogenic drivers.

Conclusions

Finally, this study concluded that consolidative radiotherapy to the primary lesion in metastatic NSCLC after response to first-line systemic therapy was well tolerated and significantly improved PFS without impacting toxicity.

Article Information and Declarations

Data availability statement

Raw data are available upon reasonable request.

Ethics statement

Ethics committee approval was obtained from the Menoufia Faculty of Medicine. all participants signed an informed consent. The trial was registered at clinicalTrials.gov with ID (NCT04776083).

Author contributions

All authors contributed to the recruitment of patients, their management, data collection and writing of the manuscript.

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None.

Conflict of interest

The authors declare that have no conflict of interests.

Supplementary material

None.

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