

Local Consolidation Therapy versus Observation for Oligometastatic Non Small Cell Lung Cancer Patients: Phase II Randomized Trial

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Abstract

Background and Objective: Based on retrospective trials, most progression sites after first line systemic therapy for metastatic non small cell lung cancer (NSCLC) were the primary disease sites rather than new sites. Therefore we conducted phase II randomized study to determine whether oligometastatic NSCLC without disease progression after first line chemotherapy, have prolonged progression free survival when treated with local consolidation therapy of residual disease followed by surveillance compared with no local consolidation therapy (observation). **Patients and Methods:** Forty eight eligible patients were randomized to either immediate or no local consolidation radiotherapy. 26 patients of immediate local consolidation radiotherapy received 3 D-conformal radiation therapy to primary tumor site and metastatic sites of disease. 22 patients were followed up by observation. **Results:** Patients in local consolidation arm had significantly better progression free survival (PFS) compared with patients in observation group. Median PFS was 9.5 months (95% CI 7.8 - 11.08) in local consolidation arm and 4.5 months (95%CI 3.9 - 5.7) in observation arm. Patients in local consolidation arm had longer median time to appearance of new metastatic sites (10 months CI 9.3 - 12.6) than those patients in observation arm (4.5 months CI 4.2 - 6.9). Median overall survival (OS) of patients in local consolidation arm was 12 months (95% CI 12.1 - 18.01) and in observation arm 10 months (95% CI 8.7 - 13.8). One year OS rate was 42.3% in local consolidation arm and 31.8% in observation arm; 2 year OS rate was 23.1% in local consolidation arm and only 4.5% in observation arm. **Conclusion:** Local consolidation radiotherapy is simple, safe, efficient, and not expensive treatment for oligometastatic non small cell

lung cancer after upfront chemotherapy. Local consolidation radiotherapy achieved significantly prolonged progression free survival and delayed appearance of new metastatic sites. Phase III studies are recommended to test benefit of local consolidation radiotherapy to gain prolonged progression free survival and overall survival. Also, define optimal patients' subgroups that are more likely to benefit of local consolidation radiotherapy.

Keywords

Lung Cancer, Oligometastatic, Conformal Thoracic Radiotherapy

1. Introduction

Lung cancer is the leading cause of cancer related deaths and represents the second most common cancer in both men and women [1]. Non-small cell lung cancer (NSCLC) accounting for more than 80% of primary lung cancers [2].

Nearly half of all patients with NSCLC present with metastatic disease. Disseminated NSCLC has classically been considered incurable and given the poor prognosis. The median survival is 8 - 10 months with palliative chemotherapy, consisting of a cisplatin or carboplatin doublet plus a third-generation agent [3].

Despite, the breakthrough in the management of advanced non small cell lung cancer with receptor tyrosine kinase inhibitors (TKI) and immunotherapy, efficacy of these advances remains limited to achieve long term progression free survival of relatively small group of metastatic non small cell lung cancer [4] [5] [6].

Based on retrospective trials, the most progression sites after first line systemic therapy for metastatic non small cell lung cancer (NSCLC) were the primary disease sites rather than new sites [7].

Hellman and Weichselbaum in 1995 described the term oligometastatic disease, and they hypothesized midst clinical stage between regional and extensive metastatic stage. Oligometastatic disease is group of patients with few numbers of metastatic sites; those patients may benefit from radical treatment and gain long term survival [8].

In addition, some preclinical and translational analyses suggested that stage IV disease with oligometastatic disease reflects a more indolent phenotype that could benefit from local ablative therapy (e.g. surgery or radiotherapy) for consolidation [9] [10]. Furthermore, these growing evidences have been recognized in National Comprehensive Cancer Network (NCCN) and European Society For Medical Oncology (ESMO) guidelines, which Consider radical local treatment for elected patients with oligometastatic disease [11] [12].

Oligometastases definition differs between studies despite of those studies stated that patients with oligometastases can be treated radically with local treatment, such as surgery or radiotherapy [13] [14] [15].

The exact definition of oligometastatic NSCLC remains to be agreed upon.

Also, It is not completely understood whether differences in tumor biology, treatment approaches, or both can adequately explain the different course of the disease, or whether local treatment at all sites of disease should be attempted [16] [17] [18].

Therefore we conducted phase II study to determine whether oligometastatic NSCLC without disease progression after first line chemotherapy, have prolonged progression free survival when treated with local consolidation therapy of residual disease followed by surveillance compared with no local consolidation therapy (observation). Also, investigate whether it would be possible to obtain a significant 1 and 2 year survival in these patients when treated radically.

2. Patient & Methods

After approving by Institutional Review Board of Mansoura faculty of Medicine (IRB-MFM). This is prospective randomized phase II trial was conducted in Clinical Oncology & nuclear Medicine department, Mansoura University Hospital between the period January 2015 to January 2018.

2.1. Study Objectives

The primary objective of this study was to determine whether oligometastatic NSCLC without disease progression after first line chemotherapy, have prolonged progression free survival when treated with local consolidation therapy of residual disease followed by surveillance compared with no local consolidation therapy (observation). Also, assessments of predictors of Progression free survival.

The secondary objectives of this study were to determine the overall survival, safety and tolerability of local consolidation therapy, time to appearance of new metastasis.

2.2. Inclusion Criteria

Patients included in this study, had the following criteria: pathologically confirmed NSCLC, ≥ 18 years of age, stage IV disease according to the 7th edition of the American Joint Committee on Cancer staging system, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , ≤ 5 metastases (not including the primary tumor) and have no evidence of disease progression after standard first-line therapy 4 - 6 cycles of platinum-doublet chemotherapy.

2.3. Exclusion Criteria

Patients were excluded from this study, if the patient had congestive heart failure or history of uncontrolled angina and arrhythmias, and malignant pleural effusion could not controlled by aspiration. Patients who had complete response to first line chemotherapy were also not eligible for randomization.

2.4. Treatment Plan

Forty eight eligible patients who received 4 - 6 cycles of induction chemotherapy,

without evidence of RECIST progression. They were randomized to either immediate or no local consolidation radiotherapy. All patients would be followed until progression of disease is documented or the end of the study (January 2018), whichever comes first. Patients with metastases involving the brain or spinal cord, or metastatic lesions causing symptoms requiring palliation may be treated radiotherapy prior to the completion of induction chemotherapy (randomization). Magnetic resonance imaging (MRI) scan of the brain with contrast, and CT scan of the chest/abdomen/pelvis with contrast. Other studies, such as a bone scan, and aspiration of pleural fluid done if clinically indicated. Those imaging were done after first-line therapy to assess the number of metastatic sites.

2.5. Induction Chemotherapy

Induction chemotherapy consists of 4 - 6 cycles of platinum doublet therapy, either cisplatin or carboplatin in combination with gemcitabine. Cisplatin and gemcitabine protocol consisted of cisplatin at dose of 70 mg/m² on day 1 and gemcitabine at dose of 1250 mg/m² on day 1 and 8. Carboplatin and gemcitabine protocol consisted of Carboplatin AUC 5 Day 1 and Gemcitabine 1200 mg/m² Days 1 & 8. Each cycle was repeated every 3 weeks. Complete blood cell counts, serum creatinine and complete liver functions were required before each cycle. Anti-emetic and supportive cares were used for each patient as required.

2.6. Immediate Local Consolidation Therapy (LCT) Arm

Twenty six patients who undergo LCT will receive radiation to primary tumor site and metastatic sites of disease by 3 D-conformal radiation therapy. After the completion of LCT the patient will be followed with surveillance until progression.

2.7. 3D-Conformal Radiotherapy

Twenty six patients were planned via 3D-conformal radiotherapy. Computed tomography (CT) for the planning was performed in inspiration while the patient was lying in a supine position with arms elevated above the head. Patients were asked to hold the breath as maximal as possible during treatment. The planning CT scan of the whole thorax was done with a slice thickness of 10 mm. the breast-board was utilized for ideal position of the patient. The CT images were transferred to the 3D planning system. Organs at risk (lung, spinal cord, esophagus, heart and liver), gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV) were delineated. The GTV was defined as the gross mass demonstrated by planning CT images. GTV contoured the primary tumor plus involved pathological lymph nodes (≥ 10 mm). The CTV was defined by adding 10 mm around the primary tumor. The PTV included the CTV with margins of 5 to 10 mm. Dose volume histograms (DVHs) were used to optimize the therapeutic plan.

We followed the recommendations of Graham *et al.* [19] for the dose-volume constraints definition. The maximum 20 Gy volume (V20) was tolerated to be

50% for ipsilateral (IL), 30% for contralateral (CL) and 40% for both lungs. The mean lung dose for the ipsilateral lung had not to be more than 25 Gy. The maximum dose to the spinal cord was 50 Gy. The maximum of 10 cm of the esophagus was permitted to receive 60 Gy.

The irradiation was delivered by multiple field arrangements using photons with energy of 6 - 15 MV. Usually, three to five coplanar ports were used. The treatment was performed in conventional fractionation, 5 days a week, with a dose of 2 Gy per fraction 5 days per week to total dose 60 Gy.

2.8. Observation (No LCT) Arm

Four to six cycles of platinum-based chemotherapy are the standard of care for initial treatment of metastatic non small cell lung cancer followed by observation. Twenty two patients were followed up by observation. Observation arm was defined as close surveillance, with follow-up without any cytotoxic treatment until progression.

2.9. Radiotherapy for Oligometastatic Sites

Radiation to metastatic sites was delivered with 3 D conformal therapy. Radiation simulation was dependent on the site being treated. Definitive radiotherapy to the metastatic lesion with a biologically effective dose for $\alpha/\beta = 10$ Gy (BED10) of ≥ 60 Gy. Dose of radiation 30 Gy/10 fraction over 2 weeks.

2.10. Follow-Up & Toxicity Evaluation

Treatment toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4. During conformal radiotherapy treatment, weekly assessments of toxicity were done. Acute toxicity was defined as adverse events that occurred within 90 days from the beginning of radiotherapy and late toxicity occurred more than 90 days after starting of radiotherapy. After completion of treatment, the patients underwent contrast-enhanced CT scanning of the chest and abdomen and MRI of the brain every 3 months for 2 years, and every 6 months thereafter. Bone scan was performed every 6 months for 2 years, and every 12 months thereafter.

2.11. Statistical Analysis

Statistical analysis was conducted using SPSS program version 20. Descriptive statistics were given to summarize the patient characteristics by the treatment arms [immediate LCT and observation (No LCT)]. Chi-square test or Fisher's exact test used to compare patient characteristics between the two arms. Time to progression-free survival (PFS) and overall survival (OS) were determined using the Kaplan-Meier method from first day of randomization till disease progression (PFS) or death or last follow up (OS) to provide the median value and 95% CI. Survival curves were calculated from life tables. Log-rank test was used to compare survival distribution between the two arms. Cox regression model was

applied to correlate PFS and OS with potential covariates in both the univariate and multivariate analyses. All applied statistical tests were two-sided, and a p-value less than 0.05 were considered statistically significant.

3. Results

Patients' characteristics of 48 patients who received 4 - 6 cycles of induction chemotherapy without evidence of RECIST progression were listed in **Table 1**. Median age of patients was 57 years (range 29 - 75). There were 33 male and 15 female, 60% of patients had ECOG performance status 0 - 1. Eligible 48 patients were randomized to either immediate local consolidation therapy arm (included 26 patients) or observation arm (included 22 patients) between the periods January 2015 to January 2018 with median follow up 18 months (range 6 - 30 month).

The site of metastasis counted at randomization for 48 patients, the bone was the most frequent site of metastasis (21 patients), followed by metastatic lung lesion (18 patients), Brain lesion (11 patients), and suprarenal lesion (3 patients). Three patients had single metastasis, Two patients had single brain metastasis where underwent surgical resection followed by whole brain irradiation 30 Gy over two weeks, five days per week. The third patients had single metastatic pulmonary nodules.

Patients and tumor characteristics of both arms were listed in **Table 2**. The two groups were balanced as regard age, sex, performance status, pathological type tumor stage, Node stage, response to treatment, number of metastasis, ALK/EGFR status, and sites of metastasis.

3.1. Progression Free Survival (PFS)

Patients in local consolidation arm had significantly better progression free survival compared with patients in observation group ($p \leq 0.001$) **Figure 1**. Median PFS was 9.5 months (95% CI 7.8 - 11.08) in local consolidation arm and 4.5 months (95%CI 3.9 - 5.7) in observation arm. One year PFS rate was 76.9% in local consolidation arm and 0% in observation arm (all the patients in observation arm were progressed during first year).

Cox regression analysis of factors potentially associated with PFS was done. The following parameters were analyzed: age, sex, performance status, T stage, N stage, EGFR/ALK mutation, CNS metastasis, and site of metastasis. In univariate analysis, site of metastasis (single site versus multiple sites) was the only significant variable ($p = 0.01$) (HR 2.93) (95% CI 1.29 - 665). However in multivariate analysis, age ($p = 0.02$, HR 0.23, 95% CI 0.06 - 0.81) and CNS metastasis ($p \leq 0.001$, HR 40.9, 95% CI 6.1 - 276.4) were independent predictors for PFS (**Table 3**).

Patients in local consolidation arm had longer median time to appearance of new metastatic sites (10 months CI 9.3 - 12.6) than those patients in observation arm (4.5 months CI 4.2 - 6.9) (**Figure 2**).

Table 1. Patient characteristics.

characteristics	Number (48 patients)	%
Age		
(Mean \pm SD)	56.8 \pm 10.8	
Median (range)	57 (29 - 75)	
Sex		
Male	33	68.8%
Female	15	31.2%
ECOG performance status		
0	1	2.1%
1	28	58.3%
2	19	39.6%
Pathology		
squamous cell carcinoma	18	37.5%
adenocarcinoma	18	37.5%
Others	12	25%
T Stage		
1	4	8.3%
2	16	33.3%
3	20	41.7%
4	8	16.7%
N Stage		
1	9	18.8%
2	19	39.6%
3	14	29.2%
4	6	12.5%
Response to chemotherapy		
Partial	20	41.7%
Stationary	28	58.3%
Number of metastasis		
1	3	6.3%
2	11	22.9%
3	19	39.6%
4	10	20.8%
5	5	10.4%
EGFR		
Negative	15	31.3%
Positive	5	10.4%
Not applicable	28	58.3%
ALK		
Negative	19	39.6%
Positive	1	2.1%
Not applicable	28	58.3%
CNS metastasis		
Yes	11	22.9%
No	37	77.1%
Site of metastasis		
Single organ	19	39.6%
Multiple organ	29	60.4%

Table 2. Patient characteristics of local consolidation RT and observation groups.

Characteristics	Local consolidation RT (n=26)	Observation (n = 22)	P value
Age (years)			
<60	16 (61.5%)	12 (54.5%)	0.77
≥60	10 (38.5%)	10 (45.5%)	
Sex			
Male	16 (61.5%)	17 (77.3%)	0.35
Female	10 (38.5%)	5 (22.7%)	
ECOG performance status			
0 - 1	17 (65.4%)	12 (54.5%)	0.56
2	9 (34.6%)	10 (45.5%)	
Pathology			
Squamous cell carcinoma	10 (38.4%)	8 (36.4%)	0.46
Adenocarcinoma	9 (34.6%)	9 (40.9%)	
others	7 (27%)	5 (22.7%)	
T stage			
T1/T2	13 (50%)	7 (31.8%)	0.25
T3/T4	13 (50%)	15 (68.2%)	
N stage			
N0/N1	14 (53.8%)	14 (63.6%)	0.57
N2/N3	12 (46.2%)	8 (36.4%)	
Response to Treatment			
Partial	13 (50%)	7 (31.8%)	0.25
Stationary	13 (50%)	15 (68.2%)	
Number of metastasis			
1 - 3	21 (80.8%)	12 (54.5%)	0.07
4 - 5	5 (19.2%)	10 (45.5%)	
EGFR			
Negative	8 (30.8%)	7 (31.8%)	0.96
Positive	3 (11.5%)	2 (9.1%)	
Not applicable	15 (57.7%)	13 (59.1%)	
ALK			
Negative	11 (42.3%)	8 (36.4%)	0.52
Positive	0 (0%)	1 (4.5%)	
Not applicable	15 (57.7%)	13 (59.1%)	
CNS metastasis			
Yes	5 (19.2%)	6 (27.3%)	0.73
No	21 (80.8%)	16 (72.7%)	
Site of metastasis			
Single organ	14 (53.8%)	6 (27.3%)	0.06
Multiple organ	12 (46.2%)	16 (72.7%)	

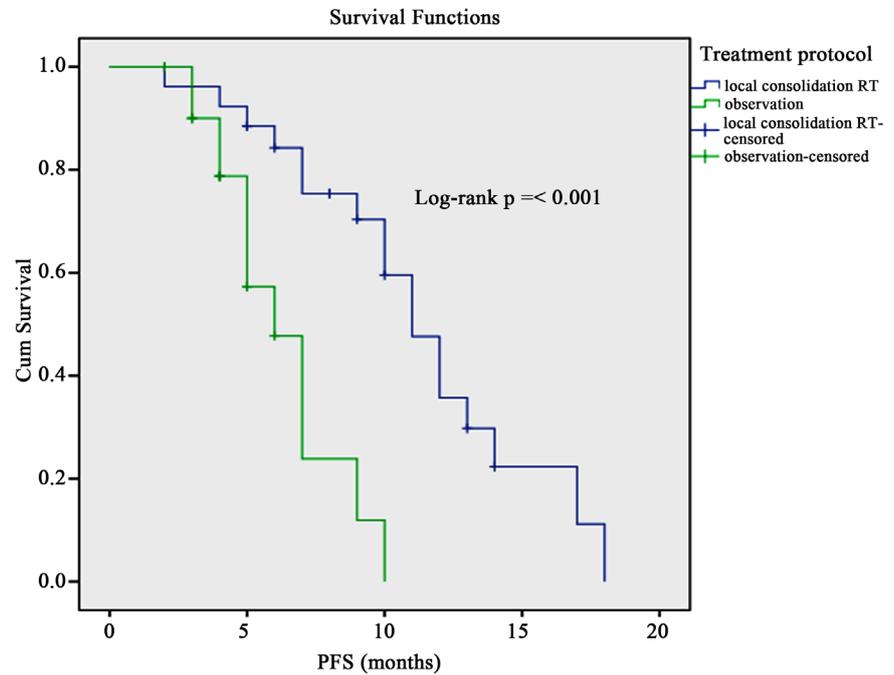


Figure 1. Kaplan-Meier curve for progression free survival (PFS).

Table 3. Cox regression analysis of clinical factors affected PFS.

Characteristics	Univariate analysis		Multivariate analysis	
	Univariable HR (95% CI)	P value	Univariable HR (95% CI)	P value
Age (years) <60 versus \geq 60	1.24 (0.58 - 2.6)	0.58	0.23 (0.06 - 0.81)	0.02
Sex Male versus Female	2.21 (0.89 - 5.48)	0.09	1.9 (0.44 - 8.16)	0.39
PS 0 - 1 versus 2	1.24 (0.57 - 2.68)	0.59	1.42 (0.48 - 4.19)	0.52
T stage T1/T2 versus T3/T4	0.95 (0.45 - 1.99)	0.88	0.83 (0.28 - 2.42)	0.73
N stage N0/ N1 versus N2/N3	0.78 (0.36 - 1.67)	0.52	0.44 (0.15 - 1.26)	0.12
Number of metastasis 1 - 3 versus 4 - 5	0.83 (0.22 - 3.1)	0.77	0.66 (0.13 - 3.38)	0.62
EGFR Negative versus Positive	1.2 (0.71 - 2.05)	0.49	2.17 (0.79 - 5.98)	0.13
ALK Negative versus Positive	1.78 (0.85 - 3.76)	0.13	2.47 (0.86 - 7.18)	0.09
CNS metastasis Yes versus No	1.56 (0.45 - 5.45)	0.49	40.9 (6.1 - 276.4)	<0.001
Site of metastasis Single organ versus Multiple organ	2.93 (1.29 - 6.65)	0.01	2.76 (0.84 - 9.12)	0.09

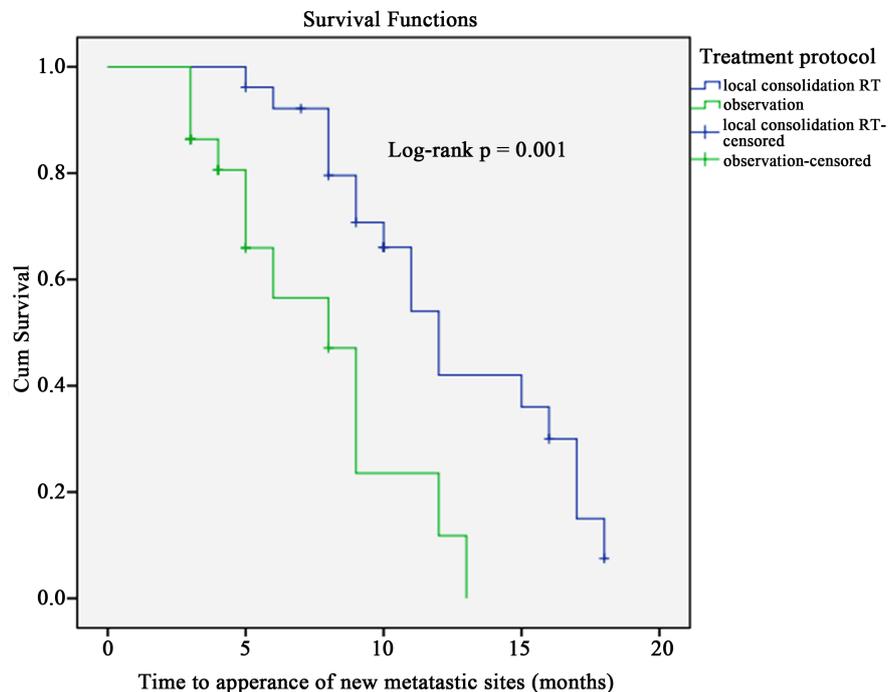


Figure 2. Kaplan-Meier curve for time to appearance of new metastatic sites.

3.2. Overall Survival (OS)

Patients in local consolidation arm had a statistically significant better overall survival than those patients in observation arm ($p = 0.005$) **Figure 3**. Median OS of patients in local consolidation arm was 12 months (95% CI 12.1 - 18.01) and in observation arm 10 months (95% CI 8.7 - 13.8). One year OS rate was 42.3% in local consolidation arm and 31.8% in observation arm, 2 year OS rate was 23.1% in local consolidation arm and only 4.5% in observation arm.

Cox regression analysis of factors potentially associated with OS was done **Table 3**. CNS metastasis ($p = 0.04$, HR 4.21, 95% CI 1.07 - 16.66) was the only significant predicting factor for OS in univariate analysis. In multivariate analysis, age ($p = 0.01$, HR 0.21, 95% CI 0.06 - 0.69) and CNS metastasis ($p = 0.002$, HR 13.9, 95% CI 2.68 - 72.24) were independent predictors for OAS **Table 4**.

3.3. Toxicity

No treatment related death (Grade IV) toxicity was reported during local consolidation radiotherapy. Acute radiation esophagitis and pneumonitis were the commonest but most of these toxicities were mild to moderate and treated with supportive management.

There were one patient (3.8%) with grade III pneumonitis and also one patients (3.8%) developed grade III esophagitis.

Late radiation toxicity was rare. No grade III and IV toxicity was detected. Grade I late lung toxicity was found in 7 patients (27%). Also, grade I late esophageal toxicity was observed in 2 patients (7.8%). Only grade I late skin toxicity was detected in one patient (3.8%).

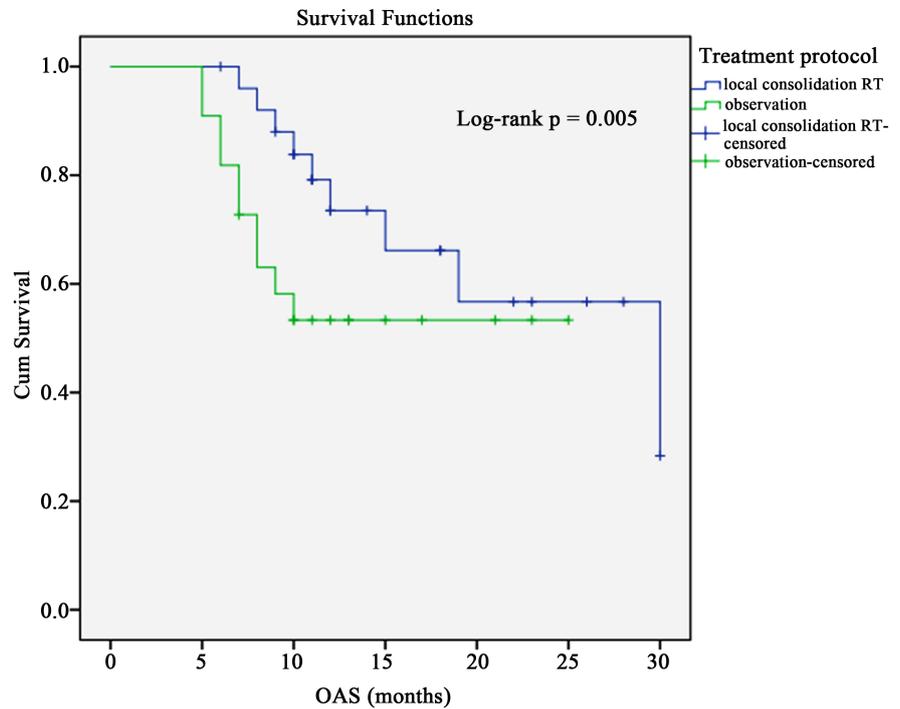


Figure 3. Kaplan-Meier curve for overall survival.

Table 4. Cox regression analysis of clinical factors affected OS.

Characteristics	Univariate analysis		Multivariate analysis	
	Univariable HR (95% CI)	P value	Univariable HR (95% CI)	P value
Age (years) <60 versus \geq 60	0.62 (0.29 - 1.35)	0.23	0.21 (0.06 - 0.69)	0.01
Sex Male versus Female	1.5 (0.61 - 3.72)	0.38	2.28 (0.55 - 9.42)	0.25
PS 0 - 1 versus 2	0.65 (0.39 - 1.79)	0.65	0.84 (0.29 - 2.49)	0.76
T stage T1/T2 versus T3/T4	0.7 (0.34 - 1.46)	0.34	0.69 (0.25 - 1.91)	0.48
N stage N0/N1 versus N2/N3	0.91 (0.42 - 1.96)	0.8	0.56 (0.19 - 1.66)	0.29
Number of metastasis 1 - 3 versus 4 - 5	1.4 (0.63 - 3.16)	0.41	0.83 (0.22 - 3.1)	0.77
EGFR Negative versus Positive	0.99 (0.58 - 1.67)	0.95	1.76 (0.76 - 4.1)	0.19
ALK Negative versus Positive	1.88 (0.88 - 4.04)	0.12	2.46 (0.87 - 6.97)	0.09
CNS metastasis Yes versus No	4.21 (1.07 - 16.66)	0.04	13.9 (2.68 - 72.24)	0.002
Site of metastasis Single organ versus Multiple organ	1.98 (0.89 - 4.42)	0.09	1.96 (0.67 - 5.69)	0.22

4. Discussion

Nearly half of patients with non small cell lung cancer presented with stage IV disease. Stage IV non small cell lung cancer remains incurable disease to treat and cure [2]. Oligometastatic theory was initially described in 1995 by Hellman and Weichselbaum which could reevaluate treatment strategies and therapeutic outcome for this incurable entity.

Fairchild *et al.* 2008 conducted comprehensive review of thirteen randomized controlled trials of palliative thoracic radiotherapy for lung cancer stated that high dose palliative thoracic radiotherapy (35 Gy 10 BED) improves chest symptoms and one year overall survival compared with lower radiotherapy dose and the major factor of treatment failure of stage IV non small cell lung cancer is metastasis [20].

Another systematic review showed that increasing total radiation dose and fractionation to primary lung tumors might prolong patient survival [21].

Phase II prospective, single arm trial was conducted by De Ruyscher *et al.* in 40 patients with one to five metastases treated with surgery or radiotherapy combined with systemic chemotherapy. The median PFS was 12.1 months and median OAS was 13.5 months [17].

Another prospective phase II study included 24 stage IV patients with one to six sites of extra cranial metastasis who progressed on systemic chemotherapy were treated with concurrent radiotherapy with erlotinib until progression. The median PFS was 14.7 months and median OS was 20.4 months [22].

Because of lacking of randomized prospective trials, there is still questions regarding improved DFS or OS with radical thoracic irradiation, so the current study was conducted to evaluate whether oligometastatic NSCLC without disease progression after first line chemotherapy, have prolonged progression free survival when treated with local consolidation therapy of residual disease followed by surveillance compared with no local consolidation therapy (observation).

The present study showed that Patients in local consolidation arm had significantly better progression free survival compared with patients in observation group. Median PFS was 9.5 months (95% CI 7.8 - 11.08) in local consolidation arm and 4.5 months (95% CI 3.9 - 5.7) in observation arm. Also, Patients in local consolidation arm had longer median time to appearance of new metastatic sites (10 months CI 9.3 - 12.6) than those patients in observation arm (4.5 months CI 4.2 - 6.9).

Our previous observation was in accordance with recently phase II trials conducted by Gomez *et al.* [23] and Iyengar *et al.* [24].

Gomez *et al.* assessed progression free survival between aggressive local consolidation therapy versus observation or maintenance therapy in patients with limited metastatic non small cell lung cancer three or fewer after first line systemic therapy. This study demonstrated median PFS 11.9 months in the local consolidation group compared to 3.9 months in the observation. Also, time to

appearance of new metastatic sites was longer in patients in local consolidative therapy group (11.9 months) than those patients in the observation group (5.7 months) [23].

The other phase II randomized study of consolidative radiotherapy for limited metastatic (primary plus up to 5 metastatic sites) non small cell lung cancer showed that statistically significant improvement in progression free survival from 3.5 to 9.7 months with adding local consolidative radiotherapy for patients who achieve partial or stable response after induction chemotherapy versus those patients with maintenance chemotherapy Iyengar *et al.* [24].

In the current study, old age and CNS metastasis were independent predictors for poor PFS and OS, this observation is consistent with finding from a study formulate prognostic models for survival in oligometastatic non small cell lung cancer. 309 patients with one to five metastasis were treated with SABR. Several risks were identified for poor prognosis, including being male, intracranial metastasis, synchronous disease and non adenocarcinoma histology [25]. Furthermore, a randomized phase III trial of stereotactic radiosurgery versus observation for patients with oligometastatic non small cell lung cancer limited to the brain, stated that no clinical benefit of local aggressive radiotherapy [26].

5. Conclusion

Local consolidation radiotherapy is simple, safe, efficient, and not expensive treatment for oligometastatic non small cell lung cancer after upfront chemotherapy. Local consolidation radiotherapy achieved significantly prolonged progression free survival and delayed appearance of new metastatic sites. Phase III studies are recommended to test benefit of local consolidation radiotherapy to gain prolonged progression free survival and overall survival. Also, it defines optimal patients' subgroups that are more likely to benefit of local consolidation radiotherapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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