BMJ Open

Standard Maintenance Therapy versus Local Consolidative Radiation Therapy and Standard Maintenance Therapy in 1-5 sites of Oligometastatic Non-Small Cell Lung Cancer: A Study Protocol of Phase III Randomized Controlled Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043628
Article Type:	Protocol
Date Submitted by the Author:	10-Aug-2020
Complete List of Authors:	Tibdewal, Anil; Tata Memorial Hospital, Radiation Oncology Agarwal, JaiPrakash; Tata Memorial Hospital, Radiation Oncology Srinivasan, Shashank; Tata Memorial Hospital, Radiation Oncology Mummudi, Naveen; Tata Memorial Hospital, Radiation Oncology Noronha, Vanita; Tata Memorial Hospital, Medical Oncology Prabhash, Kumar; Tata Memorial Hospital, Medical Oncology Patil, Vijay ; Tata Memorial Hospital, Medical Oncology Purandare, Nilendu; Tata Memorial Hospital, Nuclear Medicine Janu, Amit; Tata Memorial Centre, Radiodiagnosis Kannan, Sadhna; Tata Memorial Hospital, Clinical Research Secretariat
Keywords:	Radiation oncology < RADIOTHERAPY, CHEMOTHERAPY, Respiratory tract tumours < THORACIC MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title Page

Title: Standard Maintenance Therapy versus Local Consolidative Radiation Therapy and Standard Maintenance Therapy in 1-5 sites of Oligometastatic Non-Small Cell Lung Cancer: A Study Protocol of Phase III Randomized Controlled Trial

Authors: Dr. Anil Tibdewal[1*], Dr. Jaiprakash Agarwal[1], Dr. Shashank Srinivasan[1], Dr. Naveen Mummudi[1], Dr. Vanita Noronha[2], Dr. Kumar Prabhash[2], Dr. Vijay Patil[2], Dr. Nilendu Purandare[3], Dr. Amit Janu[4], Dr. Sadhana Kannan[5].

[1] Department of Radiation Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India.

[2] Department of Medical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India.

[3] Department of Nuclear Medicine, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India.

[4] Department of Radiodiagnosis, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India.

[5] Clinical Research Secretariat, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India.

***Corresponding Author: Dr. Anil Tibdewal**

Assistant Professor,

Department of Radiation Oncology

Tata Memorial Centre, Mumbai, India

Email: aniltibdewal@gmail.com

Telephone: 91-22-2417 7030

Abstract

Introduction: Two-phase II randomized studies have shown a significant benefit of local consolidation therapy in oligometastatic NSCLC. This phase III RCT will evaluate the efficacy of local consolidation radiation therapy in OM NSCLC after completion of initial systemic therapy.

Methods and Analysis: This is a single-center phase III randomized controlled trial of OM NSCLC patients. One hundred ninety patients will undergo 1:1 randomization to either standard maintenance therapy (Control Arm) or local consolidation radiation therapy and standard maintenance therapy (Experimental Arm). Patients will be stratified into the number of OM sites (1-2 vs 3-5), nodal metastases (N0-N1 vs N2-N3) and presence or absence of brain metastases. Stereotactic body radiation therapy (SBRT) to all the oligometastatic sites and definitive RT to primary disease will be given in the experimental arm. The primary endpoint is overall survival and secondary endpoints include progression-free survival, local control of OM sites, new distant metastases free survival, objective response rate, toxicity and quality of life. Translation endpoint include circulating tumor cells and radiomics using texture analysis.

Ethics and Dissemination: All patients will be provided with a written informed consent form which needs to be signed before randomization. The study is approved by the institutional ethics committee-II (project number 3445) and registered with Clinical Trials Registry – India, CTRI/2020/04/024761, dated April 21st, 2020.

Keywords: Local consolidation radiation therapy, Non-small cell lung cancer, Oligometastases, Stereotactic body radiation therapy, Quality of life.

Article Summary

Strengths and Limitations of this study

- Single Centre phase III study assessing role of local consolidation radiation therapy in oligometastatic (OM) NSCLC
- Randomization after initial systemic therapy with no progressive disease
- Practical eligibility criteria for timely recruitment
- SBRT to all oligometastatic sites
- Translational endpoints of circulating tumor cells and radiomics analysis

Introduction

Systemic therapy is the standard of care for patients with metastatic non-small cell lung cancer (NSCLC). Tyrosine kinase inhibitors (TKI) have significantly improved survival outcomes for patients with an actionable oncogene mutation like epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) [1–4]. In patients with programmed death/ ligand receptor (PD-1/PD-L1) expression, immune checkpoint inhibitors (ICI) also improves outcomes compared to systemic therapy alone [5,6]. Patients who do not have oncogene mutations and are not eligible for immunotherapy have a worse prognosis with median OS ranging from 10-13 months as compared to median OS of 18-26 months for patients treated with TKI or immunotherapy[4,6].

Metastatic NSCLC with limited sites of metastases referred to as oligometastases (OM) has shown better prognosis than those with widespread metastases[7,8]. The OM state was proposed as an intermediate stage of cancer with a spread between localized disease and widespread metastases[9,10]. The significance of the OM paradigm is that selected patients could be cured with radical local therapies[11]. There has been much debate as to the definition of oligometastatic disease in NSCLC. Recently, the European consensus definition for synchronous oligometastatic NSCLC was published. These include patients with a maximum of five metastatic lesions involving a maximum of three organs and all can be treated with radical local ablative therapy [12,13]. It is recommended not to consider histology and genomic background. (ref to be added).

The question remains why oligometastatic disease should behave differently than widespread metastatic disease. Patterns of failure analyses from limited metastatic NSCLC suggest that disease progression most often occurs at sites of existing disease at baseline rather than at new sites[14–16]. Hence, aggressive treatment of limited metastatic sites could potentially remove the dominant disease that could seed other sites in the future. Various retrospective studies have proven the role of definitive local therapy in oligometastases[17,18]. Two-phase II studies performed by Gomez et al. and Iyengar et al. showed that local consolidative therapy in addition to systemic therapy has a role in oligometastatic NSCLC. Gomez et al. randomized 1-3 sites of OM NSCLC patients to local consolidative therapy with or without maintenance therapy or to maintenance treatment alone. They showed a significant median PFS benefit in favor of local consolidative therapy (11.9 months vs 3.9 months, p=0.005). Long term results

also showed an OS benefit of 41 months vs 17 months [19,20]. Iyengar et al. randomized 29 patients to maintenance chemotherapy (CT) alone vs SABR followed by maintenance chemotherapy. As opposed to the study by Gomez et al. they enrolled patients with negative EGFR/ALK mutations and up to 5 metastatic sites. They showed a significant improvement in PFS with SABR (9.7 months vs 3.5 months, p=0.01). The SINDAS trial is the only phase III randomized trial with results presented at the recent ASCO meeting. The study randomized patient with EGFR mutation and ≤ 5 OM sites to either TKI alone or SBRT plus TKIs. The study showed a significant median PFS (20.2 vs 12.5 months, p<0.001) and OS (25.5 vs 17.4 months, p<0.001) respectively [21].

Although there has been promising data for the addition of local consolidative therapy to standard systemic therapy for oligometastatic NSCLC, these studies remain nondefinitive as they included small patient numbers. The only reported phase III RCT has exclusively selected patients with EGFR mutation[21]. These patients have a different natural history and outcomes for those who do not have EGFR mutations [22]. Hence, we initiated a phase III RCT to ascertain the role of addition of local consolidative radiation therapy (LCRT) to standard maintenance therapy (SMT) in oligometastatic NSCLC patients with up to 5 metastatic lesions and negative oncogene mutations.

Materials and Methods

This study is designed as a single institution, open-label, phase-III RCT, approved by the institutional ethics committee-II (IEC-II) (project number 3445). All NSCLC patients with up to 5 metastatic sites at presentation will be screened for this study. Patients who have completed standard systemic therapy and response imaging shows no progressive disease (PD) as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 will be eligible for this study. If found eligible under eligibility criteria (Table 1), patients will be explained about the study protocol by the study investigators in their native language and interested patients will be given an IEC approved written informed consent document available in English, Hindi and Marathi language (Supplement file 1).

Patients will be randomized in a 1:1 ratio to SMT alone (control arm), and LCRT + SMT (experimental arm). Patients will be stratified by the number of metastatic sites (1-2 vs 3-5), nodal metastases (N0-N1 vs N2), and brain metastases (present vs absent). Independent biostatistician of the institute will perform a computer-generated randomization sequence based on stratification factors.

Patient and Public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this study.

Objectives and Endpoints

The primary objective of this study is to assess the efficacy of LCRT after initial systemic therapy in oligometastatic NSCLC patients.

Primary Endpoint

To compare the overall survival (OS) between SMT arm and LCRT+ SMT arm where OS is defined as the time from the date of randomization to the date of death due to any cause.

Secondary Endpoints

1. Progression-free survival (PFS) - the time from the date of randomization until the date of disease progression, or until death in the absence of progression, whichever is earlier.

2. Local control for sites treated with LCRT – defined as the absence of PD (complete response, partial response, or stable disease).

3. New distant metastases free survival (DMFS) - the time from the date of randomization until the emergence of new distant metastases or death, whichever is earlier.

4. Objective response rate (complete response [CR] + partial response [PR])

5. Patient-reported outcomes using the EORTC QOL core questionnaire (QLQ-C30) and the corresponding lung cancer module (QLQ-LC13)

6. Treatment-related toxicity assessed using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 5.

Exploratory endpoints

1. Textural features of primary and metastatic sites using the TexRAD software (TexRAD ltd. Cambridge UK)

2. Differences in the textural features between pre and post-treatment images in the experimental arm and their correlation with survival outcomes.

3. Correlation of circulating tumor cells (CTCs) with the survival outcomes.

Table 1: Eligibility criteria for the study

Inclusion criteria:	**Exclusion criteria:**
1) Age > 18 years 2) ECOG performance status of 0-2 3) Pathologically proven diagnosis of NSCLC 4) 1-5 sites of metastatic disease not including the primary tumor and regional nodes (≤ 3 metastatic lesions in one organ will be eligible) 5) Patients should have received at least 4-6 cycles of systemic therapy without progression on response Imaging 6) Patients suitable for definitive therapy to the primary disease 7) All the oligometastatic lesions should be radiologically visible and suitable for SBRT 8) Adequate end organ function with CBC/differential obtained within 15 days before registration on the study, with adequate bone marrow function defined as follows: • Absolute neutrophil count (ANC) ≥ 500 cells/mm^3 • Platelets ≥ 50,000 cells/mm^3 • Hemoglobin ≥ 8.0 g/dl (Use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable); 9) Negative serum or urine pregnancy test for females of child-bearing potential, within 14 days before study registration 10) Patients willing for written informed consent and must be willing to comply with the specified follow up schedule	1) Progressive disease after initial systemic therapy 2) Positive oncogene mutations (EGFR/ALK/ROS) 3) More than 5 sites of oligo metastases 4) Metastatic lesion size >5 cm 5) More than three metastatic lesions in one organ 6) Malignant peritoneal disease 7) Malignant pleural effusion 8) Leptomeningeal disease 9) Brain metastases in the brain stem 10) Clinical or radiological evidence of spinal cord compression or metastases within 2 mm of the spinal cord on MRI 11) Severe, active co-morbidity defined as follows: • Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months • Transmural myocardial infarction within the last 6 months • Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration 12) Prior history of radiation therapy to the thorax 13) Previous history of malignancy within the last 3 years

Specific scenarios for Inclusion

1) Patients who underwent ablative RT or surgery or RFA for metastatic sites at presentation or during systemic therapy will be eligible provided the site is under control and the total number of oligometastatic sites at the time of study entry (treated site included) is ≤ 5.
2) Palliative RT for symptomatic bony metastases will be eligible provided the treated site is under control and further ablative doses of radiation can be delivered.
3) Patients with vertebral metastases who underwent surgical decompression, or stabilization followed by palliative RT will be eligible in the study provided the treated site is under control and the patient has ≤ 5 sites (treated site included).

Pre-randomization assessment

Eligible patients will undergo response assessment PET-CT or contrast-enhanced CT of thorax, abdomen, and pelvis after the completion of 4-6 cycles of standard systemic therapy. Complete history and thorough physical examination including PS assessment, baseline laboratory tests (including but not limited to complete blood count, renal function tests and liver function tests), 2D Echocardiography, and gadolinium contrast-enhanced MR Brain if not done earlier. Patients who do not have a progressive disease as per RECIST 1.1 will be eligible.

Figure 1- Study schema

Defining the number of Oligometastases

All metastatic sites at presentation and on follow up imaging will be confirmed by an experienced radiologist and will be discussed in multidisciplinary joint clinics. The involvement of adjacent vertebrae by direct extension would be counted as one site and not two sites of metastases. Indeterminate parenchymal lung nodule or any suspicious lung lesion on baseline imaging will be again evaluated on the response imaging for its metastatic confirmation. If required, biopsy confirmation will be preferred but is not mandatory. Primary tumor and regional nodes' feasibility for definitive RT will be assessed by the study investigators before randomization. Non-regional nodes will be counted as an individual metastatic site. Patients who have received palliative RT for symptomatic bone and brain metastases during the initial period will be evaluated for local control of those sites. Additional ablative doses will be decided as per the study investigators' discretion.

Control Arm – Standard Maintenance Therapy

All patients in this arm will receive standard maintenance therapy which includes chemotherapy, immunotherapy, or observation. SMT will be decided by the treating medical oncologist. Maintenance systemic therapy should start within 4-8 weeks of randomization. Palliative radiation therapy to existing metastatic sites in this arm will be done on clinical or radiological worsening. Acceptable RT doses include 8 Gy times one or two fractions or 20 Gy in five fractions. No ablative doses to metastatic sites are allowed in this arm.

Experimental Arm – Local Consolidative Radiation Therapy + SMT

Patients in this arm will receive LCRT with SBRT to all oligometastatic sites and definitive RT to primary disease including involved regional nodes. SMT will be given as discussed in arm A. LCRT will be started within 4 weeks of randomization. Maintenance systemic therapy can be started concurrently or after completion of LCRT within 4 weeks. SBRT doses are given in Table 2. Definitive radiation for the primary and nodal disease would be done similarly as in locally advanced NSCLC with hypofractionation schedule to a dose of 45-55 Gy in 15-22 fractions. Doses will be decided depending upon normal tissue tolerances and at radiation oncologist's discretion.

Table 2: LCRT doses for oligometastatic sites

Oligometastatic site	Location	Dose per fraction (Gy)	Number of fractions	Total Dose	Frequency
Primary (if N0) and Lung metastases	Peripheral	12	5	60 Gy	Alternate day
	Central	7.5	8	60 Gy	Daily/Alternate
	Ultra-central	5	10	50 Gy	Daily/Alternate
Bone	Spine	8 - 12	3 - 2	24 Gy	Alternate day
	Any other	7	5	35 Gy	Daily/Alternate
Brain	Single	18-24	1	18-24	Single
	1-3 lesion	18-24 or 5	1 or 10	18-24 or 50	Single/Daily
Adrenal	NA	7 – 10 Gy	5	35 – 50 Gy	Daily/Alternate
Liver	Any	6 – 10 Gy	5	30 – 50 Gy	Daily/Alternate

Radiotherapy planning and delivery

All patients in the experimental arm will undergo CT-based planning which should completely cover all the areas of interest so that a composite dose distribution can be created for all metastatic sites. Ideally, patient position will be preferred to remain the same across all treatment sites except brain metastases. Four-dimensional CT (4D-CT) will be used to encompass tumor and organ motion for moving metastatic sites. Target volume delineation will be done as per the consensus guidelines for individual sites e.g. international spinal consortium guidelines for spinal metastases [23]. A high precision technique like SBRT will be used for oligometastatic sites. Treatment planning will be done using intensity-modulated radiation therapy (IMRT) or volumetric modulated Arc therapy (VMAT).

Radiomics

Texture analysis of medical images like CT and MRI assess heterogeneity of tumors and other benign lesions[24,25]. It evaluates the distribution of grey levels, coarseness, and regularity. As a radiomics endpoint, texture analysis will be done on pre and post-treatment imaging and their significance and correlation will be analyzed separately.

Circulating Tumor Cells

In this study, the exploratory translational objective is to evaluate the significance of circulating tumor cells in the blood at baseline and subsequent follow-up. Circulating tumor cells have been identified as a prognostic marker in different tumor subtypes [26,27]. Serial follow up of CTCs in blood could predict clinical recurrence earlier than the radiological recurrence.

Participant withdrawal/discontinuation:

The principal investigator can discontinue the treatment whenever deemed necessary if the patient has significant toxicities or in life-threatening clinical scenarios. Patients can withdraw from the study without giving any reasons, however, reasons for withdrawal would be preferred for study documentation. Any data prior to withdrawal will be used for the study related outcome analysis.

Safety monitoring:

The data safety monitoring committee of the institute will monitor the progress of the study at regular intervals. Study modifications/amendments will be informed to IRB for approval, study sponsors, and will be uploaded in the clinical trials registry-India. All toxicities, treatment

interruptions or discontinuation and protocol deviations will be recorded and inform by the study investigators to the institutional review board as specified by the institutional guidelines.

Statistics:

Randomization: All eligible patients will be stratified according to the number of metastatic sites (1-2 vs 3-5), nodal status (N0-N1 vs N2-N3), and brain metastases (present vs absent). Patients will then undergo 1:1 randomization by an independent biostatistician with permuted block randomization.

Sample size calculation

The results of the phase II study of Gomez et al demonstrated a median OS of 17 months in the SMT alone arm and 41.2 months in SMT + LCT arm. For this phase III study, we expected an absolute increase in median OS of 10 months ie. to 27 months with a hazard ratio (HR) of death of 0.63 in the SMT plus LCRT (experimental arm). To detect this difference, with 80% power and a two-sided alpha of 0.05, 148 events will be required, 80 in the control arm and 68 in the experimental arm. Assuming a 10% drop out rate, the total sample size would be 206 (103 in the control arm and 103 in the experimental arm). We intend to accrue 40-45 patients per year for a 5 year accrual period with a minimum follow up of two years. The total study duration is seven years.

Analysis

Study-related data will be collected in an electronic case record form (eCRF) and will be uploaded in a restricted-access database (REDCap). Data will be available to principal investigators and the statistical team of the study in a password protected computer folder. Patient baseline characteristics will be summarized by study arm and control arm. Chi-square test or Fisher's exact test will be applied to compare patient characteristics between the two arms. The primary endpoint of OS will be calculated as per the intention-to-treat analysis. OS and PFS will be calculated using the Kaplan-Meier method and log-rank test will be used for comparison between groups. Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with OS and PFS. Chi-square test with Pearson's or Fisher's exact test will be used to compare the ORR between the two treatment arms. A similar test will be used to estimate the incidence of adverse events in each treatment arm (both acute and chronic toxicities). A p-value≤0.05 in a two-tailed test will

be considered statistically significant. Statistical analyses will be performed using SPSS version 25.0 (Statistical Package for Social Sciences) and STATA version 14.

QOL Analysis

The EORTC QLQ-LC13 is a 13-item questionnaire grouped, while the QLQ-C30 comprises a 30-item questionnaire. Raw scores will be standardized by linear transformation such that the final scores ranged between 0 and 100. Higher scores on the global QOL and functional scales represent a better QOL, whereas high symptom scale scores indicate significant symptoms or greater difficulty. Repeated-measures analysis of variance (RM-ANOVA) will be used to assess the interaction of time and group with time as within-subject factor and group as a between-subject factor with respect to EORTC QLQ 30 and LC30 from baseline to till the last follow-up.

Follow up evaluation and toxicity assessment

All patients accrued in the control arm will be followed up every 3 monthly (± 4 weeks) for the first 2 years and then 6 monthly (± 6 weeks) afterward till 5 years and thereafter annually (Table 3). Patients in the experimental arm during LCRT treatment will be reviewed once weekly for symptom and acute toxicity assessment if any. Post LCRT completion follows up will be done similarly as in the control arm. Adherence to protocol treatment and timely follow up of participants will be encouraged by the study investigators and team members through proper counselling, resolving queries and by allowing easy access to them. Any serious adverse events during treatment and at follow up will be documented, informed to IRB, managed appropriately, and will be followed up till resolution. At each visit, history and physical examination, ECOG PS, toxicity assessment using NCI CTC v5.0 will be recorded. Acute toxicity is defined as symptoms occurring within 90 days of the first fraction of radiotherapy. Late toxicity is defined as symptoms occurring beyond 90 days. Efficacy assessment will be done with CECT imaging of the disease sites at every follow-up. On equivocal suspicion of recurrent or PD, PET-CT or biopsy will be done. If biopsy not feasible, repeat imaging will be done after 4-8 weeks. MRI Brain will be done on clinical suspicion based on neurological worsening. EORTC QOL questionnaires will be completed by patients at 3, 6, and 12 months. If symptomatic before the scheduled follow up visit, relevant imaging will be done to rule out progression.

Table 3: Follow up visits schedule

Assessment	Before randomization	1st follow up at 3 months (± 4 weeks)	Every 3 month till 2 years (± 4 weeks)	Six monthly till 5 years (± 6 weeks)
Physical examination	x	x	x	x
Performance status	x	x	x	x
RO assessment	x	x	x	x
CECT (T+A+P)	x	x	x	x
Toxicity evaluation	x	x	x	x
MRI Brain	x	As required	As required	As required
PET CT	Not required (preferred)	Not required	As required	As required
QOL questionnaires	x	x	x (At 6 and 12 months)	-

Treatment at the progression:

Isolated progression at existing or new sites will be evaluated for local ablative therapies including surgery, SBRT, or radiofrequency ablation in both the arms. For limited or widespread metastases, subsequent lines of chemotherapy or immunotherapy will be decided at the investigator's discretion depending upon PS at the time of progression. Symptomatic sites will be offered palliative RT as per the existing institutional policies. Follow up schedule after progression will be adjusted to match the existing schedules within ± 6 weeks to avoid duplication of visits.

Quality assurance:

Strict adherence to quality assurance protocols will be ensured for patients undergoing SBRT or definitive RT in the experimental arm. Full quality assurance guidelines will be published separately.

Confidentiality:

Study participants' names and personal information will be held in strict confidence and will not be shared publicly. Participant details in case record forms, safety reports, and correspondence to IRB will be done with the study identification number and participant's

initials. Study investigators will maintain a master list with the participant's identification details.

Data sharing statement

Deidentified participant data from this study will not be shared publicly, however, the full protocol along with the primary analysis of the outcomes will be published in a peer reviewed indexed journal.

Discussion:

Oligometastatic disease deserves attention owing to the increasing evidence from various retrospective and prospectively randomized studies. Two-phase II randomized studies in NSCLC patients have shown significant benefit in PFS (Table 4). Adequately powered well-conducted phase III RCT is needed to generate level I evidence to support the efficacy of local ablative therapies in OM NSCLC. There are two similar phase III RCT in progress for assessment of local ablative therapy in combination with systemic therapy (Table 5).

The SARON trial (NCT02417662) is a multicenter, randomized phase III trial being conducted in 30 hospitals in the United Kingdom and plans to recruit 340 patients with oligometastatic EGFR, ALK, and ROS1 mutation-negative NSCLC (1-3 sites of synchronous metastatic disease at least one of which must be extracranial). Patients will receive either standard systemic therapy only or standard systemic therapy plus radical radiotherapy or SBRT to their primary tumors (and mediastinal nodes where present) and SBRT/SRS to all metastatic sites. The primary end-point of the study is overall survival.

The OMEGA trial (NCT03827577) is a phase III randomized trial being conducted in Italy which proposes to recruit 195 patients with synchronous or metachronous oligometastatic NSCLC with up to 3 metastatic sites. The study will include both oncogene mutation-positive and negative patients and they will be randomized to receive either standard systemic therapy alone (platinum doublet chemotherapy or TKI or immunotherapy) or standard systemic therapy followed by SBRT, surgical resection or radiofrequency ablation (RFA). The primary endpoint of the study is overall survival.

Our institute sees approximately 2500 new lung cancer patients annually. The proposed study is a single-center study and will recruit patients with ≤ 5 OM sites after completion of initial

planned standard systemic therapy. This study will also include patients who have been treated with palliative RT at presentation and if controlled at the time of randomization. The possibility of further ablative doses at those particular sites will be ascertained by the radiation oncologist. The study is currently awaiting funding from extramural grants and will start recruitment once funding is arranged.

Table 4: Prospective published studies of local consolidative therapy in OM NSCLC

Author, year	Study design	No. of patients	No. of sites	Intervention	Med FU (months)	Inclusion	Median Outcomes in months
Gomez et al (NSCLC)[19]	RCT – II CRT Arm No CRT	25 24	≤3	LCT + MT Vs MT/O alone	38.8	Synchronous#	PFS 14.4 Vs 4.4 OS 41.2 Vs 17
Iyengar et al (NSCLC)[28]	RCT - II	14 15	≤5	SABR + MT Vs MT alone	9.6	Synchronous	PFS 9.7 vs 3.5
Palma et al (various primaries)[29]	RCT - II	66 33	≤5	SABR +SOC vs SOC alone	26	Synchronous or metachronous	OS 41 Vs 28,
Sutera et al (various primaries)[30]	Phase II	147 (lung-32)	≤5	SABR	41.3	Synchronous or metachronous	OS 42.3 (Lung OS – 26.8)
Ruysscher et al (NSCLC)[31]	Phase II	40	≤5	SABR	27.7	Synchronous	OS – 13.5
Petty et al (NSCLC) [32]	Phase II	29	≤ 5	SBRT	24.2	Synchronous	OS – 28.4 PFS – 11.2
Collen et al (NSCLC) [33]	Phase II	26	≤ 5	SBRT	16.4		OS – 23 PFS – 11.2
Arrieta et al (NSCLC) [34]	Phase II	37	≤5	RCT	32.5	Synchronous#	OS – not reached PFS – 23.5

includes oncogene mutation-positive patients

Abbreviations: RCT – randomized controlled trial, OM – oligometastases, NSCLC – non-small cell lung cancer, TNBC – triple-negative breast cancer, SMT – standard maintenance therapy, SBRT – stereotactic body radiation therapy, LAT – local ablative therapy, SOC – standard of care, LCRT – local consolidation radiation therapy, OS – Overall survival, PFS – progression-free survival

Table 5: Ongoing Randomized Studies in Oligometastatic NSCLC

	SARON	OMEGA	CORE	PROMISE-005	NRG LU 002	Current Study
Trial ID	NCT02417662	NCT03827577	NCT02759783	NCT03808337	NCT03137771	CTRI/2020/04/024761
Country	UK	Italy	UK	USA	Multicentric	India
Trial Design	RCT III	RCT III	RCT II/III	RCT II	RCTII/III	RCT III
No. of OM sites	≤3	≤3	≤3	≤5	≤3	≤5
Presentation	Synchronous at least 1 extracranial site	Synchronous or metachronous	Metachronous	Synchronous or metachronous	Synchronous or metachronous (extracranial)	Synchronous
Primary Site	NSCLC	NSCLC	Breast, Prostate, NSCLC	TNBC, NSCLC	NSCLC	NSCLC
Oncogene mutation	Negative*	Negative and Positive	--	Negative and Positive	Negative	Negative
Target accrual	340	195	245	142	300	206
Control Arm	SMT	Systemic therapy	SOC	SOC	SMT	SMT
Experimental Arm	RT to primary and SBRT for OM	Systemic therapy followed by LAT	SBRT followed by SOC	SBRT plus SOC	LCT + SMT	LCRT + SMT
Primary end point	OS	OS	PFS/OS	PFS	PFS/OS	OS
Estimated year of completion	2022	2022	2024	2022	2022	2024

*Negative indicates for de-novo stage IV non-small cell lung cancer

Abbreviations: RCT – randomized controlled trial, OM – oligometastases, NSCLC – non-small cell lung cancer, TNBC – triple-negative breast cancer, SMT – standard maintenance therapy, SBRT – stereotactic body radiation therapy, LAT – local ablative therapy, SOC – standard of care, LCRT – local consolidation radiation therapy, OS – Overall survival, PFS – progression-free survival

Author contributions: Concept and design of the study – AT and JPA. The initial draft of Protocol – AT, JPA. The final draft of the protocol - AT, JPA, SS, NM, KP, VN, VP, NP, AJ, and SK. All authors read and approved the final protocol

Funding: The study is awaiting funds from extramural grants. Funding bodies will not have any role in study design modifications, data collection, and analysis of the study.

Competing interests: Dr. VN has received institutional research funding from Amgen, Sanofi India Ltd, Dr. Reddy's Laboratories Inc., Intas Pharmaceuticals, and Astra Zeneca Pharma India Ltd. All research grants have been paid to the institution. Dr. Kumar Prabhash has received research funding from Dr. Reddy's Laboratories Inc., Fresenius Kabi India Pvt. Ltd., Alkem Laboratories, Natco Pharma Ltd., BDR Pharmaceuticals Intl. Pvt. Ltd, and Roche Holding AG (all research grants paid to the institution and are unrelated to this study project). The rest of the authors declare that they have no competing interest in the proposed study protocol.

Ethics approval and consent to participate: The study is approved by the institutional ethics committee of Tata Memorial Hospital (TMH IRB project number – 3445). Written informed consent will be obtained from all the patients for study interventions, biomarkers and radiomics part of the study. The study is registered prospectively with Clinical Trials Registry – India, CTRI/2020/04/024761, dated April 21st, 2020.

Consent for publication: Not applicable

Availability of data and materials: Additional information on the protocol is available by contacting the corresponding author. There is no data reported in this manuscript.

Acknowledgments: None

Figure legends

Figure 1: Study schema

References:

1 Solomon BJ, Mok T, Kim D-W, *et al.* First-Line Crizotinib versus Chemotherapy in ALK -Positive Lung Cancer . *N Engl J Med* 2014;**371**:2167–77. doi:10.1056/nejmoa1408440

2 Soria J-C, Ohe Y, Vansteenkiste J, *et al.* Osimertinib in Untreated EGFR -Mutated Advanced Non–Small-Cell Lung Cancer . *N Engl J Med* 2017;**378**:113–25. doi:10.1056/nejmoa1713137

3 Rosell R, Carcereny E, Gervais R, *et al.* Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;**13**:239–46. doi:10.1016/S1470-2045(11)70393-X

4 Patil VM, Noronha V, Joshi A, *et al.* Phase III study of gefitinib or pemetrexed with carboplatin in EGFR-mutated advanced lung adenocarcinoma. *ESMO Open* 2017;**2**:10–8. doi:10.1136/esmoopen-2017-000168

5 Reck M, Rodriguez-Abreu D, Robinson AG, *et al.* Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2016;**375**:1823–33. doi:10.1056/NEJMoa1606774

6 Mok TSK, Wu YL, Kudaba I, *et al.* Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2019;**393**:1819–30. doi:10.1016/S0140-6736(18)32409-7

7 Ashworth AB, Senan S, Palma DA, *et al.* An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* 2014;**15**:346–55. doi:10.1016/j.cllc.2014.04.003

8 Van den Begin R, Engels B, Collen C, *et al.* The METABANK score: A clinical tool to predict survival after stereotactic radiotherapy for oligometastatic disease. *Radiother Oncol* 2019;**133**:113–9. doi:10.1016/j.radonc.2019.01.001

9 Hellman S, Weichselbaum RR. Oligometastases. J. Clin. Oncol. 1995;**13**:8–10. doi:10.1200/jco.1995.13.1.8

10 Weichselbaum RR, Hellman S. Oligometastases revisited. Nat. Rev. Clin. Oncol. 2011;**8**:378–82. doi:10.1038/nrclinonc.2011.44

11 Gomez DR, Tang C, Zhang J, *et al.* Local consolidative therapy vs. Maintenance therapy or observation for patients with oligometastatic non–small-cell lung cancer: Long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol* 2019;**37**:1558–65. doi:10.1200/JCO.19.00201

12 Dingemans AMC, Hendriks LEL, Berghmans T, *et al.* Definition of Synchronous Oligometastatic Non–Small Cell Lung Cancer—A Consensus Report. *J Thorac Oncol*

2019;**14**:2109–19. doi:10.1016/j.jtho.2019.07.025

13 Lievens Y, Guckenberger M, Gomez D, *et al.* Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. *Radiother Oncol* 2020;**148**:157–66. doi:10.1016/j.radonc.2020.04.003

14 Rusthoven KE, Hammerman SF, Kavanagh BD, *et al.* Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis. *Acta Oncol (Madr)* 2009;**48**:578–83. doi:10.1080/02841860802662722

15 Patel SH, Rimner A, Foster A, *et al.* Patterns of initial and intracranial failure in metastatic EGFR-mutant non-small cell lung cancer treated with erlotinib. *Lung Cancer* 2017;**108**:109–14. doi:10.1016/j.lungcan.2017.03.010

16 Al-Halabi H, Sayegh K, Digamurthy SR, *et al.* Pattern of failure analysis in metastatic EGFR-mutant lung cancer treated with tyrosine kinase inhibitors to identify candidates for consolidation stereotactic body radiation therapy. *J Thorac Oncol* 2015;**10**:1601–7. doi:10.1097/JTO.0000000000000648

17 Parikh RB, Cronin AM, Kozono DE, *et al.* Definitive primary therapy in patients presenting with oligometastatic non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2014;**89**:880–7. doi:10.1016/j.ijrobp.2014.04.007

18 Xu Q, Wang Y, Liu H, *et al.* Treatment outcome for patients with primary NSCLC and synchronous solitary metastasis. *Clin Transl Oncol* 2013;**15**:802–9. doi:10.1007/s12094-013-1008-2

19 Gomez DR, Blumenschein GR, Lee JJ, *et al.* Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 2016;**17**:1672–82. doi:10.1016/S1470-2045(16)30532-0

20 Nsclc LC, Elamin YY, Gomez DR, *et al.* Local Consolidation Therapy (LCT) After First Line Tyrosine Kinase Inhibitor (TKI) for Patients With EGFR Mutant Metastatic Non e small-cell. *Clin Lung Cancer* 2019;**20**:43–7. doi:10.1016/j.cllc.2018.09.015

21 Wang X, Zeng M. First-line tyrosine kinase inhibitor with or without aggressive upfront local radiation therapy in patients with EGFRm oligometastatic non-small cell lung cancer: Interim results of a randomized phase III, open-label clinical trial (SINDAS) (NCT02893332). *J Clin Oncol* 2020;**38**:9508–9508. doi:10.1200/jco.2020.38.15_suppl.9508

22 Mak RH, Doran E, Muzikansky A, *et al.* Outcomes After Combined Modality Therapy for EGFR -Mutant and Wild-Type Locally Advanced NSCLC. *Oncologist* 2011;**16**:886–95. doi:10.1634/theoncologist.2011-0040

23 Cox BW, Spratt DE, Lovelock M, *et al.* International spine radiosurgery consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 2012;**83**:e597–605. doi:10.1016/j.ijrobp.2012.03.009

24 Dou TH, Coroller TP, van Griethuysen JJM, *et al.* Peritumoral radiomics features predict distant metastasis in locally advanced NSCLC. *PLoS One* 2018;**13**:1–15. doi:10.1371/journal.pone.0206108

25 Aerts HJWL, Velazquez ER, Leijenaar RTH, *et al.* Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun* 2014;**5**. doi:10.1038/ncomms5006

26 Alix-Panabières C, Pantel K. Clinical applications of circulating tumor cells and circulating tumor DNA as liquid biopsy. Cancer Discov. 2016;**6**:479–91. doi:10.1158/2159-8290.CD-15-1483

27 Lindsay CR, Faugeroux V, Michiels S, *et al.* A prospective examination of circulating tumor cell profiles in non-small-cell lung cancer molecular subgroups. *Ann Oncol Off J Eur Soc Med Oncol* 2017;**28**:1523–31. doi:10.1093/annonc/mdx156

28 Iyengar P, Wardak Z, Gerber DE, *et al.* Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: A phase 2 randomized clinical trial. *JAMA Oncol* 2018;**4**:1–4. doi:10.1001/jamaoncol.2017.3501

29 Palma DA, Olson R, Harrow S, *et al.* Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019;**393**:2051–8. doi:10.1016/S0140-6736(18)32487-5

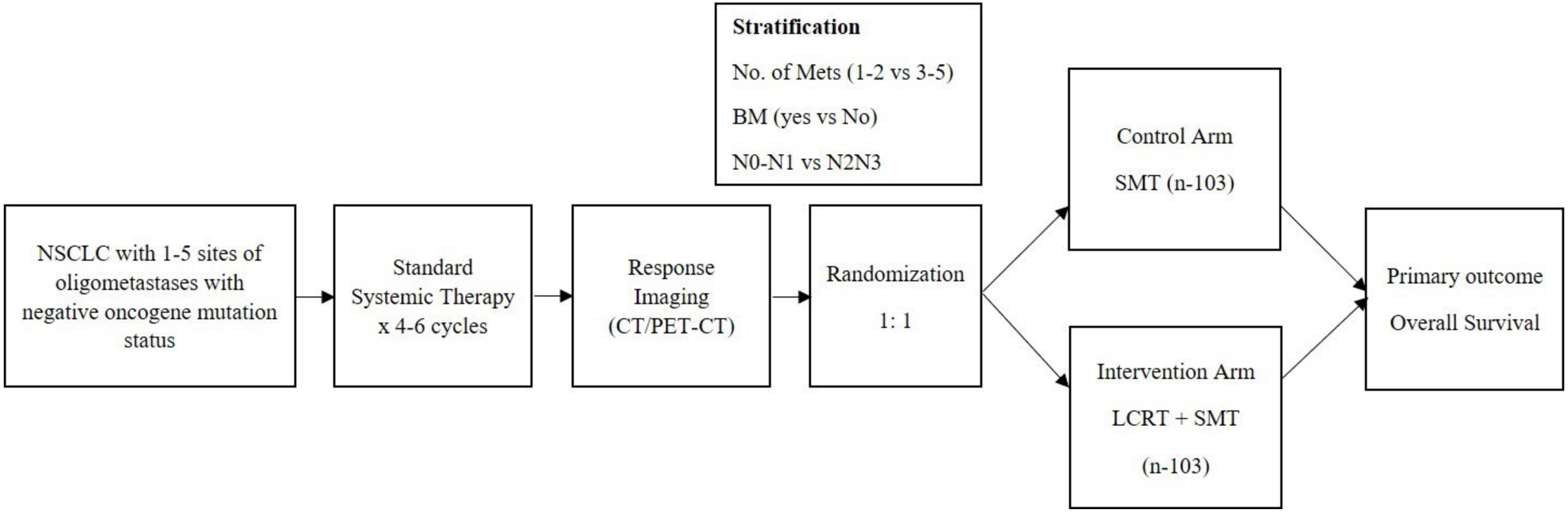
30 Sutera P, Clump DA, Kalash R, *et al.* Initial Results of a Multicenter Phase 2 Trial of Stereotactic Ablative Radiation Therapy for Oligometastatic Cancer. *Radiat Oncol Biol* 2019;**103**:116–22. doi:10.1016/j.ijrobp.2018.08.027

31 De Ruysscher D, Wanders R, Hendriks LE, *et al.* Progression-Free Survival and Overall Survival Beyond 5 Years of NSCLC Patients With Synchronous Oligometastases Treated in a Prospective Phase II Trial (NCT 01282450). *J Thorac Oncol* 2018;**13**:1958–61. doi:10.1016/j.jtho.2018.07.098

32 Petty WJ, Urbanic JJ, Ahmed T, *et al.* Long-Term Outcomes of a Phase 2 Trial of Chemotherapy With Consolidative Radiation Therapy for Oligometastatic Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys* 2018;**102**:527–35. doi:10.1016/j.ijrobp.2018.06.400

33 Collen C, Christian N, Schallier D, *et al.* Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients. *Ann Oncol* 2014;**25**:1954–9. doi:10.1093/annonc/mdu370

34 Arrieta O, Barrón F, Maldonado F, *et al.* Radical consolidative treatment provides a clinical benefit and long-term survival in patients with synchronous oligometastatic non-small cell lung cancer: A phase II study. *Lung Cancer* 2019;**130**:67–75. doi:10.1016/j.lungcan.2019.02.006


Stratification
No. of Mets (1-2 vs 3-5)
BM (yes vs No)
N0-N1 vs N2N3
NSCLC with 1-5 sites of oligometastases with negative oncogene mutation status
Standard Systemic Therapy x 4-6 cycles
Response Imaging (CT/PET-CT)
Randomization 1: 1
Control Arm
SMT (n-103)
Intervention Arm
LCRT + SMT
(n-103)
Primary outcome
Overall Survival

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	17
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	17

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-5
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	5

		be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome.	6

		Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9,12
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity,	11

		if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	5
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	10

Notes:

- 32: Supplement 1 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 26. June 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Standard Maintenance Therapy versus Local Consolidative Radiation Therapy and Standard Maintenance Therapy in 1-5 sites of Oligometastatic Non-Small Cell Lung Cancer: A Study Protocol of Phase III Randomized Controlled Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043628.R1
Article Type:	Protocol
Date Submitted by the Author:	07-Dec-2020
Complete List of Authors:	Tibdewal, Anil; Tata Memorial Hospital, Radiation Oncology Agarwal, JaiPrakash; Tata Memorial Hospital, Radiation Oncology Srinivasan, Shashank; Tata Memorial Hospital, Radiation Oncology Mummudi, Naveen; Tata Memorial Hospital, Radiation Oncology Noronha, Vanita; Tata Memorial Hospital, Medical Oncology Prabhash, Kumar; Tata Memorial Hospital, Medical Oncology Patil, Vijay ; Tata Memorial Hospital, Medical Oncology Purandare, Nilendu; Tata Memorial Hospital, Nuclear Medicine Janu, Amit; Tata Memorial Hospital, Radiodiagnosis Kannan, Sadhna; Tata Memorial Hospital, Clinical Research Secretariat
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology, Qualitative research, Respiratory medicine
Keywords:	Radiation oncology < RADIOTHERAPY, CHEMOTHERAPY, Respiratory tract tumours < THORACIC MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title Page

Title: Standard Maintenance Therapy versus Local Consolidative Radiation Therapy and Standard Maintenance Therapy in 1-5 sites of Oligometastatic Non-Small Cell Lung Cancer: A Study Protocol of Phase III Randomized Controlled Trial

Authors: Dr. Anil Tibdewal[1*], Dr. Jaiprakash Agarwal[1], Dr. Shashank Srinivasan[1], Dr. Naveen Mummudi[1], Dr. Vanita Noronha[2], Dr. Kumar Prabhash[2], Dr. Vijay Patil[2], Dr. Nilendu Purandare[3], Dr. Amit Janu[4], Dr. Sadhna Kannan[5].

[1] Department of Radiation Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India.

[2] Department of Medical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India.

[3] Department of Nuclear Medicine, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India.

[4] Department of Radiodiagnosis, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India.

[5] Clinical Research Secretariat, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India.

***Corresponding Author: Dr. Anil Tibdewal**

Assistant Professor,

Department of Radiation Oncology

Tata Memorial Centre, Mumbai, India

Email: aniltibdewal@gmail.com

Telephone: 91-22-2417 7030

Abstract

Introduction: Two-phase II randomized studies have shown a significant benefit of local consolidation therapy in oligometastatic NSCLC. This phase III RCT will evaluate the efficacy of local consolidation radiation therapy in OM NSCLC after completion of initial systemic therapy.

Methods and Analysis: This is a single-center phase III randomized controlled trial of OM NSCLC patients. One hundred ninety patients will undergo 1:1 randomization to either standard maintenance therapy (Control Arm) or local consolidation radiation therapy and standard maintenance therapy (Experimental Arm). Patients will be stratified into the number of OM sites (1-2 vs 3-5), nodal metastases (N0-N1 vs N2-N3) and presence or absence of brain metastases. Stereotactic body radiation therapy (SBRT) to all the oligometastatic sites and definitive RT to primary disease will be given in the experimental arm. The primary endpoint is overall survival and secondary endpoints include progression-free survival, local control of OM sites, new distant metastases free survival, objective response rate, toxicity and quality of life. Translation endpoint include circulating tumor cells and radiomics using texture analysis.

Ethics and Dissemination: All patients will be provided with a written informed consent form which needs to be signed before randomization. The study is approved by the institutional ethics committee-II (project number 3445) and registered with Clinical Trials Registry – India, CTRI/2020/04/024761, dated April 21st, 2020.

Keywords: Local consolidation radiation therapy, Non-small cell lung cancer, Oligometastases, Stereotactic body radiation therapy, Quality of life.

Strengths and Limitations of this study

- Used consensus definition for number of OM sites
- Randomization after initial systemic chemotherapy if no progression
- Practical eligibility criteria for timely recruitment
- SBRT to all oligometastatic sites
- Translational endpoints of circulating tumor cells and radiomics analysis

Introduction

Systemic therapy is the standard of care for patients with metastatic non-small cell lung cancer (NSCLC). Tyrosine kinase inhibitors (TKI) have significantly improved survival outcomes for patients with an actionable oncogene mutation like epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) [1–4]. In patients with programmed death/ ligand receptor (PD-1/PD-L1) expression, immune checkpoint inhibitors (ICI) also improves outcomes compared to systemic therapy alone [5,6]. Patients who do not have oncogene mutations and are not eligible for immunotherapy have a worse prognosis with median OS ranging from 10-13 months as compared to median OS of 18-26 months for patients treated with TKI or immunotherapy[4,6].

Metastatic NSCLC with limited sites of metastases referred to as oligometastases (OM) has shown better prognosis than those with widespread metastases[7,8]. The OM state was proposed as an intermediate stage of cancer with a spread between localized disease and widespread metastases[9,10]. The significance of the OM paradigm is that selected patients could be cured with radical local therapies[11]. There has been much debate as to the definition of oligometastatic disease in NSCLC. Recently, the European consensus definition for synchronous oligometastatic NSCLC was published. These include patients with a maximum of five metastatic lesions involving a maximum of three organs and all can be treated with radical local ablative therapy [12,13]. It is recommended not to consider histology and genomic background. (ref to be added).

The question remains why oligometastatic disease should behave differently than widespread metastatic disease. Patterns of failure analyses from limited metastatic NSCLC suggest that disease progression most often occurs at sites of existing disease at baseline rather than at new sites[14–16]. Hence, aggressive treatment of limited metastatic sites could potentially remove the dominant disease that could seed other sites in the future. Various retrospective studies have proven the role of definitive local therapy in oligometastases[17,18]. Two-phase II studies performed by Gomez et al. and Iyengar et al. showed that local consolidative therapy in addition to systemic therapy has a role in oligometastatic NSCLC. Gomez et al. randomized 1-3 sites of OM NSCLC patients to local consolidative therapy with or without maintenance therapy or to maintenance treatment alone. They showed a significant median PFS benefit in favor of local consolidative therapy (11.9 months vs 3.9 months, p=0.005). Long term results also showed an OS benefit of 41 months vs 17 months [19,20]. Iyengar et al. randomized 29

patients to maintenance chemotherapy (CT) alone vs SABR followed by maintenance chemotherapy. As opposed to the study by Gomez et al. they enrolled patients with negative EGFR/ALK mutations and up to 5 metastatic sites. They showed a significant improvement in PFS with SABR (9.7 months vs 3.5 months, p=0.01). The SINDAS trial is the only phase III randomized trial with results presented at the recent ASCO meeting. The study randomized patient with EGFR mutation and ≤ 5 OM sites to either TKI alone or SBRT plus TKIs. The study showed a significant median PFS (20.2 vs 12.5 months, p<0.001) and OS (25.5 vs 17.4 months, p<0.001) respectively [21].

Although there has been promising data for the addition of local consolidative therapy to standard systemic therapy for oligometastatic NSCLC, these studies remain nondefinitive as they included small patient numbers. The only reported phase III RCT has exclusively selected patients with EGFR mutation[21]. These patients have a different natural history and outcomes for those who do not have EGFR mutations [22]. Hence, we initiated a phase III RCT to ascertain the role of addition of local consolidative radiation therapy (LCRT) to standard maintenance therapy (SMT) in oligometastatic NSCLC patients with up to 5 metastatic lesions and negative oncogene mutations.

Materials and Methods

This study is designed as a single institution, open-label, phase-III RCT, approved by the institutional ethics committee-II (IEC-II) (project number 3445). The study schema is shown in figure 1. All NSCLC patients with up to 5 metastatic sites at presentation will be screened for this study. Patients who have completed standard systemic therapy and response imaging shows no progressive disease (PD) as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 will be eligible for this study. If found eligible under eligibility criteria (Table 1), patients will be explained about the study protocol by the study investigators in their native language and interested patients will be given an IEC approved written informed consent document available in English, Hindi and Marathi language (Supplement file 1).

Patients will be randomized in a 1:1 ratio to SMT alone (control arm), and LCRT + SMT (experimental arm). Patients will be stratified by the number of metastatic sites (1-2 vs 3-5), nodal metastases (N0-N1 vs N2), and brain metastases (present vs absent). Independent biostatistician of the institute will perform a computer-generated randomization sequence based on stratification factors. The study is expected to start from Jan 2021 and will continue for at least 5 years thereafter.

Patient and Public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this study.

Objectives and Endpoints

The primary objective of this study is to assess the efficacy of LCRT after initial systemic therapy in oligometastatic NSCLC patients.

Primary Endpoint

To compare the overall survival (OS) between SMT arm and LCRT+ SMT arm where OS is defined as the time from the date of randomization to the date of death due to any cause.

Secondary Endpoints

1. Progression-free survival (PFS) - the time from the date of randomization until the date of disease progression, or until death in the absence of progression, whichever is earlier.

2. Local control for sites treated with LCRT – defined as the absence of PD (complete response, partial response, or stable disease).

3. New distant metastases free survival (DMFS) - the time from the date of randomization until the emergence of new distant metastases or death, whichever is earlier.

4. Objective response rate (complete response [CR] + partial response [PR])

5. Patient-reported outcomes using the EORTC QOL core questionnaire (QLQ-C30) and the corresponding lung cancer module (QLQ-LC13)

6. Treatment-related toxicity assessed using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 5.

Exploratory endpoints

1. Textural features of primary and metastatic sites using the TexRAD software (TexRAD ltd. Cambridge UK)

2. Differences in the textural features between pre and post-treatment images in the experimental arm and their correlation with survival outcomes.

3. Correlation of circulating tumor cells (CTCs) with the survival outcomes.

Table 1: Eligibility criteria for the study

Inclusion criteria:	**Exclusion criteria:**
1) Age > 18 years 2) ECOG performance status of 0-2 3) Pathologically proven diagnosis of NSCLC 4) 1-5 sites of metastatic disease not including the primary tumor and regional nodes (≤ 3 metastatic lesions in one organ will be eligible) 5) Patients should have received at least 4-6 cycles of systemic therapy without progression on response Imaging 6) Patients suitable for definitive therapy to the primary disease 7) All the oligometastatic lesions should be radiologically visible and suitable for SBRT 8) Adequate end organ function with CBC/differential obtained within 15 days before registration on the study, with adequate bone marrow function defined as follows: • Absolute neutrophil count (ANC) ≥ 500 cells/mm^3 • Platelets ≥ 50,000 cells/mm^3 • Hemoglobin ≥ 8.0 g/dl (Use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable); 9) Negative serum or urine pregnancy test for females of child-bearing potential, within 14 days before study registration 10) Patients willing for written informed consent and must be willing to comply with the specified follow up schedule	1) Progressive disease after initial systemic therapy 2) Positive oncogene mutations (EGFR/ALK/ROS) 3) More than 5 sites of oligo metastases 4) Metastatic lesion size >5 cm 5) More than three metastatic lesions in one organ 6) Malignant peritoneal disease 7) Malignant pleural effusion 8) Leptomeningeal disease 9) Brain metastases in the brain stem 10) Clinical or radiological evidence of spinal cord compression or metastases within 2 mm of the spinal cord on MRI 11) Severe, active co-morbidity defined as follows: • Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months • Transmural myocardial infarction within the last 6 months • Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration 12) Prior history of radiation therapy to the thorax 13) Previous history of malignancy within the last 3 years

Specific scenarios for Inclusion

1) Patients who underwent ablative RT or surgery or RFA for metastatic sites at presentation or during systemic therapy will be eligible provided the site is under control and the total number of oligometastatic sites at the time of study entry (treated site included) is ≤ 5.
2) Palliative RT for symptomatic bony metastases will be eligible provided the treated site is under control and further ablative doses of radiation can be delivered.
3) Patients with vertebral metastases who underwent surgical decompression, or stabilization followed by palliative RT will be eligible in the study provided the treated site is under control and the patient has ≤ 5 sites (treated site included).

Pre-randomization assessment

Eligible patients will undergo response assessment PET-CT or contrast-enhanced CT of thorax, abdomen, and pelvis after the completion of 4-6 cycles of standard systemic therapy. Complete history and thorough physical examination including PS assessment, baseline laboratory tests (including but not limited to complete blood count, renal function tests and liver function tests), 2D Echocardiography, and gadolinium contrast-enhanced MR Brain if not done earlier. Patients who do not have a progressive disease as per RECIST 1.1 will be eligible.

Defining the number of Oligometastases

All metastatic sites at presentation and on follow up imaging will be confirmed by an experienced radiologist and will be discussed in multidisciplinary joint clinics. The involvement of adjacent vertebrae by direct extension would be counted as one site and not two sites of metastases. Indeterminate parenchymal lung nodule or any suspicious lung lesion on baseline imaging will be again evaluated on the response imaging for its metastatic confirmation. If required, biopsy confirmation will be preferred but is not mandatory. Primary tumor and regional nodes' feasibility for definitive RT will be assessed by the study investigators before randomization. Non-regional nodes will be counted as an individual metastatic site. Patients who have received palliative RT for symptomatic bone and brain metastases during the initial period will be evaluated for local control of those sites. Additional ablative doses will be decided as per the study investigators' discretion.

Control Arm – Standard Maintenance Therapy

All patients in this arm will receive standard maintenance therapy which includes chemotherapy, immunotherapy, or observation. SMT will be decided by the treating medical oncologist. Maintenance systemic therapy should start within 4-8 weeks of randomization. Palliative radiation therapy to existing metastatic sites in this arm will be done on clinical or radiological worsening. Acceptable RT doses include 8 Gy times one or two fractions or 20 Gy in five fractions. No ablative doses to metastatic sites are allowed in this arm.

Experimental Arm – Local Consolidative Radiation Therapy + SMT

Patients in this arm will receive LCRT with SBRT to all oligometastatic sites and definitive RT to primary disease including involved regional nodes. SMT will be given as discussed in arm A. LCRT will be started within 4 weeks of randomization. Maintenance systemic therapy can be started concurrently or after completion of LCRT within 4 weeks. SBRT doses are given in Table 2. Definitive radiation for the primary and nodal disease would be done similarly as in locally advanced NSCLC with hypofractionation schedule to a dose of 45-55 Gy in 15-22 fractions. Doses will be decided depending upon normal tissue tolerances and at radiation oncologist's discretion.

Table 2: LCRT doses for oligometastatic sites

Oligometastatic site	Location	Dose per fraction (Gy)	Number of fractions	Total Dose	Frequency
Primary (if N0) and Lung metastases	Peripheral	12	5	60 Gy	Alternate day
	Central	7.5	8	60 Gy	Daily/Alternate
	Ultra-central	5	10	50 Gy	Daily/Alternate
Bone	Spine	8 - 12	3 - 2	24 Gy	Alternate day
	Any other	7	5	35 Gy	Daily/Alternate
Brain	Single	18-24	1	18-24	Single
	1-3 lesion	18-24 or 5	1 or 10	18-24 or 50	Single/Daily
Adrenal	NA	7 – 10 Gy	5	35 – 50 Gy	Daily/Alternate
Liver	Any	6 – 10 Gy	5	30 – 50 Gy	Daily/Alternate

Radiotherapy planning and delivery

All patients in the experimental arm will undergo CT-based planning which should completely cover all the areas of interest so that a composite dose distribution can be created for all metastatic sites. Ideally, patient position will be preferred to remain the same across all treatment sites except brain metastases. Four-dimensional CT (4D-CT) will be used to encompass tumor and organ motion for moving metastatic sites. Target volume delineation will be done as per the consensus guidelines for individual sites e.g. international spinal consortium guidelines for spinal metastases [23]. A high precision technique like SBRT will be used for oligometastatic sites. Treatment planning will be done using intensity-modulated radiation therapy (IMRT) or volumetric modulated Arc therapy (VMAT).

Radiomics

Texture analysis of medical images like CT and MRI assess heterogeneity of tumors and other benign lesions[24,25]. It evaluates the distribution of grey levels, coarseness, and regularity. As a radiomics endpoint, texture analysis will be done on pre- and post-treatment imaging and their significance and correlation will be analysed separately.

Circulating Tumor Cells

In this study, the exploratory translational objective is to evaluate the significance of circulating tumor cells in the blood at baseline and subsequent follow-up. Circulating tumor cells have been identified as a prognostic marker in different tumor subtypes [26,27]. Serial follow up of CTCs in blood could predict clinical recurrence earlier than the radiological recurrence.

Participant withdrawal/discontinuation:

The principal investigator can discontinue the treatment whenever deemed necessary if the patient has significant toxicities or in life-threatening clinical scenarios. Patients can withdraw from the study without giving any reasons, however, reasons for withdrawal would be preferred for study documentation. Any data prior to withdrawal will be used for the study related outcome analysis.

Safety monitoring:

The data safety monitoring committee of the institute will monitor the progress of the study at regular intervals. Study modifications/amendments will be informed to IRB for approval, study sponsors, and will be uploaded in the clinical trials registry-India. All toxicities, treatment

interruptions or discontinuation and protocol deviations will be recorded and inform by the study investigators to the institutional review board as specified by the institutional guidelines.

Statistics:

Randomization: All eligible patients will be stratified according to the number of metastatic sites (1-2 vs 3-5), nodal status (N0-N1 vs N2-N3), and brain metastases (present vs absent). Patients will then undergo 1:1 randomization by an independent biostatistician with permuted block randomization.

Sample size calculation

The results of the phase II study of Gomez et al demonstrated a median OS of 17 months in the SMT alone arm and 41.2 months in SMT + LCT arm. For this phase III study, we took median OS of 17 months in the standard arm from Gomez et al and are expecting an increment of 10 months in the experimental arm with hazard ratio of 0.63 based on previous single arm phase II studies [28,29]. To detect this difference, with 80% power and a two-sided alpha of 0.05, 148 events will be required, 80 in the control arm and 68 in the experimental arm. Assuming a 10% drop out rate, the total sample size required would be 206 (103 in the control arm and 103 in the experimental arm). We intend to accrue 40-45 patients per year for a 5-year accrual period with a minimum follow up of two years. The total study duration is seven years.

Analysis

Study-related data will be collected in an electronic case record form (eCRF) and will be uploaded in a restricted-access database (REDCap). Data will be available to principal investigators and the statistical team of the study in a password protected computer folder. Patient baseline characteristics will be summarized by study arm and control arm. Chi-square test or Fisher's exact test will be applied to compare patient characteristics between the two arms. The primary endpoint of OS will be calculated as per the intention-to-treat analysis. OS, PFS and DMFS will be calculated using the Kaplan-Meier method and log-rank test will be used for comparison between the groups. Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with OS and PFS. Chi-square test with Pearson's or Fisher's exact test will be used to compare the ORR between the two treatment arms. A similar test will be used to estimate the incidence of adverse events in each treatment arm (both acute and chronic toxicities). A p-value$\leq$0.05 in a two-tailed

test will be considered statistically significant. Statistical analyses will be performed using SPSS version 25.0 (Statistical Package for Social Sciences) and STATA version 14.

QOL Analysis

The EORTC QLQ-LC13 is a 13-item questionnaire grouped, while the QLQ-C30 comprises a 30-item questionnaire. Raw scores will be standardized by linear transformation such that the final scores ranged between 0 and 100. Higher scores on the global QOL and functional scales represent a better QOL, whereas high symptom scale scores indicate significant symptoms or greater difficulty. If data from one assessment point will be missing, then the last observation carry forward (LOCF) method will be used to impute the missing subsequent values. To account for possible bias due to imputation, sensitivity analyses will be performed by conducting a complete case analysis. Repeated-measures analysis of variance (RM-ANOVA) will be used to assess the interaction of time and group with time as within-subject factor and group as a between-subject factor with respect to EORTC QLQ 30 and LC30 from baseline to till the last follow-up.

Follow up evaluation and toxicity assessment

All patients accrued in the control arm will be followed up every 3 monthly (± 4 weeks) for the first 2 years and then 6 monthly (± 6 weeks) afterward till 5 years and thereafter annually (Table 3). Patients in the experimental arm during LCRT treatment will be reviewed once weekly for symptom and acute toxicity assessment if any. Post LCRT completion follows up will be done similarly as in the control arm. Adherence to protocol treatment and timely follow up of participants will be encouraged by the study investigators and team members through proper counselling, resolving queries and by allowing easy access to them. Any serious adverse events during treatment and at follow up will be documented, informed to IRB, managed appropriately, and will be followed up till resolution. At each visit, history and physical examination, ECOG PS, toxicity assessment using NCI CTC v5.0 will be recorded. Acute toxicity is defined as symptoms occurring within 90 days of the first fraction of radiotherapy. Late toxicity is defined as symptoms occurring beyond 90 days. Efficacy assessment will be done with CECT imaging of the disease sites at every follow-up. On equivocal suspicion of recurrent or PD, PET-CT or biopsy will be done. If biopsy not feasible, repeat imaging will be done after 4-8 weeks. MRI Brain will be done on clinical suspicion based on neurological worsening. EORTC QOL questionnaires will be completed by patients at 3, 6, and 12 months.

If symptomatic before the scheduled follow up visit, relevant imaging will be done to rule out progression.

Table 3: Follow up visits schedule

Assessment	Before randomization	1st follow up at 3 months (± 4 weeks)	Every 3 month till 2 years (± 4 weeks)	Six monthly till 5 years (± 6 weeks)
Physical examination	x	x	x	x
Performance status	x	x	x	x
RO assessment	x	x	x	x
CECT (T+A+P)	x	x	x	x
Toxicity evaluation	x	x	x	x
MRI Brain	If not done earlier	As required	As required	As required
PET CT	Not required (preferred)	Not required	As required	As required
QOL questionnaires	x	x	x (At 6 and 12 months)	-

Treatment at the progression:

Isolated progression at existing or new sites will be evaluated for local ablative therapies including surgery, SBRT, or radiofrequency ablation in both the arms. For limited or widespread metastases, subsequent lines of chemotherapy or immunotherapy will be decided at the investigator's discretion depending upon PS at the time of progression. Symptomatic sites will be offered palliative RT as per the existing institutional policies. Follow up schedule after progression will be adjusted to match the existing schedules within ± 6 weeks to avoid duplication of visits.

Quality assurance:

Strict adherence to quality assurance protocols will be ensured for patients undergoing SBRT or definitive RT in the experimental arm. Full quality assurance guidelines will be published separately.

Ethics and dissemination: The study is approved by the institutional ethics committee of Tata Memorial Hospital (TMH IRB project number – 3445). The study is registered prospectively

with Clinical Trials Registry – India, CTRI/2020/04/024761, dated April 21st, 2020. Written informed consent will be obtained from all the patients for study interventions, biomarkers and radiomics part of the study.

Confidentiality:

Study participants' names and personal information will be held in strict confidence and will not be shared publicly. Participant details in case record forms, safety reports, and correspondence to IRB will be done with the study identification number and participant's initials. Study investigators will maintain a master list with the participant's identification details.

Data sharing statement

Deidentified participant data from this study will not be shared publicly, however, the full protocol along with the primary analysis of the outcomes will be published in a peer reviewed indexed journal.

Discussion:

Oligometastatic disease deserves attention owing to the increasing evidence from various retrospective and prospectively randomized studies. Two-phase II randomized studies in NSCLC patients have shown significant benefit in PFS (Table 4). Adequately powered well-conducted phase III RCT is needed to generate level I evidence to support the efficacy of local ablative therapies in OM NSCLC. There are two similar phase III RCT in progress for assessment of local ablative therapy in combination with systemic therapy (Table 5).

The SARON trial (NCT02417662) is a multicenter, randomized phase III trial being conducted in 30 hospitals in the United Kingdom and plans to recruit 340 patients with oligometastatic EGFR, ALK, and ROS1 mutation-negative NSCLC (1-3 sites of synchronous metastatic disease at least one of which must be extracranial). Patients will receive either standard systemic therapy only or standard systemic therapy plus radical radiotherapy or SBRT to their primary tumors (and mediastinal nodes where present) and SBRT/SRS to all metastatic sites. The primary end-point of the study is overall survival.

The OMEGA trial (NCT03827577) is a phase III randomized trial being conducted in Italy which proposes to recruit 195 patients with synchronous or metachronous oligometastatic NSCLC with up to 3 metastatic sites. The study will include both oncogene mutation-positive and negative patients and they will be randomized to receive either standard systemic therapy alone (platinum doublet chemotherapy or TKI or immunotherapy) or standard systemic therapy followed by SBRT, surgical resection or radiofrequency ablation (RFA). The primary endpoint of the study is overall survival.

Our institute sees approximately 2500 new lung cancer patients annually. The proposed study is a single-center study and will recruit patients with ≤ 5 OM sites after completion of initial planned standard systemic therapy. This study will also include patients who have been treated with palliative RT at presentation and if controlled at the time of randomization. The possibility of further ablative doses at those particular sites will be ascertained by the radiation oncologist. The study is currently awaiting funding from extramural grants and will start recruitment once funding is arranged.

Table 4: Prospective published studies of local consolidative therapy in OM NSCLC

Author, year	Study design	No. of patients	No. of sites	Intervention	Med FU (months)	Inclusion	Median Outcomes in months
Gomez et al (NSCLC)[19]	RCT – II CRT Arm No CRT	 25 24	≤3	LCT + MT Vs MT/O alone	38.8	Synchronous#	PFS 14.4 Vs 4.4 OS 41.2 Vs 17
Iyengar et al (NSCLC)[30]	RCT - II	14 15	≤5	SABR + MT Vs MT alone	9.6	Synchronous	PFS 9.7 vs 3.5
Palma et al (various primaries)[31]	RCT - II	66 33	≤5	SABR +SOC vs SOC alone	26	Synchronous or metachronous	OS 41 Vs 28,
Sutera et al (various primaries)[28]	Phase II	147 (lung-32)	≤5	SABR	41.3	Synchronous or metachronous	OS 42.3 (Lung OS – 26.8)
Ruysscher et al (NSCLC)[32]	Phase II	40	≤5	SABR	27.7	Synchronous	OS – 13.5
Petty et al (NSCLC) [29]	Phase II	29	≤ 5	SBRT	24.2	Synchronous	OS – 28.4 PFS – 11.2
Collen et al (NSCLC) [33]	Phase II	26	≤ 5	SBRT	16.4		OS – 23 PFS – 11.2
Arrieta et al (NSCLC) [34]	Phase II	37	≤5	RCT	32.5	Synchronous#	OS – not reached PFS – 23.5

includes oncogene mutation-positive patients

Abbreviations: RCT – randomized controlled trial, OM – oligometastases, NSCLC – non-small cell lung cancer, TNBC – triple-negative breast cancer, SMT – standard maintenance therapy, SBRT – stereotactic body radiation therapy, LAT – local ablative therapy, SOC – standard of care, LCRT – local consolidation radiation therapy, OS – Overall survival, PFS – progression-free survival

Table 5: Ongoing Randomized Studies in Oligometastatic NSCLC

	SARON	**OMEGA**	**CORE**	**PROMISE-005**	**NRG LU 002**	**Current Study**
Trial ID	NCT02417662	NCT03827577	NCT02759783	NCT03808337	NCT03137771	CTRI/2020/04/024761
Country	UK	Italy	UK	USA	Multicentric	India
Trial Design	RCT III	RCT III	RCT II/III	RCT II	RCT II/III	RCT III
No. of OM sites	≤3	≤3	≤3	≤5	≤3	≤5
Presentation Primary Site Oncogene mutation	Synchronous at least 1 extracranial site NSCLC Negative*	Synchronous or metachronous NSCLC Negative and Positive	Metachronous Breast, Prostate, NSCLC --	Synchronous or metachronous TNBC, NSCLC Negative and Positive	Synchronous or metachronous (extracranial) NSCLC Negative	Synchronous NSCLC Negative
Target accrual	340	195	245	142	300	206
Control Arm Experimental Arm	SMT RT to primary and SBRT for OM	Systemic therapy Systemic therapy followed by LAT	SOC SBRT followed by SOC	SOC SBRT plus SOC	SMT LCT + SMT	SMT LCRT + SMT
Primary end point	OS	OS	PFS/OS	PFS	PFS/OS	OS
Estimated year of completion	2022	2022	2024	2022	2022	2024

*Negative indicates for de-novo stage IV non-small cell lung cancer

Abbreviations: RCT – randomized controlled trial, OM – oligometastases, NSCLC – non-small cell lung cancer, TNBC – triple-negative breast cancer, SMT – standard maintenance therapy, SBRT – stereotactic body radiation therapy, LAT – local ablative therapy, SOC – standard of care, LCRT – local consolidation radiation therapy, OS – Overall survival, PFS – progression-free survival

Author contributions: Concept and design of the study – AT and JPA. The initial draft of Protocol – AT, JPA. The final draft of the protocol - AT, JPA, SS, NM, KP, VN, VP, NP, AJ, and SK. All authors read and approved the final protocol

Funding: The study is awaiting funds from intramural and extramural grants. Funding bodies will not have any role in study design modifications, data collection, and analysis of the study.

Competing interests: Dr. VN has received institutional research funding from Amgen, Sanofi India Ltd, Dr. Reddy's Laboratories Inc., Intas Pharmaceuticals, and Astra Zeneca Pharma India Ltd. All research grants have been paid to the institution. Dr. Kumar Prabhash has received research funding from Dr. Reddy's Laboratories Inc., Fresenius Kabi India Pvt. Ltd., Alkem Laboratories, Natco Pharma Ltd., BDR Pharmaceuticals Intl. Pvt. Ltd, and Roche Holding AG (all research grants paid to the institution and are unrelated to this study project). The rest of the authors declare that they have no competing interest in the proposed study protocol.

Consent for publication: Not applicable

Availability of data and materials: Additional information on the protocol is available by contacting the corresponding author. There is no data reported in this manuscript.

Acknowledgments: None

Figure legends

Figure 1: Study schema

References:

1 Solomon BJ, Mok T, Kim D-W, *et al.* First-Line Crizotinib versus Chemotherapy in ALK -Positive Lung Cancer . *N Engl J Med* 2014;**371**:2167–77. doi:10.1056/nejmoa1408440

2 Soria J-C, Ohe Y, Vansteenkiste J, *et al.* Osimertinib in Untreated EGFR -Mutated Advanced Non–Small-Cell Lung Cancer . *N Engl J Med* 2017;**378**:113–25. doi:10.1056/nejmoa1713137

3 Rosell R, Carcereny E, Gervais R, *et al.* Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;**13**:239–46. doi:10.1016/S1470-2045(11)70393-X

4 Patil VM, Noronha V, Joshi A, *et al.* Phase III study of gefitinib or pemetrexed with carboplatin in EGFR-mutated advanced lung adenocarcinoma. *ESMO Open* 2017;**2**:10–8. doi:10.1136/esmoopen-2017-000168

5 Reck M, Rodriguez-Abreu D, Robinson AG, *et al.* Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2016;**375**:1823–33. doi:10.1056/NEJMoa1606774

6 Mok TSK, Wu YL, Kudaba I, *et al.* Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2019;**393**:1819–30. doi:10.1016/S0140-6736(18)32409-7

7 Ashworth AB, Senan S, Palma DA, *et al.* An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* 2014;**15**:346–55. doi:10.1016/j.cllc.2014.04.003

8 Van den Begin R, Engels B, Collen C, *et al.* The METABANK score: A clinical tool to predict survival after stereotactic radiotherapy for oligometastatic disease. *Radiother Oncol* 2019;**133**:113–9. doi:10.1016/j.radonc.2019.01.001

9 Hellman S, Weichselbaum RR. Oligometastases. J. Clin. Oncol. 1995;**13**:8–10. doi:10.1200/jco.1995.13.1.8

10 Weichselbaum RR, Hellman S. Oligometastases revisited. Nat. Rev. Clin. Oncol.

2011;**8**:378–82. doi:10.1038/nrclinonc.2011.44

11 Gomez DR, Tang C, Zhang J, *et al.* Local consolidative therapy vs. Maintenance therapy or observation for patients with oligometastatic non–small-cell lung cancer: Long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol* 2019;**37**:1558–65. doi:10.1200/JCO.19.00201

12 Dingemans AMC, Hendriks LEL, Berghmans T, *et al.* Definition of Synchronous Oligometastatic Non–Small Cell Lung Cancer—A Consensus Report. *J Thorac Oncol* 2019;**14**:2109–19. doi:10.1016/j.jtho.2019.07.025

13 Lievens Y, Guckenberger M, Gomez D, *et al.* Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. *Radiother Oncol* 2020;**148**:157–66. doi:10.1016/j.radonc.2020.04.003

14 Rusthoven KE, Hammerman SF, Kavanagh BD, *et al.* Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis. *Acta Oncol (Madr)* 2009;**48**:578–83. doi:10.1080/02841860802662722

15 Patel SH, Rimner A, Foster A, *et al.* Patterns of initial and intracranial failure in metastatic EGFR-mutant non-small cell lung cancer treated with erlotinib. *Lung Cancer* 2017;**108**:109–14. doi:10.1016/j.lungcan.2017.03.010

16 Al-Halabi H, Sayegh K, Digamurthy SR, *et al.* Pattern of failure analysis in metastatic EGFR-mutant lung cancer treated with tyrosine kinase inhibitors to identify candidates for consolidation stereotactic body radiation therapy. *J Thorac Oncol* 2015;**10**:1601–7. doi:10.1097/JTO.0000000000000648

17 Parikh RB, Cronin AM, Kozono DE, *et al.* Definitive primary therapy in patients presenting with oligometastatic non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2014;**89**:880–7. doi:10.1016/j.ijrobp.2014.04.007

18 Xu Q, Wang Y, Liu H, *et al.* Treatment outcome for patients with primary NSCLC and synchronous solitary metastasis. *Clin Transl Oncol* 2013;**15**:802–9. doi:10.1007/s12094-013-1008-2

19 Gomez DR, Blumenschein GR, Lee JJ, *et al.* Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell

lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 2016;**17**:1672–82. doi:10.1016/S1470-2045(16)30532-0

20 Nsclc LC, Elamin YY, Gomez DR, *et al.* Local Consolidation Therapy (LCT) After First Line Tyrosine Kinase Inhibitor (TKI) for Patients With EGFR Mutant Metastatic Non e small-cell. *Clin Lung Cancer* 2019;**20**:43–7. doi:10.1016/j.cllc.2018.09.015

21 Wang X, Zeng M. First-line tyrosine kinase inhibitor with or without aggressive upfront local radiation therapy in patients with EGFRm oligometastatic non-small cell lung cancer: Interim results of a randomized phase III, open-label clinical trial (SINDAS) (NCT02893332). *J Clin Oncol* 2020;**38**:9508–9508. doi:10.1200/jco.2020.38.15_suppl.9508

22 Mak RH, Doran E, Muzikansky A, *et al.* Outcomes After Combined Modality Therapy for EGFR -Mutant and Wild-Type Locally Advanced NSCLC. *Oncologist* 2011;**16**:886–95. doi:10.1634/theoncologist.2011-0040

23 Cox BW, Spratt DE, Lovelock M, *et al.* International spine radiosurgery consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 2012;**83**:e597–605. doi:10.1016/j.ijrobp.2012.03.009

24 Dou TH, Coroller TP, van Griethuysen JJM, *et al.* Peritumoral radiomics features predict distant metastasis in locally advanced NSCLC. *PLoS One* 2018;**13**:1–15. doi:10.1371/journal.pone.0206108

25 Aerts HJWL, Velazquez ER, Leijenaar RTH, *et al.* Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun* 2014;**5**. doi:10.1038/ncomms5006

26 Alix-Panabières C, Pantel K. Clinical applications of circulating tumor cells and circulating tumor DNA as liquid biopsy. Cancer Discov. 2016;**6**:479–91. doi:10.1158/2159-8290.CD-15-1483

27 Lindsay CR, Faugeroux V, Michiels S, *et al.* A prospective examination of circulating tumor cell profiles in non-small-cell lung cancer molecular subgroups. *Ann Oncol Off J Eur Soc Med Oncol* 2017;**28**:1523–31. doi:10.1093/annonc/mdx156

28 Sutera P, Clump DA, Kalash R, *et al.* Initial Results of a Multicenter Phase 2 Trial of Stereotactic Ablative Radiation Therapy for Oligometastatic Cancer. *Radiat Oncol Biol* 2019;**103**:116–22. doi:10.1016/j.ijrobp.2018.08.027

29 Petty WJ, Urbanic JJ, Ahmed T, *et al.* Long-Term Outcomes of a Phase 2 Trial of Chemotherapy With Consolidative Radiation Therapy for Oligometastatic Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys* 2018;**102**:527–35. doi:10.1016/j.ijrobp.2018.06.400

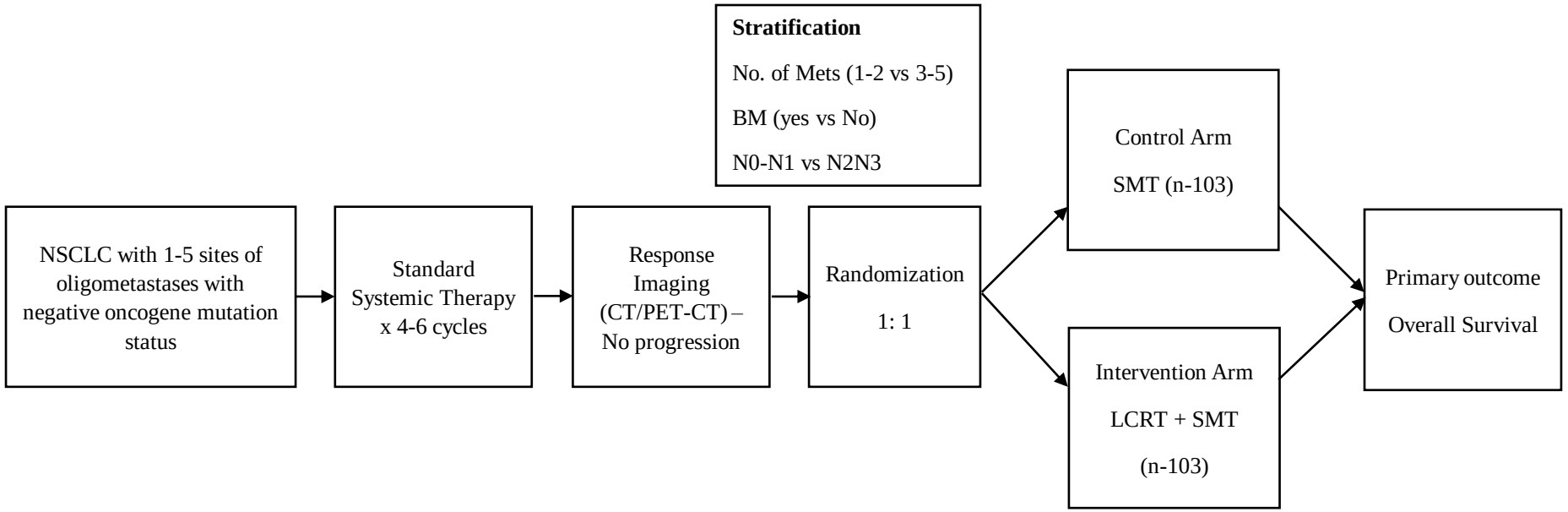
30 Iyengar P, Wardak Z, Gerber DE, *et al.* Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: A phase 2 randomized clinical trial. *JAMA Oncol* 2018;**4**:1–4. doi:10.1001/jamaoncol.2017.3501

31 Palma DA, Olson R, Harrow S, *et al.* Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019;**393**:2051–8. doi:10.1016/S0140-6736(18)32487-5

32 De Ruysscher D, Wanders R, Hendriks LE, *et al.* Progression-Free Survival and Overall Survival Beyond 5 Years of NSCLC Patients With Synchronous Oligometastases Treated in a Prospective Phase II Trial (NCT 01282450). *J Thorac Oncol* 2018;**13**:1958–61. doi:10.1016/j.jtho.2018.07.098

33 Collen C, Christian N, Schallier D, *et al.* Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients. *Ann Oncol* 2014;**25**:1954–9. doi:10.1093/annonc/mdu370

34 Arrieta O, Barrón F, Maldonado F, *et al.* Radical consolidative treatment provides a clinical benefit and long-term survival in patients with synchronous oligometastatic non-small cell lung cancer: A phase II study. *Lung Cancer* 2019;**130**:67–75. doi:10.1016/j.lungcan.2019.02.006


Stratification
No. of Mets (1-2 vs 3-5)
BM (yes vs No)
N0-N1 vs N2N3
NSCLC with 1-5 sites of oligometastases with negative oncogene mutation status
Standard Systemic Therapy x 4-6 cycles
Response Imaging (CT/PET-CT) – No progression
Randomization 1: 1
Control Arm SMT (n-103)
Intervention Arm LCRT + SMT (n-103)
Primary outcome Overall Survival

Informed Consent form

Patient information sheet (PIS) and Informed Consent form (ICF) document

Standard maintenance therapy versus local consolidative radiation therapy and standard maintenance therapy in 1-5 sites of oligometastatic Non-small cell lung cancer (NSCLC): A Phase III Randomized Controlled Trial

Anil Tibdewal, JP Agarwal, Kumar Prabhash, Naveen Mummudi, Vanita Noronha, Amit Joshi, Vijay Patil, Nilendu Purandare, Amit Janu, Abhishek Mahajan, Rajiv Kumar, Tapas Dora and Sadhana Kannan.

1. Information to participate in the research project

This document explains the study for which you are being considered as participant. Before consenting for the study, it is important that you read and understand the research questions, additional benefits, possible risks and study related procedures. Please feel free to approach the study team for clarifying any doubts for asking any question arising in relation to the study being proposed. You are also free to discuss with your family members of and before deciding about study participation. If you decide to participate in the study then you will have to sign the consent form. By signing the form, you are stating that you understand the information about the study, agree to the treatment procedure and willing to take part in the study.

Radiotherapy is a standard treatment for metastatic non-small cell lung cancer. In metastatic setting, radiotherapy is general given for palliative setting. However, even in metastatic setting, if the patients have limited number of metastatic sites usually less than 5 then this condition is called Oligometastases. In oligometastatic non-small cell lung cancer, patients after completion of systemic therapy has no evidence of progression then can be treated with radical radiotherapy to all the oligometastatic sites with curative intent. This therapy has resulted in better outcomes than maintenance systemic therapy alone (observation or more chemotherapy). In this study, we want to study the effects of local consolidative radiation therapy (LCRT) to all sites of oligometastatic disease in addition to standard maintenance therapy for its beneficial effects in improving the overall survival.

2. Nature and purpose of this study

Version No. 1.0, 04/01/2020

All consecutive oligometastatic NSCLC patients with 1-5 sites of metastases initially treated with 4-6 cycles of systemic therapy will be screened for this study. Patients without evidence of progressive disease will be eligible for this study. The study will involve 300 patients. Patients willing for participation will be asked to sign the written informed consent form. Subsequently, these patients will be randomly allocated to receive maintenance therapy in the form of observation or further chemotherapy OR local consolidative radiation therapy to all initial sites of Oligometastases and standard maintenance therapy i.e half of the patients in the trial will continue to receive TKI alone and half will receive TKI + local consolidative Radiation therapy. The study team with the help of computers will do the treatment allocation after checking pertinent details regarding your disease condition. You have equal chance of receiving RT on not receiving it. In every other aspect, the treatment will be the same. If you are allocated to receive radiation, it will be planned within 2- 4 weeks after you agreed to participate in this study.

3. Study Methodology

Radiotherapy for metastatic non-small cell lung cancer is a relatively simple form of treatment delivered using beams of high-energy x ray. The planning process involved taking some measurement and a computed tomography CT scan in a position necessary for the treated sites and patient comfort. The planning session usually take 20 to 40 minutes. You will receive radiation to all the metastatic sites and primary disease. During treatment, you will be set up in the same position as you were during the planning session. Radiation is usually delivered daily Monday to Friday as outpatient. Each treatment session will take about 10 to 15 minutes depending upon the sites being treated.

All participating patients will be followed up for at least five years. The first follow-up will be done at 3 months post radiotherapy completion and then subsequently you will be seen at 3 monthly interval up to 2 years in the hospital clinic for a routine examination there after you will be reviewed every six monthly for 5 years or more.

Another aspect that we would like to study the impact of local consolidative radiation treatment on your quality of life. For assessing this, you would be requested to fill in questionnaire that contains various items related to Physical, emotional and social wellbeing. You will be asked to fill this form before start of treatment and at regular intervals thereafter. Each questionnaire will take about 30 minutes to complete apart.

4. Biological and Radiomics substudy

Apart from the main study, we would like to do further research on your blood sample for circulating tumor cells & molecular studies and your radiologic images for Radiomics analysis. With your permission, we would like to preserve some parts of your cancerous tissue embedded in paraffin blocks at the pathological laboratory of Tata Memorial Hospital for 10 years. Your tissue would be stored in a way that it would not be identifiable and no one would be informed about specific findings related to you. Five ml of blood sample will be collected at baseline and at 3,6 and 12 months for the biological part of the study. Blood sample will be processed at a partner research laboratory in Pune. Other scientists or doctors may want to use this material to improve diagnosis and treatment of cancer after getting approval from the institutional ethics committee. If you agree to donate your biological material or let use of radiologic images for future studies, kindly give a separate consent for the same in addition to the main study. However, you are free to participate in the main study even if you decide not to donate the biological material.

5. Risks and side effects

Like any other treatment, RT caused side effects depending upon the area of the body being treated. The short-term general side effect in the form of redness, pigmentation or itching of the skin in the irradiated area, which is expected to subside within a month of completion of treatment. For example, if you are being treated for lung mass, RT may cause inflammation of the lung causing dry cough, shortness of breath and chest wall pain. However, these side effects are minimal by careful planning and using modern RT techniques. For further questions on side effects relating to specific sites, please consult the study team doctors. For any unforeseen radiation induced complications, patients will be managed at Tata Memorial hospital and treatment cost will be borne by the study team.

6. Costs

The study protocol will cover the cost of MRI Brain and you do not have to pay for it. You are not expected to pay for the radiation if you are allocated to receive RT. However, you will have to bear the cost of systemic therapy drugs, which you were previously taking before participating in this study and routine tests/procedure considered standard for staging, treatment and follow up. Thus, the cost of your standard treatment as well as the cost of managing any complication directly or indirectly attributable to this standard treatment would have to be borne by you or your caregivers.

7. Benefits

There are no direct monetary or financial benefits for participation in this study. We do not anticipate that any new information gained during the course of the study will benefit you directly. Many of the most effective treatments used today are the results of clinical trials done in the past. However, irrespective of your participation in the trial you will receive high standards of care. Moreover, close contact with the study team will be beneficial. Information from this study will improve our knowledge of treating non-small cell lung cancer with limited metastatic disease especially the benefits of RT.

8. Confidentiality

All information obtained during the study will be held in strict confidence. You will be identified with study number only. No names or identifying information will be used in images for any publication or presentation. Only the doctors and associates working on this study will have access to your medical charts in order to collect information on your treatment and the outcomes thereof. They will require access to your medical charts during your treatment and up to 5 years following your treatment. If you withdraw early from the study, no further collection of information from your medical charts will take place. However, information collected up to the point of withdrawal would still be used. The information in the study record will be kept confidential and the clinical chart will be kept in the Clinical Research secretariat (CRS) at TMC. Data will be stored securely and will be made available only to persons conducting the study. No reference will be made in oral or written reports, which would link you to the study.

9. Compensation

In the event of an injury occurring to the clinical trial subject, related to the intervention arm, such subject should be provided free medical management as long as required. In the event of a study related injury and death, compensation will be provided as per the institutional policy.

10. Reimbursement

You will not receive any reimbursement for the routine tests/procedures and the standard treatment that is being offered to you in the study.

11. Contact

If you have any questions regarding the study or the procedures at any time, you may contact the Principal investigator on this study, Dr. Anil Tibdewal, Room number 306 Homi Bhabha Block 3rd floor, Radiation Oncology OPD (Tel 91-22-2417 7000, Extension 6315 at Tata Memorial Hospital or Room no 1130 (Tel 24177030) at Tata Memorial Hospital between 9:30 a.m. to 5:30 p.m. In case you have any question regarding your rights as a participant or wish to clarify certain issues from a non-investigator on this study, you can contact Dr. Umesh Mahantshetty or Dr. Girish Chinnaswamy, Member Secretary IEC, Tata Memorial Hospital, Parel, Mumbai on 91-22-24177262.

12. Participation

Your participation in this study is completely voluntary. You are free to refuse participation, or to leave the study at any time. You will not be penalized or lose any benefit to which you are otherwise entitled. If you withdraw from the study prior to its completion you will receive the usual standard of care for the disease and your non- participation will not have any adverse effect on your subsequent medical treatment or relationship with the treating physician. Additionally, we may discontinue the study at any time without your consent for safety or Administrative reasons.

Informed Consent form (Main study)

Study Title: Standard maintenance therapy versus local consolidative radiation therapy and standard maintenance therapy in 1-5 sites of oligometastatic Non-small cell lung cancer (NSCLC): A Phase III Randomized Controlled Trial

Study number: _____

Subject's Name: _____

Subject's Initials: _____

Date of birth/Age: _____

1. I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that the sponsor of the research study, others working on the sponsor's behalf, IEC and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw form this trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.
4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
5. I agree to take part in the above study.

I have read the above information and agreed to participate in this study. I have received a copy of this form.

Version No. 1.0, 04/01/2020

Participant's name (print)	
Participant's signature or thumb impression and date	
Address: Qualification: Occupation: Student/Self-employed/service/Housewife/others (please tick as appropriate) and attach supporting documentation Annual Income of the subject (please attach supporting documentation)	
Phone Nos:	
Legal acceptable representative name	
Legal acceptable representative signature or thumb impression and date	
Address (Capital letters) Phone numbers	
Impartial witness's name	
Impartial witness's signature and date	
Address (capital letters) Phone numbers	
Name of PI or Co-PI/Co-I	
PI or Co-PI/Co-I signature and date	

Version No. 1.0, 04/01/2020

Informed Consent form

Study Title: Standard maintenance therapy versus local consolidative radiation therapy and standard maintenance therapy in 1-5 sites of oligometastatic Non-small cell lung cancer (NSCLC): A Phase III Randomized Controlled Trial

I hereby freely give my consent to take part in the BIOLOGICAL and Radiomics sub study for which I wish to donate the following materials/agree to let use of my radiology scan images.

Blood ☐

Tumor tissue ☐

Radiology Images ☐

Participant's name (print)	
Participant's signature and date	
Phone Nos:	
Legal acceptable representative name	
Legal acceptable representative signature and date	
Address (Capital letters) Phone numbers	
Impartial witness's name	
Impartial witness's signature and date	
Address (capital letters) Phone numbers	
Name of PI or Co-PI/Co-I	

Version No. 1.0, 04/01/2020

PI or Co-PI/Co-I signature and date	