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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 randomised controlled trial

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ABSTRACT

INTRODUCTION

Two-phase II randomised studies have shown a significant benefit of local consolidation therapy in oligometastatic non-small cell lung cancer (NSCLC). This phase III randomised controlled trial (RCT) will evaluate the efficacy of local consolidation radiation therapy (RT) in oligometastases (OM) NSCLC after completion of initial systemic therapy.

Methods and analysis

This is a single-centre phase III RCT of OM NSCLC patients. One hundred and ninety patients will undergo 1:1 randomisation to either standard maintenance therapy (control arm) or local consolidation RT and standard maintenance therapy (experimental arm).

METHODS AND ANALYSIS

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ABSTRACT

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 oncoprotein mutation like epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK).1–4 In patients with programmed death/ligand receptor expression, immune checkpoint inhibitors also improves outcomes compared with systemic therapy alone.5–6 Patients who do not have oncoprotein mutations and are not eligible for immunotherapy have a worse prognosis with median overall survival (OS) ranging from 10 to 13 months as compared with median OS of 18–26 months for patients treated with TKI or immunotherapy.7–11

Metastatic NSCLC with limited sites of metastases referred to as oligometastases (OM) has shown better prognosis than those with widespread metastases.5–8 The OM state was proposed as an intermediate stage of cancer with a spread between localised 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

Strengths and limitations of this study

- Used consensus definition for number of oligometastases sites.
- Randomisation after initial systemic chemotherapy if no progression.
- Practical eligibility criteria for timely recruitment.
- Stereotactic body radiation therapy to all oligometastatic sites.
- Translational endpoints of circulating tumour cells and radiomics analysis.
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.\textsuperscript{12,13}

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.\textsuperscript{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.\textsuperscript{17,18} Two-phase II studies performed by Gomez \textit{et al}\textsuperscript{19} and Iyengar \textit{et al}\textsuperscript{20} showed that local consolidative therapy in addition to systemic therapy has a role in oligometastatic NSCLC. Gomez \textit{et al}\textsuperscript{19} randomised 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 progression-free survival (PFS) benefit in favour 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 versus 17 months.\textsuperscript{19,21} Iyengar \textit{et al}\textsuperscript{20} randomised 29 patients to maintenance chemotherapy (CT) alone versus stereotactic ablative radiotherapy (SABR) followed by maintenance CT. As opposed to the study by Gomez \textit{et al}\textsuperscript{19} they enrolled patients with negative EGFR/ALK mutations and up to five 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 randomised trial with results presented at the recent American Society of Clinical Oncology (ASCO) meeting. The study randomised patient with EGFR mutation and \(\leq 5\) OM sites to either TKI alone or stereotactic body radiation therapy (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.\textsuperscript{22}

Although there has been promising data for the addition of local consolidative therapy to standard systemic therapy for oligometastatic NSCLC, these studies remain non-definitive as they included small patient numbers. The only reported phase III randomised controlled trial (RCT) has exclusively selected patients with EGFR mutation.\textsuperscript{22} These patients have a different natural history and outcomes for those who do not have EGFR mutations.\textsuperscript{23} 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 five 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 five 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. Patients with EGFR mutation and \(\leq 5\) OM sites will be enrolled in this study. Patients with brain metastases (BM) will be excluded from this study. The study is expected to start from January 2021 and will continue for at least 5 years thereafter.

**Figure 1** Study schema. BM, Brain metastases; CT, Computed Tomography; LCRT, local consolidative radiation therapy; NSCLC, non-small cell lung cancer; PET, positron emission tomography; SMT, standard maintenance therapy.
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 OS between SMT arm and LCRT+SMT arm where OS is defined as the time from the date of randomisation to the date of death due to any cause.

Secondary endpoints

1. PFS: the time from the date of randomisation 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 (CR), partial response (PR) or stable disease).
3. New distant metastases free survival (DMFS): the time from the date of randomisation until the emergence of new distant metastases or death, whichever is earlier.
4. Objective response rate (CR+PR).
5. Patient-reported outcomes using the EORTC Quality Of Life (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 version 5.

Exploratory endpoints

1. Textural features of primary and metastatic sites using the TexRAD software (TexRAD, Cambridge, UK).
2. Differences in the textural features between pretreatment and post-treatment images in the experimental arm and their correlation with survival outcomes.
3. Correlation of circulating tumour cells (CTCs) with the survival outcomes.

Specific scenarios for inclusion

1. Patients who underwent ablative radiation therapy (RT) or surgery or radiofrequency ablation (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 stabilisation 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).

Prerandomisation assessment

Eligible patients will undergo response assessment Positron Emission Tomography-Computed Tomography (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 performance status (PS) assessment, baseline laboratory tests (including but not limited to complete blood count, renal function tests and liver function tests), two-dimensional echocardiography and gadolinium contrast-enhanced MR brain if not done earlier. Patients who do not have a PD as per RECIST version 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 tumour and regional nodes’ feasibility for definitive RT will be assessed by the study investigators before randomisation. 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—SMT
All patients in this arm will receive SMT which includes CT, immunotherapy or observation. SMT will be decided by the treating medical oncologist. Maintenance systemic therapy should start within 4–8 weeks of randomisation. Palliative RT 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—LCRT+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 randomisation. 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 on normal tissue tolerances and at radiation oncologist’s discretion.

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 will be used to encompass tumour and organ motion for moving metastatic sites. Target volume delineation will be done as per the consensus guidelines for individual sites, for example, international spinal consortium guidelines for spinal metastases. A high precision technique like SBRT will be used for oligometastatic sites. Treatment planning will be done using intensity-modulated RT or volumetric modulated arc therapy.

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

Circulating tumour cells
In this study, the exploratory translational objective is to evaluate the significance of CTCs in the blood at baseline and subsequent follow-up. CTCs have been identified as a prognostic marker in different tumour subtypes. 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 Institutional Review Board (IRB) for approval, study sponsors, and will be uploaded in the Clinical Trials

| Table 2 | Local consolidative radiation therapy doses for oligometastatic sites |
|---------|-------------------------------------------------------------|
| **Oligometastatic site** | **Location** | **Dose per fraction (Gy)** | **Fractions (n)** | **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 |
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
Randomisation
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 randomisation by an independent biostatistician with permuted block randomisation.

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 80% power and a two-sided alpha of 0.05 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 2 years. The total study duration is 7 years.

Analysis
Study-related data will be collected in an electronic case record form 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 summarised by study arm and control arm. \( \chi^2 \) test or Fisher’s exact test will be applied to compare possible bias due to imputation, sensitivity analyses will be performed by conducting a complete case analysis. Repeated-measures analysis of variance 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.

Quality Of Life (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 standardised 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 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 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 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 analyse the effects of factors, in addition to treatment, that may be associated with OS and PFS. \( \chi^2 \) test with Pearson’s or Fisher’s exact test will be used to compare the objective response rates (ORR) between the two treatment arms.

| Assessment                  | Before randomisation | First follow up at 3 months (+4 weeks) | Every 3 months 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                                      | (at 6 and 12 months)                   | –                                   |

CECT, Contrast enhanced Computed Tomography; MRI, Magnetic Resonance Imaging; PET, Positron Emission Tomography; QOL, Quality Of Life; RO, Radiation Oncology.
| Author            | Study design | Patients (n) | Sites (n) | Intervention                                    | Med FU (months) | Inclusion            | Median outcomes in months |
|-------------------|--------------|--------------|-----------|-------------------------------------------------|-----------------|----------------------|--------------------------|
| Gomez et al<sup>19</sup> (NSCLC) | RCT-II CRT arm No CRT | 25 | ≤3 | LCT+MT vs MT/O alone | 38.8 | Synchronous* | PFS 14.4 vs 4.4 OS 41.2 vs 17 |
| Iyengar et al<sup>20</sup> (NSCLC) | RCT-II | 14 | ≤5 | SABR+MT vs MT alone | 9.6 | Synchronous | PFS 9.7 vs 3.5 |
| Palma et al<sup>21</sup> (various primaries) | RCT-II | 66 | ≤5 | SABR+SOC vs SOC alone | 26 | Synchronous or metachronous | OS 41 vs 28 |
| Sutera et al<sup>29</sup> (various primaries) | Phase II 147 (lung-32) | 40 | ≤5 | SABR | 41.3 | Synchronous or metachronous | OS 42.3 (lung OS—26.8) |
| De Ruyscher et al<sup>32</sup> (NSCLC) | Phase II | 29 | ≤5 | SBRT | 24.2 | Synchronous | OS—28.4 PFS—11.2 |
| Petty et al<sup>30</sup> (NSCLC) | Phase II | 26 | ≤5 | SBRT | 16.4 | Synchronous | OS—23 PFS—11.2 |
| Coli et al<sup>33</sup> (NSCLC) | Phase II | 37 | ≤5 | RCT | 32.5 | Synchronous* | OS—not reached PFS—23.5 |

*Includes oncogene mutation-positive patients.

LAT, local ablative therapy; LCRT, local consolidation radiation therapy; NSCLC, non-small cell lung cancer; OM, oligometastases; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiation therapy; SMT, standard maintenance therapy; SOC, standard of care; TNBC, triple-negative breast cancer.
Table 5  Ongoing randomised studies in oligometastatic NSCLC

| Trial ID          | Country | Trial design | OM sites (n) | Presentation | Primary Site | Oncogene mutation | Control arm         | Experimental arm   | Primary end point | Estimated year of completion |
|-------------------|---------|-------------|--------------|--------------|--------------|-------------------|---------------------|-------------------|-------------------|------------------------|
| SARON             | UK      | RCT III     | ≤3           | Synchronous at least 1 extracranial site | NSCLC Negative* | SMT to primary and SBRT for OM | SMT/RT to primary and SBRT for OM | Systemic therapy followed by LAT | OS                | 2022                   |
| OMEGA             | Italy   | RCT III     | ≤3           | Synchronous or metachronous NSCLC Negative and Positive | NSCLC Negative and Positive | Systemic therapy followed by SBRT | Systemic therapy followed by SBRT | Systemic therapy followed by SBRT | OS                | 2022                   |
| CORE              | UK      | RCT II/III  | ≤3           | Metachronous Breast, Prostate, NSCLC – | Negative – | SOC SBRT followed by SOC | SOC SBRT followed by SOC | SOC SBRT plus SOC | PFS               | 2024                   |
| PROMISE-005       | USA     | RCT II      | ≤5           | Synchronous or metachronous TNBC, NSCLC Negative and Positive | NSCLC Negative and Positive | SOC SBRT followed by SOC | SOC SBRT plus SOC | SOC SBRT plus SOC | OS                | 2022                   |
| NRG LU 002        | India   | RCT II/III  | ≤3           | Synchronous or metachronous (extracranial) NSCLC Negative | Negative | SMT LCT+SMT | SMT LCT+SMT | SMT LCT+SMT | PFS               | 2024                   |
| Current study     | Multicentric | RCT III     | ≤5           | Negative | Synchronous | SMT LCRT+SMT | SMT LCRT+SMT | SMT LCRT+SMT | OS                | 2024                   |

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

LAT, local ablative therapy; LCRT, local consolidation radiation therapy; NSCLC, non-small cell lung cancer; OM, oligometastases; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; SBRT, stereotactic body radiation therapy; SMT, standard maintenance therapy; SOC, standard of care; TNBC, triple-negative breast cancer.
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, Eastern Cooperative Oncology Group (ECOG) PS, toxicity assessment using NCI CTC version 5.0 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 CT 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.

**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, dated 21 April 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.

**DISCUSSION**
Oligometastatic disease deserves attention owing to the increasing evidence from various retrospective and prospectively randomised studies. Two-phase II randomised 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 multicentre, randomised phase III trial being conducted in 30 hospitals in the UK 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 tumours (and mediastinal nodes where present) and SBRT/Stereotactic radiosurgery to all metastatic sites. The primary end-point of the study is OS.

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

Our institute sees approximately 2500 new lung cancer patients annually. The proposed study is a single-centre study and will recruit patients with ≤3 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 randomisation. 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.

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