

---

## Study Protocol

### **A Phase II Open-Label Multi-center Trial of Isotoxic Hypofractionated Radiotherapy for NSCLC**

#### **ABSTRACT**

**Background:** The standard treatment for advanced unresectable non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy. However, many poor KPS or elderly patients cannot tolerate it due to their serious side effects. For patients who cannot tolerate concurrent chemoradiotherapy, conventional treatment is sequential chemoradiotherapy or radiotherapy alone. But the median survival time of sequential chemoradiotherapy and radiotherapy alone is 11-16 months. In order to improve curative effect, radiotherapy, as an important treatment method, has been tried, innovated and improved continuously. The goal of this trial is to evaluate feasibility and safety of isotoxic hypofractionated radiotherapy in patients with NSCLC.

**Methods:** This is a phase II open-label multi-center two-step non-randomised Trial. In the first stage, 12 patients will be included in the trial with radiotherapy of 3Gy per fraction. More than 3 patients had serious side effects of radiotherapy, the trial will be terminated. Otherwise, the second phase will continue, and the total number of participants was 30.

---

All patients eventually will be followed up for 5 years.

The primary endpoint is the safety of isotoxic hypofractionated radiotherapy. The secondary outcomes are time to progression (TTP), progression free survival (PFS), overall survival(OS), local control(LC).

**Discussion:** In clinical practice, the local control rate of conventional fractionated radiotherapy for NSCLC is very low. We hope that this trial can verify the safety of isotoxic hypofractionated radiotherapy.

**Trial registration:** NCT03606291, REGISTERED JULY, 30, 2018.

**Keywords:** Non-small cell lung cancer, Isotoxic hypofractionated radiotherapy

## Introduction

Lung cancer seriously harms human health and is an important cause of human death. The standard treatment for advanced unresectable non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy<sup>[1-4]</sup>. However, many patients cannot tolerate it due to its severe side effects. A meta<sup>[5]</sup> analyzed from 3 prospective Radiation Therapy Oncology Group trials (RTOG 91-06, 92-04, and 94-10) in which concurrent chemoradiotherapy for good-Karnofsky performance status(KPS) NSCLC showed that 18% of patients had to discontinue radiotherapy because of acute side effects. It is still difficult for people with good KPS to perform concurrent chemoradiotherapy, not to mention those poor KPS or elderly

---

people. Driessen<sup>[6]</sup> reported that Only 26% older patients can tolerate concurrent chemoradiotherapy, while sequential chemoradiotherapy reaches 40%. For patients who cannot tolerate concurrent chemoradiotherapy, Radiotherapy plays an irreplaceable role. In order to improve curative effect, radiotherapy, as an important treatment method, has been tried, innovated and improved continuously.

In the era before modern imaging and treatment planning design, randomized trials conducted by the radiotherapy Oncology Group (RTOG) showed that a standard treatment dose of 60-70 Gy was established using conventional fraction. But the standard dose of 60-70Gy for conventional fractionated radiation was not well controlled<sup>[7]</sup>, the median survival time was only 11-16 months<sup>[3, 8-11]</sup>. So the dose escalation had been studied. Retrospective and non randomized prospective data suggested that further dose escalating in NSCLC might be associated with better outcomes. However, Schild<sup>[12]</sup> analyzed 3600 patients with locally advanced non-small cell carcinoma. It was found that conventional fractionated radiotherapy with dose above 60Gy did not improve survival, but was significantly related to the side effects of radiotherapy above grade 3, which could significantly increase the treatment-related mortality. So escalating doses by conventional fractionated radiotherapy was not the effective method to increase curative effect. The repopulation of cancer stem cells was one of the most important factors of radiation resistance<sup>[13]</sup>.

---

That means the longer the overall treatment time , the less damage to the local tumor control <sup>[14]</sup>. So gradually increasing doses with conventional fraction did not improve overall survival as we wish.

Because of the poor efficacy of conventional fractionated radiotherapy, the research on changing the fraction method has always been a research hot spot. There are usually two methods: hyperfractionated or hypofractionated radiotherapy. Hyperfraction means multiple smaller doses of radiotherapy daily, hypofraction means fewer fractions with larger doses radiotherapy daily. Both can increase the doses which can convert into the Equivalent Dose in 2 Gy/f (EQD2) and shorten the total treatment time. CHART<sup>[15]</sup> confirmed that hyperfraction was superior to conventional radiotherapy. ECOG 2597<sup>[16]</sup> found that there was a positive statistical trend indicating a survival advantage of hyperfraction radiotherapy over conventional radiotherapy. However, this highly fractionated dose approach poses great challenges. Din<sup>[17]</sup> retrospectively included 609 patients in 4 UK centers with 55 Gy in 20 fractions, found that 2 year overall survival was 50%. Some phase I- II trials<sup>[18] [19-21] [22, 23]</sup> also confirmed the safety of hypofractionated radiation therapy.

Current general studies had adopted uniform prescription doses. However, uniform prescription doses radiotherapy resulted in individual dose deficiency as some patients could tolerate higher radiation doses without severe toxicity, but for others higher radiation doses were not

---

tolerated. Therefore, we need to perform individualized dose prescription according to maximum tolerated doses (MTD) based on normal tissue.

The MAASTRO (Maastricht Radiation Oncology clinic) in the Netherlands<sup>[24-26]</sup> study published well established results from prospective studies using individualized dose prescriptions. Patients were irradiated using an individualized prescribed total tumor dose (TTD) based on normal tissue dose constraints up to a maximal TTD of 79.2 Gy in 1.8 Gy fractions twice daily. Only sequential chemoradiation was administered. The median prescribed TTD was 64.8 Gy, grade 4 acute toxicity was 2.4% and grade 4 late toxicity was 1.8%. No patients developed grade 5 toxicity. Individualized prescribed TTD based on normal tissue dose with sequential chemoradiation showed well survival rates that come close to results of concurrent chemoradiation schedules, with acceptable acute and late toxicity. Haslett<sup>[27]</sup> reported a multicenter clinical study in which 37 patients of Stage III Non-Small Cell Lung Cancer were recruited. Radiation dose was increased until a maximum dose of 79.2 Gy in 1.8 Gy fractions twice daily was reached or 1 or more of the organs at risk met predefined constraints. A maximum dose of 79.2Gy was achieved in 37.8%. Grade 3 esophagitis was reported in 2 patients, and no patients developed grade 3 to 4 pneumonitis. But there were 3 grade 5 events: acute radiation pneumonitis, bronchopulmonary hemorrhage, and acute lung infection. The treatment-related death rate was 5.7%. Its severe toxic side

---

reaction was acceptable, although exceeding that of the MAASTRO trial.

However, considering the time consuming and effort of accelerated hyperfraction radiotherapy, clinical operation was difficult. As an alternative to accelerated hyperfraction radiotherapy, it can also provide good therapeutic results by reducing the total treatment time and providing a high biological effective dose (BED). Landau<sup>[28]</sup> reported a multicenter phase I/II clinical study in which 84 patients were recruited from eight centers: the first group received 65 Gy, 68 Gy and 71 Gy with the maximum safety limit for the esophagus, and another group received radiotherapy under the premise of ensuring the maximum safety limit of other organs (mainly the lung). The number of fractionation was 30 and the average tumor dose was 67.7 Gy. 5 cases of grade 3 esophagitis and 3 cases of grade 3 pneumonia were observed in both groups. After 35 months of follow-up, the mean overall survival rate was 36.9 months. The overall survival rate and progression free survival rate were 87.8% and 72.0% at 1 year and 68.0% and 48.5% at 2 years, respectively. All the above experiments were isotoxic individualized treatment experiments. However, the isotoxicity or individualized designs were not as comprehensive as our experiment. They did not include all organs at risk or did not achieve full individualization. Our experiment draws from the experience of MAASTRO, using an individualized prescribed total tumor dose (TTD) based on normal tissue dose constraints up to a maximal TTD, but not

---

using accelerated hyperfraction radiotherapy. The goal of this trial is to evaluate feasibility and safety of isotoxic hypofractionated radiotherapy in patients with NSCLC.

## **Methods/design**

### **Trial objectives**

#### *Primary objective*

The primary objective is to evaluate the safety of isotoxic hypofractionated radiotherapy. The safety endpoint is the number of participants with treatment-related severe adverse events, defined as the Grade **IV** radiation esophagitis, Grade **III** radiation esophagitis which results in interruption of radiotherapy for 7 days or more and Grade **III** or above radiation pneumonitis<sup>[29]</sup>.

#### *Secondary objectives*

The secondary objectives are to evaluate:

- PFS: survival defined by the time, in months, before recurrence or death at 5 years after enrolled in the trial.
- OS: survival defined by the time, in months, before death (for any reason) at 5 years after enrolled in the trial.
- TTP: survival defined by the time, in months, before tumor progression at 5 years after enrolled in the trial.

---

- LC: Percentage of patients without progression of the tumor which received radiotherapy at 3 and 5 years after enrolled in the trial.

### Study population

Patients will be considered eligible according to the following criteria.

#### Inclusion criteria:

1. Pathological or cytological diagnosis confirmed non-small cell lung cancer;
2. clinical stage according to the 8th edition of American Joint Committee on Cancer ( AJCC ), including stage III without resectable or who when SBRT/SABR are not suitable;
3. Age 18 or older<sup>[30]</sup>;
4. Life expectancy  $\geq 3$  months;
5. Karnofsky performance status  $\geq 60$ ;
6. Blood routine is normal, liver and kidney function  $\leq 2.5$  times the upper limit of normal;
7. Sequential chemotherapy is allowed, before and/or after radiotherapy;

#### Exclusion criteria :

1. Serious medical complications included pulmonary fibrosis history, myocardial infarction within 6 months, heart failure with level II and



---

above, uncontrolled heart failure, uncontrolled COPD, uncontrolled diabetes patients, etc.

2. Others who are not suitable for hypofractionated radiotherapy.

### Trial design

The present trial is a phase II open-label multi-center two-step non-randomised trial. Three centers in the China are participating in this trial (The Second Hospital of Hebei Medical University, North China Petroleum Bureau General Hospital of Hebei Medical University, No.1 Hospital of Shijiazhuang City). The aim of the study is evaluating the safety of isotoxic hypofractionated radiotherapy for patients with stage III NSCLC accord to inclusion and exclusion criteria. 12 patients are planned to be enrolled in first step and 18 patients are planned to be enrolled in second step. (Fig.1) The two-steps based on Simon's Optimal two-stage design<sup>[31]</sup>. Twelve patients in the first step will stop the trial if one of the following conditions were metted:

- 1) 4 or more patients have grade III or above radiation pneumonitis.
- 2) 4 or more patients have grade IV and above radiation esophagitis, and/or radiation esophagitis of grade III cause radiotherapy interruption for more than 1 week<sup>[29]</sup>.

In order to recruit patients, we set up publicity boards for recruiting patients in outpatient clinics and wards.

### Study process

---

The trial schema is illustrated in Fig.2.

### *Baseline examination*

At baseline, patients will undergo fiberoptic bronchoscopic biopsy or percutaneous lung biopsy , routine tumor biopsy, chest enhancement computed tomography(CT), upper abdomen CT, whole body bone scan, Brain magnetic resonance imaging(MRI), electrocardiogram(ECG), positron emission tomography /Computed Tomography (PET/CT) if the patient requests, blood carcinoembryonic antigen (CEA), blood Squamous cell carcinoma antigen (SCC), bloodneuron-specific enolase (NSE), blood Glycoantigen 125 (CA125), blood cytofragmented 19 keratin (cyfra 21-1), blood routine, blood biochemistry, coagulation routine, plasma D-dimer, urine routine, stool routine.

### *Interventions*

Isotoxic hypofractionated radiotherapy is a special type of radiotherapy that uses a hypofractionated method to give individualized doses to the tumor, at the same time ensuring normal tissue dose within the normal range. Its requirements are as follows:

1. Fraction mode: 3Gy/f.
2. radiotherapy techniques: Intensity Modulated Radiation Therapy (IMRT). Image Guided Radiation therapy (IGRT) at least once a week.
3. Breathing control: there is no requires for 4D-CT or respiratory gating

---

technology, but 4D-CT will be encouraged. Patients undergoing pre-radiotherapy training should try to calm their breathing.

4. Imaging/localization: a planning CT scan will be performed with intravenous contrast injection. Patients will be scanned and treated, in the supine position with arms cross above their head, and immobilization with thermoplastic device or vacuum cushion as per local protocols, in order to properly limit the respiratory movement. The scan will fully include target and all organs at risk. CT scans layer thickness 5 mm and scan range begin from cricoid cartilage (including full neck if special conditions), and the lower bounds consisted of complete lungs and liver. Image data is input into the IMRT planning system. The target area is outlined in the plain scan image sequence, and enhancement image sequence fusion is performed for reference. Non-small cell lung cancer target area delineation consensus: In the lung window (1600, -600 HU)<sup>[32]</sup> outline the target area of the primary lung lesion, in the mediastinal window (400, 20 HU) outline the mediastinal target area, using the involved-field irradiation, not elective node irradiation.
5. Volume definitions: the Gross tumor volume (GTV) is the primary lung lesion and lymph nodes with a short diameter larger than 1 cm on CT, or lymph nodes with a short diameter less than or equal to 1 cm but PET/CT shows positive or biopsy confirmed; Clinical target volume

---

(CTV) is GTV expand 6mm (squamous and non-adenocarcinoma), or 8mm (adenocarcinoma), 3-5mm (metastatic lymph nodes) ; PTV was based on lung respiratory dynamics observed under a simulator. External expansion for CTV was 10-15 mm. The GTV was confirmed by two radiotherapists and one radiologist. Radiotherapists outline body contours and organs at risk. IMRT was performed using 5-7 coplanar or non-coplanar fields.

6. radiation therapy prescription and organ at risk(OAR) doses:

(1) isotoxic Individualized Dose:

A. With normal tissues and organs as a toxicity-limiting condition<sup>[29]</sup>:

Spinal cord:  $0\% > 45 \text{ Gy}$ , and  $\leq 2\text{Gy}$  each time, Lung:  $V20 \leq 30\%$ ,  $V5 \leq 65\%$ ,  $MLD \leq 16\text{Gy}$ , Esophagus: highest dose  $\leq 72\text{Gy}$ .

B. Maximum limit: If the limit of any "A" is not reached, the maximum radiation dose is  $72 \text{ Gy}^{[22, 23]}$ .

(2) The lowest radiation dose:  $45\text{Gy}$ .

7. Quality Assurance:

Prior to treatment, each patient's plan must be peer-reviewed, or approved by another radiation oncologist. All radiation treatment plans must meet target dose request for OAR. Before the plan is approved, the dose for each OAR must be verified by a physicist and an oncologist.

---

### *Clinical response evaluation(CRE)*

Patients will undergo the first CRE immediately at the end of radiotherapy by CT chest, then undergo every 3 months after radiotherapy for the first 2 years, and every 6 months for the next 3 years. The results of CRT are according to response evaluation criteria in Solid Tumors(RECIST 1.1)<sup>[33]</sup>.

### *Quality of life assessment*

Each patient will be asked to fill in self-administered questionnaires (EORTC QLQ-C30 and LC13) to assess health-related quality of life (QoL). QoL will be assessed at baseline, 4 weeks after the beginning of radiotherapy and the end of radiotherapy.

### *Follow up*

The first visit will begin at 1 month after radiotherapy. Patients will be seen every 3 months post radiotherapy for the first 2 years, and every 6 months until 5 years or death after treatment. At each visit, the history and physical examination will be conducted and recorded by oncologists, and adverse events (AE) of radiation pneumonitis and radiation esophagitis will be recorded. The EORTC QLQ-C30 (version 3) and LC13 quality of life questionnaire will also need to be completed.

---

Chest enhancement CT or PET/CT will repeated in each visit, upper abdomen CT, whole body bone scan, Brain MRI will repeated every 6 months. Disease recurrence or progression should be documented by appropriate imaging or biopsies. And we will specially arrange a follow-up doctor to remind patients to review by telephone.

### Quality assurance

The trial will be performed in three centers. Patients will be recruited, treated and followed up at the radiation department of The Second Hospital of Hebei Medical University (China), North China Petroleum Bureau General Hospital of Hebei Medical University (China), No.1 Hospital of Shijiazhuang City (China). Then, at least two radiologists will check all the inclusion and exclusion criteria. Patients will be informed of the trial protocol and, on acceptance, will be enrolled into this trial. The trial will be open blinded because of the procedures employed and with an objective primary end point. The patient will be informed of the isotoxic hypofractionation group. Unacceptable treatment-related toxicity or adverse events which will be recorded in the case report form, must be judged by either the patient's treating physician or the chief investigator.

The radiotherapy target area and plan of the first two patients in each center need to be approved by the three centers before treatment. The data entry will be checked by two people, and the case report forms will be

---

locked in the filing cabinet. The chief investigator will review all case report forms every six months.

### **Statistical analysis**

The study primary end point is the safety of isotoxic hypofractionated radiotherapy. We use the PASS software to calculate the sample size according to the Simon optimal two-stage designs for phase II clinical trials<sup>[31]</sup>. The study design is with a two-sided alpha level of 0.125, and an estimated 85% power to detect increase in no radiotherapy side reaction patient of 15% i.e. 75% to 90%. Finally, we calculated that the result was 12 participants in the first step. More than 3 patients had serious side effects of radiotherapy, the trial will be terminated. Otherwise, the second step will continue, and the total number of participants was 30. Shedding, withdrawal and loss of follow-up cases will not be included in the statistical analysis. We will continue to include patients until the number of qualified patients reaches the experimental design.

### **Ethical and regulatory considerations**

The trial has been submitted and approved by a research ethics committee in each of the participating hospitals, and received clinical trials authorisations from regulatory authorities. This trial was approved by the research ethics committee of the second hospital of Hebei Medical

---

University (2018-R099). The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. If there is any important modification of the protocol, we will modify it on the official website of the clinical trial registration as soon as possible after the approval of the ethics committee. In each centre, the lead investigator will be responsible for identification, recruitment, data collection, completion of case report forms, follow-up of study patients and adherence to study protocol. Informed consent will be obtained from participants by the local lead investigator using a standard consent form and participant information sheet. Authorship will be defined as per International Committee of Medical Journal Editors guidelines. Results will be communicated at relevant international conferences, via publication and on the clinical trial registry. Data are collected using the individual trial case number on standard case report forms collated centrally by IHR and personal information will not be individually identifiable. The final trial dataset will be available to study investigators but will not be analyzed per centre.

### **Withdrawal criteria**

Situations where a study treatment may need to be interrupted for other clinical reasons will be considered. If an interruption happened, the study chief investigator will be notified in advance, and further advice sought with regards to the appropriateness of restarting study treatment. Other



---

criteria for which treatment will be withdrawn include: disease progression before completion of study treatment; withdrawal of consent for treatment and/or study participation; pregnancy; and patient non-compliance.

## **Discussion**

Isotoxic dose prescription was a new model in radiotherapy. The radiation dose was prescribed according to the tolerance dose of the nearby OAR. Meanwhile, the prescribed total tumor dose maximizes to the highest technically achievable level to increase the probability of tumor control. The strategy has the potential to overcome several limitations of conventional radiotherapy dose prescribing based on tumor volume, and is expected to increase the overall proportion of treatments for tumor control without severe toxicity <sup>[34]</sup>. The individualized radiation dose prescription is expected to further improve the efficacy of radiotherapy. In the future, further individualization of treatment may include patient specific factors, such as complications and biological tumor characteristics, such as hypoxia, growth factors and cytokines, gene changes and imaging data, giving personalized PTV boundaries and improving dose volume parameters and dose limits for patient tumor characteristics.

In conclusion, individual prescription radical radiotherapy based on normal tissue dose limitation has a good prospect. In addition, we expect

---

that the isotoxic individualized radiotherapy regimen can be safely applied with acceptable acute and late toxicity, which may be the basis of phase III prospective randomized trials and ultimately prove the superiority of this individualized method.

## **Abbreviations**

4D: Four dimensional; AE: Adverse Event; AJCC: American Joint Committee on Cancer; ALT: Alanine aminotransferase; BED: Biological effective dose; BID: Twice A Day; CT: Computed Tomography; CTV: Clinical Target Volume; Dmax: Maximum Dose; COPD: Chronic Obstructive Pulmonary Disease; EORTC: European Organization for Research and Treatment of Cancer; FEV1: Forced Expiratory Volume in 1 second; GTV: Gross Tumour Volume; Gy: Gray; ICORG: Ireland Co-operative Oncology Research Group; IMRT: Intensity-modulated radiation therapy; IGRT: Image Guided Radiationtherapy; KPS: Karnofsky; LC: local control; Mg: Milligram; ml: Millilitre; MLD: mean lethal dose; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; MAASTRO: Maastricht Radiation Oncology; NSCLC: Non-small cell lung cancer; OAR: Organ at risk; OS: Overall Survival; OS: Overall survival; PET/CT: Computerised Tomography-Positron Emission Tomography; PTV: Planning Target Volume; PFS: Progress free survival; QoL: Quality of Life; RT: Radiation therapy; RTOG: Radiation Therapy Oncology Group; RTQA:

---

Radiotherapy quality assurance; SABR: Stereotactic ablative radiotherapy;  
SBRT: Stereotactic body radiotherapy; TNM: Tumor/Nodes/Metastases;  
TTP: Time to progression;

### **Ethics approval and consent to participate**

The study will be performed in accordance with the declaration of Helsinki and the Ethical Guidelines for Clinical Research by the Ministry of Health, Labor, and Welfare in China<sup>[35]</sup>. The trial has been submitted and approved by a multi-centre research ethics committee in each of the participating hospital, and received clinical trials authorisations from regulatory authorities (The Second Hospital of HMU: 2018-R099). written informed consent will be obtained from all patients.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

All information will be provided in the published articles.

5010 words.

## **References**

1. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non-Small-Cell Lung Cancer. *Journal of clinical oncology*. 2010;28(13):2181-90.
2. O'Rourke N, Roqué I Figuls M, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev*. 2010;16(6):CD002140.
3. Curran WJ, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs Concurrent

- 
- Chemoradiation for Stage III Non-Small Cell Lung Cancer: Randomized Phase III Trial RTOG 9410. JNCI : Journal of the National Cancer Institute. 2011;103(19):1452-60.
4. Sause W, Kolesar P, Taylor IV S, Johnson D, Livingston R, Komaki R, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest. 2000;117(2):358-64.
  5. Machtay M, Hsu C, Komaki R, Sause WT, Swann RS, Langer CJ, et al. Effect of overall treatment time on outcomes after concurrent chemoradiation for locally advanced non-small-cell lung carcinoma: analysis of the Radiation Therapy Oncology Group (RTOG) experience. Int J Radiat Oncol Biol Phys. 2005;63(3):667-71.
  6. Driessen EJM, Schulkes KJG, Dingemans AC, van Loon JGM, Hamaker ME, Aarts MJ, et al. Patterns of treatment and survival among older patients with stage III non-small cell lung cancer. Lung Cancer. 2018;116:55-61.
  7. Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Pajak TF. A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83-11. J Clin Oncol. 1990;8(9):1543-55.
  8. Zatloukal P, Petruzella L, Zemanova M, Havel L, Janku F, Judas L, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung cancer (Amsterdam, Netherlands). 2004;46(1):87-98.
  9. Huber RM, Flentje M, Schmidt M, Pöllinger B, Gosse H, Willner J, et al. Simultaneous Chemoradiotherapy Compared With Radiotherapy Alone After Induction Chemotherapy in Inoperable Stage IIIA or IIIB Non-Small-Cell Lung Cancer: Study CT99/97 by the Bronchial Carcinoma Therapy Group. Journal of clinical oncology. 2006;24(27):4397-404.
  10. Belderbos J, Uitterhoeve L, van Zandwijk N, Belderbos H, Rodrigus P, van de Vaart P, et al. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). European Journal of Cancer. 2006;43(1):114-21.
  11. Groen HJM, van der Leest AHW, Fokkema E, Timmer PR, Nossent GD, Smit W, et al. Continuously infused carboplatin used as radiosensitizer in locally unresectable non-small-cell lung cancer: a multicenter phase III study. Annals of oncology. 2004;15(3):427-32.
  12. Schild SE, Fan W, Stinchcombe TE, Vokes EE, Ramalingam SS, Bradley JD, et al. Toxicity Related to Radiotherapy Dose and Targeting Strategy: A Pooled Analysis of Cooperative Group Trials of Combined Modality Therapy for Locally Advanced Non-Small Cell Lung Cancer. 2019;14(2):298-303.
  13. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta oncologica. 2009;27(2):131-46.
  14. Baumann M, Dörr W, Petersen C, Krause M. Repopulation during fractionated radiotherapy: much has been learned, even more is open. International Journal of Radiation Biology. 2009;79(7):465-7.
  15. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Parmar M, et al. Continuous,

- 
- hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. *Radiotherapy and oncology*. 1999;52(2):137-48.
16. Belani CP, Wang W, Johnson DH, Wagner H, Schiller J, Veeder M, et al. Phase III Study of the Eastern Cooperative Oncology Group (ECOG 2597): Induction Chemotherapy Followed by Either Standard Thoracic Radiotherapy or Hyperfractionated Accelerated Radiotherapy for Patients With Unresectable Stage IIIA and B Non–Small-Cell Lung Cancer. *Journal of clinical oncology*. 2005;23(16):3760-7.
  17. Din OS, Harden SV, Hudson E, Mohammed N, Pemberton LS, Lester JF, et al. Accelerated hypo-fractionated radiotherapy for non small cell lung cancer: Results from 4 UK centres. *Radiotherapy and Oncology*. 2013;109(1):8-12.
  18. Cheung P, Cheung P, Faria S, Faria S, Ahmed S, Ahmed S, et al. Phase II study of accelerated hypofractionated three-dimensional conformal radiotherapy for stage T1-3 N0 M0 non-small cell lung cancer: NCIC CTG BR.25. *JNCI : Journal of the National Cancer Institute*. 2014;106(8):dju164-dju.
  19. Lin Q, Liu Y-E, Ren X-C, Wang N, Chen X-J, Wang D-Y, et al. Dose escalation of accelerated hypofractionated three-dimensional conformal radiotherapy (at 3 Gy/fraction) with concurrent vinorelbine and carboplatin chemotherapy in unresectable stage III non-small-cell lung cancer: A phase I trial. *Radiation oncology (London, England)*. 2013;8(1):201-.
  20. Westover KDMDP, Loo BWMDP, Gerber DEMD, Iyengar PMDP, Choy HMD, Diehn MMDP, et al. Precision Hypofractionated Radiation Therapy in Poor Performing Patients With Non-Small Cell Lung Cancer: Phase 1 Dose Escalation Trial. *International Journal of Radiation Oncology, Biology, Physics*. 2015;93(1):72-81.
  21. Cagney DN, Thirion PG, Dunne MT, Fleming C, Fitzpatrick D, O'Shea CM, et al. A Phase II Toxicity End Point Trial (ICORG 99-09) of Accelerated Dose-escalated Hypofractionated Radiation in Non-small Cell Lung Cancer. *Clinical oncology (Royal College of Radiologists (Great Britain))*. 2018;30(1):30-8.
  22. Cagney D, Thirion P, Dunne M, Fleming C, Fitzpatrick D, O'Shea C, et al. A phase II toxicity end point trial (ICORG 99-09) of accelerated dose-escalated hypofractionated radiation in non-small cell lung cancer. *Clinical Oncology*. 2018;30(1):30-8.
  23. Thirion P, Holmberg O, Collins CD, O'Shea C, Moriarty M, Pomeroy M, et al. Escalated dose for non-small-cell lung cancer with accelerated hypofractionated three-dimensional conformal radiation therapy. *Radiotherapy and Oncology*. 2004;71(2):163-6.
  24. van Baardwijk A, Bosmans G, Bentzen SM, Boersma L, Dekker A, Wanders R, et al. Radiation dose prescription for non–small-cell lung cancer according to normal tissue dose constraints: an In silico clinical trial. *International Journal of Radiation Oncology\*Biology\*Physics*. 2008;71(4):1103-10.
  25. van Baardwijk A, Bosmans G, Boersma L, Wanders S, Dekker A, Dingemans AMC, et al. Individualized radical radiotherapy of non–small-cell lung cancer based on normal tissue dose constraints: a feasibility study. *International Journal of Radiation Oncology\*Biology\*Physics*. 2008;71(5):1394-401.
  26. van Baardwijk A, Wanders S, Boersma L, Borger J, Öllers M, Dingemans A-MC, et al. Mature results of an individualized radiation dose prescription study based on normal tissue constraints in stages I to III non–small-cell lung cancer. *Journal of Clinical Oncology*.

- 
- 2010;28(8):1380-6.
27. Haslett K, Bayman N, Franks K, Groom N, Harden SV, Harris C, et al. Isotoxic Intensity Modulated Radiation Therapy in Stage III Non-Small Cell Lung Cancer: A Feasibility Study. *Int J Radiat Oncol Biol Phys.* 2021;109(5):1341-8.
  28. Landau DBM, Hughes LN, Baker AM, Bates ATM, Bayne MCMD, Counsell NM, et al. IDEAL-CRT: A Phase 1/2 Trial of Isotoxic Dose-Escalated Radiation Therapy and Concurrent Chemotherapy in Patients With Stage II/III Non-Small Cell Lung Cancer. *International Journal of Radiation Oncology, Biology, Physics.* 2016;95(5):1367-77.
  29. (NCI) TNCI. Randomized phase II trial of individualized adaptive radiotherapy using during-treatment FDG-PET/CT and modern technology in locally advanced non-small cell lung cancer (NSCLC)(RTOG 1106/ACRIN 6697). RTOG 1106/ACRIN 6697. 2016.
  30. McPartlin AJ, Chaudhry S, Swindell R, Bayman N, Burt P, Chittalia A, et al. The largest UK single centre series using hypofractionated radical radiotherapy for NSCLC in the very elderly. *Lung Cancer.* 2013;81(1):144.
  31. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials.* 1989;10(1):1-10.
  32. Guangying Z TZ, Lvhu W, Xianshu Gao, Junjie Wang, et al. Consensus and controversy on target delineation of non-small cell lung cancer. *Chinese Journal of Radiation Oncology.* 2008;17(6):432-6.
  33. Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1—Update and clarification: From the RECIST committee. *European journal of cancer (1990).* 2016;62:132-7.
  34. Zindler JD, Thomas CR, Jr., Hahn SM, Hoffmann AL, Troost EG, Lambin P. Increasing the Therapeutic Ratio of Stereotactic Ablative Radiotherapy by Individualized Isotoxic Dose Prescription. *J Natl Cancer Inst.* 2016;108(2).
  35. Association WM. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA.* 2013;310(20):2191-4.

## Figure legends

Fig.1 Methodology design of the IHR study

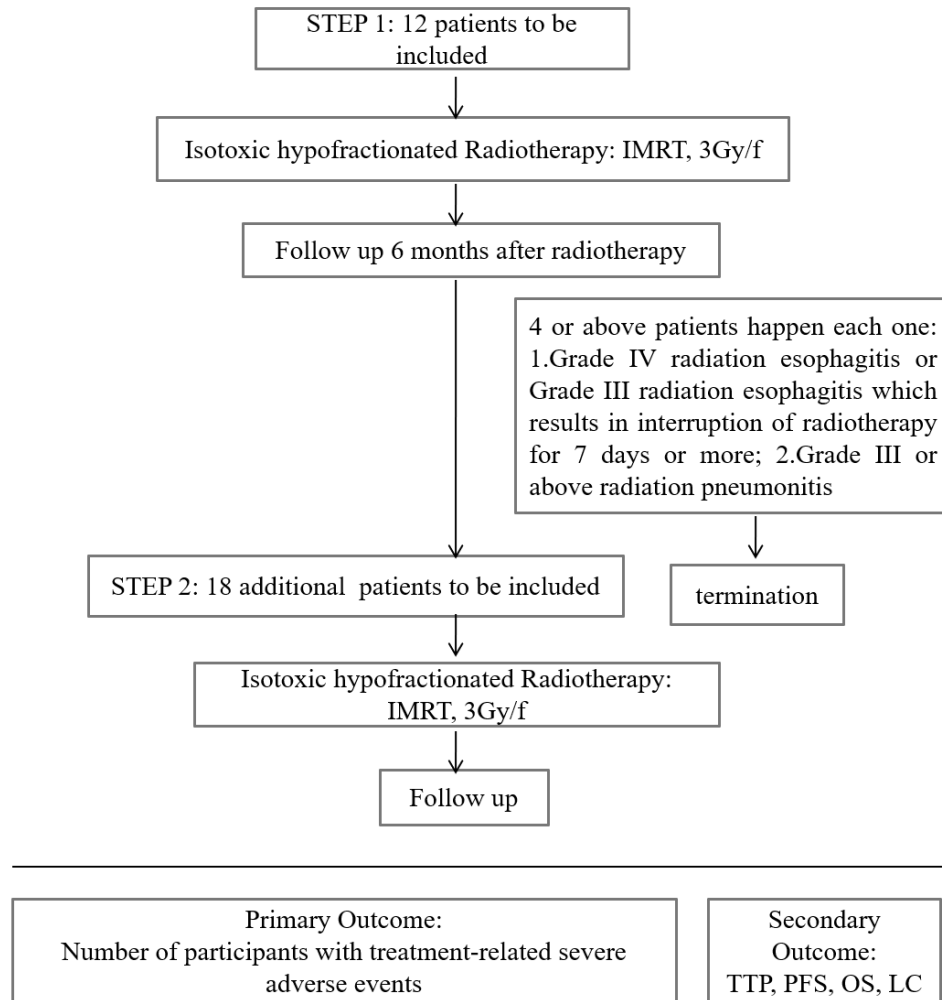


Fig.2 Schematic representation of the IHR study

