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Personalized radiation therapy through functional lung avoidance and response-adaptive dose escalation: utilizing multimodal molecular imaging to improve the therapeutic ratio (FLARE RT)

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Study Summary

Title	*Personalized radiation therapy through response-adaptive dose escalation and functional lung avoidance: utilizing multimodal molecular imaging to improve the therapeutic ratio (FLARE RT)*
Short Title	*FLARE RT*
Protocol Number	*CCIRB 9599*
Phase	*Phase II*
Methodology	*Single Arm Open-Label*
Study Duration	*5 yrs.*
Study Center(s)	*University of Washington Medical Center*
Objectives	*To utilize mid-treatment FDG PET/CT tumor response to select non-responding patients for dose escalation, while utilizing functional lung avoidance to mitigate toxicity. Changes in tumor FDG uptake on mid-treatment PET/CT (24 Gy nominal) will divide patients into "responders" and "non-responders". Responders will receive 60 Gy to their tumor per standard of care; non-responders will undergo dose escalation to 74 Gy. All patients will receive functional lung avoidance radiation treatment via SPECT/CT imaging with ^{99m}Tc-MAA and ^{99m}Tc-SULFUR COLLOID to accurately identify and preferentially spare functional lung. Primary endpoint of this study will be 2-yr. overall survival.*
Number of Subjects	*The projected enrollment number is 60 in order to meet the study goal of 50 evaluable subjects.*
Diagnosis and Main Inclusion Criteria	*Patients diagnosed with stage IIB-III non-small cell lung cancer receiving definitive chemoradiation.*
Study Product, Dose, Route, Regimen	*All scans are FDA approved for use with patients: ^{18F}FDG-PET/CT and SPECT/CT with ^{99m}Tc-MAA and ^{99m}Tc-Sulfur Colloid*
Duration of administration	*Beyond standard of care imaging, some patients may undergo a repeat baseline protocol specific FDG-PET/CT, and be considered research, then a PET/CT mid-treatment, and 2 SPECT/CT scans (pre-treatment and 3 months post-treatment).*

Statistical Methodology	*Primary endpoint of the study will be 2 yr. overall survival, compared to the 60 Gy cohort of RTOG 0617 (57% 2yr OS). With an estimated improvement to 72% 2yr OS, we will need 49 patients to test for superiority of FLARE RT at 80% power and 5% Type I error. Secondary endpoints will include toxicity, and in particular CTCAE v4 grade 2 or higher pneumonitis, and 1 yr. local control, progression-free survival, and pulmonary function test decline. We will also collect plasma and urine for future correlative studies.*

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1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Radiation is a major treatment option for patients with locally advanced non-small cell lung cancer (NSCLC), but current treatment regimens result in suboptimal tumor control with local failures up to 50% and 5-year overall survival (OS) of 10-20%, while carrying substantial risk of toxicity, with grade 3+ pulmonary toxicity seen in approximately 20% of patients (1-4). We propose to improve the therapeutic ratio by limiting pulmonary toxicity risk through radiation dose avoidance of functional lung defined on ventilation/perfusion SPECT/CT and increasing local control through FDG-PET/CT guided tumor dose escalation in select patients at high risk of local failure. We will explore several questions with clinical significance: (1) whether the combination of selective tumor dose escalation and functional lung avoidance synergistically impacts patient outcomes, (2) whether patient selection based on early FDG PET response can improve the potential survival benefit from PET-guided dose escalation, (3) whether radiation dose burden to functional lung better predicts clinical lung toxicity than radiation dose burden to anatomic lung, and (4) whether image parameters of spatial and functional heterogeneity in lung can select patients prior to treatment who are at highest risk of pulmonary toxicity. Answers to such questions within the scope of this pilot trial will support the launch of a multi-center trial that can definitively assess the efficacy of FLARE RT. Development of functional lung imaging heterogeneity tools and FLARE RT planning tools will enable radiation oncologists and radiologists to more precisely manage and deliver care to cancer patients.

1.2 Local Control Impacts Survival in Locally Advanced NSCLC

Although current treatments have dose limiting toxicities including pulmonary toxicity, local control after radiation treatment is still suboptimal at around 50%. When patients die from NSCLC, both metastatic sites of disease and disease in the chest contribute to the causes of deaths (5). The lack of local control of lung tumor is clearly correlated with worse survival, and the death-rate for patients with intra-thoracic disease recurrence is similar to death-rate for patients with metastatic disease (6-8). In the CHART randomized trial testing different radiation dose/fractionation schemes, improving the local control from 20% to 29% resulted in improvement in median survival from 10 months to 28 months (9). Therefore, local control of lung tumors does impact the overall survival in patients with locally advanced lung cancer.

1.3 Radiation Dose Escalation Can Improve Local Control in NSCLC, but Uniform Dose Escalation Is Detrimental

Dose-escalation studies have shown promising local control rates when radiation dose is escalated above the standard 60 Gy in conventional fractionation. One study looking at 122 patients receiving definitive radiation treatment for lung cancer, without surgery, found that each 1 Gy increase in dose resulted in approximately 1.25% improvement in

5-year local control (3). For patients treated to 63-69 Gy, 5-year local control was 12%, versus 49% for patients treated to >90 Gy. The same trend is seen for 5-year OS, 4% versus 28% for the lower dose versus higher dose groups, respectively. Analysis of multiple patient series has found that a 1 Gy increase in dose leads to 3-4% improvement in survival and local control (10).

The potential survival advantage from dose escalation beyond 60 Gy was tested in a randomized trial in RTOG 0617, where patients with locally advanced NSCLC were treated to 60 Gy versus 74 Gy (11). Surprisingly, results showed that uniform dose escalation to the entire tumor volume in all patients is inferior to standard dose radiation. Local control and OS were worse in the 74 Gy arm versus the 60 Gy arm. Exact cause of the inferior outcome in the higher dose arm is unclear, but higher heart radiation dose was found to be associated with worse outcomes, and heart dose was higher in the 74 Gy arm compared to the 60 Gy arm. It is unknown if the higher heart dose is truly the cause of increased mortality, or a surrogate marker for other poor prognostic variables that were unbalanced between the two randomized arms. For example, multiple surgical series have found subcarinal lymph node involvement and multi-station mediastinal nodal involvement to be associated with poor survival in patients in lung cancer (12-14). The same effect is seen in patients treated with chemoradiation (15). Both subcarinal disease and multi-station nodal disease are associated with higher radiation dose to the heart (16). Therefore, it is possible that the higher heart dose in the higher dose arm is a surrogate for mediastinal nodal involvement, which is well known to have a negative impact on survival.

These results highlight the importance of selecting the right patient population for dose escalation, since not all patients experience local failures after 60 Gy, and only patients who would have experienced local failure would potentially benefit from escalated radiation dose beyond 60 Gy. Giving more radiation dose uniformly across an entire patient population will likely cause as much toxicity as benefit; therefore it is key to utilize strategies that can identify patients at high risk of local failure after conventional radiation doses of 60 Gy.

1.4 FDG PET/CT Can Select For Patients at High Risk of Local Failure and Guide Dose Escalation

Given that up to 50% of patients with NSCLC develop local recurrences after standard radiation treatment, methods to improve local control are needed. However, randomized data have shown that dose escalation in all patients leads to worse outcomes when looking at the entire patient population (11). Strategies to identify patients at high risk of local failure are needed to target therapy intensification in the group of patients who will benefit. High tumor uptake on mid-radiation treatment FDG PET relative to baseline FDG PET is associated with poorer clinical outcomes, and local recurrences after radiation treatment tend to occur inside FDG PET avid regions (17-19). It has been estimated that 60% of patients were classified as early non-responders on FDG PET and that this subpopulation had overall survival rates of 33% compared to 92% in the responder subpopulation (van Elmpt, Ollers, et al. 2012). This result highlights both the prevalence of poor tumor response early during treatment and its significant impact on patient outcomes. Further, high spatial correlation between FDG PET avid areas and

recurrent disease (20, 21) help refine the definition of high-risk treatment targets in NSCLC.

Ongoing clinical trials are defining targets on FDG PET/CT for concomitant dose escalation but do not select patients according to local failure risk. The PET boost trial in the Netherlands utilizes discrete dose escalation to FDG PET avid regions (50% SUV_{max} threshold) based on pre-treatment assessment and individualizes integral target dose boosts based on mean lung dose, but does not account for patient variability in early treatment response (22). RTOG 1106 is investigating whether tumor dose can be escalated to improve the local control rate based on FDG-PET/CT imaging at 40-46 Gy during treatment, which exploits higher achievable dose escalation following tumor volume regression (17). This adaptive dose escalation trial design to concurrently boost residual FDG PET avid regions late in therapy poses the following challenges: (1) potential for increased toxicity with little survival benefit from dose escalation in patients whose tumors have already responded to standard dose radiation therapy, (2) limited radiobiological effectiveness with 9/30 radiation treatment fractions available for dose escalation during accelerated tumor cell repopulation, and (3) enhancement of radiation-induced inflammatory response signal on late mid-therapy FDG PET/CT imaging that can confound target definition.

Patients at high local failure risk can be selected according to the quantitative change in tumor FDG PET SUV_{max} and total lesion glycolysis as early as 2-3 weeks into treatment, which is predictive of clinical outcomes (23, 24). An earlier assessment of treatment response (2-3 week time point instead of waiting until 40-46 Gy during week 4-5) has the benefit of allowing earlier implementation of dose escalation to regions at high risk of local failure. The 2-3 week mid-treatment PET/CT can select for patients who are at high risk of local relapse, and treat this high risk subpopulation with dose escalation to improve cancer control, which is another step towards personalized medicine for this patient population.

1.5 Radiation to the Lungs Causes Pulmonary Toxicity and Limits the Deliverable Dose

When improving the therapeutic ratio, dose escalation must always be weighed against potentially increased toxicity. Radiation to the lungs cause a spectrum of changes, with the two most clinically relevant changes being radiation pneumonitis (RP) and radiation induced fibrosis. Radiation pneumonitis is a disorder characterized by inflammation focally or diffusely affecting the lung parenchyma. It occurs in the subacute phase after radiation treatment, from several weeks to several months after completion of therapy. Radiation pneumonitis can be mild, causing shortness of breath that does not require intervention and resolves spontaneously, to severe, requiring steroids, oxygen, ventilation, or, if not treatable even, even death. Radiation pneumonitis is a dose-limiting toxicity in lung cancer treatment, causing worsening respiration in patients who often already have underlying lung disease, such as emphysema. Approximately 15-40% of patients develop clinically significant radiation pneumonitis after treatment with conventional radiation doses (25). Long term, lung tissue treated with radiation can develop fibrosis, and is no longer able to function in gas-exchange. This can lead to a permanent reduction in pulmonary function. Symptomatic lung damage is the major impediment to safely escalate dose to lung tumors.

1.6 Current Radiation Planning Methods are Unable to Accurately Predict Which Patients Will Develop Pulmonary Toxicity

Radiation pneumonitis and global pulmonary dysfunction are poorly predicted by current radiation planning methods, which consider all lung tissue to be equally important in pulmonary gas exchange (and equally vulnerable to radiation damage). Mean radiation dose to the lung (mean lung dose=MLD) and percent of lung volume receiving at least 20 Gy of radiation (V20) are the two most commonly used metrics for estimating risk for developing pulmonary toxicity from radiation treatment. Many other studies have tried to incorporate other variables into prediction models for radiation pneumonitis and global dysfunction, including clinical parameters as well as radiation treatment plan parameters, but the most widely used metrics for evaluating a radiation treatment plan are still MLD and V20. In a recent large international series of 836 patients, V20 was found to be predictive of radiation pneumonitis: 18% of patients receiving V20<20% (lowest lung dose group) developing symptomatic RP, 0% fatal; versus 30% symptomatic RP in the V20 between 20-30% patient group (intermediate lung dose group but still within V20 that is typically considered safe) and 1% fatal RP; versus the highest lung dose group with V20>40%, developing 36% RP and 3.5% fatality (25). This data emphasizes that even in the lowest lung dose group (according to V20), almost 20% of patients are still developing radiation pneumonitis; and even in the highest lung dose group, more than 60% of patients do not develop RP. This calls for a better method of predicting RP than the current parameters of MLD and V20.

1.7 SPECT/CT Perfusion/Ventilation Scans can Detect Heterogeneity in Lung Function

Current standard practice in radiation oncology, relying on MLD and V20 to quantify lung dose, treats all lung tissue as if it functions equally. In reality, lung tissue function is spatially heterogeneous, especially in patients with baseline lung disease such as smoking-induced COPD where ventilation and perfusion-mediated gas exchange becomes compromised. Perfusion and ventilation SPECT/CT imaging using ^{99m}Tc-labeled MAA and SULFUR COLLOID, respectively, is commonly performed as a non-invasive diagnostic imaging test of pulmonary function, is utilized by surgeons to predict post-operative lung function, and has strong potential for use in RT planning (26). Conventional RT planning based on anatomic lung dose constraints yielded large variability in dose to functional lung across patients (27) that can be accounted for in functional avoidance planning. Prior studies using planar scintigraphy and MAA SPECT perfusion scans with long-term follow-up provided strong rationale for modeling regional perfusion reduction as a function of delivered radiation dose (28, 29). Independent investigations were able to link perfusion SPECT-weighted dose to post-RT pulmonary toxicity (30, 31). However, no link was established between regional perfusion deficits and pulmonary toxicity in part due to existing technical limitations in spatial resolution and quantitative accuracy that are now achievable with modern SPECT/CT imaging techniques (32). The technical feasibility of incorporating lung function imaging heterogeneity into treatment planning has been well-established (33-37) and can be readily implemented once an imaging surrogate for radiation-induced pulmonary toxicity risk is identified.

The established clinical utility and widespread availability of perfusion and ventilation imaging using ^{99m}Tc-labeled MAA and SULFUR COLLOID SPECT/CT, respectively, make this approach most feasible for eventual incorporation of functional lung avoidance into routine radiation oncology practice.

2 Study Objectives

Primary Objective

The primary endpoint of the study will be 2 year overall survival. The primary objective will be to test the superiority of 2yr OS in the FLARE RT patient cohort over the 60 Gy cohort of RTOG 0617 (57% 2yr OS) for historical control. Based on an estimated improvement to 72% 2yr OS, we will enroll at least **49 patients** to test for superiority of FLARE RT at 80% power and 5% Type I error.

Secondary Objective

- CTCAE v4 grade 2 or higher pneumonitis incidence from FLARE RT compared to historical controls (non-inferiority test)
- 1 yr local control, progression-free survival, and pulmonary function test decline
- Identification of baseline FDG PET/CT and mid-treatment FDG PET/CT imaging biomarkers for predicting patient survival
- Identification of baseline perfusion SPECT/CT imaging biomarkers for predicting G2+ pneumonitis and PFT decline
- Collection of plasma and urine samples for future correlative studies between imaging biomarkers and cytokine biomarkers of radiation response in both tumor and normal tissue

3 Study Design

3.1 General Design

This is a phase II study that will deliver personalized radiation treatment plans by combining differential tumor dose escalation based on residual tumor SUV of mid-treatment FDG-PET/CT in select patients classified as early FDG PET non-responders, and functional pulmonary avoidance based on perfusion SPECT/CT. The long-term goal is to improve patient survival without increasing toxicity of treatment.

Trial schema is shown below in Figure 1. All patients will undergo imaging at 3 time points: 1) baseline FDG PET/CT and SPECT/CT for tumor imaging and functional lung avoidance treatment planning; 2) mid-radiation treatment (24 Gy nominal) FDG PET/CT to assess tumor response to therapy; 3) 3 months post-radiation FDG PET/CT and SPECT/CT, to assess cancer response to treatment and functional lung tissue response. Based on tumor response at the mid-treatment PET/CT, patients will either be classified as responders (receive 60 Gy per standard of care with functional lung avoidance), or non-responders (dose escalation to 74 Gy while keeping overall treatment constant at 30 fractions and avoiding functional lung). Follow up of all patients will also include standard of care evaluations (see Table 1 for study calendar).

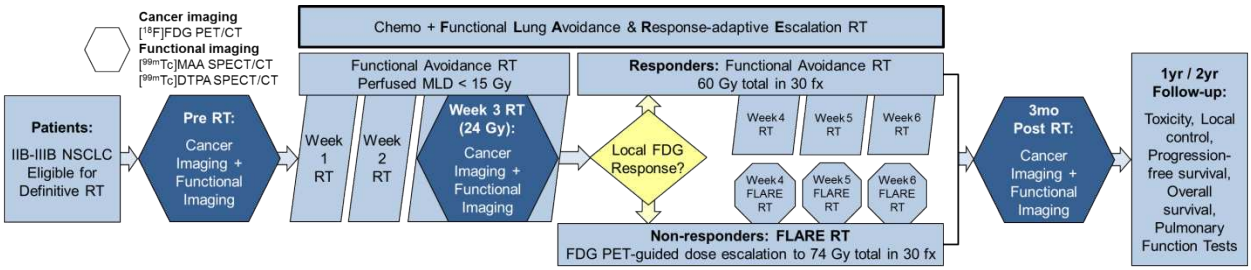

Figure 1. *Clinical trial schema for FLARE RT.*

Table 1. Study Calendar

	Pre-screen	Baseline	Mid-RT	3-Months Post-RT	1-year Post-RT
		Prior to RT Start	20-30 Gy	2-4 mo.	9-18 mo.
Informed Consent		X			
Medical History	X			X	X
Physical Exam	X		X	X	X
ECOG Performance Status	X		X	X	X
Lab Work* **	X				
Pulmonary Function Tests (PFTs) including FEV1	X			X	X
Brain CT or MRI	X				
^{18}F-FDG PET/CT Scan#	X	X[a]	X[c]	X	
SPECT/CT with ^{99m}Tc-MAA and ^{99m}Tc-SULFUR COLLOID# performed at UWMC		X[b]	*[b]	X[b]	
Blood and urine collection for future correlative studies		X**	X**	X**	

X Required for study
* Optional for study
** Optional but highly encouraged
***CBC with absolute neutrophil count and platelet count; Serum chemistries include BUN, creatinine, sodium, potassium, bicarbonate, chloride, glucose, total protein, total bilirubin, AST, ALT, alkaline phosphatase, and albumin

Scans should ideally be performed in the treatment position with treatment immobilization

[a] Baseline PET/CT scans will be done as part of routine clinical care for lung cancer staging and radiation treatment planning. For patients whose clinical scans are >1 month old or do not meet research scan quality standards, a repeat research PET/CT will be done around the time of simulation, which will be paid for by the study.

[b] All SPECT/CT scans performed will be paid for by the study.

[c] Mid-Treatment PET/CT performed will be paid for by the study. Ideally, mid-RT PET/CT to be performed between treatment fraction #12 and #13 (~24 Gy).

3.2. Statistical Plan

The primary endpoint of the study will be 2-year overall survival (OS). The primary objective will be to test the superiority of the 2-year overall survival rate in patients enrolled on the FLARE RT trial compared to the 60 Gy cohort of RTOG 0617 (57% 2yr OS) for historical control (11). RTOG 0617 was a randomized phase III trial for patients with unresectable non-small cell lung cancer (NSCLC), testing two radiation doses (60 Gy versus 74 Gy), and addition of cetixumab to standard chemoradiation. Results of RTOG 0617 established the current standard of care for NSCLC: concurrent chemoradiation to 60 Gy.

The expected 2yr OS and effect size of FLARE RT was derived from a weighted average of mid-treatment FDG PET responders (2 yr. OS = 92%, 41% of patient population) and non-responders (2 yr. OS = 33%, 59% of patient population) identified in a prospective patient series with 2 yr. OS rate (56%) in strong agreement with the 60 Gy cohort of RTOG 0617 (23). Based on data from a dose escalation meta-analysis (10) and the University of Michigan experience tumor dose escalation to 74 Gy in non-responders are expected to produce 4% relative improvement in overall survival per Gy (3). Combined with functional lung avoidance to reduce mean perfused lung dose from 20 Gy to 10 Gy and risk of clinical grade radiation pneumonitis, we predict a 72% 2yr OS in patients receiving FLARE RT.

The FLARE RT trial features a non-randomized design that selectively assigns patients to one of two arms based on early treatment response assessment on FDG PET/CT. In order to assess whether this selection strategy leads to superior 2yr OS compared to the historical control, we will perform a one sample proportionality test using all patients who complete either FLARE RT treatment arm (standard dose arm in responders + dose escalation arm in non-responders). In our cohort of at least 49 patients, the test is expected to detect a 2yr OS rate improvement relative to historical control from 57% to 72%, under assumptions of 5% Type I error rate (α=0.05), 80% power (β=0.20), and 1% margin of superiority (δ=0.01).

Secondary objectives will feature a non-inferiority proportionality test of pulmonary toxicity incidence, defined as CTCAE v4 grade 2 or higher pneumonitis, between patients receiving FLARE RT and historical rates. Interim and final statistical analyses of the clinical endpoints (local control, progression-free survival, overall survival) will consist of Kaplan-Meier estimation and Cox proportional hazard regression. We will not conduct formal subset analyses due to insufficient statistical power. However, we will assess the relative strengths of hazard ratio estimates (and 95% confidence intervals) from a few predictors, including pre-treatment and mid-treatment imaging metrics extracted from PET/CT and SPECT/CT data. The degree of correlation amongst the variables will be evaluated. We will conduct linear regression of post-treatment lung perfusion SPECT/CT changes and decline in standard pulmonary function tests (FEV1,

DLCO, etc.). Lastly, we will perform ROC analysis to associate pre-treatment lung perfusion SPECT/CT parameters with dichotomous incidence of pneumonitis.

3.3. Eligibility

Conditions for patient eligibility:

- *Pathologically proven (either histologic or cytologic) diagnosis of Stage IIB-IIIB non-small cell lung cancer (NSCLC); according to AJCC Staging, 7th edition.*
    - *Staging workup must include: brain imaging (CT head or MRI brain) and PET/CT.*
    - *Pleural effusions must have cytology to rule out malignant involvement unless too small to undergo thoracentesis per radiology*
- *Patients must be considered unresectable or inoperable*
- *Patient must not have received prior radiation for this lung cancer*
- *Patients must be having concurrent chemotherapy*
- *Nodal recurrences can be treated on this protocol but prior curative surgery for lung cancer must have been at least 6 months prior to the nodal recurrence.*
- *Patients must have measurable or evaluable disease that is FDG avid with SUV>3 on PET/CT*
- *Zubrod Performance Status 0-1;*
- *Age ≥ 18;*
- *PFTs including FEV1 within 26 weeks prior to registration; for FEV1, the best value obtained pre- or post-bronchodilator must be ≥ 0.8 liters/second or ≥ 50% predicted.*
- *CBC/differential obtained within 8 weeks prior to registration on study, with adequate bone marrow function defined as follows:*
    - *Absolute neutrophil count (ANC) ≥ 1,800 cells/mm3;*
    - *Platelets ≥ 100,000 cells/mm3;*
    - *Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable.)*
- *Serum creatinine within normal institutional limits or creatinine clearance ≥40 ml/min;*
- *Bilirubin must be within or below normal institutional limits;*
- *AST and ALT < 2.5 x the IULN;*
- *Patient must sign study specific informed consent prior to study entry.*

Conditions for patient ineligibility:

- *>10% unintentional weight loss within the past month*
- *Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years; non-invasive conditions such as carcinoma in situ of the breast, oral cavity, or cervix are all permissible.*
- *Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;*
- *Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception.*

4 Study Registration

Subjects will be registered by the FHCRC/UW Study Coordinator and entered into OnCore at seattlectms.org. A complete, signed, study consent and HIPAA consent are required for registration.

5 Radiation Therapy

5.1 Dose Specifications

All patients will undergo treatment planning at initial simulation to 60 Gy at 2.0 Gy per fraction, using perfusion SPECT/CT to guide functional lung avoidance (details below). At 24 Gy (20-30 Gy acceptable), mid-treatment FDG PET/CT will be performed, and changes in tumor SUV and total lesion glycolysis (TLG) will be assessed to divide patients into metabolic responders and metabolic non-responders (details below). Patients classified as metabolic non-responders will receive dose escalation to 74 Gy, completed in 30 fractions (starting fraction 16, there will be hypofractionated dose escalation, dividing the additional 44 Gy into the remaining 15 fractions).

5.2 Localization, simulation, and immobilization

- Volumetric treatment planning CT study will be required to define gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) (see definitions below). Each patient will be positioned in an immobilization device in the treatment position on a flat table.
- Contiguous CT slices, having 3 mm thickness through the regions harboring gross tumor and grossly enlarged lymph nodes and 8-10 mm thickness of the remaining regions are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume. The GTV, CTV, and PTV and normal organs will be outlined on all appropriate CT slices.
- A treatment planning FDG PET/CT scan and SPECT/CT scan with the patient in the treatment position is strongly encouraged for treatment planning.
- 4-dimensional radiation treatment planning is required.

5.3 Target Volumes

- Definition of the GTV: The primary tumor and clinically positive lymph nodes seen either on the planning CT (> 1 cm short axis diameter) or pretreatment PET scan (SUV > 3) will constitute the GTV.
- The ITV includes the envelope that encompasses the tumor motion for a complete respiratory cycle.
- Definition of the CTV: The CTV is defined to be the ITV plus a 0.5 cm to 1 cm margin as appropriate to account for microscopic tumor extension.
- Definition of the PTV: PTV margin should account for setup uncertainties and may be individualized but should not be less than 0.5 cm with daily imaging guidance.
- Definition of the metabolic tumor volume (MTV): the MTV is defined as the FDG PET avid volume for response assessment of total lesion glycolysis (TLG = SUV_{mean}*MTV) between baseline and mid-treatment scans.

5.4 Critical Structures

Anatomic based clinical objectives will be prioritized first in treatment planning, to ensure that functional lung avoidance radiation treatment will be at least as safe as current standard of care (details on functional lung avoidance planning below).

- Definition of perfused lung-CTV: the structure is derived by applying a fixed threshold of 70% of maximum intensity on MAA SPECT/CT (rigidly aligned to the planning CT) within the lung-CTV structure

5.5 Treatment Planning

Following the trial schema, we will deliver functional lung avoidance RT plans that meet pre-treatment functional lung objectives and PTV coverage. The treatment plans will be subsequently adapted to dose escalate after 3 weeks of RT based on a mid-treatment PET/CT (image after 24 Gy, between fraction 12-13 nominal) in select patients classified as FDG non-responders based on change in SUV_{max} (< 15% nominal) and total lesion glycolysis (< 15% nominal) reported from prior patient series with validation against local control and survival (23-24). FLARE RT plans will maintain 60 Gy base dose to the pre-treatment PTV, while delivering a concomitant boost to mid-treatment PTV (defined by 3 week PET/CT) during weeks 4-6 up to a total mean dose of 74 Gy in 30 fx. The 14 Gy mid-treatment PTV boost will be distributed according to relative mid-treatment FDG PET SUV. Patients who are classified as FDG responders (as defined above) at 3 weeks mid-RT will continue receiving functional lung avoidance RT to a total dose of 60 Gy, without plan adaptation.

The FLARE RT plans will be generated from unique FDG PET/CT and perfusion SPECT/CT objectives that redistribute dose at every image voxel away from functional lung regions and towards FDG-avid tumor regions. This combined differential avoidance [38] and differential tumor dose escalation [39-41] is a form of dose painting that creates continuous dose gradients rather than sharp dose gradients, which increases the robustness of FLARE RT to target motion and patient setup-induced uncertainties. In effect, the low spatial resolution PET and SPECT images acquired over many patient respiratory cycles define blurred targets and avoidance regions that help mitigate the effects of motion and risk of geographic miss during delivery of FLARE RT. Mathematically, FLARE RT objectives for FDG PET/CT-based dose escalation levels and MAA perfusion SPECT/CT-based dose avoidance levels are tabulated in the planning system as part of the cost function for plan optimization.

All FLARE RT planning clinical goals are listed in Table 2.

Structure	Clinical Goal	Type	Minor Violation	Major Violation
Pre-treatment PTV	V_{54Gy} = 100%	Objective	>= 95%	< 95%
	V_{60Gy} > 95%	Objective	>= 90%	< 90%
Mid-treatment PTV	Mean Dose = 74Gy	Objective	>= 66Gy	< 66Gy
	Min Dose = $60Gy + 14Gy \frac{SUV_{min}^{mid\ PTV}}{SUV_{mean}^{mid\ PTV}}$	Recommendation	-	-
	Max Dose = $60Gy + 14Gy \frac{SUV_{max}^{mid\ PTV}}{SUV_{mean}^{mid\ PTV}}$	Recommendation	-	-
	$D_{50\%}$ Min/Max DVH = $60Gy + 14Gy \frac{SUV_{median}^{mid\ PTV}}{SUV_{mean}^{mid\ PTV}}$	Recommendation	-	-
Mid-treatment PTV FDG L_i (i=1:N)	Mean Dose = $60Gy + 14Gy \frac{SUV_{mean}^{mid\ PTV\ FDG\ Li}}{SUV_{mean}^{mid\ PTV}}$	Recommendation	-	-
	Min Dose = $60Gy + 14Gy \frac{SUV_{min}^{mid\ PTV\ FDG\ Li}}{SUV_{mean}^{mid\ PTV}}$	Recommendation	-	-
	Max Dose = $60Gy + 14Gy \frac{SUV_{max}^{mid\ PTV\ FDG\ Li}}{SUV_{mean}^{mid\ PTV}}$	Recommendation	-	-
	$D_{50\%}$ Min/Max DVH = $60Gy + 14Gy \frac{SUV_{median}^{mid\ PTV\ FDG\ Li}}{SUV_{mean}^{mid\ PTV}}$	Recommendation	-	-
Lung-CTV	Mean Dose < 20Gy	Objective	<= 22Gy	> 22Gy
Lung-CTV	V_{20Gy} < 37%	Objective	<= 40%	> 40%
Lung-CTV	V_{10Gy} < 50%	Objective	<= 55%	> 55%
Lung-CTV	V_{5Gy} < 60%	Objective	<= 70%	> 70%
Perfused Lung-CTV	Mean Dose < 15 Gy	Objective	<= 20Gy	> 20Gy
Lung-CTV PERF L_i (i=1:N)	Mean Dose < $20Gy \frac{U_{mean}^{Lung-GTV}}{U_{mean}^{Lung-GTV\ PERF\ Li}}$	Recommendation	-	-
	Max Dose < $20Gy \frac{U_{mean}^{Lung-GTV}}{U_{min}^{Lung-GTV\ PERF\ Li}}$	Recommendation	-	-
	$D_{50\%}$ Max DVH< $20Gy \frac{U_{mean}^{Lung-GTV}}{U_{median}^{Lung-GTV\ PERF\ Li}}$	Recommendation	-	-
Heart	V_{60Gy} < 30%	Objective	<= 40%	>40%
Heart	V_{45Gy} < 60%	Objective	<= 70%	> 70%
Heart	V_{40Gy} < 100%	Objective	-	100%
Heart	Mean Dose < 35Gy	Objective	<= 45Gy	> 45Gy
Spinal Cord	$D_{0.03cc}$ < 50.5Gy	Objective	-	>= 50.5Gy
Esophagus	Mean Dose < 34Gy	Recommendation	-	-
Brachial Plexus	Max Dose < 66Gy	Recommendation	-	-

Table 2. FLARE RT adaptive planning objectives in select high local failure risk NSCLC patients classified as FDG PET non-responders. The composite dose of the functional avoidance RT plan administered in weeks 1-3 (15 fx) and the FLARE RT plan administered in weeks 4-6 (15 fx) would meet the following key objectives: (1) dose escalate residual FDG avid regions through linear dose redistribution at each FDG PET SUV-based dose level Li about 74 Gy mean dose to the mid-treatment PTV, (2) maintain perfused mean lung dose below 15 Gy, (3) redistribute each MAA perfusion SPECT uptake U-based dose level Li about 20 Gy mean dose to the anatomic lung. FLARE RT planning objectives will also include conventional dose-volume limits in accordance with standard clinical practice to heart, esophagus, spinal cord, etc. With

the exception of the mid-treatment PTV boost objectives, the same objectives will be applied to all remaining structures for patients selected to the functional lung avoidance arm (no dose escalation). All dosimetric objectives refer to radiation dose in units of Gray for photon therapy and Cobalt Gray Equivalent (CGE) for particle therapy.

5.6 Radiation Quality Assurance Reviews

All patients treated on this protocol will undergo standard review in the Department of Radiation Oncology. At least two physicians will review the patient history, imaging findings, tumor contours, and radiation plan.

5.7 Radiation Toxicity

Toxicity will be graded based on CTCAE 4.0. Grade 3 and higher AE's will be recorded as well as AE's that require a treatment interruption. One exception is pulmonary AE's which will be recorded at Grade 2 and higher. In accordance with institutional policy, all adverse events which in the opinion of the principal investigator are unexpected **and** related or possibly related to the research **and** serious or suggest that the research places research participants or others at greater risk of physical or psychological harm than was previously known or recognized be reported to the IRB within 10 calendar days of learning of the problem.

5.8 Criteria for Removal/Withdrawal from Treatment

Patients will be withdrawn from treatment if their clinical conditions decline so they are no longer able to tolerate x-ray / proton radiation, or are unlikely to clinically benefit from further therapy.

Patients will still receive follow up care per standard of care even if they withdraw from the study. If a subject withdraws consent to participate in the study or aspects of the study, attempts will be made to obtain permission to record at least survival data up to 6 months post-treatment.

6 Systemic Therapy

All patients must receive cytotoxic (not targeted agents) systemic therapy concurrent with radiation, but exact agent and dosing are at discretion of medical oncology.

7 Data and Safety Monitoring Plan

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring

visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human under the provisions of the DSMB, the Cancer Consortium Clinical Trial Support Office subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

7.1 Early Stopping Rules

Early stopping of this trial will be any grade 5 adverse events (AEs) occurring within ≤ 30 days after the end of treatment defined as possibly, probably, or definitely related to treatment (per CTCAE, v.4.0). All AEs will be immediately monitored and reviewed by PI.

7.2 Interim Data Review

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented or published. In general, the interim reports will contain the following information:

- Patient accrual rate with a projected completion date (while the study is still accruing)
- Total patients accrued
- Frequencies and severity of adverse events
- Compliance rates of treatment delivery

8 Data Management/Confidentiality

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique patient number to assure subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents.

Subject research files are stored in a secure place (or database). Access is restricted to authorized personnel.

References

1. Dillman RO, Herndon J, Seagren SL, Eaton WL, Jr., Green MR. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. Journal of the National Cancer Institute. 1996 Sep 4;88(17):1210-5. PubMed PMID: 8780630.

2. Sause W, Kolesar P, Taylor SI, 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 Feb;117(2):358-64. PubMed PMID: 10669675.

3. Kong FM, Ten Haken RK, Schipper MJ, Sullivan MA, Chen M, Lopez C, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. International journal of radiation oncology, biology, physics. 2005 Oct 1;63(2):324-33. PubMed PMID: 16168827.

4. Socinski MA, Rosenman JG, Halle J, Schell MJ, Lin Y, Russo S, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B nonsmall cell lung carcinoma: a modified phase I/II trial. Cancer. 2001 Sep 1;92(5):1213-23. PubMed PMID: 11571735.

5. Nichols L, Saunders R, Knollmann FD. Causes of death of patients with lung cancer. Archives of pathology & laboratory medicine. 2012 Dec;136(12):1552-7. PubMed PMID: 23194048.

6. Auperin A, Le Pechoux 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 : official journal of the American Society of Clinical Oncology. 2010 May 1;28(13):2181-90. PubMed PMID: 20351327.

7. Arriagada R. Current strategies for radiation therapy in non-small cell lung cancer. Chest. 1997 Oct;112(4 Suppl):209S-13S. PubMed PMID: 9337291.

8. Schaake-Koning C, van den Bogaert W, Dalesio O, Festen J, Hoogenhout J, van Houtte P, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. The New England journal of medicine. 1992 Feb 20;326(8):524-30. PubMed PMID: 1310160.

9. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 1999 Aug;52(2):137-48. PubMed PMID: 10577699.

10. Machtay M, Bae K, Movsas B, Paulus R, Gore EM, Komaki R, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. International journal of radiation oncology, biology, physics. 2012 Jan 1;82(1):425-34. PubMed PMID: 20980108.

11. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. The Lancet Oncology. 2015 Feb;16(2):187-99. PubMed PMID: 25601342.

12. Watanabe Y, Shimizu J, Oda M, Hayashi Y, Watanabe S, Tatsuzawa Y, et al. Aggressive surgical intervention in N2 non-small cell cancer of the lung. Ann Thorac Surg. 1991 Feb;51(2):253-61. PubMed PMID: 1846524.

13. Iwasaki A, Shirakusa T, Miyoshi T, Hamada T, Enatsu S, Maekawa S, et al. Prognostic significance of subcarinal station in non-small cell lung cancer with T1-3 N2 disease. The Thoracic and cardiovascular surgeon. 2006 Feb;54(1):42-6. PubMed PMID: 16485188.

14. Okada M, Tsubota N, Yoshimura M, Miyamoto Y, Matsuoka H. Prognosis of completely resected pN2 non-small cell lung carcinomas: What is the significant node that affects survival? The Journal of thoracic and cardiovascular surgery. 1999 Aug;118(2):270-5. PubMed PMID: 10425000.

15. Fernandes AT, Mitra N, Xanthopoulos E, Evans T, Stevenson J, Langer C, et al. The impact of extent and location of mediastinal lymph node involvement on survival in Stage III non-small cell lung cancer patients treated with definitive radiotherapy. Int J Radiat Oncol Biol Phys. 2012 May 1;83(1):340-7. PubMed PMID: 22104359.

16. Kollar LE, Bowen SR, Gopan O, Nyflot MJ, Patel SA, Zeng J, et al. Relationship between Cardiac Radiation Dose and Extent /and Location of Mediastinal Lymph Node Involvement in Stage III NSCLC Patients [Abstract]. International Journal of Radiation Oncology Biology Physics. 2015.

17. Feng M, Kong FM, Gross M, Fernando S, Hayman JA, Ten Haken RK. Using fluorodeoxyglucose positron emission tomography to assess tumor volume during radiotherapy for non-small-cell lung cancer and its potential impact on adaptive dose escalation and normal tissue sparing. Int J Radiat Oncol Biol Phys. 2009 Mar 15;73(4):1228-34. PubMed PMID: 19251094. Pubmed Central PMCID: 3381895. Epub 2009/03/03. eng.

18. Ohri N, Piperdi B, Garg MK, Bodner WR, Gucalp R, Perez-Soler R, et al. Pre-treatment FDG-PET predicts the site of in-field progression following concurrent chemoradiotherapy for stage III non-small cell lung cancer. Lung Cancer. 2015 Jan;87(1):23-7. PubMed PMID: 25468149.

19. Na F, Wang J, Li C, Deng L, Xue J, Lu Y. Primary tumor standardized uptake value measured on F18-Fluorodeoxyglucose positron emission tomography is of prediction value for survival and local control in non-small-cell lung cancer receiving radiotherapy: meta-analysis. J Thorac Oncol. 2014 Jun;9(6):834-42. PubMed PMID: 24787963. Pubmed Central PMCID: 4219540.

20. Aerts HJ, Bussink J, Oyen WJ, van Elmpt W, Folgering AM, Emans D, et al. Identification of residual metabolic-active areas within NSCLC tumours using a pre-radiotherapy FDG-PET-CT scan: a prospective validation. Lung Cancer. 2012 Jan;75(1):73-6. PubMed PMID: 21782272. Epub 2011/07/26. eng.

21. Aerts HJ, van Baardwijk AA, Petit SF, Offermann C, Loon J, Houben R, et al. Identification of residual metabolic-active areas within individual NSCLC tumours using a pre-radiotherapy (18)Fluorodeoxyglucose-PET-CT scan. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2009 Jun;91(3):386-92. PubMed PMID: 19329207. Epub 2009/03/31. eng.

22. van Elmpt W, De Ruysscher D, van der Salm A, Lakeman A, van der Stoep J, Emans D, et al. The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2012 Jul;104(1):67-71. PubMed PMID: 22483675. Epub 2012/04/10. eng.

23. van Elmpt W, Ollers M, Dingemans AM, Lambin P, De Ruysscher D. Response assessment using 18F-FDG PET early in the course of radiotherapy correlates with survival in advanced-stage non-small cell lung cancer. J Nucl Med. 2012 Oct;53(10):1514-20. PubMed PMID: 22879081. Epub 2012/08/11. eng.

24. Yossi S, Krhili S, Muratet JP, Septans AL, Campion L, Denis F. Early assessment of metabolic response by 18F-FDG PET during concomitant radiochemotherapy of non-small cell lung carcinoma is associated with survival: a retrospective single-center study. Clinical nuclear medicine. 2015 Apr;40(4):e215-21. PubMed PMID: 25546211. Epub 2014/12/30. eng.

25. Palma DA, Senan S, Tsujino K, Barriger RB, Rengan R, Moreno M, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. International journal of radiation oncology, biology, physics. 2013 Feb 1;85(2):444-50. PubMed PMID: 22682812. Pubmed Central PMCID: 3448004.

26. Toney LK, Wanner M, Miyaoka RS, Alessio AM, Wood DE, Vesselle H. Improved prediction of lobar perfusion contribution using technetium-99m-labeled macroaggregate of albumin single photon emission computed tomography/computed tomography with attenuation correction. The Journal of thoracic and cardiovascular surgery. 2014 Nov;148(5):2345-52. PubMed PMID: 24882061.

27. Bowen SR, Dhami G, Nyflot MJ, Kinahan PE, Sandison GA, Miyaoka RS, et al. Impact of Functional Lung Imaging Using Ventilation/Perfusion SPECT/CT on Planning

Objectives in Thoracic Radiation Therapy [Abstract]. Int J Radiat Oncol Biol Phys. 2014;90(1):S659.

28. Woel RT, Munley MT, Hollis D, Fan M, Bentel G, Anscher MS, et al. The time course of radiation therapy-induced reductions in regional perfusion: a prospective study with >5 years of follow-up. Int J Radiat Oncol Biol Phys. 2002 Jan 1;52(1):58-67. PubMed PMID: 11777622. Epub 2002/01/05. eng.

29. Zhang J, Ma J, Zhou S, Hubbs JL, Wong TZ, Folz RJ, et al. Radiation-induced reductions in regional lung perfusion: 0.1-12 year data from a prospective clinical study. Int J Radiat Oncol Biol Phys. 2010 Feb 1;76(2):425-32. PubMed PMID: 19632063. Epub 2009/07/28. eng.

30. Seppenwoolde Y, Engelsman M, De Jaeger K, Muller SH, Baas P, McShan DL, et al. Optimizing radiation treatment plans for lung cancer using lung perfusion information. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2002 May;63(2):165-77. PubMed PMID: 12063006.

31. Seppenwoolde Y, De Jaeger K, Boersma LJ, Belderbos JS, Lebesque JV. Regional differences in lung radiosensitivity after radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2004 Nov 1;60(3):748-58. PubMed PMID: 15465191.

32. Buck AK, Nekolla S, Ziegler S, Beer A, Krause BJ, Herrmann K, et al. Spect/Ct. J Nucl Med. 2008 Aug;49(8):1305-19. PubMed PMID: 18632825. Epub 2008/07/18. eng.

33. McGuire SM, Marks LB, Yin FF, Das SK. A methodology for selecting the beam arrangement to reduce the intensity-modulated radiation therapy (IMRT) dose to the SPECT-defined functioning lung. Phys Med Biol. 2010 Jan 21;55(2):403-16. PubMed PMID: 20019404. Epub 2009/12/19. eng.

34. McGuire SM, Zhou S, Marks LB, Dewhirst M, Yin FF, Das SK. A methodology for using SPECT to reduce intensity-modulated radiation therapy (IMRT) dose to functioning lung. Int J Radiat Oncol Biol Phys. 2006 Dec 1;66(5):1543-52. PubMed PMID: 17126212. Epub 2006/11/28. eng.

35. Das SK, Miften MM, Zhou S, Bell M, Munley MT, Whiddon CS, et al. Feasibility of optimizing the dose distribution in lung tumors using fluorine-18-fluorodeoxyglucose positron emission tomography and single photon emission computed tomography guided dose prescriptions. Med Phys. 2004 Jun;31(6):1452-61. PubMed PMID: 15259648.

36. Das SK, Ten Haken RK. Functional and molecular image guidance in radiotherapy treatment planning optimization. Seminars in radiation oncology. 2011 Apr;21(2):111-8. PubMed PMID: 21356479. Pubmed Central PMCID: 3062208. Epub 2011/03/02. eng.

37. Siva S, Thomas R, Callahan J, Hardcastle N, Pham D, Kron T, et al. High-resolution pulmonary ventilation and perfusion PET/CT allows for functionally adapted intensity modulated radiotherapy in lung cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2015 Apr 29. PubMed PMID: 25935743. Epub 2015/05/04. Eng.