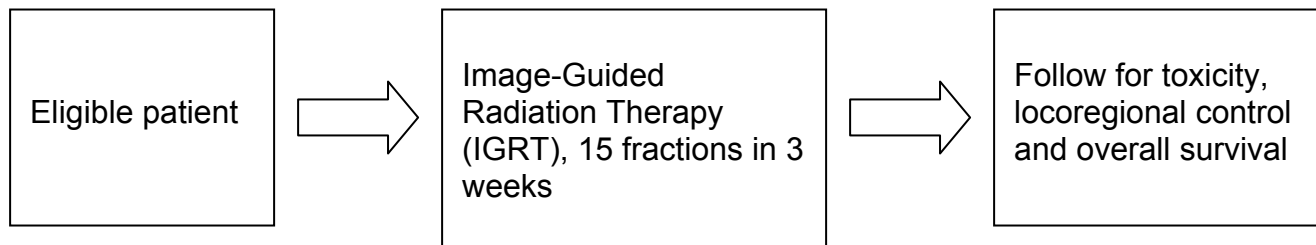


Phase I Study of Accelerated Hypofractionated Image-Guided Radiation Therapy (IGRT) in Patients with Stage II-IV Non-Small Cell Lung Cancer and Poor Performance Status

1.0 Schema



Number of patients = between 7-45 (depending on tolerance)

Patients in each dose cohort will all be treated as a single group for dose escalation. The starting dose will be 3.33 Gy per fraction for 15 fractions (total dose = 50 Gy). Subsequent cohorts of patients will receive a higher dose per fraction as follows:

<u>Cohort</u>	<u>No. Fractions</u>	<u>Dose per fraction (Gy)</u>	<u>Total Dose (Gy)</u>	<u>No. Patients</u>
1	15	3.33	50	7-15
2	15	3.67	55	7-15
3	15	4.00	60	7-15

Minimum waiting periods will be assigned between each dose cohort to observe toxicity.

ELIGIBILITY (See Section 3.0 for details)

- Stages II (not eligible for definitive surgical resection or stereotactic body radiation therapy,), III or IV non-small cell lung cancer that would benefit from local radiation therapy
- Recurrent non-small cell lung cancer that would benefit from local radiation therapy
- Zubrod performance status of 2 or greater, age > 18
- No prior radiotherapy to the chest or neck that would result in overlap of radiation therapy fields
- No chemotherapy within one week prior to study registration
- Study-specific consent form signed

2.0 Objectives

2.1 Primary Objective

2.1.1 To escalate the dose of accelerated, hypofractionated, image-guided conformal radiotherapy to a potent tumoricidal dose without exceeding the maximum tolerated dose in treatment of stage II-IV NSCLC in patients with poor performance status. The maximum tolerated dose will be defined using the following criteria:

- For determination of appropriate dose escalation, the protocol is designed to capture rates of treatment-related (definitely and probably, but not possibly related to treatment*) grade 3 adverse events (per CTCAE, v.3.0, with the exception of pulmonary function tests as noted in Section 6.9.4) related to the following specific symptoms, including:
 - Gastrointestinal: dysphagia, esophagitis, esophageal stricture/stenosis, esophageal ulceration;
 - Cardiac: pericarditis, pericardial effusion, restrictive cardiomyopathy, ventricular dysfunction (left ventricular diastolic dysfunction, left ventricular systolic dysfunction, right ventricular dysfunction);
 - Neurologic: myelitis, neuropathy (cranial and motor);

- Hemorrhage: pulmonary or upper respiratory;
- Pulmonary: decline in pulmonary function as measured by pulmonary function tests (DL_{CO}, and FEV₁,) using the modified criteria in relation to baseline (see section 6.9.4), pneumonitis, pulmonary fibrosis, hypoxia, pleural effusion, cough, and dyspnea
- Any grade 4 or 5 adverse event attributed to the therapy (definitely and probably, but not possibly related to treatment)

*Patients enrolled on this study are highly likely to have associated tobacco related cardiopulmonary co-morbidities that would result in adverse events (e.g., hospitalizations) irrespective of any cancer treatment. In published trials referenced in the introduction, adverse event analysis was confounded by problems distinguishing whether adverse events were treatment related versus part of the natural history of co-existing co-morbidities. As such, in this protocol only adverse events deemed probably and definitely related to treatment are considered for formal adverse event assessment. Adverse events deemed possibly related will be collected and reviewed but not used in adverse event analysis (e.g., for defining the maximum tolerated dose).

2.2 Secondary Objectives

- 2.2.1** To evaluate local regional tumor control and overall survival in patients with stage II-IV NSCLC and poor performance status treated with accelerated, hypofractionated, image-guided conformal radiotherapy.

3.0 Patient Selection

3.1 Conditions for patient eligibility

- 3.1.1** All patients must be willing and capable to provide informed consent to participate in the protocol.
- 3.1.2** Patients must have appropriate staging studies identifying them as AJCC stage II, III or IV non small cell lung cancer, [according to AJCC Staging, 6th edition; see appendix III], or recurrent non small cell lung cancer. Histologic confirmation of cancer will be required by biopsy or cytology.
- 3.1.3** Patients must have the potential for benefit from local therapy (at the discretion of the investigator).
- 3.1.4** The patient's Zubrod performance status must be 2 or greater.
- 3.1.5** Age ≥ 18.
- 3.1.6** The tumor must be ineligible for definitive surgical resection.
- 3.1.7** The tumor must be ineligible for stereotactic body radiation therapy.
- 3.1.8** Patients must have measurable or evaluable disease.
- 3.1.9** Women of childbearing potential and male participants must agree to use an effective method of contraception.
- 3.1.10** Patients must sign study specific informed consent prior to study entry.
- 3.1.11** No plans for concurrent chemoradiation therapy
- 3.1.12** Patients must complete all required pretreatment evaluations (section 4.0)

3.2 Conditions for patient ineligibility

- 3.2.1** Evidence of small cell histology.
- 3.2.2** Tumor eligible for definitive surgical resection.
- 3.2.3** Tumor eligible for definitive stereotactic body radiation therapy.
- 3.2.4** Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields.
- 3.2.5** Chemotherapy given within one week of study registration.
- 3.2.6** Pregnant or lactating women, as treatment involves unforeseeable risks to the embryo or fetus.