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TITLE: A PHASE I TRIAL OF INTENSITY-MODULATED RADIATION THERAPY USING A CONTRALATERAL ESOPHAGUS SPARING TECHNIQUE IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER AND LIMITED-STAGE SMALL CELL LUNG CANCER.

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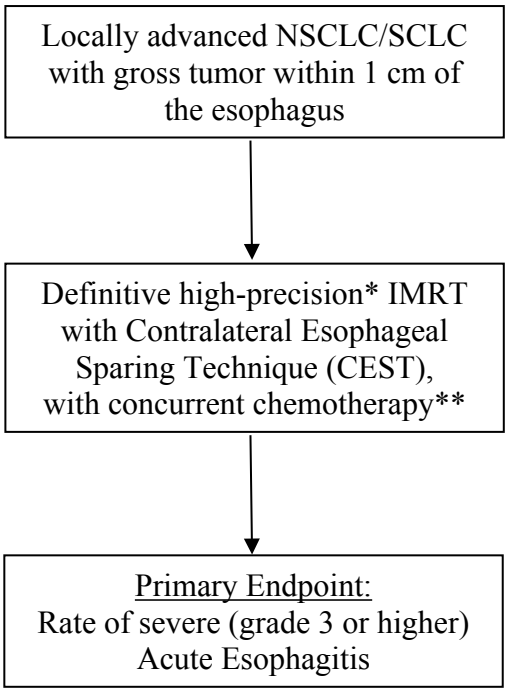
SCHEMA



NSCLC, non-small cell lung carcinoma; SCLC, small cell lung carcinoma; IMRT, intensity-modulated radiation therapy, * high-precision therapy refers to the utilization of state-of-the-art techniques that ensure adequate tumor coverage and appropriate sparing of normal organs throughout the course of radiation therapy, including custom patient immobilization, image-guided radiation therapy (IGRT) using daily cone beam CT, and adaptive treatment planning if needed, **any concurrent chemotherapy per standard of care

1. INTRODUCTION

1.1 Study Disease

Lung Cancer

Lung cancer is the leading cause of cancer death in men and women, and it is the second most common cancer. The American Cancer Society estimates 224,210 new cases in 2014 and 159,260 deaths (27% of all cancer deaths) [1]. More than 80% of lung cancers are caused by exposure to tobacco smoke. Lung cancer is divided into two histologic subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC encompasses approximately 87% of all lung cancer cases. The majority of NSCLC patients presents with either locally advanced disease or distant metastases, and are medically inoperable or have unresectable disease. Chemoradiation is the primary treatment for SCLC and unresectable, locally advanced NSCLC. It is estimated that two thirds of lung cancer patients will undergo radiation therapy.

Locally advanced NSCLC comprises approximately 30% of all patients with NSCLC and includes stages IIIA and IIIB. Standard of care for this large and heterogeneous group of patients is multimodality therapy with chemotherapy and radiation, with the possible addition of surgical resection for operable candidates [2-4]. Although locally advanced disease is considered curable, outcomes are poor with median progression-free survival of 10-13 months, median overall survival of 17-24 months, and a 2 year-survival rate of about 50%. In an attempt to improve treatment outcomes the Radiation Therapy Oncology Group (RTOG) and others have explored the use of higher radiation doses. The University of Michigan used a dose range of 60-100Gy with concurrent and adjuvant chemotherapy (Kong et al., ASTRO meeting 2011). The median survival was 15.5 and 41.9 months for doses less then and greater than 70Gy, respectively. RTOG 0617 is a randomized phase III trial comparing 74 Gy with 60 Gy using concurrent chemotherapy with carboplatin/paclitaxel, with or without cetuximab which is a monoclonal antibody directed against the epidermal growth factor receptor. Preliminary reports show higher toxicity for 74 Gy and the surprising finding that 74 Gy is associated with inferior survival outcome [5,6]. Factors predictive of worse survival on multivariate analysis included higher radiation dose and higher esophagitis grade [6]. While final publication of this trial is awaited to better assess the reasons why 74 Gy fared worse, radiation doses of > 70 Gy remain investigational. Doses of 60-66 Gy are considered the standard of care in the community [7]. The continued use of 70 Gy is supported by modern clinical trials such as RTOG 1308 or CALGB 30105 [8]. Importantly, data show that doses of ~60-63 Gy with concurrent chemotherapy are associated with ~30-50% local failure rates, which is unacceptably high [3,9-11].

SCLC is an aggressive disease that is chemosensitive yet associated with high rates of local relapse and metastases. SCLC is staged as limited stage (LS) or extensive stage disease: LS referring to disease confined to the ipsilateral hemithorax that can be safely included in a radiation portal while extensive stage disease includes all remaining patients. Approximately 30% of SCLC patients present with limited stage disease [12]. The standard of care in the treatment for SCLC is concurrent chemoradiation [13,14]. One of the limitations to concurrent chemoradiation in many patients is the development of toxicities, one common toxicity being acute esophagitis. In the randomized trial by Turrisi et al, 45 Gy given at 1.5 Gy twice daily over 3 weeks was

associated with a > 30% incidence of severe esophagitis, with 27% grade 3 esophagitis and 5% of grade 4 esophagitis [14]. The range of recommended doses in the standard of care for SCLC is 60-70 Gy when given once-daily[15].

Acute Esophagitis

Challenges for delivering an adequate radiation dose are the limitations of normal tissue tolerance. Acute esophagitis is a common toxicity in patients undergoing concurrent chemoradiation for lung cancer, often requiring treatment breaks, fluid and nutritional support, or even hospitalization (see Table 1). Importantly, treatment breaks can lower tumor control rates and reduce survival, emphasizing the need to avoid severe acute esophagitis. Concurrent chemoradiation generally results in a ~15-25% rate of severe esophagitis (RTOG Grade 3 or higher) [16]. Patients undergoing concurrent chemoradiation have an approximate 5-fold increase in the development of esophagitis as compared to patients undergoing sequential chemoradiation. In addition, the development of esophagitis has been a limitation to dose-escalation of radiation. Of note, esophagitis rates are generally similar for different concurrent chemotherapy schedules [17] (see Table 1).

Table 1. Rates of acute esophagitis in prospective trials of concurrent chemoradiation

Prospective trial	**Radiation dose**	**2D, 3D or IMRT**	**Chemotherapy**	**Esophagitis scoring system**	**G3+ acute esophagitis (%)**	**Patient number & comments**
Albain INT 0139, Lancet [2]	61.2 Gy (1.8 Gy/day)	2D	Cisplatin, Etoposide	RTOG	Arm 2: 23%	N=194 in Arm 2 (definitive chemoRT* arm)
Curran RTOG 94-10, JNCI [3]	Arm 2: 63 Gy (1.8 Gy to 45 Gy, 2 Gy to 18Gy)	2D	Arm 2: Cisplatin, VBL^	RTOG	Arm 2: 22%	N=204
Govindan CALGB, JCO [18]	70 Gy (2 Gy/day)	3D	Carboplatin, Pemetrexed	CTCAEv3.0#	Arm A: 16% Arm B: 13%	N=48 (Arm A), N=53 (B) (Group B with same chemo + cetuximab)
Furuse, JCO [4]	56 Gy (2Gy/day) Split-course	2D	Cisplatin, Vindesine, Mitomycin	ECOG 1982	[2.6%]@	N=156 in the concurrent arm
Hanna HOG, JCO [19]	59.4 Gy (45 Gy + 14.4 Gy boost; 1.8 Gy/day)	2D	Cisplatin, Etoposide	CTCAEv3.0#	17.2%	N=203
Turrisi [14]	45 Gy (1.8 Gy QD or 1.5 Gy BID)	2D	Cisplatin, Etoposide	RTOG	16% QD& 32% BID%	N= 206 QD& N= 211 BID%
RTOG 0324 [20]	63 Gy (1.8 Gy/fraction)	3D	Cetuximab, Carboplatin, Paclitaxel	CTCAEv3.0#	8%	N=87 (phase II trial)

*chemoRT=chemotherapy with concurrent radiation therapy, ^VBL=vinblastin, #Common Terminology Criteria for Adverse Events (CTCAE), @split-course reduces esophagitis rate, &QD=once daily, %BID=twice daily

Intensity-Modulated Radiation Therapy (IMRT)

IMRT is an advanced form of conformal radiation therapy, which delivers radiation to the patient via multiple fields (typically 5-7) that have non-uniform radiation fluence. IMRT uses "inverse planning", meaning that the radiation oncologist specifies the dose distribution, and the plan is calculated to deliver it. IMRT can increase dose conformality and provide greater sparing of normal tissues than traditional 3D conformal forward planning [21-24]. Despite this improved conformality around the tumor, the reported rates of grade 2 and 3 esophagitis remain relatively high. Jiang et al. reported toxicity outcomes in 165 inoperable NSCLC patients treated with definitive IMRT (median dose 66 Gy in 33 fractions) at the MD Anderson Cancer Center, of which 136 received concomitant chemotherapy [21]. The encountered incidences of Common Terminology Criteria for Adverse Events (CTCAE) grade 2 and 3 esophagitis were 70% and 18%, respectively. On long term follow-up, the development of esophagitis was associated with the late esophageal stricture in 15 patients (9%). Similarly, Kwint et al. assessed the esophagitis outcomes in 139 patients with inoperable NSCLC treated with IMRT and concomitant chemotherapy. Using a hypofractionated regimen of 64 Gy in 24 fractions, 38% of patients experienced CTCAE grade 2 esophagitis, and 22% developed grade 3 toxicity [25]. Hence, IMRT has not been shown to reduce the toxicity to the esophagus, at least not with traditional dose constraints.

1.2 Rationale for the use of the Contralateral Esophageal Sparing Technique (CEST) with IMRT

Traditional esophagus dose constraints

The dose in definitive radiation therapy for locally advanced NSCLC and SCLC is limited by normal tissues and organs, most notably lungs, spinal cord, heart, and esophagus. Concurrent chemoradiation, as evidenced in Table 1, leads to high rates of severe acute esophagitis (15-25%). Thus, there is an urgent need for improved radiation technologies, techniques, and predictors of esophagitis in the treatment of lung cancer. Many centers have tried to predict esophagitis rates using dose-volume histograms (DVH), that is, the dose of radiation given to a volume of esophagus that will result in esophagitis. The use of DVH constraints is now a common tool used to predict radiation toxcity to organs. In a large metaanalysis published in 2013, Palma et al. looked at 1,082 lung cancer patients who received concurrent chemoradiation [26]. The study found that the volume of esophagus receiving 60 Gy (V60) was the most accurate predictor of grade 2 and 3 acute esophagitis. Patients with a very low V60 <1% had a low risk of esophagitis and patients with a V60 above 17% conferred a high risk. A review by Werner-Wasik et al. summarized 11 studies that used 3D treatment planning. Unfortunately, a single best parameter was not identified to predict esophagitis, mainly because a variety of V(dose) parameters were associated with acute esophagitis [16]. This suggests that the maximum dose limits to the esophagus may not be a reliable tool to reduce esophagitis in patients undergoing concurrent chemoradiation. The recent RTOG 0617 trial has collected V60 data on all patients and is recommending keeping the mean dose to the esophagus to less than 34 Gy. Altogether, the available data indicate a lack of robust dosimetric parameters that could be used to limit the rate of severe esophagitis.

Contralateral Esophageal Sparing Technique (CEST)

In prostate cancer, IMRT is associated with low rates of radiation-induced proctitis. Sparing of the posterior rectal wall with IMRT has been of great significance in reducing the rates of rectal toxicity, while achieving high dose to the tumor-containing prostate [27-31]. At MGH, we have applied a similar technique for esophagus sparing in the treatment of lung cancer patients with IMRT since 2013. This simple technique involves outlining the half of the esophageal circumference that is located contralateral to the tumor on axial CT slices. This contralateral esophagus (CE) contour serves as a distinct avoidance structure that is used as a guide for promoting a steep dose fall-off across sections of the esophagus in close proximity to tumor. Figure 1A,B illustrates how radiation isodose lines attempt to "curve" around the CE contour.

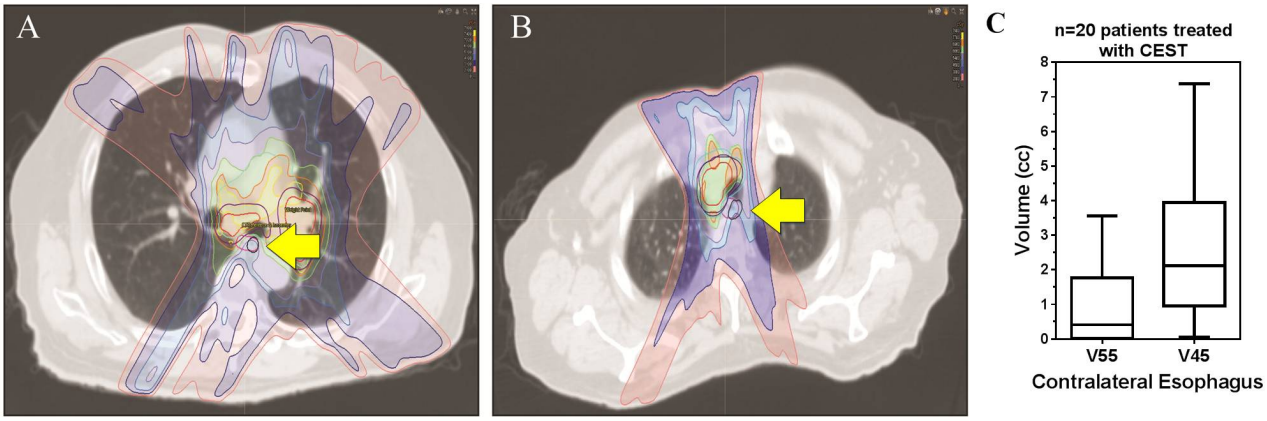


Figure 1: Sparing of contralateral esophagus (CE) with IMRT. A+B) Illustration of how the isodose lines "curve" around the contralateral esophagus (purple). In A), the tumor target is covered by the prescription dose of 70.2 Gy and a steep dose fall off across the esophagus allows for limiting the contralateral esophogus to 41 Gy. In B), the target is covered with a prescription dose of 66.6 Gy, while the contralateral esophagus is receiving 45 Gy. C) Summary of V45 and V55 value (i.e., volume of esophagus receiving 45+ Gy or 55 + Gy in 20 patients treated with this technique. Box and whiskers represent mean and range of data.

We recently analyzed our experience with CEST in 20 consecutive patients with locally advanced thoracic malignancies who received concurrent chemoradiation [32]. All patients had gross tumor within 1 cm of the esophagus. The median total radiation dose was 70.2 Gy (range, 63-72.15 Gy). Only one patient was treated with 63 Gy following an R1 resection of a paramediastinal pT3N0 NSCLC. Importantly, CEST did not compromise target coverage in any patient. Strikingly, no patient developed grade 3-4 esophagitis (RTOG score) (95% CL, 0-16%), and the rate of grade 2 esophagitis was only 20%.

Dosimetric parameters and esophagus toxicity are summarized in Table 2. The median maximum dose to the CE was 62.3 Gy (range, 47-68.2Gy), which was significantly lower than the maximum dose to the esophagus, mean 67.5 Gy (range, 61.9-72.7Gy) (paired t-test, $p<0.05$). Similarly, the median esophageal volume receiving 60 Gy or more (V60) was 5.3% (range, 0-23%), which was higher than the median CE V60 of 0.5% (range, 0-12.7%). The median CE

volume receiving 45 Gy and volume receiving 55 Gy measured 2.1 cc and 0.4 cc, respectively (Figure 1C). Overall, the CE had more favorable dosimetry in comparison to the whole esophagus, indicating effective esophagus cross section sparing.

Table 2: Characteristics of patients treated with CEST and observed acute esophagitis

Patient	TN Stage	Gross Tumor PTV (Gy)	Esophagus		Contralateral Esophagus				RTOG Acute Esophagitis Grade
			Max Dose (Gy)*	V60 (%)	Max Dose (Gy)*	V60 (cc)	V55 (cc)	V45 (cc)	
1	T2N2	69.9	69.5	18.2	65.0	0.82	3.56	7.38	1
2	TxN1	70.2	68.0	5.6	55.0	0.00	0.07	3.96	1
3	T3N2	72.0	72.7	14.9	64.8	0.59	2.34	6.28	0
4	T2N2	66.6	65.5	2.5	52.3	0.00	0.00	0.20	1
5	T2N3	72.2	66.9	5.0	65.5	0.36	1.06	5.22	1
6	T3N2	70.2	70.3	12.5	65.1	0.39	0.97	3.90	2
7	T0N2	72.0	70.8	6.0	62.5	0.06	0.18	0.86	0
8	T2N3	72.0	70.2	14.0	65.0	0.37	0.95	1.73	0
9	T3N2	72.0	72.5	8.0	65.3	0.12	0.32	1.68	1
10	T2N3	72.0	62.0	1.6	62.0	0.40	2.32	7.23	1
11	T1N2	70.2	63.6	2.0	47.0	0.00	0.00	0.05	1
12	T2N3	72.2	66.6	2.8	52.8	0.00	0.00	1.48	1
13	TxN3	66.6	65.0	10.0	55.4	0.00	0.05	1.75	2
14	T0N2	70.2	70.8	22.8	68.2	1.87	2.35	3.20	0
15	T2N1	70.0	58.7	0.0	47.0	0.00	0.00	0.05	1
16	TxN3	66.6	66.9	9.7	64.8	1.36	2.00	2.68	1
17	T3N0	63.0	65.6	4.7	59.4	0.01	0.51	2.49	1
18	T2N2	70.2	70.2	2.7	56.4	0.00	0.07	1.24	2
19	T3N0	72.0	67.04	1.9	64.1	0.00	0.02	0.34	2
20	T4N0	70.0	68.7	2.3	54.9	0.15	0.50	2.63	0

*Max Dose is defined as the dose received by 0.03 cc receiving the highest dose.

To understand how CE sparing may decrease severe esophagitis, it is important to consider the different mechanisms of radiation-induced normal tissue injury. The reason why a large dose to a small length of the spinal cord may cause severe radiation injury, such as myelopathy, is that the inactivation of even a single functional subunit (FSU) can disrupt the function of the entire organ for tissues whose FSUs are arranged in a serial fashion. In contrast, a high dose to a small volume of the lung may have little impact because the remainder of the lung will continue to function normally because its FSUs are arranged in parallel [33]. Assuming that the esophagus represents an organ with FSUs arranged in serial fashion in the longitudinal axis, high dose irradiation of the entire cross-section of the esophagus would be expected to result in whole organ dysfunction. The results suggest a model in which near-normal esophageal function is maintained by preserving the function of part of the esophageal cross-section, i.e., converting serial organ-type injury to parallel organ-type injury.

We now propose to prospectively test the utility of CEST which was developed in clinical practice. The rationale for using CEST is that, once we can reduce the rate of severe esophagitis from the published rate of 15-25% to 5% or less, we may be able to revisit the question of radiation dose escalation to > 70 Gy. Increasing the radiation dose is predicted to increase local tumor control and subsequently survival, provided that the dose increase is not associated with morbidity and mortality.

2. OBJECTIVES

2.1 Study Design

Standard therapy for both inoperable, locally advanced NSCLC and LS-SCLC involves concurrent radiation therapy and chemotherapy. The rate of grade 3+ acute esophagitis associated with these treatment regimens is generally in the order of 15-25% (Table 1). We will thus allow both locally advanced NSCLC and LS-SCLC patients to enroll.

Acceptable radiation doses for both lung cancer types range from 60 Gy to 70 Gy. We will select 70 Gy for our study, which would be predicted to result in somewhat higher esophagitis rates than 60 Gy and is thus better suited to demonstrate the superiority of CEST in terms of esophagitis reduction. We note that 70 Gy is already being used as a standard at MGH, and its use therefore does not represent a deviation from routine clinical care (see Table 2).

There is no prospective data to indicate that different concurrent chemotherapy regimens result in different rates of esophagitis. We will, therefore, allow any type of standard-of-care concurrent regimen at the discretion of the treating medical oncologist (this would be in the vast majority of cases cisplatin + etoposide, carboplatin + paclitaxel, or cisplatin/carboplatin + pemetrexed).

Currently, there are no established dosimetric parameters to guide appropriate esophageal sparing in the treatment of locally advanced lung cancer. This is highlighted by the recently opened RTOG 1308 protocol in which patients with locally advanced NSCLC are randomized to photon or proton radiation to a dose of 70 Gy. In this protocol, only a maximum esophageal dose is specified. At MGH, we have developed an IMRT-based technique to reduce radiation dose to the part of the esophagus that is located contralateral to the tumor. This approach mirrors the approach to sparing of the posterior rectum, used in the treatment of prostate cancer. In our clinical experience, esophagus sparing with IMRT-based CEST has the potential to dramatically reduce the rates of acute esophagitis, and in particular grade 3+ esophageal toxicity (Table 2). We, therefore, wish to analyze the toxicity associated with this technique in a prospective fashion.

Contralateral esophageal sparing is particularly important in patients in whom there is gross tumor (primary tumor or involved lymph nodes) in close proximity to the esophagus. We will, therefore, enroll only patients with gross tumor within 1 cm of the esophagus. A steep dose gradient between the gross tumor (which receives 70 Gy) and the contralateral esophagus wall (which is limited to a maximum dose of ~55 Gy) requires high precision delivery of radiation.

We will, therefore, require custom immobilization and daily image-guidance with cone beam CT in every patient, in order to ensure adequate tumor coverage and esophageal sparing. In addition, if changes in esophagus position are detected during the course of radiation therapy, for example due to regressing tumor which had pushed the esophagus aside, repeat (adaptive) radiation planning will be required.

Therefore, we propose to undertake a phase I study to analyze the impact of CEST on rates of acute esophagitis in patients with locally advanced NSCLC and LS-SCLC receiving definitive radiation with concurrent chemotherapy. We anticipate that sparing the contralateral esophagus from full prescription dose will result in a reduction of grade ≥3 acute esophagitis compared to historical rates of 15-25%. We will test this technique in a cohort of 20 patients with NSCLC/SCLC treated to a radiation dose of 70 Gy.

2.2 Primary Objectives

To describe the rate of grade ≥3 acute esophagitis using CTCAE v4 in patients with locally advanced NSCLC or LS-SCLC, located in close proximity to the esophagus, who undergo concurrent IMRT with CEST and chemotherapy.

2.3 Secondary Objectives

As a main secondary objective we will describe the rates of acute esophagitis using the historical RTOG scoring scale, in order to facilitate comparisons with published clinical trials. We will describe the general toxicities of treatment, which, because combined radiation/chemotherapy is the standard of care, will reflect routine clinical practice. Because reducing the dose to parts of the esophagus in close proximity to the tumor can theoretically lead to underdosing of tumor during the course of treatment, we will also assess local and regional failure rates.

Secondary objectives are thus:

1) To describe the rates of acute esophagitis using the historical RTOG scoring system
2) To describe general toxicities of radiation treatment using CTCAE v4.0
3) To analyze local and regional failure rates
4) To determine overall survival time

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study.

3.1.1 Histologically or cytologically proven diagnosis of NSCLC or SCLC. In cases where the histology and cytopathology results are consistent with a carcinoma but immunohistochemistry stains are indeterminate and unable to support the lungs as the most

likely site of origin, the diagnosis of NSCLC or SCLC may be established in conjunction with the radiographic and clinical picture.

3.1.2 For NSCLC, patients with clinical stage IIB-IV patients (AJCC, 7th ed.) are eligible, and for SCLC, limited-stage patients are eligible, if documented to be a candidate for definitive radiation and concurrent chemotherapy in the radiation oncologist or medical oncologist clinic note.

- Stage IV NSCLC patients are eligible only if they have a solitary brain metastasis
- Patients with non-malignant pleural effusion are eligible.
    - If a pleural effusion is present, the following criteria must be met to exclude malignant involvement:
        - When pleural fluid is visible on both the CT scan and on a chest x-ray, a pleuracentesis is required to confirm that the pleural fluid is cytologically negative.
        - Exudative pleural effusions are excluded, regardless of cytology;
        - Effusions that are minimal (ie, not visible on chest x-ray) that are too small to safely tap are eligible.

3.1.3 Gross tumor (primary tumor or involved lymph node) must be within 1 cm of esophagus on the most recent chest CT scan.

3.1.4 ECOG performance status 0-1 within 30 days prior to registration;

3.1.5 Age ≥ 18

3.1.6 Women of childbearing potential must indicate that there is not a possibility of being pregnant at the time of enrollment or have a negative serum pregnancy test prior to the initiation of radiation therapy.

3.1.7 Women of childbearing potential and male participants must practice adequate contraception.

3.1.8 Patient must provide study-specific informed consent prior to study entry.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Greater than minimal, exudative, or cytologically positive pleural effusions

3.2.2 Tumor suspected or known to invade the esophagus

3.2.3 Prior chemotherapy if this precludes administration of concurrent chemotherapy for protocol treatment. Note that induction chemotherapy is allowed as long as concurrent chemotherapy is possible.

3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields

3.2.5 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.2.6 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.7 Any history of allergic reaction to chemotherapies used

3.3 Inclusion of Women and Minorities

We do not expect that the inclusion or exclusion criteria will impact the enrollment of women, minorities, or other underrepresented populations as lung cancer affects people of all genders, races, and socioeconomic classes.

4. PRETREATMENT EVALUATIONS/MANAGEMENT

Baseline studies include the following minimum diagnostic workup, which is standard-of-care:

- History/physical examination, including vital signs with weight, blood pressure, heart rate, oxygen saturation, documentation of smoking history, alcohol use, acid reflux, and pre-chemotherapy laboratory tests as per standard-of-care within 30 days prior to registration;
- FDG-PET scan for staging within 90 days prior to registration.
- CT chest/abdomen scan with IV contrast for staging within 90 days prior to registration.
    - MRI scan with IV contrast of the brain (preferred) or CT scan of the brain with iv contrast within 90 days prior to registration.*PET and CT may be combined in a single study. If a subject has an allergy to IV dye or refuses, non-contrast scans will be acceptable.*
- Optional FLT-PET Scan (Refer to Section 9)
    - *A pregnancy test will be conducted before the scan for women of child-bearing potential.*

5. REGISTRATION PROCEDURES

5.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registration must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

5.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #**:** REGIST-101) must be followed.

5.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Coordinating Center by the Multi-center Coordinator. All sites should contact the Multi-center Coordinator to verify dose level availabilities prior to consent.

Following registration, participants should begin protocol therapy within 5 weeks. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive a protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellation as soon as possible.

6. RADIATION TREATMENT PLAN

Radiation therapy will consist of high-precision IMRT that utilizes custom patient immobilization, 4D CT planning, daily image guidance, and adaptive planning as needed. A total dose of 70 Gy at 2 Gy per fraction over 7 weeks will be delivered to all gross tumor using a shrinking field technique.

6.1 Dose Specifications:

Initial fields: 44 Gy at 2 Gy/fraction
At least 99% of the CTV (clinical target volume, see 6.4 below) will be covered with 100% of prescription dose (i.e., 44 Gy). At least 99% of the CTV plus margin (PTV1, see 6.4 below) will be covered by at least 90% of prescription dose (i.e., 39.6 Gy).

Boost fields: 26 Gy at 2 Gy/fraction
At least 99% of the ITV (internal target volume, see 6.4 below) will be covered with 100% of prescription dose (i.e., 26 Gy, for a total dose of 70 Gy). At least 99% of the ITV plus margin (PTV2) will be covered by at least 90% of the prescription dose (i.e., 23.4 Gy).

Target coverage may not be compromised in order to spare normal organs at risk (OAR). If OAR sparing cannot be achieved with the above coverage specifications, the study PI will decide on a case-by-case basis whether the gross tumor can be covered at least in part by a lower dose that remains within the standard of care, such as 22 Gy to the PTV2 boost volume (for a total 66 Gy) (i.e., ~94% of 70 Gy).

6.2 Technical Factors

a. IMRT will be delivered with megavoltage equipment at 6 MV energy.

b. IMRT will be planned and carried according to standard institutional practice and guidelines. Typically no more than 5 beams should be used in order to minimize low dose lung exposure.

c. IMRT planning may not use multicriteria optimization (MCO) so that techniques and results of this study will be applicable to institutions that do not have MCO planning capability in future trials. However, in cases where only MCO-planned IMRT would provide adequate esophagus and OAR sparing without compromising target coverage, the study PI will make a determination as to whether this will be allowable.

d. In patients where respiratory peak-to-peak motion of the tumor exceeds 1.5 cm or if needed to meet lung DVH constraints, respiratory gating is permissible and will be performed according to institutional practice.

6.3 CT simulation

Custom patient immobilization is required to ensure precise and reproducible positioning. All simulations will be done on CT scanners capable of acquiring 4D CT image data sets. The slice thickness through tumor-containing regions should be 2.5 mm. The imaging session will consist of acquisition of a free-breathing treatment planning CT image data set and a 4D CT image data set consisting of 0% to 90% phase CT sets representative of a single respiratory cycle, as per individual institutional practice.

CT images should be acquired with the application of intravenous contrast for the free breathing scan component, unless medically contraindicated. Omission of intravenous contrast for non-medical reasons is discouraged but permissible if a diagnostic chest CT scan with IV contrast is available to guide the delineation of mediastinal target volume and critical normal tissue structures. Oral esophageal contrast may not be used as it can interfere with dosimetric calculations.

Repeat 4D CT scanning during the treatment course to take advantage of tumor regression or adjust for anatomical changes including changing esophagus position for adaptive purposes is strongly recommended.

6.4 Treatment Planning/Target Volumes

Visible gross tumor should be outlined on each CT slice. For the identification of parenchymal lung tumor, lung windows should be used. For the identification of tumor in the mediastinum including lymph nodes, an appropriate soft tissue window should be used. Interpolation is allowed.

The use of the average intensity projection of the 4D CT data set as reference scan is recommended.

For the purpose of this protocol, the following target volumes are defined:

GTV The gross tumor volume (GTV) is all known gross disease visible on the 50% (exhale) phase of the 4D planning CT modified as necessary based on diagnostic CT and PET images. Mediastinal lymph nodes are considered involved if they are FDG-avid on PET or biopsy-proven (for example, on mediastinoscopy). Suspicious lymph nodes that are PET negative may also be included at the treating physician's discretion, for example if they are > 1 cm in short axis diameter, lie in a predicted path of lymphatic spread, or have a necrotic center.

ITV For the purpose of this protocol, the internal target volume (ITV) will be defined as GTV plus internal margin for respiratory tumor motion. Generation of the ITV will be performed as per institutional practice. The ITV should encompass all gross disease on all respiratory phase and maximum intensity projection (MIP) scans.

CTV The clinical target volume (CTV) is derived by adding an automatic 5-8 mm margin around the ITV for microextension of tumor. The CTV should be extended beyond the automatic margin to include areas of likely subclinical disease, including atelectatic lung, postobstructive changes, and likely lymphatic drainage routes. However, comprehensive elective nodal irradiation (ENI) is not allowed and careful consideration must be given to any increase in lung V5 or V20 that may result from an increase in the CTV volume that could limit delivery of the prescription dose to the gross tumor. The CTV should be manually constricted if it extends into normal tissue structures that do not contain microscopic spread such as lumen of a vessel, vertebral body, and esophagus.

PTV1 The planning target volume (PTV) entails a margin that accounts for variations in treatment delivery, including variations in setup between treatments. The PTV1 should be 5 mm around the CTV. Manual editing of PTV is not allowed even if this

were to minimize overlap with critical normal tissue structures such as the esophagus.

PTV2 The planning target volume 2 (PTV2) is obtained by adding a 5 mm margin around the ITV. Manual editing of PTV is not allowed even if this were to minimize overlap with critical normal structures.

6.5 Critical Normal Structures

The following normal tissue structures should be generated for every subject except where indicated:

- right and left lung
- combined lungs minus ITV
- thoracic spinal cord
- spinal cord + 5 mm margin
- esophagus (entire length),
- heart (contour the pericardial sac from the apex of the heart to a level of ~1 cm inferior to the pulmonary artery bifurcation), unless all disease is located above the heart
- left ventricle, unless all disease is located above the left ventricle
- ipsilateral brachial plexus, if there is disease above the aortic arch that would potentially put the brachial plexus at risk
- contralateral esophagus (CE) from 2 cm above the most superior slice that contains PTV1/2 to 2 cm inferior to the most inferior slice that contains PTV1/2 – see below

The CE should be contoured as a distinct avoidance structure that will be used as a guideline for promoting a steep dose fall-off across sections of the esophagus in close proximity to tumor. This is illustrated in Figures 2 and 3 below. On an axial slice, identify the cross-sectional half of esophagus that is opposite to the gross tumor. This can be the posterior half, left or right half, or oblique half. Figure 2 illustrates examples of CE contours. Figure 3 shows examples of CE contours in patients. On slices where the esophagus is located within 1 cm of the ITV, the CE should be contoured at least 5 mm away from the ITV edge. This is helpful in order to allow a sufficient gap for adequate dose fall-off to occur beyond the ITV. As a result, the CE may be reduced to a quarter or less of the esophagus' cross section in cases where the esophagus abuts the ITV. To facilitate planning, it is recommended that the CE does not overlap with any PTV. Thus, after creating the 5 mm PTV expansion, the CE may be modified by subtracting the PTV volume. There is no minimum size for the CE on an axial slice, hence, if after subtracting out the PTV there is only a small sliver of CE or no CE left on a given slice, that is allowable though not desirable. The rationale underlying this approach is that tumor coverage has always priority over esophagus sparing.

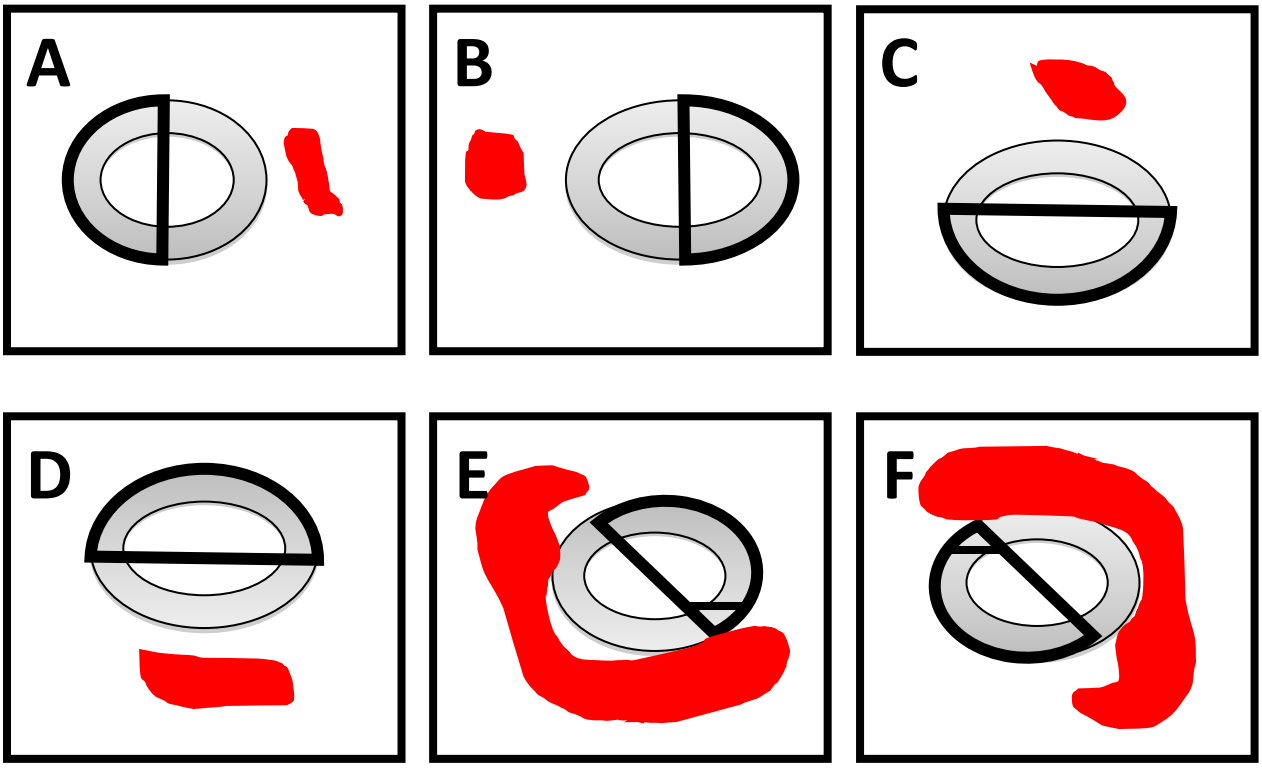


Figure 2. Illustrated above are examples of the contralateral esophagus contour (solid black outline) in relation to gross tumor (red). In A and B, the CE is drawn opposite to the tumor, resulting in right and left lateral contours. In C and D, the CE is drawn posteriorly and anteriorly, respectively. In E and F, the CE is drawn in obliquely, given that the tumor "wraps" around the esophagus (gray). In the latter (E/F), the CE may be edited to introduce a gap of ~ 5 mm for a steep dose gradient between tumor (70 Gy) coverage and the CE (max 55 Gy) (additional black line). Note that the PTV extension around the gross tumor is 5 mm and that the minimum dose to the PTV2 is 63 Gy. The PTV should not overlap with the CE. Note that a minimum cross section area of the esophagus is not defined as target coverage must be ensured at all times.

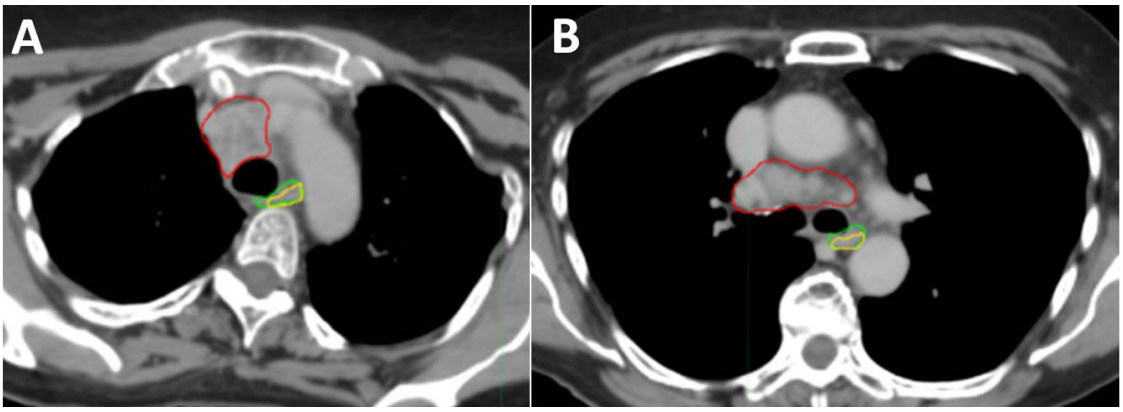


Figure 3: This figure illustrates contouring of the CE contours (yellow) in relation to the internal target volume (red) and esophagus (green).

Every effort must be made to respect dose constraints to critical organs at risk (OAR) as outlined below.

Table 3. OAR Dose Constraints

OARs	Constraints	Deviations
Combined Lungs	V5 ≤ 65% V20 ≤ 35%	V20 ≤ 40%, acceptable if subject has excellent lung function
Spinal Cord	max 45 Gy	No deviations permitted
Spinal Cord + 5mm	V45 ≤ 1% max 50 Gy	The V45 constraint may only be exceeded in cases where gross tumor is in close vicinity to the spinal cord.
Brachial Plexus	max 60 Gy	max 66 Gy, acceptable if there is gross tumor in close proximity
Heart	V40 ≤ 40% max 70 Gy	guideline only
Left Ventricle	V40 ≤ 10% max 45 Gy	guideline only
Esophagus	max 72 Gy V40 ≤ 40% V60 ≤ 15%	guideline only
Contralateral Esophagus (CE)	max 60 Gy V55 ≤ 0.5cc V45 ≤ 2.5cc	max 63 Gy V55 ≤ 3.0cc V45 ≤ 7.5cc deviations from these constraints are permitted if otherwise tumor coverage would be compromised
All max doses refer to a dose to a 0.03 cc volume V(dose) refers to the volume that receives at least the indicated dose		

6.6 Treatment Verification

Daily pre-treatment cone beam CT (CBCT) must be obtained. CBCT should be matched using the planning CT as reference. Preportal orthogonal kV images are allowed if CBCT is not available. Physician review of soft tissue anatomy and target matching at least once per week is recommended.

6.7 Quality Assurance

Documentation Requirements: per institutional standard, no specific requirements
Compliance Criteria: N/A

6.8 Radiation Quality Assurance Reviews

Treatment on protocol follows the standard-of-care for IMRT treatments including physics checks and phantom-based verification of monitoring units prior to first treatments.

6.9 Radiation Adverse Events

Radiation side effects are divided into those that occur acutely (during course of radiation therapy and up to 3 months after completion of treatment) and those that occur later (>3 months post-radiation). Acute side effects are typically common and transient, while late normal tissue complications are generally rare but they can be severe and/or permanent. All participants will be seen weekly by their treating radiation oncologist while undergoing therapy. IMRT with CEST is not expected to be associated with any more side effects than normally observed. These are:

>10%:
Fatigue
Mild to moderate dermatitis
Mild, moderate, or severe esophagitis
Dry cough
Mild to moderate pneumonitis

1-10%:
Moist desquamation of skin
Stricture of the esophagus
Severe pneumonitis, requiring oxygen support
Severe or permanent dyspnea or hypoxia
Fracture of ribs or vertebral body
Decreased neutrophil count

<1% (serious or life-threatening):
Esophageal obstruction or perforation
Fistula formation
Severe hemoptysis
Pneumonitis requiring ventilation
Myocardial infarction
Constrictive pericarditis
Severe congestive heart failure
Cardiac arrhythmias
Transverse myelitis
Brachial plexopathy
Skin ulceration
Radiation-induced cancer

All adverse events experienced by participants will be collected from the time of the first dose of

study treatment, through the study, and until the final study visit. Participants continuing to experience toxicity at the off-study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

Radiation-related side effects will be managed per clinical standard-of-care.

Consider holding radiation therapy for neutropenia (ANC < 500 cells/mcl) as per routine clinical care, because radiation can theoretically lower counts further. Hold radiation therapy for any febrile neutropenia. If neutropenia-related treatment break is > 3 days, subject will be removed from the primary endpoint analysis because prolonged treatment breaks will reduce the risk of severe esophagitis.

Treatment should not be interrupted for grade 2 dermatitis. However, in the case of impending or actual grade 3 dermatitis (moist desquamation), treatment breaks cumulatively of up to 3 days are allowable. However, should treatment breaks exceed 3 days the subject will be removed from the primary endpoint analysis because prolonged treatment breaks will reduce the risk of severe esophagitis. The subject may resume radiation once the skin toxicity has resolved to grade 2 or less.

6.9.1 Acute esophagitis

Esophagitis is common with combined radiation therapy and chemotherapy. Esophagitis should not be reason enough to interrupt or delay daily radiation treatment provided that oral intake is sufficient. Subjects will be advised to follow diet restrictions that include avoiding alcoholic, acidic, or spicy foods. Subjects should refrain from smoking. Medications for the treatment of esophagitis include proton pump inhibitors, a mixture of 2% viscous lidocaine, diphenhydramine, aluminum hydroxide/magnesium hydroxide/simethicone, narcotic pain medications as needed, and sucralfate suspension on a case-by-case basis.

Esophagitis will be graded according to the CTCAE v4 as well as the RTOG scoring system. We will use both scoring systems to facilitate comparisons with published esophagitis rates.

CTCACE v4

Grade	1	2	3	4	5
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death

RTOG Scale

Grade	1	2	3	4	5
Esophagitis	Mild dysphagia or odynophagia, requiring topical anesthetic, non-narcotic agents or soft diet	Moderate dysphagia or odynophagia, requiring narcotic agents or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss (>15% of pre-treatment baseline), requiring nasogastric feeding	Complete stricture, ulceration, perforation, or fistula	Death

6.10 Radiation Adverse Event Reporting

6.11 Definitions

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment, even if the event is not considered to be related to the study. Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be SAE are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen

- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

The severity of the AE should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Expectedness
Adverse events can be 'Expected' or 'Unexpected.'

- Expected Adverse Event
  Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list or is included in the Informed Consent as a potential risk.
- Unexpected Adverse Event
  For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list or is not included in the Informed Consent as a potential risk.

Attribution

- Attribution is the relationship between an adverse event or serious adverse event and the study treatment, radiation therapy. Attribution will be assigned as follows:
  Definite – The AE is clearly related to the study treatment.
  Probable – The AE is likely related to the study treatment.
  Possible – The AE may be related to the study treatment.
  Unlikely - The AE is doubtfully related to the study treatment.
  Unrelated - The AE is clearly NOT related to the study treatment

For the purpose of this study protocol, we will assess all toxicities and events that a subject experiences irrespective of etiology, but we will only report AE that are possibly, probably, or definitely related to radiation therapy.

6.12 Procedures for AE and SAE Recording and Reporting

Reporting participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs, whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the CTEP Active Version of the NCI

Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

6.13 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator. Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

6.14 Reporting to the Study Sponsor

SAE Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Henning Willers, MD, PI
Tel. 617-726-5184
Fax. 617-726-3603
hwillers@partners.org

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Non-SAE Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

6.15 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

6.16 Reporting to the Food and Drug Administration (FDA)

N/A

6.17 Reporting to the NIH Office of Biotechnology Activities (OBA)

N/A

6.18 Reporting to the Institutional Biosafety Committee (IBC)

N/A

6.19 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

6.20 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any

unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

7 DRUG THERAPY

All patients will receive standard concurrent chemotherapy as prescribed by their treating medical oncologist. Most common regimens include cisplatin and etoposide, carboplatin and paclitaxel and cisplatin/carboplatin and pemetrexed. These regimens when combined with radiation are associated with comparable rates of esophagitis (Table 1). Induction chemotherapy prior to concurrent chemotherapy and radiation is allowed. Side effects in relation to chemotherapy will be managed per standard of care and are not reportable as AE for purposes of this trial. In addition, adjuvant therapies within or outside a separate clinical trial are allowed and include chemotherapy and immune checkpoint inhibitor therapy at the discretion of the treating physicians.

8 SURGERY

Patients will undergo definitive radiation/chemotherapy. Surgery is not allowed on this protocol

9 CORRELATIVE STUDIES

9.1 18F-Fluorothymidine-PET (FLT-PET/CT)

In addition to the study requirements, we would like to include 2 optional FLT-PET/CT scans, 1 baseline scan within 1 week before treatment start and a mid-treatment scan during treatment week 3 (+/- 1 week). The injection dose for 18F- FLT will be not more than 10mCi. The baseline FLT-PET/CT will include an attenuation correction chest CT and the week 3 FLT-PET/CT will include a diagnostic chest CT. The total radiation dose from the FLT-PET/CT imaging will be approximately 37.51 mSv, equivalent to approximately 12.1 years of normal background radiation.

The difference between these FLT-PET/CT scans and the standard FDG-PET is that the FLT tracer has been introduced to specifically image tumor proliferation, while FDG is not intrinsically tumor specific and is also taken up by inflammatory cells. FLT is phosphorylated by thymidine kinase 1, a key enzyme in the salvage pathway of DNA synthesis. Thymidine Kinase 1 is up-regulated during the S-phase of the cell cycle; therefore FLT uptake is dependent on cell proliferation. It has been shown in lung cancer that FLT correlates better than FDG with the proliferation activity, and multiple studies have reported that FLT-PET is useful to measure early tumor response to chemotherapeutic agents.

We hypothesize that FLT-PET/CT can also be used as an early response indicator to concurrent chemo-radiation for lung cancer, which could enable personalized treatment approaches depending on changes in tumor proliferation.

10 TISSUE/SPECIMEN SUBMISSION

N/A

11 PARTICIPANT ASSESSMENTS

Baseline evaluation tests and scans are to be conducted as outlined in Section 4. Assessments during radiation therapy should be made once per week. Follow-up assessments should be done per routine clinical care as detailed below and obtained within 4 weeks of the protocol-specified date.

	Pre-Stud	**Concurrent radiation/chemotherapy**							**Follow-up[ef]**
Weeks		1	2	3	4	5	6	7	
Radiation Therapy		X----------							
Tissue diagnosis	X								
Informed consent	X								
History[a]	X								
Physical exam[b]	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X
Laboratory studies [c]	X	X	X	X	X	X	X	X	X
Toxicity and adverse event monitoring[d]	X	X	X	X	X	X	X	X	X[f]
CT chest/abdomen	X								X[e]
FDG-PET scan	X								As clinically indicated
FLT-PET/CT scan (optional) [g]	X			X					
Brain MRI, or Head CT	X								As clinically indicated

a. History must include smoking status/history, alcohol use, and acid reflux history

b. Including weight and vital signs include blood pressure, heart rate, oxygen saturation

c. Laboratory tests may include complete blood count with differential, basic metabolic panel (Na, K, Cl, CO2, BUN, creatinine, glucose, calcium), magnesium, liver function tests (albumin, total protein, alkaline phosphatase, total and direct bilirubin, ALT, AST). These tests will be up to the discretion of the treating medical oncologist depending on chemotherapy regimen and tolerance. These may be obtained only in part or less often than once per week. During long-term follow up after chemotherapy laboratory tests are at the discretion of the treating physician.

d. Toxicity assessment must include smoking status, alcohol use, GERD/reflux, supportive medications including pain medications needed, intravenous fluids needed.

e. Follow up visits and scans per routine standard of care. CT scan of the chest generally includes upper abdomen with liver and adrenal glands and thus does not require a separate CT abdomen during follow-up. Continue CT scans every 3 months (+/- 4 weeks) for year 1 and every 3-4 months for year 2 (+/- 4 weeks), which reflects standard-of-care. CT scans outside this schedule, will be allowed if needed per standard of care and will not be marked as a minor deviation.

f. Subjects who have at least grade 2 esophagitis at the end of the radiation therapy course should be seen at least every other week until esophagitis is resolved.

g. The optional FLT-PET/CT scan will be completed at baseline, within 1 week prior to treatment start and during treatment week 3 (+/- 1 week). A pregnancy test will be conducted before the scan for women of child-bearing potential.

12 DATA COLLECTION

The Office of Data Quality (ODQ) will collect, manage, and monitor data for this study.

The schedule for completion and submission of case report forms (paper or electronic) to the ODQ is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with OnCore
On Study Form	Within 14 days of registration
Treatment Form	Within 10 days of completion of treatment
Toxicity and Adverse Event Report Form	Within 10 days of completion of treatment and within 10 days of protocol specified follow up visit
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints Definitions

The historical rate of severe (grade 3+) acute esophagitis in the treatment of locally advanced NSCLC or LS-SCLC with radiation and concurrent chemotherapy is in the order of 15-25% (Table 1). Grade 3 esophagitis is a serious effect of treatment that can be associated with hospital admission, treatment interruptions, and reduced local tumor control and survival. Here, we will test a novel esophagus sparing technique (CEST) to reduce the rate of grade 3+ esophagitis. Specifically, we hypothesize that CEST will reduce the rate of grade 3+ esophagitis to 5% or less in a study cohort of 20 patients with locally advanced NSCLC or LS-SCLC treated with definitive IMRT to 70 Gy at 2 Gy/fraction using CEST and concurrent standard-of-care chemotherapy.

Primary endpoint:
Rate of grade 3+ acute esophagitis occurring during and up to 3 months after the last day of radiation therapy using CTCAEv4

Secondary endpoints:

1. Rates of acute esophagitis using the historical RTOG scoring scale
2. General toxicities of treatment using CTCAEv4
3. Two-year local and regional failure rates
4. Two-year overall survival rate

13.2 Sample Size, Accrual Rate and Study Duration

In our clinical experience with CEST, the observed rate of grade 3+ acute esophagitis has been 0%. In contrast, the published rate of grade 3+ esophagitis in this patient population is 15-25%, With the primary goal of estimating the rate of grade 3+ acute esophagitis in this study population a sample size of 20 subjects was chosen to guarantee that if no more than one subject is observed with grade 3+ esophagitis, the one-sided upper limit of the 90% confidence interval (CI) would not exceed 20% (exact value 18%). In addition, a sample size of 20 subjects provides a two-sided exact binomial 90% CI of (0.25%, 21.6%) for a good grade 3+ esophagitis rate of 5%.This means that even if we were to observe as many as 3-5 cases of severe esophagitis out of 20 participants results would still be in keeping with the extent of toxicity that standard-of-care treatment produces. Because CEST is designed to reduce the rate of acute esophagitis it is not expected that this technique would lead to a rate of grade 3+ esophagitis that is higher than what is observed with standard-of-care treatment. Therefore, grade 3+ esophagitis is not defined as a dose-limiting toxicity in this protocol.

At MGH and NWH, we see approximately 60 patients with locally advanced, inoperable NSCLC or LS-SCLC every year. At least 80% of patients receive concurrent chemotherapy/radiation. We anticipate that up to 10 patients may be enrolled onto other high-priority national treatment protocols. Of the remaining patients, we estimate that ~50% will be eligible for this study, in particular due to the requirement of having gross tumor within 1 cm of the esophagus. We expect that 75% of these patients will enroll onto the protocol. Hence, we will accrue ~14 subjects per year. We expect that no more than 25% of participants may have unplanned treatment interruptions of > 3 days for reasons other than grade 3+ esophagitis, which would lead to removal from primary endpoint analysis (see below). These participants will thus have to be replaced for the purpose of analyzing the primary endpoint based on a sample size of 20 subjects. Therefore, we may need up to ~25 participants, so that up to 2 years will be required to complete enrollment. An additional 2-year follow up will be necessary after the last participant enrolled to assess locoregional control and survival rates, for a total study duration of 4 years.

Participants will be removed from study when any of the criteria listed below applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

- Disease progression
- Illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

Any subject removed from the study for any of the reasons above will be replaced in order to

maintain the sample size of 20 subjects required for the primary endpoint.

In addition, subjects will be excluded from primary endpoint analysis in the following scenarios:

- Treatment interruption for any reason other than acute esophagitis resulting in a break of > 3 radiation treatment days. This includes treatment-associated toxicity other than esophagitis.
- Less than full chemotherapy given concurrently with radiation therapy:
  - only 1 cycle of cisplatin and etoposide (given every 3 or 5 weeks) received concurrently
  - only 1 cycle of cisplatin or carboplatin and pemetrexed (given every 3 weeks) received concurrently
  - only 1-4 cycles of carboplatin/paclitaxel (once weekly) received concurrently

Subjects removed from primary endpoint analysis for these reasons will remain on study and will still be analyzable for secondary endpoints 2-4. Subjects will be replaced in order to maintain the sample size of 20 subjects. Based on our own clinical experience, it is estimated that no more than 1 in 4 subjects will experience treatment toxicity other than esophagitis (such as severe neutropenia) that warrants treatment interruption or will receive less than full dose chemotherapy or have any other reasons for withdrawal from protocol therapy.

13.3 Stratification Factors

Not applicable

13.4 Interim Monitoring Plan

Not applicable

13.5 Analysis of Primary Endpoints

Determination of number of patients with grade 3 or higher acute esophagitis according to CTCAEv4. Exact binomial confidence intervals will be calculated for grade 3+ esophagitis and other toxicities of interest.

13.6 Analysis of Secondary Endpoints

1. Rates of acute esophagitis using the historical RTOG scoring scale:
Determination of number of patients with grade 3 or higher acute esophagitis according to RTOG.

2. General toxicities of treatment using CTCAEv4
Determination of number of patients with grade 3 or higher toxicities according to CTCAEv4.

3. Two-year local and regional failure rates

Crude frequencies and rates of isolated local and regional recurrence, as defined below, will be calculated.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline. Changes in the diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

Measurable disease: Measurable disease is the presence of at least 1 lesion that can be accurately measured in at least one dimension with longest diameter > 10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Target lesions: The primary lung tumor and the hilar/mediastinal lymph nodes judged as involved should be identified as the target lesions and recorded and measured at baseline and with each follow-up imaging evaluation. The longest diameter (LD) of the target lesions will be calculated from the pre-treatment diagnostic chest CT scan with IV contrast, using pulmonary windowing for the primary tumor soft tissue windowing for involved lymph nodes, and reported as the baseline LD. The baseline LD will be used as a reference by which to characterize the objective tumor response. Local treatment effects in the vicinity of the tumor target may make determination of tumor dimensions difficult. For example, bronchial or bronchiolar damage may cause patchy consolidation around the tumor that over time may coalesce with the residual tumor. In cases in which it is indeterminate whether consolidation represents residual tumor or treatment effect, a PET/CT scan should be obtained for further characterization. If findings remain indeterminate, it should be assumed that the observed abnormalities represent residual tumor.

Non-target lesions: All other lesions, including small lesions < 10 mm and truly non-measurable lesions.

Response Criteria:
Complete Response (CR): Disappearance of all target lesions; this will be made based on CT image evaluation.
Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD; ideally, this will be made based on CT image evaluation.
Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions (new lesions must be > slice thickness). Ideally, this determination will be made based on CT image evaluation**.** If the criteria for PD are met, the patient should undergo either PET scan imaging and/or a direct biopsy of the targeted tumor for evaluation as to whether local or regional failure exists as defined below.
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Local failure (LF): Refers to the primary treated tumor after protocol therapy and corresponds to meeting both of the following two criteria:
(1) Increase in tumor dimension of 20% as defined as an increase in the sum of diameters of

target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) following RECIST criteria. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions within the ITV is also considered progression).
(2) The measurable tumor with criteria meeting PD should be avid on PET imaging with uptake of a similar intensity as the pretreatment staging PET, or the measurable tumor should be biopsied confirming viable carcinoma.
Marginal failure, i.e., PET-positive or biopsied measurable tumor within 1 cm of the PTV, will be counted as LF. The EORTC criteria for post-treatment PET evaluation may be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathologic for cancer recurrence vs. inflammation. It will be necessary to measure the distance of site of failure from the esophagus.
Regional failure (RF): This is defined as progression of nodal target lesions or the appearance of non-target lesions in either hilum, the mediastinum, or supraclavicular fossa. The measurable tumor with criteria meeting PD should be avid on PET imaging with uptake of a similar intensity as the pretreatment staging PET, or the measurable tumor should be biopsied confirming viable carcinoma. It will be important to measure the distance the failure occurs from the esophagus.
Distant failures (DF): This will be disease progression in sites not included as LF or RF above. Diagnosis will be made by CT, PET, or MRI as per clinical protocol. If imaging findings are not definitive biopsy confirmation is recommended.

4. Two-year overall survival (OS) rate

Follow-up time will be calculated from the date of registration to the date of death or the last follow-up date on which the patient was reported alive. OS rates will be estimated using the Kaplan-Meier method.

State of patient at last follow up – This refers to the state of the patient at the last follow up on the study. This will be scored as alive, dead (if dead, state cause of death), or lost to follow up.

13.7 Reporting and Exclusions

Reporting will take place at two separate time points. Initially, reporting on esophagitis will occur within 3 months of the last study patient completing radiation therapy. After two years of minimum follow up, an additional report will include local failure, regional failure, and overall survival.

Participants who never start protocol therapy are excluded ("inevaluable") from analyses. Participants who are removed from primary endpoint analysis for reasons specified above will be eligible for secondary endpoint analyses.

13.8 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.9 Evaluation of the Primary Efficacy Endpoint

Not applicable

14 REGULATORY CONSIDERATIONS

14.1 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

14.2 Multicenter Guidelines

NA

14.3 Collaborative Agreements Language

NA

14.4 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

14.5 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant 's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

14.6 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
  Title 21 Part 11 – Electronic Records ; Electronic Signatures
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
  Title 21 Part 50 – Protection of Human Subjects
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  Title 21 Part 54 – Financial Dis closure by Clinical Investigators
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
  Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
  Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State Laws

- DF/HCC research policies and procedures
http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unitcru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

14.7 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

14.8 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

15 PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.