Using FDG-PET Acquired During the Course of Radiation Therapy to Individualize Adaptive Radiation Dose Escalation in Patients with Non-Small Cell Lung Cancer

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Using FDG-PET Acquired During the Course of Radiation Therapy to Individualize Adaptive Radiation Dose Escalation in Patients with Non-Small Cell Lung Cancer

**Study Objectives:** To determine 2 year local-regional progression free survival in patients with non-small cell lung cancer (NSCLC) when an adaptive plan is applied based on repeat PET-CT imaging during the course of radiation therapy (during RT), and investigate if there is an improvement compared to those treated with conventional radiation therapy without field and/or dose modification.

**Study hypothesis:** During-RT PET-CT based adaptive radiation can deliver a higher total dose to the active tumor, and will thus improve the local-regional tumor control without increasing the normal tissue complication probability (NTCP) of the lung.

**Eligible subjects:** Patients with newly diagnosed or recurrent stage I-III NSCLC who have unresectable or inoperable disease, without contraindications to radiation, who require a dose of ≥63 Gy for radiation, with or without chemotherapy.

**Design:** All patients will receive individualized conformal radiation therapy to a ≤17.2% rate of NTCP (mean lung dose corrected to 2 Gy per fraction less than 20 Gy) for estimated pneumonitis. The radiation dose will be delivered 2.1+ Gy per daily fraction, with the treatment duration limited to 30 fractions, and total radiation dose limited to 63-86 Gy. Patients, particularly those with stage III disease and good performance status, will be considered for treatment with concurrent and consolidation chemotherapy with carboplatin plus paclitaxel. Each patient will have CT resimulation and PET-CT after a normalized isoeffective dose (NID) at 2 Gy per fraction of 40-50 Gy is delivered. The first 50 Gy (NID) of radiation will be given based on a target defined by PET and CT acquired prior to the start of radiation, and the remaining dose will be delivered to the target defined by PET-CT acquired during the course of radiation. In addition to maintaining a lung NTCP of ≤17.2%, the radiation dose is prescribed such that (when normal tissue constraints permit) pre-RT PTV, pre-RT CTCTV, and during-RT CTPTV will receive at least 50, 60 and 70 Gy NID, respectively. The local-regional tumor control will be compared to historical controls from University of Michigan.

**Statistical Considerations:** Long-term results from UMCC 9204 showed the local tumor control was significantly associated with total radiation dose; a 1 Gy increment was associated with a 1% improvement in local progression free survival. After 63-69 Gy radiation, local-regional progression free survival was 44%, 34%, and 29% for 1, 2, and 3 years, respectively (with a median survival of 10 months). Based on preliminary results, dose can be escalated by an average of 38% (approximately 20 Gy if 60 Gy is considered to be the standard) if the PET-CT target during treatment is used for the remaining part of radiation therapy. By using this adaptive measure, we expect to achieve up to a 20% improvement in 2 year local-regional progression free survival compared to controls treated with conventional dose prescription and technique without application of adaptive measure. Forty-two evaluable cases, accrued over a three-years time period, will be necessary to detect the hypothesized improvement with 80% power with 5% type I error.
Using FDG-PET-CT Acquired During the Course of Radiation Therapy to Individualize Adaptive Radiation Dose Escalation in Patients with Non-Small Cell Lung Cancer

UMCC 2007.123

ELIGIBILITY CHECKLIST

Patient Name: ________________________________ Reg #: _______________________

1. _____ (Y or N) Does the patient have FDG-avid and pathologically proven non-small cell lung cancer? If No, ______ (Y) Does the patient have FDG-avid and clinically diagnosed non-small cell lung cancer?

2. _____ (Y) Is the patient 18 years of age or older?

3. _____ (Y) Is the patient’s Karnofsky performance status ≥ 60?

4. _____ (Y) Does the patient have Stage I-III disease?

5. _____ (Y) Does the patient have unresectable or inoperable disease?

6. _____ (N) Is there any evidence of a malignant pleural or pericardial effusion?

7. _____ (Y) Does the patient have a hemoglobin ≥ 10 mg/dl?

8. _____ (Y or N) Will the patient receive chemotherapy? If yes, ______ (Y) Is WBC ≥ 3000/mm³, ANC ≥ 1500/mm³, and platelet count ≥ 100,000/mm³? AND ______ (Y) Is total bilirubin ≤ 3.0 mg/dl, AST and ALT ≤ 4x ULN, and serum creatinine ≤ 2.0 mg/dl?

9. _____ (N) Does the patient have serious intercurrent disease?

10. _____ (N) Is the patient pregnant?

11. _____ (Y) If the patient is a female with reproductive capability, is she willing to use effective contraception?

12. _____ (N) Does the patient have any component of small cell lung carcinoma?

13. (N) Did the patient have previous thoracic irradiation such that composite radiation would significantly overdose critical structures?

14. _____ (Y) Has the patient signed informed consent?

Investigator: ________________________________ Date: _______________________


1. OBJECTIVES

1.1 Primary objective: To determine 2 year local-regional progression free survival in patients with non-small cell lung cancer treated with radiation therapy with or without chemotherapy, when the radiation treatment field is adapted and/or radiation dose is escalated during the course of radiation therapy based on repeat FDG PET-CT imaging, and investigate if there is an improvement compared to those treated with conventional radiation therapy without field and/or dose modification during the course of treatment.

1.2 Secondary objectives:

   1.2.1 To determine whether this technique permits escalation of radiation therapy dose to the tumor volume.
   1.2.2 To determine the effect of such an escalated dose prescription on survival.
   1.2.3 To report the treatment toxicity associated with functional image-guided adaptive radiotherapy.
   1.2.4 To determine if there is a relationship between plasma concentration of TGFβ1 or other molecules and treatment outcomes.

2. BACKGROUND

In this section, we will discuss the following topics: 1) The challenge in treating NSCLC and the role of radiation; 2) the effect of radiation dose escalation, duration, fractionation and chemotherapy; 3) preliminary results; and 4) rationale and hypothesis for this proposed study.

2.1 The Challenge in Treating NSCLC and the Role of Radiation

Lung cancer is the leading cause of cancer death in the United States and worldwide. In 2006, there will be an estimated 174,470 new cases of and 162,460 deaths related to lung cancer in the United States, of which 80% to 85% will be non-small-cell lung cancers (NSCLC). The majority of the patients are inoperable or unresectable at the time of diagnosis, due to the presence of locally advanced disease (40%), distant metastases (40%) or co-morbid conditions [1, 2]. Radiation therapy plays an important role in every stage of NSCLC. It is the principal mode of treatment for medically inoperable patients with early stage disease [3], and important local-regional treatment for unresectable locally advanced disease. Very frequently, radiation therapy is required for palliative purposes for patients with stage IV disease. It is estimated that 64% of patients require RT at least once, with about 45% receiving it as part of their initial treatment [3].

Despite advances in radiation technology, treatment outcomes remain poor. Using modern techniques, current radiation therapy applies a uniform dose prescription of 60 Gy or slightly higher and generates a five-year overall survival rate of less than 10%, [4, 5, 6]. Local tumor failure remains a major problem after radiation-based non-surgical treatment. After radiation with or without neoadjuvant chemotherapy, our prior trial, UMCC 9204, showed ultimate local failure in 70% of patients [4]. After neoadjuvant chemoradiotherapy in CALGB 9433, 90% of patients failed locally with 45% having local failure alone [4, 5]. After neoadjuvant and concurrent chemoradiation with radiation doses of 60-74 Gy, Socinski et al reported that 46% patients initially had local failure [7]. Evaluation by bronchoscopy and biopsy one year after treatment completion revealed pathologic local-regional control rates of only 15%–17% after 65 Gy of radiation with neoadjuvant therapy [8].

2.2 Radiation Dose, Escalation, Duration, Fractionation and Chemotherapy

2.2.1 Radiation Dose Escalation and Effect

Several studies have suggested that if high doses of radiation could be delivered safely, treatment outcomes may improve. A dose-response relationship over the range of 40-60 Gy was established by RTOG 73-01 in which 376 patients were randomized between 40 Gy split-course radiation or a continuous-fractionation schedule of 40 Gy, 50 Gy or 60 Gy. The intrathoracic failure rates at 3 years in these arms were 44%, 52%, 42% and 33% respectively [2, 9]. Although the study did not show improved overall survival with higher dose therapy, review of the results from other RTOG trials led to the conclusion that local tumor control is significantly correlated with improved survival [2]. This has formed the base of the current standard dose prescription in radiation therapy.
Using 3D CT-based conformal RT techniques, several radiation dose escalation studies have shown that doses much higher than 60–70 Gy are feasible [10-19]. In the settings of radiation alone or sequential chemoradiotherapy, RTOG 9311 escalated the dose to 83.8 Gy for patients with V20 (lung volume receiving > 20 Gy) < 37.5%, using daily fractions of 2.15 Gy [20]. Investigators from Memorial Sloan-Kettering Cancer Center safely escalated to a dose of 84 Gy for NTCP of less than 25% [17]. Using a lung volume-based escalation scheme, we have demonstrated that doses of 92.4 and 102.9 Gy in 2.1 Gy daily fractions can be delivered safely with minimal toxicity if the mean lung dose is sufficiently small [14, 19]. Higher doses appear to be associated with better local tumor control and survival in medically inoperable or unresectable NSCLC [4, 21]. For stage I NSCLC, retrospective studies from Duke University and Washington University reported that patients who received ≥ 70 Gy had better local tumor control than those who received < 70 Gy [13, 22]. More than 64 Gy was associated with superior survival in patients with stage III NSCLC disease based on a recent retrospective analysis from the Memorial Sloan-Kettering Cancer Center [21]. In an extensive literature review, Vijayakumar, et al. estimated that a dose of 80 Gy was required for 90% local control in lung cancer [7]. For patients with newly diagnosed or recurrent stage I-III disease, multivariate analysis of UMCC 9402 found the radiation dose to be the only significant factor for local tumor control and overall survival and demonstrated a positive relationship between dose and local-regional control, as well as overall survival, with doses between 63 and 103 Gy [4]. An increase of 1 Gy was associated with a > 1% improvement in the five-year tumor control rate, and a 3% decrease in the risk of death. Higher radiation doses may therefore be beneficial to patients with inoperable/unresectable NSCLC (Figure 3). A recent secondary analysis from RTOG trials has demonstrated a 2% reduction in the risk of death with each increase of 1 Gy biological equivalent dose [23]. Bogart et al. used > 2.25 Gy daily fractions to a total nominal dose of up to 84 Gy (range: 60–84) and reported a promising overall tumor response rate of 88% (35% complete response and 53% partial response), 3-5 year local tumor control rate of 80%, median survival of 38 months, and three-year overall survival of 60% in early stage medically inoperable NSCLC [15].

Local tumor control is directly correlated with long term survival. Local-regional disease can not only lead to death due to local effects within the chest, it can also serve as a source for metastatic dissemination. Arriagada et al. reported that local progression or relapse correlated with poorer survival [5]. In RTOG 73-01, the death rate in patients with intra-thoracic failure was similar to that in patients with distant metastases, and an increased survival was observed in patients with complete tumor response [2, 3]. In the CHART trial, local control rates of 20% and 29% were associated with median survivals of 9.9 months and 27.9 months, respectively [6]. In EORTC, Schaake-Koning et al. demonstrated a similar correlation between local control rate and survival [1].

### 2.2.2 The Duration of Radiation Therapy

A problem with traditional dose-escalation using conventional fractionation schedules is that the overall treatment time increases considerably. For example, some patients in UMCC 9204 received treatment for over 10 weeks. Extension of treatment duration may allow tumor re-population and decrease the probability of local tumor control and survival.

In RTOG 83-11, the dose associated with the highest survival was 69.6 Gy, rather than higher dose levels, which were often associated with extended treatment duration and delays due to acute esophagitis. Indeed, survival at two and five years was significantly better in patients who completed treatment in the planned time, as compared with those who had treatment interruptions (24% vs. 13% at two years and 10% vs. 3% at five years) [24]. In a large phase III trial reported by Saunders et al., 563 patients were randomized into two groups treated with either standard RT (60 Gy in 2 Gy fractions, Monday through Friday in six weeks), or continuous hyperfractionated accelerated RT (CHART, 54 Gy delivered over 12 consecutive days) [25]. Two-year survival was superior in the CHART arm (29% vs. 20%; P = .008) despite its lower biological equivalent dose (BED) (72 Gy for the conventional arm versus 62 Gy for CHART). It is conceivable that the improved survival with CHART was a result of the decreased overall treatment time. ECOG 2597 compared 64 Gy in 32 fractions over 6.5 weeks with hyperfractionated accelerated radiation therapy (HART) (57.6 Gy/36 fx/3 weeks) after induction chemotherapy in locally advanced, stage III NSCLC, and reported a trend toward improved survival in the accelerated arm [26]. An early analysis estimated that the tumor control probability of NSCLC decreases 1.6% per day after a six-week duration of RT [27]. In a recent secondary analysis of three RTOG trials in patients with stage III NSCLC who were treated with immediate concurrent chemoradiotherapy, prolonged treatment time was significantly associated with poorer survival [23]. The latter translated into a 2% increase in the risk of
death for each day of prolongation in therapy. Thus, every effort should be made to limit treatment duration and avoid treatment delays. Currently, there are investigative efforts to increase daily fraction size to escalate total radiation dose without extending the treatment duration. One approach involves dose escalation using 2.25 Gy daily fractions (once or twice daily) while limiting treatment duration to six weeks [11]. This approach was used to escalate to 87.8 Gy in patients with limited lung volumes. Another approach is to use a higher fraction dose every day while limiting the treatment duration to five weeks [28]. We previously performed a dose escalation study with a limit of 6 weeks, the results of which will be summarized in a later section (Preliminary Results).

2.2.3 Effect of Radiation Fractionation

Another question related to radiation dose escalation is the choice of fractionation. Hyperfractionated RT delivers multiple smaller fractions each day, and was an area of interest for clinical trials to prevent excessive late tissue toxicities, such as radiation pneumonitis, that result from large daily fractions. However, randomized clinical trials have not demonstrated a clear advantage for hyperfractionated RT in NSCLC [24, 29, 30]. With radiation alone, RTOG 8311 tested total tumor doses ranging from 60 to 79.2Gy (60, 64.8, 69.6, 74.5, and 79.2 Gy) and showed superior results with 69.6 Gy in 1.2 Gy fractions twice-daily when compared to 60 Gy in 2 Gy fractions once a day with a similar BED and treatment duration [24]. Although there was no reduction of radiation pneumonitis, the apparent survival benefit in this phase I/II trial was used to justify the inclusion of hyperfractionated radiation therapy in subsequent trials, such as RTOG 8808 and RTOG 9410 [29, 30]. In the setting of neoadjuvant chemotherapy, RTOG 8808 failed to show a significant advantage of hyperfractionated radiation. Using concurrent chemoradiotherapy, RTOG 9410 compared sequential chemoradiotherapy with single daily fraction RT, concurrent chemoradiotherapy, or hyperfractionated RT and concurrent chemotherapy. The hyperfractionated arm was associated with an increased incidence of esophagitis and inferior survival compared to the daily fractionated concurrent arm [30]. Trials using hyperfractionated and accelerated radiation, such as the aforementioned CHART and HART, resulted in increased mortality in patients treated with concurrent chemotherapy, and higher esophagitis rates (25% for HART vs. 16% for conventional RT). In summary, hyperfractionated schemes are not recommended due to the lack of a significant survival benefit in phase III trials, increased toxicity in conjunction with chemotherapy, and the logistical burden to patients and radiation departments. Although the published data are limited, there does appear to be a trend toward benefit for an increased dose per fraction in patients treated for early stage disease with radiation therapy alone [11] and for locally advanced disease with chemoradiotherapy [28].

2.2.4 Combination of Chemotherapy in NSCLC

The standard of care for patients with stage III unresectable NSCLC is combined chemoradiotherapy. The results with RT alone for stage III tumors that are deemed unresectable or marginally resectable are poor, with five-year survival rates of 5%–7% [2, 5, 6]. Radiation therapy alone is only used to treat patients who cannot tolerate chemotherapy. The addition of neoadjuvant chemotherapy resulted in a 2–4 month extension in median survival and 8%–20% improvement in 2–3-year overall survival [31, 32] in at least three randomized trials: CALGB 9433 [5], RTOG8808/ECOG4588 [6], and a French study [8]. The French study also reported a significant reduction in distant recurrence rate.

**Sequential vs. Concurrent Chemoradiotherapy.** Several prospective randomized trials examining the treatment of patients with stage III unresectable NSCLC have demonstrated superior results with concurrent chemoradiotherapy compared to sequential chemoradiotherapy, with a 2–3 month extension in median survival and 7%–10% improvement in 3–5-year survival, albeit with increased toxicity [30, 33, 34]. In patients with locally advanced NSCLC who are medically fit, concurrent chemoradiotherapy is considered as a standard therapy.

**Adjuvant or Induction Chemotherapy with Concurrent Chemoradiotherapy.** Although there is general agreement on the principle of using combined modality therapy with a concurrent regimen for stage III unresectable NSCLC, there is controversy over the optimal approach and sequence in this population. A number of phase II and III trials have evaluated the use of either induction or consolidation chemotherapy [26, 35-39]. Researchers from the University of North Carolina reported a median survival of 24 months in patients treated with induction paclitaxel/carboplatin (CP) followed by concurrent chemoradiotherapy. However, CALGB 39801, a phase III study comparing concurrent chemoradiotherapy alone to induction CP followed by concurrent chemoradiotherapy failed to show a significant survival difference between the two arms, with a
median survival of 14.0 months in the induction arm versus 11.4 months in the concurrent alone arm \((P = .154)\) [40]. A median survival of 26 months, the best survival result reported thus far for unresectable stage III NSCLC, was reported from a phase II trial (SWOG 9504) using docetaxel as consolidation chemotherapy [38]. The median overall survival from the locally advanced multiple modality protocol (LAMP) was 13.0, 12.7, and 16.3 months with sequential chemoradiotherapy, concurrent chemoradiotherapy after induction CP, and concurrent chemoradiotherapy followed by consolidation CP, respectively [26]. Although the LAMP was not powered to definitively address differences between arms, it suggested that concurrent chemoradiotherapy followed by consolidation chemotherapy resulted in the best median survival. Although large phase III trials are still warranted to determine the optimal combination of chemotherapy and radiotherapy and recent HOG study failed to show a benefit of adjuvant docetaxol [41], yet a common practice in patients with good performance status is concurrent chemotherapy followed by consolidation chemotherapy in the United States [39].

2.3 Preliminary Results

2.3.1 Radiation Dose Effect

From 1992-2000, we conducted a radiation dose escalation study (UMCC 9204) from which long-term results were recently published [42]. A total of 122 patients with inoperable/unresectable newly diagnosed or recurrent stage I-IIII NSCLC were enrolled. Using 3-D conformal radiation therapy and limiting the lung volume irradiated, we treated 106 patients with 63 to 103 Gy in 2.1 Gy fractions. With a median follow-up of 8.5 years, median survival is 17 months, and 5-year overall survival is 13%. Multivariate analysis revealed that radiation dose \((p=0.0006)\) was the most significant predictor for survival. The 5-year survival rates were 4%, 22% and 28% for patients receiving 63-69 Gy, 74-84 Gy, and 92-103 Gy, respectively. The 5-year local control rates were 12%, 35% and 49% for 63-69 Gy, 74-84 Gy, and 92-103 Gy, respectively. With each 1 Gy increment of radiation, 5-year local control improved by 1.25% and the risk of death decreased by 3%.

Radiation dose effect varies with the tumor size [43]. High-dose radiation is more important for patients with larger tumors, and may be effective in reducing the adverse outcome associated with large GTV. Our recent retrospective analysis of 114 patients with medically inoperable NSCLC showed that there was a significant interaction between radiation dose and GTV \((p < .001)\). In patients with BED \(< 79.2 \text{ Gy} \text{(n=68)}, \text{the median OS for patients with GTV} > 51.8 \text{ cm}^3 \text{ and } \leq 51.8 \text{ cm}^3 \text{ was 18.2 and 23.9 months, respectively (p = .015). If BED was }> 79.2 \text{ Gy (n=46)}, \text{no significant difference was found between GTV groups (p = .681). For patients with GTV} > 51.8 \text{ cm}^3 \text{(n=45), the median OS in those with BED} > 79.2 \text{ Gy and } \leq 79.2 \text{ Gy was 30.4 and 18.2 months, respectively (p < .001); If GTV was } \leq 51.8 \text{ cm}^3 \text{(n=45), the difference was no longer significant (p = .577). This study suggested radiation dose is more important for patients with larger tumors, and may be effective in reducing the adverse outcome associated with large GTV.}

Radiation is a significant factor for patients with stage III NSCLC treated with combined chemotherapy. Proportional hazards regression of 137 stage III NSCLC showed that BED was also a significant prognostic factors associated with the risk of death \((HR=0.96 \text{ each Gy, 95% CI: 0.95-0.97, p=0.001}) [44]. For those patients who received concurrent chemo therapy, the hazard ratio of BED for the risk of death was 0.97 each Gy \((95\% \text{ CI: 0.95-0.99, } p=0.013)\). BED also remained a significant independent prognostic factor in patients treated with chemotherapy and radiation in the dose range of 60-66 Gy \((HR=0.91, 95\% \text{ CI: 0.84-0.99, p=0.041})\).

2.3.2 Challenges in Radiation Dose Escalation----Normal Tissue Dose Limit

The toxicity of radiation in UMCC 9204 has also been recently reported [45]. A total 109 patients were prescribed protocol radiation therapy, with 106 completing at least 63.1 Gy, and 84 completing more than 69 Gy. The trial was stopped at a maximum dose of 103 Gy. With long-term follow-up for toxicity, we demonstrated that much higher doses of radiation than are traditionally administered can be safely delivered to patients with NSCLC when the dose to normal lung tissue is limited. With an average mean lung dose (MLD) of 14 Gy \((95\% \text{ CI 4-24 Gy})\) and a median follow-up of 110 months, 17 patients (16%) had grade 2-3 pneumonitis, 15 (14%) grade 2-3 fibrosis, and 17 (16%) grade 2-3 esophagitis. There was no grade 4-5 lung toxicity. Grade 2-3 lung toxicity was not associated with the dose prescribed to the tumor, but was significantly \((P<0.001)\) associated with normal lung dosimetric parameters, such as MLD, volume of lung receiving at least 20 Gy \((V20)\), and the normal tissue complication probability (NTCP) of the lung. Using cut-offs of 30% for \(V20, 20 \text{ Gy for MLD and 10\% for NTCP}, \) these factors have positive predictive values of 50-71% and negative
predictive value of 85-89% for lung toxicity. There were no significant difference between the models based on various dosimetric factors and NTCP.

In UMCC 9204, we also found that the maximum tolerated dose of radiation for patients with Veff > 0.31 was 65 Gy even in patients treated with radiation alone or sequential chemotherapy and radiation. Using concurrent chemotherapy, UMCC 2003-073 intended to accelerate daily dose twice a week to escalate dose without increasing radiation duration for patients with stage III NSCLC. Among the 17 patients given protocol prescription, the majority of patients received less than 70 Gy due to esophageal or cord constraints (21%) or lung volume limitations (40%), primarily due to large tumor volumes.

2.3.3 Changes of Radiation Volume and Activity During the Course of Fractionated Radiation

Changes of Tumor Activity on PET GTV and its Potential for Adaptive Dose Escalation [46]: We have also recently completed a pilot study on patients with stage I-III NSCLC treated with ≥ 60 Gy of fractionated RT with or without chemotherapy. In this study, FDG-PET-CT scans were acquired within 2 weeks prior to RT, after the delivery of 45 Gy, and 3 months after completion of RT. PET scans were evaluated qualitatively by a radiologist and by quantification of FDG-uptake in regions of interest. Peak activities in primary tumors and in normal lung were determined relative to the mean intravascular background in the aortic arch. FDG-avid tumor volumes were contoured on PET using the same autothresholding value for all scans within each patient. 3D-CRT plans were generated, first using only the pre-RT scans, then adapted to the during-RT PET volume. We demonstrated that peak tumor FDG-activity reduced significantly during RT after 45 Gy (P<0.0001). The relative peak activities were 5.0±2.5, 2.4±1.0, and 1.7±0.7 in the pre-, during- and post-RT scans, respectively. FDG activity on the during-RT scan correlated significantly with post-RT measures (R^2=0.7, p<0.0001). Complete metabolic response during-RT was associated with complete response on post-RT PET and CT scans (Fisher’s exact p=0.009). There was no significant change in FDG activity in normal lung during RT, although a significant increase was seen on the post-RT PET (p=0.01). After 45 Gy of radiation, FDG-avid tumors also decreased significantly in volume (p=0.04). The mean reduction in PET gross tumor volume was 48±31%, and such reduction was significantly more than that of CTGTV.

Changes of PET-CT GTV and its Potential for Adaptive Dose Escalation [47]: We have performed dosimetric studies on adapting the changes in tumor volumes in 11 patients with stage I-III NSCLC who had a PET-CT scan performed in the treatment position after 40-50 Gy during the course of fractionated radiation. GTV was contoured on pre-RT and during-RT PET-CT scans using identical window and level settings. The lungs, heart, esophagus, and cord were also contoured consistently between the two scans and from patient to patient. Using the same margins for clinical and planning target volumes and the same beam arrangement, 2 plans were generated for each patient based on: A) pre-RT target to 15% lung NTCP; B) pre-RT target to 50 Gy, then adaptation of the plan to the during-RT PET-CT target to a 15% lung NTCP (or BED of 100 Gy in 2 Gy daily fractions or other maximum dose constraints specified by the protocol). In 5 patients with very small tumors (less than 100 cc), the dose for 15% NTCP based on the original tumor was already above 100 Gy (if the dose was prescribed at 2 Gy daily fractions), in which case further dose escalation may not have been clinically meaningful. Among 6 cases with larger tumors, dose was able to be escalated by an average of 20 Gy BED for tumor.

2.4 Rationale and Hypothesis for this Proposed Study

As the mainstay of local treatment for inoperable/unresectable NSCLC, radiation therapy has not generated optimal local tumor control; despite significant advancement in radiation technology, the majority of patients ultimately develop local failure. Data from our institution and others has demonstrated that high dose radiation is associated with improved local control and survival, approximately with a 1% improvement for each 1Gy of dose escalation. While a NTCP of 17.2% is considered a relatively safe lung limit, a significant portion of patients cannot receive an adequate dose for tumor control, even with the use of highly conformal techniques. Although it is sometimes associated with the proximity of tumor to critical structures, the most common reason is excessive tumor volume. Our preliminary data have demonstrated that there is a decrease in maximum FDG activity and FDG-avid tumor volume at 45 Gy normalized isoeffect dose (NID) for tumor at 2 Gy fractions during a course of fractionated radiotherapy. Adapting the planning target volume to this decreased tumor volume with a fixed composite NTCP of 17.2% allows escalation of the total BED to the tumor by an average of 20%. In this trial, we will repeat CT simulation and PET-CT at 40-50 Gy NID, and redefine the treatment target based on this PET-CT scan acquired during treatment. The total dose for each
patient, limited within the range of 64-102 Gy NID for lung toxicity, will be determined by the dose corresponding to
a 17.2% probability of grade ≥2 lung toxicity based on the available NTCP model. Radiation will be given once a day,
five days a week, for a total of 30 fractions in 6 weeks. The initial daily fraction dose will be based on the Veff, and
will range from 2.1 Gy to 2.85 Gy. Daily physical doses for the adaptive phase could go up to 5.0 Gy. We
hypothesize that the during-RT PET-CT-based adaptive therapy will allow us to dose escalate (i.e., raise the daily dose
to the reduced target volume for the remainder of the treatment) in the majority of patients and meet the dose limits of
normal structures, thus improving local tumor control without increasing normal tissue toxicity. This will also allow us
to use the lung NTCP to deliver adaptive dose escalation to active tumor regions and limit the incidence of
pneumonitis simultaneously.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Patients must have FDG-avid and pathologically proven non-small cell lung cancer. If pathology not
definitive, the patient needs to have a clinically diagnosed non-small cell lung cancer, which is also
FDG-avid.

3.1.2 Patients must be 18 years of age or older.

3.1.3 Patients must have Karnofsky performance score ≥ 60 (See Appendix A)

3.1.4 Patients must have clinical AJCC Stage I-IIIB, with unresectable or inoperable disease

3.1.5 Patients must have no evidence of a malignant pleural or pericardial effusion

3.1.6 Patients must have hemoglobin ≥ 10 gm/dl. Transfusions or medications may be used to achieve this
criterion

3.1.7 Patients must have reasonable organ and marrow functions as defined below if chemotherapy is
considered:
- WBC ≥3,000/mm³
- absolute neutrophil count ≥ 1,500/mm³
- platelets ≥100,000/mm³
- total bilirubin ≤ 3.0 mg/dl
- AST (SGOT) and ALT (SGPT) ≤ 4 X institutional upper limit of normal
- creatinine ≤ 2.0 mg/dl

3.1.8 Patients must not have serious intercurrent diseases per the judgment of the treating physician.

3.1.9 Patient must be willing to use effective contraception if female with reproductive capability.

3.1.10 Patients must be informed of the investigational nature of this study and given written informed
consent in accordance with institutional and federal guidelines

3.2 Exclusion Criteria

3.2.1 Patients with any component of small cell lung carcinoma are excluded from this study.

3.2.2 Prior radiotherapy to the thorax such that composite radiation would significantly overdose critical
structures, either per estimation of the treating radiation oncologist or defined by failure to meet
normal tissue tolerance constraints.

3.2.3 Pregnant women are excluded from this study because radiation has the potential for teratogenic or
abortifacient effects.

3.2.4 Prisoners are excluded for this study.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4. PRE-TREATMENT EVALUATIONS/ENROLLMENT PROCEDURES

4.1 Pre-treatment Clinical Evaluations: The following clinical evaluations should be done within the specified
times prior to the start of treatment:

4.1.1 Complete history and physical examination should be performed within 4 weeks

4.1.2 Weight and Karnofsky performance status should be evaluated within 2 weeks
4.1.3 CBC with differential, complete chemistry panel including alkaline phosphatase, creatinine, serum albumin, total bilirubin and AST/ALT should be done within 2 weeks
4.1.4 CT scan (if possible with IV contrast) of chest and upper abdomen including the liver and adrenals should be done within 6 weeks
4.1.5 MRI or CT of the brain with contrast is required for patient with stage II and III disease and should be done within 6 weeks
4.1.6 A total body FDG-PET scan is required within 2 weeks from CT simulation. PET scan performed outside hospital is allowed if it can be transferred to our treatment planning system and the image is quality assured. A bone scan is optional, pending the decision of the treating physician.
4.1.7 Complete pulmonary function tests should be done within 6 weeks
4.1.8 Blood samples for biomarkers should be drawn within 2 weeks

All the tests above, except biomarker measurements, are part of routine staging work-ups.

4.2 Enrollment Procedures

Patients will be enrolled once all eligibility criteria are met. Expired studies need to be repeated if out of specified time frame. The Eligibility Checklist must be completed in its entirety. The completed, signed, and dated checklist will be retained in the patient’s study file.

5 PLAN OF TREATMENT AND STUDY PROCEDURES

5.1 Concurrent Chemo-Radiation Based Treatment Regimen

All the patients will be treated with radiation with or without chemotherapy. All patients will receive individualized conformal radiation therapy up to a 17.2% rate of NTCP for estimated grade ≥2 pneumonitis (mean lung dose less than 20 Gy at 2 Gy per fraction). The radiation dose will be delivered in daily fraction of ≥2.1 Gy, with the treatment duration limited to 30 fractions, and total radiation dose limited to 63-86 Gy physical dose; 64-102 Gy NID at 2 Gy per fraction for lung toxicity assessment; 63.5-92 Gy NID at 2 Gy per fraction for tumor. Selected patients, particularly those with stage II or III disease and good performance status, can be considered for treatment with concurrent and consolidation chemotherapy with carboplatin plus paclitaxel. Each patient will have CT resimulation and PET-CT after a dose of 40-50 Gy NID at 2 Gy per fraction for tumor is delivered. The first 50 Gy NID at 2 Gy per fraction for tumor of radiation will be given based on targets defined by PET and CT acquired prior to radiation start, and the remaining dose will be delivered to the target defined by PET-CT acquired during the course of radiation. In addition to having a lung NTCP of ≤17.2%, the radiation dose is prescribed such that (when normal tissue constraints permit) pre-RT PTV, pre-RT CTV, and during-RT CTPTV will receive at least 50, 60 and 70 Gy (2 Gy equivalent dose for tumor), respectively. See schema of the treatment plan below:

Schema of the overall treatment plan.

5.2 Radiation Therapy

5.2.1 Radiation Dose/Fractionation

Dose: The total tumor dose of radiation for each patient will be assigned to be consistent with the 17.2% target iso-NTCP of grade 2 or higher radiation pneumonitis, estimated by the Lyman-Kutcher-Berman (LKB) model (previously used in UMCC 9204; 2 Gy equivalent lung normalization doses up to 103 Gy). This iso-NTCP method associates a normalization dose with each lung Veff value in a continuous fashion ranging from 64 Gy to 102 Gy NID at 2 Gy per fraction for lung toxicity (Figure 5.2.1). The initial LKB model parameter set is
derived from an University of Michigan-Netherlands Cancer Institute combined analysis, based on 382 patients [48]. NTCP for the altered fractionation schedule will be corrected based on Linear/Quadratic model, with assumption of alpha/beta ratio of 2.5 Gy for lung, 10 Gy for tumor. Radiation dose will be prescribed to the ICRU reference point (isocenter), with the aim of coverage to the target volume by the 90-95% isodose surface. Tissue heterogeneity correction will be applied for all the dose calculations.

**Lung Iso-NTCP**

The curve above shows the relationship between the lung NID at 2 Gy per fraction) and lung Veff for a less than 20 Gy mean lung dose (NID at 2 Gy per fraction) (17.2% risk of grade 2 or higher radiation pneumonitis) as predicted by our lung NTCP model. The equivalent curves below are plotted as a function of total physical dose over 30 fractions and NID of 2 Gy per fraction for tumor effect, respectively.

**Fractionations/Radiation Duration:** Radiation will be delivered once a day, for a total of 30 fractions. The dose per fraction will be ≥2.1 Gy daily so that all the radiation (63-86 Gy physical dose; 63.5-92 Gy NID of 2 Gy per fraction for tumor; 64-102 Gy NID at 2 Gy per fraction for lung) will be delivered within 30 fractions (~6 weeks). The figure above shows an iso-NTCP relating to relationship between lung Veff and lung normalization total dose at 2 Gy per fraction. While the dose of the prescription in general changes with the Veff, 64 Gy NID at 2 Gy per fraction size for lung will be given for patients with Veff of 0.0.31-0.325 or greater and 102 Gy NID at 2 Gy per fraction for lung will be the upper limit for patients with Veff ≤0.19. In addition to have a lung NTCP of 17.2%, the radiation dose is prescribed so that the pre-RT PTV, pre-RT CTCTV, and during-RT...
CTPTV will receive at least 50, 60 and 70 Gy (2 Gy equivalent dose), respectively. Detailed dose fractionations for each patient should be individualized based on the NTCP/V_{eff} table (Appendix D – Table 1). The summary of physical doses is shown in Table 2 (Appendix D).

5.2.2 Typical Radiation Volume Definitions (See Appendix D – Table 3)

Treatment volume for the first plan (dose of at least 50 Gy NID at 2 Gy per fraction for tumor): The initial planning target volume (PREPTV) based on composite GTVs from pretreatment CT1 (Exhale and Inhale) and PET1. CT1GTV will be a composite volume of the primary tumor mass and any hilar or mediastinal lymph nodes greater than or equal to 1 cm on both exhale and inhale CT (or 4D CT), plus any abnormal findings detected on, bronchoscopy and/or mediastinoscopy, if applicable. The primary tumor will be contoured on CT images under a standard lung window and level for its lung borders and under mediastinal window and level for the borders adjacent to mediastinum. The nodes will be drawn using a mediastinal window and level. In cases with extensive atelectasis and/or pneumonia where tumor margins are obscure, volumes are left to the judgment of the participating radiation oncologist. GTV of involved nodes will be called as GTVN, and GTV of primary tumor will be named as GTV. Unless it is otherwise specified, GTVs are for both PET and CT data sets. PET1GTV of both primary tumor and nodal disease on PET scan will also be contoured and will be composited with that of the CT1GTV to make the total PREGTV. The initial clinical target volume (PRECTV) will consist of composite PREGTV and approximate 0.5 cm margin for microscopic extension. Radiographically uninvolved supraclavicular nodes, para-tracheal nodes and subcarinal nodes will NOT be intentionally included in the PRECTV. The PREPTV will consist of PRECTV plus a minimal 0.5 cm margin for set-up error and an individualized margin for organ motion. For 3 phase scans, this margin ranged 0.5 to 1.0 cm for patients simulated by 3 phase simulation. Smaller margins can be used for Active Breathing Control or voluntary gating or motion compensated patients. The PREPTV will receive at least 50 Gy (NID at 2 Gy per fraction for tumor) and the PRECTV should receive at least 60 Gy (NID at 2 Gy per fraction for tumor).

Treatment volume for the second plan: The PET2PTV is defined based on the during-RT PET-CT and consists of the PET2GTV plus at least a 1 cm expansion. The PET2GTV should be auto-contoured using the same absolute threshold value as was used to define the pre-RT PET GTV (PET1GTV).

The during-RT CT PTV (CT2PTV) will consist of the CT2GTV and at least a 1 cm margin. It should receive at least 70 Gy (if the dose is escalated above 70 Gy).

Figure 5.2.2 - The schema of target volumes
5.2.3 Technique

Position/Immobilization /Simulation: Patients will usually be positioned and immobilized using standard technique. Simulation CT scans of the chest will be performed either under natural breath, three phases with breath held at the end of voluntary inhale, at the end of voluntary exhale, and while breathing freely, and multiple phases of 4D scans, with IV contrast as indicated. If three phases of CT scans are applied, CTGTV will be contoured on the end of inhale and exhale phases of scans, and the composite GTV will be used for the based CT PTV.

Treatment planning: All patients will undergo computed tomography and PET based treatment planning for conformal radiation therapy. GTV definition, CTV margin, and PTV margin are as described above. The treatment technique and number of fields will be optimized individually. DVHs will be used to predict the potential for normal tissue damage and will also provide objective criteria for the selection of an appropriate treatment plan. Suitable treatment plans will be those which minimize lung Veff while maintaining dose to other critical organs at risk (OARs) below specified limits while also providing acceptable target volume coverage. With the tumor and critical organ constraints described in further detail below, the goal of the treatment planner will be to develop a plan that provides the lowest possible lung Veff and thus highest prescription dose.

Target Volume Coverage: For treatment plans limited by the dose to normal lung (the standard case), the treatment planning goal will typically be to encompass the PTV with at least the 90-95% (relative to the normalization point/prescription) isodose surface while limiting the maximum isodose to <115%. For PTVs which overlap or come near other critical OARs which would then limit the PTV dose to values lower than those allowed by the normal lung Veff, greater PTV dose heterogeneity will be allowed by relaxing the minimum isodose specification in the region near the OAR. In these cases the dose to the rest of the PTV should be adjusted as uniformly as possible up to the limit permitted by the dose to normal lung while still maintaining the upper level dose heterogeneity limit. If, in these latter cases, doses to other OARs still limit the prescription dose or excessive dose heterogeneity is realized, a dose lower than that indicated by the normal lung Veff value may be assigned to the PTV given that the PREPTV, PRECTV, and CT2PTV will receive at least 50, 60 and 70 Gy NID at 2 Gy fraction per fraction for tumor, respectively.

Organs at Risk Tolerances: All of the critical organs listed below will be contoured into the treatment planning system when they are included in the field of irradiation. If any of these tolerance doses cannot be met, the prescription dose may be decreased heterogeneously according to these limits. For example, if a patient with a relative small NTCP can not receive high dose to mediastinal nodes due to dose limits of cord or esophagus, a plan may be generated to give higher dose to the primary to generate 17.2% lung NTCP, while giving less dose to the nodes to meet the cord tolerance.

Spinal Cord: The spinal cord must remain below a dose biologically equivalent to 50 Gy in 2 Gy fractions.
Esophagus: Initially, the Veff computed for the esophagus with a normalization dose biologically equivalent to 72 Gy in 2 Gy fractions must be less than 1/3.
Heart: The Veff computed for the heart with a normalization dose biologically equivalent to 40 Gy and 65 Gy in 2 Gy fractions must be less than 1 and 1/3, respectively.
Lung: The Veff computed for both lungs for the prescription dose must be limited by NTCP of 17.2% as described above.

Treatment Equipment: Megavoltage equipment is required with effective photon energies of 6 MV (preferred) or higher. The minimum treatment distance shall be 100 cm to the isocenter. Electron beams may be used to boost superficial chest wall primaries.

Blocking: All fields must be individually shaped to exclude structures and lung not within the target volume. Divergent custom-made blocks or multi-leaf collimation will be used.
5.3 **Chemotherapy Administration**

### 5.3.1 Concurrent chemotherapy

For selected patients with stage II or III disease and good performance status, chemotherapy will be administered weekly concurrent with radiation. Carboplatin (AUC 2, IV) and Paclitaxel (40 mg/m², IV) will be started on week 1 of thoracic radiotherapy and will be continued weekly for six weeks. Patients may receive chemotherapy on any day of the week from Monday to Friday, but the day of administration should remain constant during the course of chemoradiotherapy. A one-day shift in the day of weekly chemotherapy infusion will be allowed if necessary.

#### Weekly Concurrent Chemotherapy Regimen

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Infusion Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>40 mg/m²</td>
<td>IV</td>
<td>60 minutes</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 2</td>
<td>IV</td>
<td>30 minutes</td>
</tr>
</tbody>
</table>

Paclitaxel 40 mg/m² IV will be given by one hour infusion. Paclitaxel is mixed in non-PVC containers per the usual guidelines of the pharmacy.

Carboplatin will be given at AUC 2 over 1/2 hour immediately after paclitaxel using the Calvert formula: calculated dose of carboplatin (mg) = target AUC x (GFR + 25) (GFR as per the Cockroft-Gault or Jelliffe formula). NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

*Note: Occasionally, the infusions may take longer than the stated time above. If Paclitaxel is given within 90 minutes and Carboplatin is given within 60 minutes, these will not be considered deviations.*

Prior to receiving carboplatin and paclitaxel, all patients should receive standard pre-medication. One standard that is recommended is:

- Dexamethasone 20 mg orally 12 and 6 hours before paclitaxel or 20 mg IV just prior to paclitaxel
- Diphenhydramine 50 mg IV (or equivalent) prior to paclitaxel
- Cimetidine 300 mg IV (or equivalent, ranitidine 50 mg or famotidine 20 mg) prior to paclitaxel
- Granisetron 2 mg orally (or equivalent) prior to chemotherapy

### 5.3.2 Consolidation Chemotherapy

Consolidation chemotherapy will start approximately 4-6 weeks after the completion of radiotherapy when esophagitis and chemo-induced neuropathy are grade 1 or less, and ANC > 1500 and platelet count > 100,000. Carboplatin (AUC 6, IV) and Paclitaxel (200 mg/m², IV) will be given on day 1. This will be repeated every 21 days for a total of 3 cycles. Administration of carboplatin and paclitaxel and standard pre-medications have been described in section 5.2.1. However, during consolidation chemotherapy, paclitaxel 200 mg/m² will be administered over 3 hours.

#### Consolidation Chemotherapy Regimen

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Infusion Time</th>
<th>Days for administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>200mg/m²</td>
<td>IV</td>
<td>3 hours</td>
<td>q 21 days × 3 cycles</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 6</td>
<td>IV</td>
<td>½ hour</td>
<td>q 21 days × 3 cycles</td>
</tr>
</tbody>
</table>
5.4 **Supportive Care Guidelines**

Nutritional support is recommended for all patients. Supportive care with medications will be determined by participating physician, based on each individual situation. Suggested management for acute radiation pneumonitis includes bed rest, bronchodilators, and corticosteroids. Oxygen and even assisted ventilation may be necessary for severe cases. Treatment of esophagitis varies with the severity of the patient’s symptoms. Diet adjustment and narcotic management may be sufficient for grade 2 esophagitis. Nutritional support via gastric tube or jejunostomy tube may be initiated upon development of grade 3-4 esophagitis, per mutual preference of the physician and patient.

5.5 **Duration of Therapy**

In the absence of treatment delays due to adverse events, treatment may continue through completion of concurrent chemoradiotherapy and consolidation chemotherapy or until one of the following criteria applies:

- Local-regional disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient’s condition render the patient unacceptable for further treatment in the judgment of the investigator.

If treatment is interrupted due to a non-dose-limiting adverse event or any reason other than toxicity, such as a holiday, bad weather, or a transportation problem, the duration of therapy will be extended accordingly. If a patient misses a day of radiation and chemotherapy, then the weekly chemotherapy should be delivered the next day and the missed radiation fraction will be given after the completion of planned treatments.

Patients who exhibit local-regional tumor progression will discontinue all study procedures and will be medically managed. For the purposes of the research, they will continue to be followed for toxicity and survival. These patients may be treated with other agents.

6 **DOSE MODIFICATIONS**

Dose of radiation and chemotherapy will be modified independently.

6.1 **Radiation dose modifications**

Radiation treatment will be stopped if a patient develops severe lung toxicity at any point during the course of radiation therapy. It will be the decision of the treating physician if the patient should continue protocol treatment and the timing of restart treatment.

6.2 **Chemotherapy dose modifications**

6.2.1 Chemotherapy dosage modifications for toxicity during concurrent chemoradiotherapy.

<table>
<thead>
<tr>
<th>Hematologic Toxicity</th>
<th>Peripheral Neuropathy</th>
<th>Dysphagia</th>
<th>Paclitaxel Dose</th>
<th>Carboplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC ≥ 1000 AND Platelets ≥ 80 K AND Grade 0 – 1 AND Grade 0 – 1</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC 500-999 OR Platelets 50-79 K OR Grade 2</td>
<td>50%</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC &lt; 500 OR Platelets &lt; 50 K OR Grade 3-4 OR Grade 3-4</td>
<td>Hold*</td>
<td>Hold*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenic fever Neutropenic fever</td>
<td>Hold*</td>
<td>Hold*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Resume chemotherapy when relevant toxicity becomes ≤ grade 1.
6.2.2 Chemotherapy dosage modifications for toxicity during **consolidation chemotherapy**:

6.2.2.1 All toxicity will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. Dose modifications or delays in administration of paclitaxel or carboplatin may be based on results from local laboratories. A maximum of three dose reductions will be allowed per patient.

6.2.2.2 **Dose Modification Table**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Carboplatin Dose</th>
<th>Paclitaxel Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (starting dose)</td>
<td>AUC 6</td>
<td>200 mg/m²</td>
</tr>
<tr>
<td>-1</td>
<td>AUC 5</td>
<td>175 mg/m²</td>
</tr>
<tr>
<td>-2</td>
<td>AUC 4</td>
<td>150 mg/m²</td>
</tr>
<tr>
<td>-3</td>
<td>AUC 3</td>
<td>135 mg/m²</td>
</tr>
</tbody>
</table>

6.2.2.3 **Hematological Toxicity**

The absolute neutrophil count must be ≥ 1500/mm³ and the platelet count must be ≥ 100,000/mm³ to receive chemotherapy on Day 1 of each cycle.

Dose modifications must be made according to the criteria specified in the table below:

<table>
<thead>
<tr>
<th>Previous Cycle</th>
<th>Next Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC nadir (/mm³)</td>
<td>Platelet nadir (/mm³)</td>
</tr>
<tr>
<td>≥ 500 AND 50,000</td>
<td>No</td>
</tr>
<tr>
<td>&lt; 500 OR &lt; 50,000</td>
<td>No</td>
</tr>
<tr>
<td>&lt; 1000 AND Any</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Note: Granulocyte colony-stimulating factor (G-CSF) may be used in case of hematological toxicity. If G-CSF is used, it should be used in accordance with the American Society of Clinical Oncology (ASCO) guidelines.

Treatment with carboplatin and paclitaxel may be delayed for up to 2 weeks until the ANC is ≥ 1500/mm³ and the platelet count is ≥ 100,000/mm³. Patients should begin the next cycle as soon as possible after appropriate hematologic recovery.

No dose reductions will be made for anemia. Patients may be supported with packed red blood cell transfusions and/or erythropoietin.

6.2.2.4 **Hepatic Dysfunction**

The SGOT or SGPT and bilirubin values on Day 1 of each cycle should be used to determine the dose of paclitaxel on the next cycle.

<table>
<thead>
<tr>
<th>SGOT/SGPT (Day 1 of each cycle)</th>
<th>Bilirubin (Day 1 of each cycle)</th>
<th>Paclitaxel Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4 × upper limit of normal AND 3.0 mg/dl</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>&gt; 4 × upper limit of normal OR &gt; 3.0 mg/dl</td>
<td>Hold dose*</td>
<td></td>
</tr>
</tbody>
</table>
*If paclitaxel is held due to hepatic toxicity, carboplatin should also be withheld and administered when the paclitaxel is resumed. No dose reductions of carboplatin will be made for hepatic toxicity. If recovery of hepatic toxicity exceeds 2 weeks, consolidation chemotherapy with paclitaxel and carboplatin should be discontinued.

6.2.2.5 Neurologic Toxicity

Paclitaxel doses should be modified for neurologic toxicity based upon the worst grade experienced during the preceding cycle. Dose modifications made for neurotoxicity are permanent reductions.

<table>
<thead>
<tr>
<th>Sensory Neuropathy (CTC Grade)</th>
<th>Paclitaxel Dose</th>
<th>Carboplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>2</td>
<td>↓ one dose level</td>
<td>No change</td>
</tr>
<tr>
<td>≥ 3</td>
<td>Hold*</td>
<td>No change</td>
</tr>
</tbody>
</table>

*May restart with dose reduction of two dose levels when neuropathic toxicity improves to ≤ grade 1.

6.2.2.6 Hypersensitivity Reactions

Patients who have had a mild to moderate hypersensitivity reaction to paclitaxel have been successfully re-challenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended.

Symptoms should be managed as follows:

**Grade 1** - Complete paclitaxel infusion. Supervise at bedside. No treatment required.

**Grade 2** - Stop paclitaxel infusion. Give diphenhydramine 25 mg IV and dexamethasone 10 mg IV. Resume paclitaxel infusion after recovery of symptoms at a low rate, 20 ml/hour for 15 minutes, then 40 ml/hour for 15 minutes, then, if there are no further symptoms, resume the paclitaxel infusion at full dose rate until complete. If symptoms recur, stop paclitaxel infusion and after full recovery continue with carboplatin.

**Grade 3 or 4** - Stop paclitaxel infusion. Give diphenhydramine IV and dexamethasone IV, as above. Add epinephrine or bronchodilators if indicated. The patient should not be rechallenged with paclitaxel and will discontinue protocol treatment.

6.2.2.7 Other Toxicity

For any drug-related Grade 3 or 4 toxicity not mentioned above, except anemia, lymphopenia, or nausea, treatment with paclitaxel and carboplatin should be withheld for a maximum of 14 days until the toxicity improves to ≤ Grade 1. Treatment may then be resumed at a one dose level reduction. For Grade 1 or 2 toxicities, no dose reduction should be made.

7 **DRUG INFORMATION**

7.1 **Paclitaxel (Taxol)**

Description: Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water.
Mechanism of Action: Paclitaxel affects microtubule formation during interphase and mitosis with a mechanism distinct from the vinca alkaloids.

Human Toxicology: Hematologic toxicity includes myelosuppression. Gastrointestinal toxicities include nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase) hepatic failure and hepatic necrosis. Cardiac complications may include arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, and lightheadedness. Neurologic morbidity may manifest as sensory changes (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights, blurred vision, and scintillating scotoma. Anaphylactoid and urticarial reactions (acute), flushing, rash, and pruritus are also possible. In addition, alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration), and radiation recall reactions are described.

Formulation: Paclitaxel is available in sterile solution concentrates in 5, 16.7, 25 and 50mL multi-dose vials in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. Paclitaxel will be diluted at the appropriate dose, in D5W, USP, in 5% polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. NOTE: Formation of a small number of fibers in solution (NOTE: acceptable limits established by the USP Particular Matter Test for LVP’s) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (eg: Millex-GV Millipore Products) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

Storage and Stability: Paclitaxel vials should be stored between 2°-25°C (36°-77°F). Vials will be labeled with shelf-life. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

Supplier: Commercially available and should be purchased by a third party.

Premedications: Dexamethasone, diphenydramine (or equivalent) and an H2-receptor antagonist are recommended before paclitaxel administration.

### 7.2 Carboplatin (Paraplatin)

Description: Carboplatin is supplied as a sterile lyophilized powder.

Mechanism of action: Carboplatin inhibits DNA synthesis through intracellular platinum complexes to form intrastrand, interstrand and protein cross-linking through covalent binding of DNA molecules. Carboplatin is considered to be cell cycle phase-nonspecific, but recent studies have shown complex and variable effects on the cell cycle.

Human Toxicology: Adverse effects include myelosuppression, nausea, vomiting, peripheral neuropathy, ototoxicity, hepatic toxicity, electrolyte imbalance, hypomagnesaemia, hypercalcemia and allergic reaction.

Formulation: Carboplatin is supplied as a sterile lyophilized powder available in a single-dose vial containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol. Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:
<table>
<thead>
<tr>
<th>Vial Size</th>
<th>Diluent Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>5 ml</td>
</tr>
<tr>
<td>150 mg</td>
<td>15 ml</td>
</tr>
<tr>
<td>450 mg</td>
<td>45 ml</td>
</tr>
</tbody>
</table>

These dilutions all produce a carboplatin concentration of 10 mg/ml.

Storage and Stability: Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light. When prepared as directed, carboplatin solutions are stable for eight hours at room temperature; since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded eight hours after dilution.

Supplier: Commercially available and should be purchased by a third party

Premedication: Antiemetics and hydration are recommended before carboplatin administration.

8 CORRELATIVE TRANSLATIONAL STUDY

Using Blood Markers to Predict Tumor Control and Treatment Toxicity

8.1 Background

Patients with similar stage of disease respond to treatment differently in terms of both tumor control and treatment related toxicity. With advancement in the field, we have recently learned that expression of many specific molecules in the tumor was associated with the prognosis and predictive of responsiveness to certain treatments. Zhang et al evaluated the prognostic value of the protein expression of excision repair cross-complementation group 1 (ERCC1) and RRM1 (regulatory subunit of ribonucleotide reductase) in tumors of early stage NSCLC treated with surgical resection alone [49]. High expressions of both these two specific proteins were significantly associated with improved survival. The tumoral RRM1 expression was a major predictor of tumor response to gemcitabine/platinum chemotherapy [50]. Most interestingly, changes in blood nucleosomal DNA fragments, cytokeratin-19 fragments (CYFRA 21-1), ERCC1 protein polymorphisms or serum carcinoembryonic antigens specifically identify a subgroup of patients with insufficient therapy response at the early treatment phase and showed to be valuable for disease management [50-53]. The EGFR mutation status in the blood was consistent with that in the tumor tissue, suggesting a potential value of studying biomarkers in the blood [54].

To predict normal tissue toxicities, transforming growth factor beta 1 (TGFβ1) has been most extensively studied for pneumonitis [55] and non-lung toxicities [56]. Researchers from Duke University reported that the plasma TGFβ1 level at the end of radiation correlated with symptomatic lung toxicity in patients treated with definitive radiation therapy [57-58]. Kong et al. further demonstrated that loss of a tumor suppressor gene, mannose 6-phosphate insulin-like growth factor-2 receptor, contributed to increased TGFβ1 levels and subsequent radiation-induced pneumonitis in patients with NSCLC [59]. In patients with lung cancer treated with escalated dose of radiation, Anscher et al. found a significant correlation between TGFβ1 levels and late non-pulmonary grade 3 and radiation toxicity [57]. A recent study from the University of Michigan has shown that radiation induced elevation of TGFβ1 levels during the course of external beam conformal radiation therapy is highly correlated with occurrence of grade ≥2 radiation pneumonitis. Other cytokines are also involved in lung toxicity. Interleukin-6 (IL-6), a major mediator of the acute-phase inflammatory response, synthesized by a variety of cells in the lung parenchyma including the alveolar macrophages, type II pneumocytes, T lymphocytes, and lung fibroblast, also has increased mRNA expression in macrophages and a trend toward increased plasma concentrations after thoracic RT [60-62]. IL-6 actively participates in the inflammatory process of lymphocytic alveolitis (radiation pneumonitis) both in experimental models and in human lung diseases by stimulating inflammatory cells, particularly lymphocytes and macrophages. Chen et al reported that pretreatment IL-6 level may serve as a predictor for radiation pneumonitis [61-62]. Serial plasma IL-6 was consistently higher for the pneumonitis group. Recent study also showed promising results on single
nucleotide polymorphisms (SNP) of several specific genes of white blood cells are associated with radiation induced acute and late toxicities [63-64].

There are many other molecules involved in the processes of tumor response and radiation normal tissue toxicity. The advances in cytokine arrays, proteomic and genomic techniques have now made it possible to evaluate many of these proteins and genes together for their association with treatment outcome.

8.2 The primary objective of this correlative study

The primary objective of this correlative study is to study if molecular markers (proteomic or genomic) in the blood circulation predict tumor control and radiation toxicity. The primary endpoints for tumor control are defined as 2 year local-regional progression free survival and overall survival. The primary endpoints for radiation toxicity are grade 2 and above lung, heart and esophageal toxicity.

8.3 Rationale/Hypotheses

The most significant advantage of blood as a source of the tissue specimen for biomarkers research is its availability for early prediction, continuous monitoring and the minimally invasive procedure associated with its sampling. Because it circulates in the body and carries molecules released or shed from tumors and normal tissues in response to tumor or external stimuli, blood has a potential to serve as a surrogate marker for the individual’s intrinsic genomic responsiveness of the tumor and normal tissue to radiation. Additionally, an individual’s blood is relatively plentiful (about 5 liters) and stable in volume, and therefore more reliable for quantitative analyses. Recent studies have shown correlations of genomic mutations (such as EGFR) between blood and tumor tissue and between expression of certain gene/protein (such as ERCC1) and tumor responses to chemotherapeutic regimens. For radiation toxicity prediction, the levels of cytokine/proteomic markers and presence of certain specific gene polymorphisms in the blood as well as the changes of the levels during and after treatment were correlated with radiation induced lung toxicity after completion of conventional fractionated 3DCRT. We hypothesize that changes in expression of blood markers will reflect tumor response and lung damage at the molecular level, and thus predict clinical tumor control and toxicity.

The primary endpoints for this translational research are 2 year local-regional tumor progression free survival and grade 2 and above treatment toxicity or adverse events, which include toxicity of lung, heart, and esophagus. The primary goal of this correlative translational analysis is to examine if any proteomic or genomic marker in the blood during the course of 3DCRT is predictive of tumor control outcome and or radiation toxicity. Specifically, we will: 1) explore the correlation of cytokine array, proteomic analysis, and genomic analysis of blood samples with 3 months tumor response and 2 year progression free survival. 2) explore the correlation of TGFβ1, IL-6 (and many other cytokines), proteomic profile and yet-to-be identified proteins, genomic profiles, and molecular specific SNPs in the blood prior to and during the course of 3DCRT with the occurrence of grade >= 2 adverse events after completion of 3DCRT.

8.4 Research Design

Blood samples will be collected at baseline, during the course of 3DCRT, and during follow-up visits. Plasma/serum samples will be prepared strictly per protocol (Appendix E). TGFβ1 measurement, cytokine array, proteomic analysis, global gene expression profile, and molecule specific SNPs (such as ATM, TGFβ1) will be performed using established methods in the core services of the institution, or the laboratories of the principal investigator, co-investigator or their collaborators. Genomic and proteomic profile will be performed and will be correlated to tumor response at 3 months and 2 year progression-free survival. The levels of plasma TGFβ1, other cytokines/proteins, and SNPs of multiple genes during the course of 3DCRT will be assessed for its prediction of grade 2 and above adverse events after completion of 3DCRT. Multivariate analysis will also be performed with combination of all the significant biopredictors with lung dosimetric parameters. Model testing will be performed by maximum likelihood method and area under curve of receptive operative curves. Depending on the number of patients with blood samples collected, the nature of the analysis could also be graphic display and descriptive.
8.5 Statistical considerations for correlative translational study:

The utility of biomarkers, including TGFβ1, a cytokine array, and specified proteomic and genomic markers, in predicting the prognosis of patients treated under this protocol will be estimated using a stepwise proportional hazards (Cox regression) model. Demographical and clinical variables known to predict local-regional progression-free survival, such as age, sex, disease stage and Karnofsky status, will be entered as regressors, and then the biomarkers, assessed at baseline, will be added in a stepwise fashion. This will allow us to identify putative markers for survival, even if there are more variables than observations. Regression coefficient will be reported with 90% Wald-type confidence intervals. This is a hypothesis-generating, rather than a hypothesis testing, endpoint, so the power is not calculated and there are no plans for validation within the current protocol.

To predict radiation toxicity, we will use logistic regression to relate grade ≥ 2 adverse events as a function of the change in TGFβ1, IL-6 and other cytokine or proteomic makers measured during RT and during treatment. A similar analysis plan will be used to that of the efficacy analysis.

9 TOXICITIES TO BE MONITORED AND REPORTED

9.1 Severe Lung Toxicity

Severe lung toxicity includes grade 3 or higher radiation pneumonitis and grade 3 or above clinical fibrosis. Diagnosis and grading of radiation pneumonitis and clinical fibrosis are listed on the table below.

Table 9.1. Diagnosis and Grading System for Radiation Pneumonitis and Clinical Fibrosis

<table>
<thead>
<tr>
<th>Radiation Pneumonitis</th>
<th>Clinical Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
</tr>
<tr>
<td>Minimal or mild symptoms of dry cough AND/OR dyspnea on exertion; AND without evidence of tumor progression or other etiology; AND with radiographic evidence of acute pneumonitis</td>
<td>Radiographic evidence of radiation fibrosis without or with minimal dyspnea</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
</tr>
<tr>
<td>Persistent dry cough requiring narcotic antitussive agents or steroid; AND/OR dyspnea at rest; AND without evidence of tumor progression or other etiology; AND with radiographic evidence of acute pneumonitis, and requiring steroid for treatment</td>
<td>Radiographic evidence of radiation fibrosis; AND dyspnea with minimal effort but not at rest, not interfering with activities of daily living</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
</tr>
<tr>
<td>Severe cough, unresponsive to narcotic antitussive agent; AND/OR dyspnea at rest; AND with radiographic evidence of acute pneumonitis; AND requiring oxygen (intermittent or continuous) for treatment</td>
<td>Radiographic evidence of radiation fibrosis at rest, interfering with activities of daily living; AND home oxygen indicated</td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
</tr>
<tr>
<td>Radiation pneumonitis causes respiratory insufficiency requiring assisted ventilation</td>
<td>Radiation fibrosis causes respiratory insufficiency, requiring assisted ventilation</td>
</tr>
<tr>
<td>Grade 5</td>
<td></td>
</tr>
<tr>
<td>Radiation pneumonitis directly contributes to the cause of the death</td>
<td>Radiation fibrosis directly contributes to the cause of the death</td>
</tr>
</tbody>
</table>

9.2 Severe Acute Esophageal Toxicity

Severe acute esophageal toxicity is defined as persistent grade 3 or higher esophageal toxicity occurring within 3 months of the start of radiation therapy. According to the RTOG acute radiation morbidity scoring criteria for esophagitis, grade 3 is defined as severe dysphagia or odynophagia with dehydration or weight loss > 15% from treatment baseline, requiring a feeding tube, IV fluids, or hyperalimentation. Grade 4 is defined as esophagitis causing life-threatening consequences, such as perforation, obstruction, or fistula formation. Grade 5 is severe
esophagitis directly contributing to death. Persistent grade 3 esophageal toxicity is defined as esophageal toxicity dependent on a feeding tube, IV fluids, or hyperalimentation longer than 6 weeks after the completion of radiation therapy.

The incidence of severe acute esophageal toxicity is expected to be lower than 5%. Since only pneumonitis is modeled by the NTCP function, doses to the lung will not be adjusted if excess severe esophageal toxicity occurs. Instead, the normalization dose to the esophagus will be adjusted if at least 2 of the first 10 patients, or 4 of the first 20 patients, or 5 of the first 30 patients experience severe acute esophageal toxicity as described.

9.3 **Other Toxicities**

Other toxicities will be monitored and reported using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

10 **STUDY CALENDAR**

10.1 **Pretreatment and during treatment studies**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pretreatment</th>
<th>Weekly During Chemotherapy / RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical</td>
<td>Within 4 wks</td>
<td>X</td>
</tr>
<tr>
<td>Weight and KPS</td>
<td>Within 2 wks</td>
<td>X</td>
</tr>
<tr>
<td>Tumor measurement</td>
<td>Based on treatment planning CT</td>
<td></td>
</tr>
<tr>
<td>Chest and upper abdomen CT*</td>
<td>Within 6 wks</td>
<td>X</td>
</tr>
<tr>
<td>CBCP, differential</td>
<td>Within 2 wks</td>
<td>X</td>
</tr>
<tr>
<td>Electrolytes, creatinine, liver function tests</td>
<td>Within 2 wks</td>
<td>As Clinically Indicated</td>
</tr>
<tr>
<td>Complete pulmonary function tests</td>
<td>Within 6 wks</td>
<td></td>
</tr>
<tr>
<td>Bone scan</td>
<td>Optional</td>
<td></td>
</tr>
<tr>
<td>Head CT or MRI #</td>
<td>Within 6 wks</td>
<td></td>
</tr>
</tbody>
</table>
| PET scan                               | Within 2 wks, before or after, treatment planning CT | X
| Blood drawing for biomarkers           | Within 2 wks          | Every 2 wks                     |
| Toxicity evaluation                    | Within 4 wks          | X                              |

* High-resolution CT is preferred.
# Only required for Stage II and III diseases.
a. PET-CT scan will be repeated after patient has received 40-50 Gy NID of radiotherapy
b. If receiving chemotherapy.
## 10.2 Follow-up calendar

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Time since the end of RT</th>
<th>Frequency of Follow-up</th>
<th>Q 3 months</th>
<th>Q 6 months</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight and KPS</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor measurement</td>
<td>3 mo only</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest and upper abdomen CT**</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CBCP, differential</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Electrolytes, creatinine, liver function tests</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity evaluation</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood drawing for biomarkers</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Timing of follow-up: From 2 months to 15 months = (+/-) 2 week window. For 18 months to 60 months = (+/-) 1 month window.

** High-resolution CT is preferred

a: Chest CT will be done at 3 months if patient did not receive chemotherapy. If patient did receive chemotherapy, Chest CT will be done approximately 1 month after last consolidation cycle. At 6 months and later, chest CT will be done every 6 months.

b: Pulmonary function tests will be done at 3 and 12 months.

c: If a patient experiences severe toxicity (as defined in 9.1 and 9.2) and returns for clinical evaluation at a time not designated on study calendar, TGF β1 and other molecules will be drawn.

Note: PET scans, bronchoscopies, bone scans, pulmonary function tests, and head CTs or MRIs may be done post-treatment as part of routine clinical care, to assist with disease or toxicity evaluation. If these are done, the results may be used for research purposes.

## 11 STUDY ENDPOINTS

### 11.1 Primary Endpoint

The primary endpoint is 2-year local-regional tumor control rate, which is defined by local progression free survival at 2 years from the end of radiation. Local-regional progression is defined on CT scan based on RECIST Criteria (Appendix C)

### 11.2 Secondary Endpoints

11.2.1 Severe lung toxicity, as defined in section 9.1

11.2.2 Severe acute esophageal toxicity, as defined in section 9.2

11.2.3 Other tumor control measures: tumor response (based RECIST criteria in appendix C); distant progression; time to local-regional progression; time to distant progression, 1-, 2-, 3- and 5-year overall survival rate.

11.2.4 The dose of radiation to generate an estimated 17.2% lung NTCP for grade 2 or higher radiation pneumonitis.

11.2.5 The levels of blood markers during treatment and follow up until disease progression.
The primary objective of this clinical trial is to assess local-tumor control when the radiation dose is escalated by adaptive radiation planning using mid-course FDG-PET-CT scanning, based upon the assumption that radiotherapy treatment until that point has reduced the tumor volume, and to examine if the local-regional tumor control is improved compared to historical controls when radiation was given by conventional radiation therapy without changes of the fields during the course. The primary endpoint of interest is two-year local-regional progression-free survival. Long-term results from UMCC 9204 estimate 2-year local-regional progression-free survival to be 34% for those patients who received between 63 and 69 Gy (average 66 Gy) radiotherapy. Analysis of that data indicated that a 1 Gy increase in dose delivered was associated with a 1% improvement in local-regional progression-free survival. Based upon the investigator’s preliminary data simulating adaptive midcourse escalation based on FDG-PET-CT imaging, the dose is expected to be escalated by 20 Gy if the adaptive plan is used after 50 Gy has been delivered. If we assume a 20 Gy increase above the standard dose of 66 Gy, then we would estimate that local-regional progression-free survival would increase to 54%. In order to test this hypothesis, with 5% type I error and 80% power, we need to accrue and treat 42 patients. This assumes the use of a chi-square test, with a one-sided alternative, with patients who die, progress locally or regionally, or are lost-to-follow-up classified as having an event. Figure 12.1 illustrates the sample size necessary if the dose escalation is varied as a percent of the increase above 60 Gy, resulting in a corresponding difference in improvement in local-regional progression-free survival, based upon our assumption of a 1% increase in the two-year rate for each 1 Gy increase in radiation dose delivered. The sample sizes are calculated based upon 5% type I error and 80% power.

Figure 12.1 - The relationship between sample size and the level of dose escalation.
12.2 Study Duration

Given our institutions’ past experience with this patient population, it is anticipated that 15 patients per year can be accrued to this treatment protocol, at a minimum. If we assume this conservative estimate, it should take nearly 3 years to accrue the necessary patients, and another 2 years of follow-up to observe the study’s primary endpoint, resulting in a 5-year study period.

12.3 Evaluable Patients

Patients who receive a NID of 60 Gy (at 2 Gy fraction size) or more will be considered evaluable for the primary objective. Subjects will be registered to the study until 42 patients meet this criterion, and all evaluable patients registered to the study will be included in the analysis of the Primary Objective, and Secondary Objectives 2 and 4. All patients who receive at least one treatment will be included for the analyses of Secondary Objectives 1 and 3.

12.4 Analysis Plan

The primary endpoint, local-regional progression-free survival, by definition will be an observable endpoint for every patient. All patients will be followed for a minimum of two-years, or until death or local-regional progression for each patient. In the event that a patient is lost-to-follow-up, prior to progression or death, the patient will be considered to have met our definition for an event for the product-limit estimate. Standard unconditional logistic regression models will be used to characterize potential associations between the dichotomous outcome with clinical characteristics. Clinical characteristics will included but not be limited to patient’s age at diagnosis, stage of disease, concomitant chemotherapy, radiotherapy dose, dose-volume parameters (GTV, PTV, etc.), occurrence of toxicity during therapy. Wald-type p-values 5% or less will be considered statistically meaningful.

Secondary endpoints for this trial include, summary of whether mid-course FDG-PET-CT imaging has allowed for intra-patient dose-escalation, to report overall survival using this adaptive escalation technique, to report treatment related toxicities, and to explore if there exists any association between the levels of biomarkers in circulating TGFβ1 level and treatment-related toxicity. Total biological equivalent dosing difference between the 6-week prescribed plan using pre-RT imaging, will be compared to the dose delivered using the adaptive planning technique. At a minimum the number of patients for which dose escalation was possible will be reported, along with the mean and standard deviation in the dose increase for the population. Correlations between pre-RT tumor sizes, distance from important anatomical structures and the dose increase, may be explored using the rank method of Spearman. Overall survival of all patients will be estimated using the product-limit method of Kaplan and Meier. Patients known to be alive at the time of analysis will be censored at their last clinical visit. Toxicities as defined in section 9.1-9.3 will be reported as proportions with exact binomial confidences intervals. Standard unconditional logistic regression techniques will be used to explore potential associations between the levels of TGFβ1 and other molecules the occurrence of treatment-related toxicity. The relationship will be explored by dichotomizing toxicity events by meaningful grade and/or by the type of toxicity (e.g. pneumonia vs. fibrosis).

12.5 Stopping Rules

12.5.1 Efficacy

Three months after the twentieth patient is accrued, the median local-regional progression free survival will be estimated on the first 20 patients. If the median survival is nine months or less, the trial will be closed due to inadequate efficacy. The operating characteristics of this rule were determined by Monte Carlo simulation as follows. Accrual is anticipated to be 14 patients/year. One-year local-regional progression free survival in UMCC 9204 was 44%, corresponding to a median survival of 10.1 months. Patient arrival was simulated to be uniform (1.17/month), survival simulated according to an exponential model, and median survival estimated three months after the twentieth patient was accrued by means of the product-limit (Kaplan-Meier) survival function estimate. If the local-regional progression free survival in the current trial was only as good as that of UMCC 9204, the stopping rule had an 0.21 probability of halting.
the trial. If the local-regional progression free survival at one year was reduced to 0.26 (40% worse than UMCC 9204), the probability of the trial halting early was 0.75.

12.5.2 Safety

If six or more of the first 20 patients experience clinically significant lung toxicity (grade 3 and above), the trial will be halted due to lack of safety. The operating characteristics of the trial are determined from the binomial distribution as follows; the therapeutic plans have a target rate of lung toxicity of no more than 0.172. If that is the true probability of lung toxicity, the stopping rule will halt the trial with probability 0.11. If the probability of lung toxicity is actually 0.33, the trial will be halted with probability 0.69. If the probability of lung toxicity is 0.37 or greater, the probability the trial will be halted is at least 0.81.

13 REPORTING ADVERSE EVENTS

Adverse event (AE) will be reported using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

13.1 Adverse events will be reported according to the Standard AE Reporting guidelines of the University of Michigan Medical School Institutional Review Board (IRBMED) except for as outlined below.

13.2 The following adverse events are excluded from the study-specific SAE reporting:

13.2.1 All moderate events (grade 2) and hematologic serious events (grade 3) due to the patient’s cancer or the treatment which are common toxicities and expected. These will be noted in the patient’s medical records.

13.2.2 Social or psychological trauma which is typical for patients undergoing treatment for cancer and/or the people with whom they have relationships. Events of this type that are severe in nature will be reported per the guidelines.

13.2.3 Hospitalization secondary to expected cancer morbidity:

13.2.3.1 Admission for palliative care or pain management

13.2.3.2 Admission for management of pre-existing co-morbidity such as COPD and congested heart failure

13.2.3.3 Admission for management of non-protocol related deep venous thrombosis or pulmonary embolism

13.1.2.4 Planned hospitalizations for surgical procedures, either related or unrelated to the patient’s cancer.

13.1.2.5 Emergency Department visits not related to study treatment

14 DATA AND SAFETY MONITORING

14.1 The Radiation Oncology Department will ensure the integrity of systems for monitoring trial data and participant safety. Monitoring will be performed on a regular basis, with minutes obtained and conclusions of the monitoring reported to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Board. Recommendations that emanate from monitoring activities will be reviewed by the responsible official (the principal investigator in this case) and addressed. The department has the responsibility of informing trial investigators concerning the data and safety monitoring policy and procedures. The Institutional Review Board will be provided feedback on a regular basis, including findings from adverse-event reports, and recommendations derived from data and safety monitoring.

14.2 Experts in all scientific disciplines needed to interpret the data and ensure patient safety will conduct monitoring activities. Clinical trial experts, biostatisticians, bioethicists and clinicians knowledgeable about the disease and treatment under study will be part of the monitoring group, as needed. Specifically, the investigators (including the protocol statistician) and the data
managers/study coordinators will participate in these meetings. Co-investigators from participating affiliates can be teleconferenced. At a minimum, the following people will be involved in each meeting: Principal Investigator, statistician, study coordinator or designee. All co-investigators listed on the protocol cover page will be invited to the meeting, with the intention that at least those with currently enrolled patients will attend. If unable to attend a meeting, the minutes will be sent to those members for review.

14.3 Data and safety monitoring committees will meet in open sessions held every month at minimum. Participants in the review of confidential data and discussions regarding continuance or stoppage of the study will have no conflict of interest and no financial stake in the research outcome.

14.4 Activities of the DSMB members will include, at the minimum:

14.4.1 Review the research protocol and plans for data and safety monitoring
14.4.2 Evaluate the progress of intervention trial(s), including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome. Monitoring will also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.
14.4.3 Make recommendations to the Cancer Center, IRB and investigators concerning continuation or conclusion of the trial(s).
14.4.4 Protect the confidentiality of the trial data and the results of monitoring

14.5 Confidentiality will be maintained during the phases of the trial including monitoring, preparation of interim results, review, and response to monitoring recommendations. Exceptions may be made under circumstances where there are serious adverse events or when it is deemed appropriate for patient safety.

14.6 In response to the Standard Operating Procedure of CTO, minor protocol calendar deviations (those which do not affect patient safety or eligibility) may be recorded in a batch in log format. The date for each individual deviation occurrence will be reported on the deviation log. The deviation log will be submitted with DSM reports to the Cancer Center, and to the IRB at the time of scheduled continuation.


# APPENDIX A

## KARNOFSKY PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>
APPENDIX B

ANATOMICAL STAGING FOR LUNG CANCER
(AJCC, 6th Edition)

TNM CATEGORIES (Note Definitions)

Primary Tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

T0 No evidence of primary tumor.

Tis Carcinoma in situ.

T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus,* (i.e., not in the main bronchus).

T2 Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura; Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.

T3 Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion.**

*Note: The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

**Note: Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathological examination of pleural fluid are negative for tumor. In these cases, fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph nodes metastasis.

N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor.

N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s).

N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis

M1 Distant metastasis present

Note: M1 includes separate tumor nodule(s) in a different lobe (*ipsilateral or contralateral*)

### STAGE GROUPING

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<th>N0</th>
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APPENDIX C

RECIST CRITERIA

Response Criteria

Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

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

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

Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Incomplete Response/ Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of “non-target” lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.
<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
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<th>Overall Response</th>
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Note:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.” Every effort should be made to document the objective progression, even after discontinuation of treatment.

- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

**Confirmatory Measurement/Duration of Response**

**Confirmation**

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be 12 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 12 weeks.

**Duration of overall response**

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

**Duration of Stable Disease**

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.
## Table 1 (Normalized Iso-effective and Physical Dose Tables)

<table>
<thead>
<tr>
<th>NTCP</th>
<th>Normal Lung</th>
<th>Total Dose (Gy)</th>
<th>Initial Dose per fx (Gy)</th>
<th>Normal Lung Effective Dose (2 Gy Eqv) (2 Gy = 2.5 Gy)</th>
<th>Normal Lung Effective Dose (2 Gy Eqv) (0 = 10 Gy)</th>
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### # Fractions for >43 Gy (Gy Eqv) Tumor Dose

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<th>NTCP</th>
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<th>Normal Lung Effective Dose (2 Gy Eqv) (2 Gy = 2.5 Gy)</th>
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<td>Normal Lung Veff Lung</td>
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<td>Physical Dose at this point (Gy)</td>
<td># Fractions for &gt;50 Gy (2 Gy Equiv) Tumor Dose</td>
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</tbody>
</table>

1. Initial prescription from columns B, F, and G based on Veff(row) that would yield nor more than a 17.2% NTCP if treated to total dose in Column C
2. 2nd PET performed after fraction number in Column D
3. 2nd part of prescription written for number of fractions in Column I (from same row as initial part of prescription), at a dose per fraction somewhere between the original dose per fraction in Column B and the maximum value in Column H, up to a maximum additional dose in Column J for a total dose somewhere between Columns C and K, all consistent with maintaining an NTCP of no more than 17.2% for the composite plan
4. Exception to (3) just above is for original Veff > 0.307 (i.e., last Veff row), where if new PET volume does not allow reduced lung irradiation, doses per fraction down to 1.8 Gy may be required for the last 6 treatments to keep the NTCP for the composite plan below 17.2%
### Table 3 Image and Target Descriptions

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<th>Image Type</th>
<th>Name</th>
<th>Description</th>
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</thead>
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<td>Exhale or EX1</td>
<td>Initial Exhale CT planning dataset</td>
</tr>
<tr>
<td>CT</td>
<td>Inhale or IN1</td>
<td>Initial Inhale CT planning dataset</td>
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<td>PET</td>
<td>PET1</td>
<td>Initial Free Breathing PET dataset</td>
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<td>Initial Free Breathing or Exhale PET CT dataset</td>
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<td>PET2</td>
<td>PET2GTV</td>
<td>autotracked with same parameters as PET1GTV</td>
<td></td>
</tr>
<tr>
<td>CT2</td>
<td>CT2GTV</td>
<td>as entered by the physician</td>
<td>50 Gy + Boost to 17.2% NTCP</td>
</tr>
<tr>
<td>CT2</td>
<td>CT2PTV</td>
<td>~1 cm expansion of CT2GTV</td>
<td>70 Gy</td>
</tr>
<tr>
<td>EX1</td>
<td>EXTERNAL</td>
<td>Autotracked external surface</td>
<td></td>
</tr>
<tr>
<td>EX1</td>
<td>R_LUNG</td>
<td>Autotracked Rt lung</td>
<td>17.2%NTCP to R_Lung + L_Lung - GTV</td>
</tr>
<tr>
<td>EX1</td>
<td>L_LUNG</td>
<td>Autotracked Lt lung</td>
<td></td>
</tr>
<tr>
<td>EX1</td>
<td>HEART</td>
<td>Drawn in by DOSIM</td>
<td>≤1.00 Veff to 45 Gy ≤ 0.34 Veff to 65 Gy</td>
</tr>
<tr>
<td>EX1</td>
<td>ESOPHAGUS</td>
<td>Drawn in by DOSIM</td>
<td>≤ 0.34 Veff to 72 Gy</td>
</tr>
<tr>
<td>EX1</td>
<td>CORD</td>
<td>Drawn in by DOSIM</td>
<td>≤ 50 Gy</td>
</tr>
</tbody>
</table>

**Example**

\[
\text{EX1GTV + IN1GTV + PET1GTV} = \text{PREGTV} \\
\text{PREGTV} + 0.5\text{cm} = \text{PRECTV} \text{ Tx to } 60 \text{ Gy} \\
\text{PRECTV + (min)0.5cm} = \text{PREPTV} \text{ Tx to } 50 \text{ Gy} \\
\text{PET2GTV auto tracked using the same ratio as previous PET} \\
\text{PET2GTV + (min)0.5cm} = \text{PET2PTV} \text{ Boost Tx up to } 17.2\% \text{ NTCP for lung} \\
\text{CT2GTV +~1cm} = \text{CT2PTV} \text{ Tx to } 70 \text{ Gy}
\]
Blood Sample Collection and Correlative Research Procedures

1. Blood Sample Collection for Translational Research

1.1 Blood Sample Drawing and Handling
Samples for TGFβ and other cytokine measurement and proteomic analysis need to be handled gently and carefully to avoid platelet degradation or contamination [65]. Needles of large gauge (19-21G) should be used to minimize platelet-contamination from hemolysis. Blood will be collected in two standard blood collection tubes (one purple top and one red top). Blood samples can be drawn in the clinic or blood lab, and temporarily placed vertically at a 4°C until plasma/serum are prepared within 2 hours of collection.

1.2 Collection of Plasma and Buffy Coat Samples
a. Collect one 5-10 ml tube of blood using one EDTA (purple top) tube and Invert gently one to two times to mix with anticoagulant
b. Store the blood at 4°C or ice as soon as possible (the time of samples setting in room temperature should be less than 5 minutes).
c. Centrifuge under ~ 3000xG at 4°C for 30 minutes
d. Carefully pipette and transfer ~1ml aliquots of plasma into 4-5 CRYOVIAL® Polypropylene Tubes, keeping the pipet tip at least 5 mm above the buffy coat (at the level of the thickest arrow) to avoid platelets contamination.
e. Remove the buffy coat cells carefully and place into one 1ml CRYOVIAL® Polypropylene Tubes labeled “buffy coat” (it is okay if a few packed red cells are inadvertently collected in the process).
f. Place tops on CRYOVIAL® Polypropylene Tubes and make sure tops of CRYOVIAL® Polypropylene Tubes are on securely.
g. Tubes should be clearly labeled as indicated.
h. Place tubes in a Styrofoam holder and then place into a zip lock bag.
i. Store samples at -80°C until assay
1.3 Serum Sample Preparation
   a. Collect one 5-10 ml tube of blood without coagulants (Red-topped tube).
   b. Sit at room temperature for 30 min to allow clot formation.
   c. Centrifuge in a standard clinical centrifuge ~ 3000xG RPM at 4°C for 30 minutes
   d. Transfer ~1ml aliquots of separated serum into 4-5 CRYOVIAL® Polypropylene Tubes
   e. Place tops on CRYOVIAL® Polypropylene Tubes and make sure tops are secured.
   f. Tube should be clearly labeled as serum as indicated.
   g. Place tubes in a Styrofoam holder and then place into a zip lock bag.
   h. Store samples at -80°C until assay.

1.4 Sample Labeling
   Each label will contain the following:
   Protocol Number:
   Patient ID number (Case number):
   Date of Sampling: (mm/dd/yy)
   Time of blood collection:
   Time of sample collection:
   Sample Type (plasma, serum, or buffy coat):
   Site ID Number:

1.5 Plasma, serum, and buffy coat will be saved in:

   Radiation Oncology/Biology Laboratory of Dr. Feng-Ming Kong
   Room 4410, Med Sci I / SPC 5637
   1301 Catherine Street, Ann Arbor, MI 48109-5637
   Telephone: 734-764-3324/ 734-330-3284/ 734-709-6888
   Pager: 734-936-6266 extension 13022 or 14613

1.6 Confidentiality/Storage
   All samples will be de-identified and stored at -80°C until assay.

   1.6.1 Upon receipt, the specimen will be labeled with the protocol number and the patient’s case number only. The blood/database will only include the following information: the number of specimens received and the date the specimens were received. No clinical information will be kept in the database.

   1.6.2 Specimens will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be trashed.

2.0 Assays for cytokine, proteomic and genomic markers will be performed in the core services of the institution, or the laboratories of the principal investigator, co-investigator or their collaborators. Updated technique will be used to secure the best results of the research