A PHASE II RANDOMIZED TRIAL WITH CAPTOPRIL IN PATIENTS WHO HAVE RECEIVED RADIATION THERAPY +/- CHEMOTHERAPY FOR STAGE II-IIIB NON-SMALL CELL LUNG CANCER, STAGE I CENTRAL NON-SMALL CELL LUNG CANCER, OR LIMITED-STAGE SMALL-CELL LUNG CANCER

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0123

A PHASE II RANDOMIZED TRIAL WITH CAPTOPRIL IN PATIENTS WHO HAVE RECEIVED RADIATION THERAPY +/- CHEMOTHERAPY FOR STAGE II-IIIB NON-SMALL CELL LUNG CANCER, STAGE I CENTRAL NON-SMALL CELL LUNG CANCER, OR LIMITED-STAGE SMALL-CELL LUNG CANCER

SCHEMA (5/15/06)

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Patient Population:  (See Section 3.0 for Eligibility) [5/15/06]
Stage II-IIIb non-small cell lung cancer or Stage I central NSCLC (excluding peripheral coin lesions) or limited-stage small-cell lung cancer (nonmetastatic disease that is receiving radiotherapy, and the target is confined to a single radiation treatment area); Planned total dose of ≥ 45 Gy delivered to the target volume; > 25% of lung receiving > 20 Gy, if receiving radiotherapy alone.

Required Sample Size: 205
(Y) 1. Has the histology or cytology confirmed as a non-small or small-cell primary lung carcinoma?

(Y) 2. Is the patient ≥ 18?

(Y) 3. Is the Zubrod Performance Status 0-1?

(Y) 4. Will a total dose of ≥ 45 Gy be delivered to the target volume, and > 25% of total lung volume receiving > 20 Gy, if receiving radiotherapy alone?

(Y) 5. Will a 3D planning CT be accomplished to measure lung volume irradiated?

(N) 6. Is there a hypersensitivity to ACE inhibitors?

(N) 7. Requirement for ACE inhibitor for hypertension or congestive heart failure?

(Y) 8. Blood pressure > 110 (Systolic) and > 60 (Diastolic)?

(Y) 9. Have required pretreatment evaluations been performed within timelines and value parameters as per Section 3.1?

(Y/N) 10. Has the patient had surgery?

(Y) If yes, was procedure performed < pneumonectomy?

(N) 11. Does the patient have collagen vascular disease, i.e., lupus and scleroderma?

(N) 12. Is the patient pregnant?

(N) 13. Is the patient taking lithium, methotrexate, or procainamide?

(Y) 14. If applicable, has the patient agreed to utilize an effective form of contraception?

(continued on next page)
Institution # ________

RTOG 0123

ELIGIBILITY CHECKLIST — STEP 1 (12/16/03)

Case # ________

(page 2 of 3)

The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed?
3. Is the patient eligible for this study?
4. Date the study-specific Consent Form was signed? (must be prior to study entry)
5. Patient’s initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
11. Gender
12. Patient’s Country of Residence
13. Zip Code
14. Patient’s Insurance Status
15. Will any component of the patient’s care be given at a military or VA facility?
16. Treatment Start Date
17. Treatment Assignment

(continued on next page)
Institution #

RTOG 0123

Case #

Eligibility Checklist — Step 1 (5/15/06)

________________ 18. Medical Oncologist’s Name

____________(Y/N) 19. Blood kept for research in current study?

____________(Y/N) 20. Blood kept for cancer research?

____________(Y/N) 21. Blood kept for medical research?

____________(Y/N) 22. Allow contact for future research?

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ___________________________ Date ______________________
Institution # __________
RTOG 0123

Case # __________
(Assigned in Step 1)

1. Name of institutional person registering case
2. Patient Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
3. Verifying Physician
4. Patient ID Number
5. (Y/N) Patient able to continue protocol treatment?
6. If no, reason that the patient cannot continue to Step 2? (Progression of disease, patient refusal, physician preference, other)
7. Specify amount of lung irradiated (< 25%, 25-37%, or > 37%)
8. (Y/N) Has the patient had prior lung surgery?
9. (Y/N) Has the patient received or is the patient receiving chemotherapy?
10. Treatment Start Date
11. Treatment Assignment

Completed by ______________________________ Date __________________
1.0 INTRODUCTION

1.1 Scientific Background/ Rationale

It is estimated that 171,600 new cases of non-small cell lung cancer will be diagnosed in the United States during the year 1999. During that same year, it is expected that 160,000 lung cancer related deaths will occur. Unlike many other cancer sites, the five-year survival for lung cancer has remained relatively unchanged over the last 20 years. Unfortunately, the majority of patients continue to present with locally advanced, unresectable disease that is managed with primary thoracic irradiation often delivered with or without neo-adjuvant or concurrent chemotherapy. The dose limiting toxicity associated with curative thoracic radiation is pulmonary pneumonitis. Radiation pneumonitis and radiation-induced pulmonary fibrosis are refractive to management. As a result, lung tolerance is a major dose-limiting factor in the curative/palliative radiotherapeutic management of thoracic and mediastinal tumors. Several common chemotherapy agents are pneumotoxic, and decrease radiation tolerance of the lung in patients receiving combined modality therapy. Current radiotherapy and multiagent chemotherapy regimens for limited-stage small-cell lung and unresectable non-small cell lung cancer are associated with high locoregional failure rates at three years, suggesting that higher radiation doses might improve local control provided the attendant pneumotoxicity could be managed medically. Strategies to increase pulmonary tolerance to radiation and chemotherapy agents, therefore, could decrease the incidence and/or severity of therapy-related pneumotoxicity in patients treated conventionally, or might enable the oncologist to treat local-regional lung cancer more aggressively without further increase in pulmonary toxicity. Captopril is an interesting candidate in this regard.

1.2 Captopril

Since its introduction in 1980, the angiotensin-converting enzyme (ACE) inhibitor captopril has become a well-established treatment for hypertension and congestive heart failure. Approximately 5 to 10 million hypertensives now take captopril. Captopril has also been reported to improve clinical status in patients with primary pulmonary hypertension, chronic obstructive pulmonary disease, diabetic renovascular disease, and rheumatoid arthritis. Captopril has also been shown to improve postmyocardial survival and reduce morbidity and mortality due to major cardiovascular events in the survival and ventricular enlargement trial (SAVE). As a thiol compound, moreover, captopril (1\-(2S)-3-mercapto-2-methylpropionyl-L-proline) exhibits several interesting biological actions in addition to ACE inhibition. For example, captopril is a radical scavenger, and can form copper complexes that exhibit superoxide dismutase-like activity. The drug stimulates interleukin-2 (IL-2) release by concavalin-A-stimulated mouse splenocytes and inhibits platelet aggregation by a mechanism involving blockage of calcium influx. The latter phenomenon has been observed both in vitro and in hypertensive patients. Captopril partially reverses pulmonary and renal insufficiency in experimentally induced intravascular coagulation in rats. This ancillary action of the drug is particularly interesting clinically, because the plasma of lung cancer patients has been reported to be abnormally prothrombogenic. Experimental data demonstrate that captopril ameliorates pulmonary hypertension induced by chronic hypoxia or by the pyrrolizidine alkaloid monocrotaline in rats. The drug suppresses increased vascular permeability induced by histamine and serotonin in rat skin and inhibits spontaneous age-associated myocardial fibrosis in rats. Work in our laboratory and others has shown captopril to be an antimitotic and antiangiogenic agent. We have also demonstrated the ability of captopril to modulate the hormone receptor concentration of mammary ductal carcinoma cells and inhibit the proliferation in culture.

More recently in our laboratory, Ward et al. have shown that captopril administration decreases pulmonary artery pressure in rats exposed to radiation. This lowering of pulmonary artery pressure is evident before the effect of captopril on the systemic blood pressure of the rats becomes apparent. These data are the first direct evidence of a specific effect of captopril on the pulmonary circulation.

Of greatest relevance to this protocol, captopril has been reported to ameliorate the radiation-induced pulmonary endothelial dysfunction and pulmonary fibrosis in rats and to delay the onset of radiation-induced pulmonary arterial hypoperfusion in that species. The effect of captopril in the lung has been shown to be evaluable by high-resolution computed tomography.

In the experiments done at Northwestern, adult male Sprague-Dawley rats were exposed to single doses of 10, 20, or 30 Gy of $^{60}$Co gamma rays to a 3.5 cm$^2$ right hemithorax port. These rats were compared to sham irradiated controls. The treated rats were given feed containing 0.12% captopril. Four markers of endothelial dysfunction were measured: ACE activity, plasminogen activator activity, prostacyclin, and...
thromboxane production. All four markers were significantly improved with the addition of captopril. A subsequent experiment similar in design utilized controls and two doses of captopril in the treated groups (0.05% and 0.10%). The lung wet weight, hydroxyproline content, collagen, and mast cell accumulation were reduced in the captopril treated rats.

A subsequent experiment utilized fractionated radiation of various doses, randomizing groups of rats to control feed or feed containing captopril. In rats exposed to 60 Gy in 10 fractions, a transient rise at 4 weeks in computed tomography lung density was seen in the control group — but not in the captopril treated rats. Both groups returned to normal at 8 weeks. In rats irradiated to 80 Gy in 10 fractions, the transient rise at 4 weeks was seen in both groups. The density in the control group continued to increase while the captopril treated rats returned to near normal at 8 weeks. Pulmonary histology noted a reduction in interstitial connective tissue in the irradiated rats. In a bone marrow model, rats which were given chemotherapy and total body irradiation preparative regimes were noted to have significantly less lung parenchymal damage with the addition of captopril versus controls.

These various experiments have noted consistent reductions in pulmonary damage in rats treated with captopril when compared to controls. In all studies, captopril was administered after completion of irradiation. It is reasonable to hypothesize that these actions could be seen in humans.

In addition to the lung, captopril has been shown to ameliorate radiation reactions in the kidney, skin, heart, and small intestine. In addition, captopril has been shown to reduce fibrosis in both the rat kidney and liver as well as the lung. In a rat model, captopril has also been shown to be prophylactic against bone marrow transplant nephropathy. Captopril also decreases the frequency of malignant tumors in irradiated rat skin. Thus, the ability of captopril to modify radiation reactions in normal tissues appears to be neither species- nor tissue-specific. In these rat studies, captopril was effective at a regimen (25 to 50 mg/kg/day, p.o.), which appeared to be free of significant side effects for up to one year of continuous drug administration. This regimen is approximately 12 to 25 times higher than the standard antihypertensive dose in humans, based on equivalent body weight. It is hoped that safe human doses of Captopril will offer a clinically relevant benefit. While the mechanism of therapeutic efficacy is currently not clear, these data suggest a novel application for captopril in the management of radiation injury in dose limiting organs.

1.3 Late Effects

The clinical syndromes of pneumonitis and fibrosis are associated with radiation therapy and several cytotoxic drugs, including bleomycin, methotrexate, mitomycin, nitrosoureas, alkylating agents, and vinca alkaloids. The clinical pathologic course is biphasic and is dependent upon the dose and volume of lung exposed. Lower doses of lung irradiation produce subclinical pathologic effects that can be expressed by added insult such as infection or drugs.

Pneumonopathy might be a better term, since this is not an infective process. The clinical syndrome usually occurs one to three months after completion of radiation or drug therapy, but occasionally an accelerated phase of the syndrome develops within a period of days after an offending drug is administered. Symptomatic pneumonitis occurs in approximately 5-15% of patients irradiated for mediastinal lymphoma, lung or breast cancer. Higher rates are seen in patients irradiated for thymomas. The severity of symptoms of the acute pneumonitis syndrome is dependent on the degree of pulmonary involvement. There may be low-grade fever, non-specific respiratory symptoms such as congestion, cough, and fullness in the chest. In more severe cases, dyspnea, pleuritic chest pain, and non-productive cough may be present. Later, small amounts of sputum, which can be bloodstained, may be produced. Physical signs in the chest are usually absent, but evidence of consolidation is sometimes found in the region corresponding to pneumonitis. Pleural friction rub or pleural fluid may be detected. When tolerance doses are exceeded, pneumonitis can be very severe and produce acute respiratory distress with the patient experiencing spiking temperatures and acute cor pulmonale that can lead to death. Patients who survive this phase experience a protracted period of pneumonitis - possibly several months. It does not, however, persist indefinitely. This is the stage at which the mortality and most of the morbidity occur.

Generally, the pneumonitic phase with the acute symptoms is relatively short in duration. After the acute phase there is the intermediate phase during which the histologic changes described continue, but in which the symptoms would not be as marked. This progresses to the eventual fibrotic phase. In contrast to the acute reaction, chronic effects of cytotoxic therapy are observed from months to years following treatment, even though histologic/biochemical changes are evident sooner. Pulmonary fibrosis develops insidiously in
the previously irradiated field, and stabilizes after one or two years. The clinical symptomatology related to radiographic changes is proportional to the extent of the lung parenchyma involved and the patients' pre-existing pulmonary reserves. Most patients with radiation fibrosis are asymptomatic. In a few patients, particularly those with severe pneumonitis, chronic respiratory failure may be present: dyspnea on effort, reduced exercise tolerance, orthopnea, cyanosis, sometimes chronic cor pulmonale, and finger clubbing. Symptoms are generally minimal if fibrosis is limited to less than 50% of one lung.\textsuperscript{56} if the volume increases above this limit, dyspnea may manifest clinically, and progressive chronic cor pulmonale leading to right heart failure may occur.

The late lung injury is characterized by progressive fibrosis of alveolar septa thickened by bundles of elastic fibers. The alveoli collapse and are obliterated by connective tissue. These changes can lead to the radiographic appearance of lung scarring on chest radiography, corresponding to the shape of the radiation portal. However, with contraction of the zone of fibrosis, the match to the radiation field may be less obvious. Utilizing CT, the correspondence of the area of fibrosis to the high dose region of the isodose curves is more apparent and helps in establishing the diagnosis. Eventually, the previously irradiated lung can develop dense fibrotic nodules, especially in the area of previous tumor.\textsuperscript{57}

Mild deterioration in pulmonary function may occur as fibrosis develops. There is a reduction in maximum breathing capacity, which is particularly evident in patients with bilateral radiation fibrosis. Tidal volume usually decreases, and frequency tends to increase, resulting in an overall moderate increase in minute ventilation.\textsuperscript{58} Most studies have found these changes to persist indefinitely, with little recovery. Improvements in pulmonary function resulting from radiation response of lung tumors may compensate for losses caused by radiation fibrosis.\textsuperscript{59,61} Pulmonary function tests do not demonstrate significant changes when small volumes of lung are irradiated due to functional compensation of adjacent lung regions\textsuperscript{62} and therefore are not an ideal endpoint for measurement of radiation-induced lung injury. Diffusion capacity may be the best assessment of whole organ function since it is least likely to be effected by compensatory changes in unirradiated portions of the lung.

1.4 Quality of Life

Radiotherapy is known to be useful in the palliation of symptoms in lung cancer patients, and symptom reduction is associated with improved quality of life (QOL).\textsuperscript{64} A recent study of NSCLC patients receiving radiotherapy alone indicated that the QOL of patients deteriorated by the end of radiotherapy but improved to pretreatment levels within one month.\textsuperscript{65} However, aggressive chemotherapy and radiotherapy increase treatment-related toxicity, which may impair long-term QOL.\textsuperscript{66-67} The alleviation or prevention of pulmonary fibrosis may be associated with improved QOL.

In this project, QOL will be assessed through the use of a disease- and site-specific instrument, the European Organization for Research and Treatment of Cancer (EORTC) multidimensional core questionnaire (QLQ-30)\textsuperscript{68-69} with its accompanying lung cancer-specific module (QLQ-LC-13). The QLQ-30 previously has been used in lung cancer patients in a number of settings: evaluating anti-emetic regimens,\textsuperscript{70} non-small cell lung cancer patients treated with radiation therapy\textsuperscript{71} and non-small cell lung cancer patients treated with chemotherapy and radiotherapy.\textsuperscript{72} Patients treated with radiation therapy have been shown to have increased problems with dyspnea as reported through the QLQ-LC 13.\textsuperscript{71} Since the main goal of this study is to assess the effects of captopril on lung toxicity, special attention will be paid to those questions relating to dyspnea.

1.5 Biochemical Markers

MIP-1\(\alpha\) is a member of the C-C chemokine supergene family, which includes RANTES, macrophage inflammatory protein-1b (MIP-1\(B\)), monocyte chemotactant protein-1 (MCP-1), HC-14, and I-309. The C-C supergene family, grouped on chromosome 17, is so named because of the juxtaposition of the first two cysteine residues at the amino terminus. \textit{In vitro} studies have shown that MIP-1\(\alpha\) is chemokinetic for neutrophils and chemotactic for mononuclear phagocytes and lymphocytes. Appropriately stimulated T lymphocytes, alveolar macrophages, neutrophils, monocytes, and fibroblasts have been identified as cellular sources of MIP-1\(\alpha\) protein. In addition, it has been shown MIP-1\(\alpha\) stimulates IL-1, IL-6, and TNF production.\textsuperscript{73-74}

To determine the \textit{in vivo} function of MIP-1\(\alpha\), Cook/Smithies et al. at the University of North Carolina used homologous recombination in mouse strain 129-derived embryonic stem (ES) cells to generate a deletion in the MIP-1\(\alpha\) gene. The deletion included 300 nucleotides of DNA upstream of the mRNA start site, as well as the first exon and half of the second exon of the MIP-1\(\alpha\) gene. Injection of these cells into C576BL/6J blastocyes produced nine chimeras, five of which transmitted the mutant MIP-1\(\alpha\) allele to the offspring. Matings between F1 heterozygotes (+/-) yielded offspring of the MIP-1\(\alpha\) genotypes (+/+) (+/), and (-/-)
in Mendelian proportions. Pulmonary inflammation and expression of MIP-1α was then examined in both cohorts of (+/+ and (-/-) animals following infection with influenza virus. When the inflammatory response was assessed at day 6-7, the lungs of the (+/+ mice were observed to be inflamed and edematous, while the (-/-) lungs appeared to be less severely affected. Histologic sections of lung were graded for inflammation between 0 and +4 based on the extent of mononuclear cell infiltration and tissue damage. As concluded by the authors, MIP-1α contributes to influenza-virus mediated pneumonitis. Additional data, utilizing this mouse system and further supporting the importance of MIP-1α in the "chemokine-to-cytokine" cascade resulting in pneumonitis, has been reported by Salazar-Mather et al.

Data supporting the postulate that MIP-1α is involved in radiation-induced pneumonitis comes from animal experiments with bleomycin-induced lung injury. Much like radiation pneumonitis, bleomycin-induced lung injury is a multicomponent event; early in the response, mice develop a diffuse alveolitis characterized by the recruitment and subsequent activation of macrophages and lymphocytes. In data reported by Smith et al., a time-dependent expression of MIP-1α protein was observed in CBA mice (+/+ followed an exposure to bleomycin. MIP-1α was observed to peak at 2 days and again later at 16 days. This temporally correlated with an observed elevation of lymphocytes and granulocytes at 2 days and a subsequent peak in macrophage accumulation at 12 days post-bleomycin challenge.

In addition to the data presented in our preliminary data section, the most direct evidence for radiation inducing MIP-1α and its subsequent importance in mediating lung injury, comes from Pannoskalitsis-Mortari et al. The investigators examined the profiles of chemokines produced locally in the lung (parenchyma and bronchial lavage fluid) and systemically (serum) during the generation of idiopathic pneumonia syndrome (IPS) in the peri-bone marrow transplant (BMT) period. These experiments were performed in C57BL/6 mice. Animals in the treatment groups received a 7.5 Gy irradiation (total body) with or without Cytoxan chemotherapy (120 mg/kg). Protein and mRNA levels for MIP-1α were preferentially induced in the lung by day 7 post-allogeneic BMT and correlated with the clinical development of severe IPS. Compared to untreated controls, statistically significant elevations in bronchial lavage fluid MIP-1α levels were also discerned. Perhaps more relevant to this application, serum MIP-1α levels were markedly increased at 7 days post-treatment in those mice developing severe IPS. As concluded by the authors, these data are important as we develop strategies to circumvent the inflammatory events leading to IPS, or specific to our application, radiation pneumonitis/fibrosis.

Clinical data in support of our proposal comes from Hasegawa et al. To discern the relationship between MIP-1α in the pathogenesis of the pulmonary fibrosis associated with diffuse systemic sclerosis (dSSc), serum MIP-1α levels were collected from normal controls and patients with dSSc. Serum MIP-1α was only detectable in 3 of the 20 normal patients sampled (range 9 pg/ml - 15 pg/ml) compared to 10/26 patients with dSSc (p = < .05). Patients with elevated MIP-1α levels (≥ 2 standard deviations from the mean) had pulmonary fibrosis more frequently than those with normal MIP-1α levels; 56% versus 21% respectively (p = < .05). The authors concluded that MIP-1α plays an important role in induction and/or the development of pulmonary fibrosis in SSc patients via recruiting macrophages and CD8+ T cells to the affected lungs. Table 1 reflects the consistency in MIP-1α levels from controls tested from a number of clinical studies. From our review of the literature, it would appear MIP-1α levels in the 0.0 - 15.0 pg/ml would represent "normal" levels. The observations reported by Hasegawa are supported by Bolster et al. Bronchoalveolar lavage fluid was collected from patients with systemic sclerosis (SSc), with or without alveolitis, and from normal control subjects. There were significant differences between groups in the lavage fluid concentrations of MIP-1α levels (p = 0.009); MIP-1α levels in SSc patients with alveolitis were much higher than those in SSc patients without alveolitis or in the normal controls.
In summary, preliminary data from a number of laboratories would suggest MIP-1α is likely an important mediator of radiation induced pulmonary injury. In conjunction with our phase II clinical trial, this application describes our strategy to discern if serum MIP-1α levels are altered during a course of thoracic radiation, and further, determine if these temporal changes predict for the clinical development of radiation pneumonitis and/or fibrosis in conjunction with other cytokines (IL-1, IL-6, TNF α).

RTOG 91-03 was a study of pulmonary function in patients receiving radiation therapy for non-small cell lung cancer (NSCLC). The objectives of RTOG 91-03 were four-fold. First, to estimate the serial changes of pulmonary function before and after definitive thoracic irradiation; second, to identify the nature and frequency of radiation-related alteration of parameters of pulmonary physiology; third, to identify factors which are predictive of acute and late lung toxicity; fourth, to correlate biochemical markers with acute and late lung toxicities. Preliminary analyses of this study indicate that TNFα, IL-1 and IL-6 may have a role in the development of clinically significant lung damage. Neither TNFα nor IL-6 was related to acute lung toxicity by logistic regression analysis. Late lung toxicity was defined using the RTOG/EORTC Late Radiation Morbidity Scoring Criteria. Thirty percent of the patients experienced a grade 2-4 late lung toxicity; pretreatment TNFα level was associated with the development of grade 2-4 late lung toxicity (p= 0.06). As TNFα levels increased, so did the risk of lung damage. This was also observed at TNFα levels at 50 Gy and 60 Gy (p= 0.07). In a recursive analysis, IL-1 and IL-6 combined to predict late lung toxicity. Patients with IL-1 of zero and IL-6 of less than or equal to 51 at 50 Gy were one-third less likely to develop late lung toxicity than patients with higher levels of IL-1 or IL-6.

### Dose Volume Relationship to Pulmonary Toxicity (5/15/06)

This study will stratify patients on the basis of the total lung volume receiving greater than 20 Gy (V 20). The Washington University experience reported by Graham, et al. revealed a critical volume effect and threshold dose for the development of pneumonitis. Their evaluation of 99 patients showed that the incidence of radiation pneumonitis was strongly correlated with the percentage of total lung receiving greater than 20 Gray:

<table>
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<th>Total Lung Volume &gt; 20 Gy (%)</th>
<th>Incidence of Pneumonitis (%)</th>
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<td>&lt; 25</td>
<td>0-4</td>
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<tr>
<td>25-37</td>
<td>2-12</td>
</tr>
<tr>
<td>&gt; 37</td>
<td>19-30</td>
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The trial reported by Graham included only 42% of the patients receiving chemotherapy both sequentially and concurrently. There is accumulating evidence that concurrent chemotherapy and radiotherapy is associated with a significantly increased risk of pulmonary toxicity. In a study reported by Tsujino, et al., even with a V 20 receiving ≤ 20%, the six-month cumulative incidence of ≥ grade 2 radiation pneumonitis was 8.7%, rising to 85% with a V 20 receiving ≥ 31%. A recent article by Fay, et al. noted an overall rate of radiation pneumonitis of 15 % at six months with the use of concurrent chemoradiotherapy. In addition, a recent prospective CALBG trial utilizing induction and concurrent chemoradiotherapy noted an extremely high rate of significant toxicity in patients with a V 20 ≥ 40%, with 4 of 11 patients experiencing grade 4 or 5 pulmonary toxicity. Based on the above data, patients in this study will be stratified according to the percentage of total lung volume receiving greater than 20 Gy, along the following points: < 25%, 25-37% and > 37%. The minimum total dose to the target volume is 45 Gy. Patients with < 25% of the lung receiving > 20 Gy only are eligible if receiving concurrent chemoradiotherapy.
2.0 OBJECTIVES

Hypothesis: We hypothesize that captopril, when given after pulmonary radiation, will ameliorate radiation-induced pulmonary damage.

2.1 Primary: Test the ability of captopril to alter the incidence of pulmonary damage at 12 months after treatment in a group of patients at significant risk for pulmonary toxicity

2.2 Secondary: To investigate the pulmonary expression of MIP-1α, TNF-α, IL-1 and IL-6 at specific time intervals (see Section 11.1)

2.3 Secondary: Prospectively analyze whether the European Organization for Research and Treatment for Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the lung cancer module (QLQ-L13) scales are consistent in their measurement of pre-therapy symptoms and ensuing changes after therapy for patients with primary lung cancer, including effects related to the addition of captopril.

2.4 Secondary: Determine if captopril’s effect on pulmonary toxicity persists after completion of drug delivery

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED.

3.1 Eligibility (5/15/06)

3.1.1 Stage II-IIIB non-small cell lung cancer or Stage I central NSCLC (peripheral coin lesions excluded) or limited-stage small-cell lung cancer (nonmetastatic disease that is receiving radiotherapy, and the target is confined to a single radiation treatment area)

3.1.2 Patients must be ≥ 18 years of age.

3.1.3 Zubrod Performance Status 0-1

3.1.4 Planned total dose of ≥ 45Gy be delivered to the target volume and > 25% of total lung volume receiving > 20 Gy, if receiving radiotherapy alone

3.1.5 3D planning CT to measure lung volume irradiated

3.1.6 Surgery < pneumonectomy (i.e. lobectomy or segmentectomy) allowed

3.1.7 Induction or concomitant chemotherapy allowed (either during radiotherapy or during therapy with captopril)

3.1.8 The 3D computerized tomography radiation planning scan must be done prior to radiotherapy; it should not be repeated at registration or randomization.

3.1.9 Current and firm commitment to continue contraception adequate to prevent pregnancy during treatment; radiation and captopril are contraindicated in pregnancy.

3.1.10 Registration within 7 days prior to radiation therapy OR during radiation therapy up to 48 hours prior to observation or captopril

3.1.11 The following pretreatment evaluations must be obtained within 2 weeks prior to registration and within 2 weeks prior to randomization*, meeting the following criteria:

- Physical examination with blood pressure: Systolic > 110, Diastolic > 60;
- Absolute granulocyte count ≥ 1,000/mm³; platelets ≥ 75,000/mm³;
- Hg > 9.0g/dl (may transfuse, if necessary, to Hg > 9); BUN < 25 mg/dl; serum creatinine < 1.6mg/dl; serum bilirubin <1.5 mg/dl; SGOT < 2X normal;
- Serum Na+ and serum K+ within institutional normal;
- Urine protein <10 mg/dl; urine glucose negative;
- Negative serum pregnancy test for women of childbearing potential.

*NOTE: If the patient is registered within 2 weeks prior to randomization, pretreatment evaluations will be done once and will not be repeated.

3.1.12 Signed study-specific informed consent prior to registration

3.2 Conditions For Patient Ineligibility (11/23/04)

3.2.1 Current pregnancy

3.2.2 Requirement for angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonists for hypertension or congestive heart failure

3.2.3 Collagen vascular disease, i.e., lupus and scleroderma; patients with rheumatoid arthritis are eligible.

3.2.4 Known hypersensitivity to ACE inhibitors

3.2.5 Patients on lithium, methotrexate, or procarbamide medication

3.2.6 Unwillingness to adhere to protocol
4.0 PRETREATMENT EVALUATIONS/MANAGEMENT (5/15/06)

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Highly Recommended Evaluations/Management

Note that these evaluations/interventions are highly recommended but are not required.

- Serum collection for biochemical marker analysis;
- Quality of life assessment: EORTC questionnaire (QLQ-30) with lung cancer-specific module (QLQ-LC-13)

**NOTE**: These evaluations should be obtained at registration, within 7 days prior to radiation therapy OR during radiation therapy up to 48 hours prior to observation or captopril. Institutions must document at which time point these baseline evaluations were obtained.

5.0 REGISTRATION PROCEDURES (5/15/06)

5.1 Step 1— Registration

Patients are registered within 7 days prior to the start of radiation therapy OR during radiation therapy, within 48 hours prior to observation or captopril.

5.1.1 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via [http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp](http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp)).
- A representative from the institution must complete the Password Authorization Form at [http://www.rtog.org/members/webreg.html](http://www.rtog.org/members/webreg.html) (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site ([http://www.rtog.org](http://www.rtog.org)), going to “Data Center Login” and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: [websupport@phila.acr.org](mailto:websupport@phila.acr.org).

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.
5.2  **Step 2 — Randomization**

All patients must be randomized within 48 hours prior to captopril/observation. If the patient is being registered during radiation therapy, within 48 hours prior to observation or captopril, institutions can complete Step 1, online Registration and then immediately complete Step 2, online Randomization.

**NOTE:** If patients registered in Step 1 are subsequently unable to continue protocol treatment, institutions must complete Step 2, noting that the patient cannot continue. In addition, institutions must submit case report forms as specified (see Section 12.1).

6.0  **RADIATION THERAPY**

**Note: Intensity Modulated RT (IMRT) Is Not Allowed (5/15/06)**

6.1  Radiation is to be delivered in standard fractionation to a total prescribed dose of at least 45 Gy. CT based treatment planning must be accomplished for accurate lung dose volume histograms (DVHs). CT scans should include 0.5 cm or smaller cuts through the portion of the chest that is/was within the radiation field. The remainder of the CT scan may be done with cuts up to 1 cm. CT scans should be done with IV contrast, unless there is a medical contraindication (e.g., allergy) to contrast. Interpretations (e.g., determining the extent of fibrosis and presence/absence of tumor) should be made jointly between the diagnostic radiologist(s) and the treating radiation oncologist(s). The radiation fields should be what is considered the institutions standard. A dose volume histogram of the lung should clearly depict the percentage of total lung volume receiving greater than 20 Gy including all boost therapies. Doses will be calculated with heterogeneity uncorrected. **Total lung volume is defined as the lung volume of both lungs, minus the PTV.** DVHs will be submitted to RTOG Headquarters (See Section 12.1); CT scans will not be sent to RTOG Headquarters.

7.0  **DRUG THERAPY**

7.1  **Captopril (FDA exemption granted 10/3/02)**

For those patients randomized to captopril; captopril will be given to patients after completion of radiotherapy.

7.1.1  **Drug Administration**

Captopril is formulated as a pill in potencies of 12.5, 25, 50, and 100 mg. Patients randomized to captopril will receive an initial dose of 6.25 mg *(The physician/nurse should cut a 12.5 mg pill in half for this test dose.*) If there is no significant toxicity experienced two hours following this dose, the patient will return the next day to begin protocol therapy. At that time, an initial 12.5 mg dose will be given in the physician’s office, where a single orthostatic blood pressure, pulse, and symptom check will be done after one hour.

For the first two weeks the dose will be 12.5 mg t.i.d. The dose will be increased to 25 mg t.i.d. for the second two weeks of therapy. Thereafter, the dose will be increased to 50 mg t.i.d. for the remainder of the one-year of therapy *(52 total weeks of drug administration).* **NOTE:** Each time the dose is increased, the initial dose will be given in the physician’s office, and blood pressure, pulse, and symptom check will be done after one hour Captopril should be taken one hour before meals.

See Section 7.3.1 for complete drug administration and dose escalation details.

7.1.2  **Description**

Captopril is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), which catalyzes the conversion of angiotensin I to angiotensin II. Captopril is specified chemically as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline.

7.1.3  **Formulation**

Captopril is a white to off-white crystalline powder that is soluble in water and methanol, and slightly soluble in chloroform and ethyl acetate. Captopril will be supplied as scored white tablets containing 12.5mg, 25 mg, or 50 mg, and should be stored in a dry place at room temperature between 59° – 86° F.

7.1.4  **Supply**

Captopril is commercially available. Individual investigators/treating physicians will write prescriptions for captopril for their patients.

7.2  **Adverse Effects**

- Renal: Proteinuria; kidney damage
- Hepatic: Impaired liver function; increased LFTs
- Metabolic: Hyperkalemia
7.3 Treatment Plan (5/15/06)

7.3.1 Post-radiotherapy patients will be randomized to captopril for one year versus observation. The test dose should, whenever possible, be given early in the morning on the first business day after the last fraction of radiation (Day 1 of protocol treatment). If the radiation ends on a Friday, the test dose should be given early in the morning on the next business day.

Day (−): After checking for adequate resting blood pressure (Systolic ≥ 110, Diastolic ≥ 60) and pulse (55), patients randomized to captopril will receive a test dose of 6.25 mg of captopril (The physician/nurse should cut a 12.5 mg pill in half for this test dose) and will be observed for a period of 2 hours. During these 2 hours, orthostatic blood pressure and pulse will be checked and recorded every 30 minutes. With each check of orthostatic blood pressure and pulse, the patient will be evaluated for any subjective complaints. The initial test dose and subsequent monitoring will be accomplished early in the morning. If there is no significant reduction of blood pressure (<90/60) and no significant symptomatic orthostasis, the patient will return the next day to begin protocol therapy. If the patient is on a diuretic, the diuretic should be withheld for 24 hours before the initial test dose and, on the following day, restricted to a half dose and adjusted as necessary. If there is a hypotensive episode, the patient will not receive captopril but will be followed as in the non-captopril arm.

NOTE: If a hypotensive episode occurs, give oral hydration with an electrolyte-containing solution, unless BP is < 80 mm Hg or the patient is markedly symptomatic. In that circumstance, initiate intravenous hydration with saline-containing solutions. If there is life-threatening hypotension, appropriate actions should be taken, including aggressive hydration, use of pressors, and admission to observation care. The patient should be observed for at least 4 hours and discharged if no longer symptomatic and if the BP has returned to at least 85% of baseline.

Day 1: Following the determination of adequate resting blood pressure (Systolic ≥ 110, Diastolic ≥ 60) and pulse (55), an initial 12.5 mg dose will be given in the treating physician’s office, where a single orthostatic blood pressure, pulse, and symptom check will be done after one hour.

If the patient becomes hypotensive, appropriate therapy will be initiated immediately. In most cases, administration of i.v. fluids is all that will be required. If there is no hypotensive episode, the dose of 12.5 mg will be continued for 2 weeks.

Day 15: Following the determination of adequate resting blood pressure (Systolic ≥ 110, Diastolic ≥ 60) and pulse (55), the dose will then be increased to 25 mg of captopril t.i.d. for 2 weeks. The initial dose will be given in the treating physician’s office, where a single orthostatic blood pressure, pulse, and symptom check will be done after one hour.

Day 29: Following the determination of adequate resting blood pressure (Systolic ≥ 110, Diastolic ≥ 60) and pulse (55), the dose will be increased to 50 mg of captopril t.i.d. until the completion of 52 weeks. The initial dose will be given in the treating physician’s office, where a single orthostatic blood pressure, pulse, and symptom check will be done after one hour.

NOTE: Patients must be instructed to return two days prior to each dose escalation for physical exam, CBC, and serum chemistries, as outlined in Section 11.1. In each case, if no adverse reactions occur (see 7.4), the patient will return to the principal investigator's office, where the dose of captopril will be increased, and orthostatic blood pressure and pulse will be monitored as outlined above.

If there is a hypotensive episode that responds to fluids at any captopril dose level, the patient will be brought back the next day and the previous dose level will be administered (e.g., if the episode occurred at 12.5 mg, the next day dose will be 6.25 mg). A single orthostatic blood pressure, pulse, and symptom check will be done after one hour. If there is a hypotensive episode with 6.25 mg, the patient will not receive further captopril but will be followed as in the non-captopril arm. If the patient does not
have a hypotensive episode to the reduced dose, this dose will be continued t.i.d. and escalated every 2 weeks with the same protocol as described above.

Patients will be required to keep a Pill Diary; these will be retained at the institution. Captopril compliance will be reported on the Treatment Summary Form (See Section 12.1).

The dose levels of captopril are based on the SAVE study as that was a large cohort of normotensive patients taking captopril for a non-blood-pressure-related medical problem. Since this is a phase two randomized trial, there will be no placebo controlled arm.

7.3.2 Patients randomized to observation will undergo no active therapy.

7.4 Dose Modifications and Toxieties

If investigators have questions or concerns regarding discontinuing captopril or about taking patients off study, they should contact Dr. Small, the study chair, at (312) 926-6810 or Dr. Fintel, cardiology chair, at (312) 908-2745.

7.4.1 Patients will be temporarily taken off captopril and restarted within 2 weeks at half the prior dose in the presence of:

- Cough (dry, unproductive) that the investigator feels is due to captopril, as opposed to lung cancer, COPD, infection, or radiation, or a cough that reaches grade 3
- Increased creatinine to ≥ 2.5 mg/dl
- Symptomatic orthostatic hypotension: lightheadedness, dizziness, and/or confusion with systolic blood pressure below 100

If any of the above conditions are still present two weeks later, before captopril is initiated at half dose, the patient will be taken off study.

7.4.2 Patients will be taken off study if any of the following develop:

- Skin rash or any signs or symptoms of drug allergy
- Absolute WBC < 2.0, thought to be related to captopril treatment
- Neutrophil Count < 1.0, thought to be related to captopril treatment
- Proteinuria
- Clinical diagnosis of congestive heart failure
- Persistent potassium > 5.0
- Hg < 7.5 gm/dl attributable to protocol treatment
- Increase in bilirubin > 2.0 or liver function tests > 2X normal
- Any unexpected grade 3 toxicity attributable to captopril
- The investigator decides that to continue captopril is not in the patient’s best interest.
- Noncompliance with the captopril regimen
- Noncompliance with the follow-up and testing schedule
- Recurrent disease necessitating anti-cancer therapy

(12/16/03) For Grade 2 or higher pulmonary toxicity, captopril will be discontinued immediately. Weaning from captopril is unnecessary. Treatment for pulmonary toxicity will be per institutional guidelines. If a patient is hypertensive, other medications can be initiated or augmented for optimal control of hypertension. The investigator should document whether or not the pulmonary toxicity is attributed to captopril or radiation therapy.

7.5 Adverse Events (5/15/06 5/18/11)

As of July 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. Note: All RTOG case report forms will continue to use CTCAE v. 3.0. A copy of the CTCAE v. 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm[home page](http://ctep.cancer.gov). The CTEP home page also can be accessed from the RTOG web page at [http://www.rtog.org/regulatory/regs.html](http://www.rtog.org/regulatory/regs.html). All appropriate treatment areas should have access to a copy of the CTCAE v. 4.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site [https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$_startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$_startup).
Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG website (http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx) for this information.

7.5.2 Adverse Events (AEs) — RTOG AE PHONE: 215-717-2762; 800-227-5463 ext. 4189 (available 24 hours/day)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported via AdEERS. Use the patient’s case number as the patient ID when reporting via AdEERS. AEs reported using AdEERS also must be reported on the AE case report form (see Section 12.1). NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting may be required. Reporting AEs only fulfills Data Management reporting requirements.

7.5.3 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported to RTOG (SAE PHONE: 215-717-2762, 800-227-5463 ext. 4189; available 24 hours/day) within 24 hours of discovery of the event.

Definition of an SAE: Any adverse drug experience occurring at any dose that results in any of the following outcomes:
- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Outside of regular business hours (8:30-5:00 EST), leave a message that includes the study/case numbers and the caller’s contact information. A Data Manager will return the call the next business day requesting details of the event and also will inform the caller which type of report is required for that study (5 or 10 day AdEERS). The required report must be completed in AdEERS within 5 or 10 calendar days of the initial phone report, as directed by the Data Manager taking the call. SAEs reported using AdEERS also must be reported on the AE case report form (see Section 12.1).

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG via the AE/SAE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT
Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.5.4 **Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)** [5/18/11]
AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis. If the site is reporting in CTCAE, v. 4, the event(s) maybe reported as 1) Leukemia secondary to oncology chemotherapy; 2) Myelodysplastic syndrome; or 3) Treatment-related secondary malignancy.

<table>
<thead>
<tr>
<th>RTOG Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML/MDS Report</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
</tr>
</tbody>
</table>

7.6 **AdEERS Expedited Reporting Requirements (5/15/06)**
Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days† of the Last Dose of the Investigational Agent [captopril] in this Study

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5</th>
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</thead>
<tbody>
<tr>
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<td>Expected</td>
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<td>Expected</td>
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<tr>
<td>Unrelated</td>
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<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>24-Hour; 5 Calendar Days</td>
<td></td>
</tr>
</tbody>
</table>

† Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a non-CTEP IND require reporting as follows:
AdEERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events
AdEERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

‡ Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

(5/18/11) Any medical event equivalent to CTCAE v. 4 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as
expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP-IND: Not applicable to this study.

8.0 SURGERY
Not applicable to this study.

9.0 OTHER THERAPY (11/23/04)

9.1 Permitted Therapy
9.1.1 Patients on other cooperative group or single institution lung treatment trials using radiation +/- chemotherapy are permitted on this study if all the eligibility criteria are met.
9.1.2 Amifostine use is permitted.
9.1.3 Post-radiotherapy surgery is allowed.

10.0 TISSUE/SPECIMEN SUBMISSION (5/15/06)
(For patients who have consented to submit serum; see Appendix IB)

10.1 Biochemical Markers - Rationale
Preliminary data from a number of laboratories would suggest MIP-1α is likely an important mediator of radiation induced pulmonary injury. Our purpose is to discern if serum MIP-1α levels are altered during a course of thoracic radiation, and further, determine if these temporal changes predict for the clinical development of radiation pneumonitis and/or fibrosis in conjunction with other cytokines (IL-1, IL-6, TNF α) [See Section 1.5 for details].

10.2 Serum Collection, Preparation, and Storage (see Appendix IV for collection kit and detailed instructions) [5/15/06]
10.2.1 Collect blood in a serum separator tube for MIP-1α (and associated markers) and a 5ml EDTA tube for TNF-α (and associated markers) using a 19-21 gauge needle.
10.2.2 Allow the serum tube to clot at room temperature for 30 minutes. After mixing the blood in the EDTA tube thoroughly to mix contents, rest the tube vertically at 4°C and avoid any agitation to the sample.
10.2.3 Centrifuge both tubes for 10-30 min. at 2000 x g with the brake off (~2500 rpm on a standard clinical centrifuge).
10.2.4 From the serum tube, collect supernatant and aliquot 200-500 µl into five tubes labeled "serum." From the EDTA tube, take only the top portion of supernatant (beginning from the top to 0.5-1 cm above the buffy coat) and aliquot 200-500 µl to five tubes labeled as "plasma." Always keep the tip of transfer pipette far away from the buffy coat (this is very important in order to avoid platelet contamination.). Next, carefully pipette the buffy coat, transfer into an aliquot tube, and label sample as "buffy coat".
10.2.5 Store samples at -80°C until transport/assay. Limited batching of samples is acceptable, if samples are shipped weekly or once a month; samples should not be stored for longer than one month prior to shipment. NOTE: Samples must be shipped via overnight carrier to the RTOG Tissue Bank at the address below Monday-Thursday to arrive the following business day. Shipping should be planned to avoid deliveries on weekends and/or holidays.
10.2.6 The following materials must be provided to the RTOG Tissue Bank: A Serum Submission Form documenting the date of collection of the serum and including the RTOG protocol number, the patient’s case number, and the method of storage (i.e., stored at -80°C).
10.2.7 Submit materials to:

LDS Hospital
RTOG Tissue Bank/E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626 or (801) 408-2035

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10.2.8 Serum samples will be analyzed by A. William Blackstock, Wake Forest University, (336) 716-4981, ablackst@wfubmc.edu

10.3 Reimbursement (5/15/06)

RTGO will reimburse submitting institutions $300 per case for fresh or flash frozen tissue or for buffy coat, $200 per case for a block or core of material, or $100 per case for serum/plasma. After confirmation from the RTOG Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.4 Confidentiality/Storage


10.4.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient’s case number only. The Tissue Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.4.2 The specimens will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS (5/15/06)

11.1 Study Parameters

Treatment Schedule of Tests (in months, both groups of patients)

| Test                        | Within 2 weeks of Registration | Within 2 weeks of Randomization | 0.5 | 1 | 1.5 | 3 | 4.5 | 6 | 9 | 12 | 18 | 24 | 30 | 36
<table>
<thead>
<tr>
<th></th>
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<tr>
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<td>X</td>
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<td>X</td>
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<td>X</td>
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<td>Pregnancy testf</td>
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<tr>
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<td>X</td>
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<td>X</td>
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</tr>
</tbody>
</table>

a. (12/16/03) For patients randomized to captopril arm; physical exam, CBC, urinalysis, and serum chemistries to be performed within 48 hours prior to scheduled dose escalations and for the duration of captopril therapy as specified in table.

b. BUN, Cr, Bili, SGOT, Na+, K+

c. For biochemical marker analysis; see section 10.2

d. > 36 months: see F1 instructions, Section 12.1.

e. Utilizing CTCAE, version 3.0 (See Section 11.1.2)

f. For females of childbearing potential

3. For females of childbearing potential

g. 3D treatment planning CT must be done prior to radiotherapy; it should not be repeated at registration or randomization.; scans should include 0.5 cm or smaller cuts through the portion of the chest that is/was within the radiation field. The remainder of the CT scan may be done with cuts up to 1 cm. CT scans should be done...
with IV contrast, unless there is a medical contraindication (e.g., allergy) to contrast. Interpretations (e.g., determining the extent of fibrosis and presence/absence of tumor) should be made jointly between the diagnostic radiologist(s) and the treating radiation oncologist(s).

11.1.2 (5/18/11) All acute and late adverse events from radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A copy of the CTCAE can be downloaded from the CTEP homepage (http://ctep.info.nih.gov).

11.2 Quality of Life
In this study QOL will be assessed through the use of a disease- and site-specific instrument, the European Organization for Research and Treatment of Cancer (EORTC) multidimensional core questionnaire (QLQ-30) with its accompanying lung cancer-specific module (QLQ-LC-13). Since the main goal of this study is to assess the effects of captopril on lung fibrosis, special attention will be paid to those questions relating to dyspnea.

The EORTC instrument includes both a multidimensional questionnaire addressing physical, emotional and social functioning, and global quality of life, the QLQ-30 (version 3), as well as lung cancer-specific symptom module, the QLQ-LC-13. The core survey includes a 30 question patient-related assessment of physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), and social functioning (2 items), and pain (2 items). Patient responses are rated on a Likert-type scale from 1 (not at all) to 4 (very much), where lower scores signify fewer symptoms and a better quality of life. Also ranked on a 4-point scale are questions addressing the presence and absence of dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact. Again, lower scores indicate better quality of life and fewer symptoms. A similar scale, though with a range of 1 (very poor) to 7 (excellent), ranks two additional questions related to overall physical health and overall quality of life in the past week.

The QLQ-LC-13 uses 13 lung cancer-specific questions to measure symptoms experienced within the past week, including difficulties of cough (1 item), hemoptysis (1 item), dyspnea (2 items), sore mouth (1 item), dysphagia (1 item), tingling in hands and feet (1 item), hair loss (1 item), and pain (4 items). Each item uses a scale from 1 (not at all) to 4 (very much), with 4 presenting more problems.

Psychometric testing of the QLQ-30 has included assessment in cultures with 17 different languages. The QLQ-30 and the QLQ-LC-13 have been proven to be feasible, reliable, and valid. The average time to complete both the QLQ-30 and the QLQ-LC-13 is 15-20 minutes. In one trial less than 5% of patients required assistance in completing the questionnaires, while the format and content of the questionnaire were acceptable even for patients with advanced malignant disease. The QLQ-30 has proven itself to be internally consistent and reliable, as has the QLQ-LC-13 (with the exception of the pain subscale). Symptom measures discriminated clearly between patients differing in performance status, with lung cancer symptoms decreasing and treatment toxicities increasing during therapy. Compliance has been good amongst those patients entered on therapy, with poor health status the primary reason for patient dropout from previous studies.

12.0 DATA COLLECTION (11/23/04)
Data should be submitted to:
RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (11/23/04)

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<td>Initial Evaluation Form (II)</td>
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</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Quality of Life (QL)</td>
<td></td>
</tr>
</tbody>
</table>
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Test the ability of captopril to reduce the incidence of therapy-induced lung toxicity

13.1.2 Correlated lung toxicities and biochemical markers

13.1.3 Correlate quality of life with late effects in lung cancer patients

13.1.4 Obtain two-year follow up to test if captopril’s effect on pulmonary toxicity persists after completion of drug therapy

13.2 Sample Size

13.2.1 Lung Toxicity

It is estimated that approximately 50% of the patients develop a grade 2 or higher late radiation-induced lung toxicity. Captopril may reduce this rate by 50% to 25%. According to Werner-Wasik et al., approximately 10% of the cases will develop a grade 2 lung toxicity by the end of radiation therapy. Therefore, 40% of the cases may develop ≥ grade 2 lung toxicity beyond that time. Continuing to assume a 50% reduction would indicate a drop from 40% to 20%. Assuming that captopril has no effect on the 10% of cases that develop toxicity prior to randomization, then the observable rate would be a reduction from 50% to 30%. A Fisher's exact test with a 0.050 one-sided significance level will have 80% power to detect the difference between the patients treated without captopril (50% expected toxicity) and the patients treated with captopril (30% expected toxicity) when the sample size in each group is 84.

This is a randomized phase II study because no reliable historical control for the incidence of pulmonary damage exists. Furthermore, the aim of this study is to determine whether there is efficacy in captopril, so a one-sided type I error was chosen. It is estimated that 5% of the patients will be found ineligible after the initiation of therapy, so 89 patients per arm will be required for randomization. Since patients are registered prior to all lung cancer therapy, it is assumed that 15% of the cases will not be randomized. Hence, a total of 205 patients will be required.

13.2.2 Quality of Life

The hypothesis for quality of life is improved QOL for patients not experiencing a grade 2 or worse late lung toxicity. A difference of ten points on the EORTC C-30 subscales or LC-13 is considered clinically significant. Using this clinically meaningful change threshold, patients will be classified as having improved, declined, or been stable at one year. If 25% of the patients that did not have lung toxicity have deteriorated by one year, then this study will have at least 80% power to detect that this is better than those with lung toxicity which is expected to have a 50% declined rate.

13.2.3 Biochemical Markers

According to Section 13.2.1 there will be 168 evaluable patients with serum data. A logistic regression will be used to determine the prognostic significance of each individual marker. The sample size will provide at least 84% power to find an odds ratio of at least 1.6 for an individual marker.

13.3 Patient Accrual

RTOG studies in NSCLC with more restrictive eligibility criteria have accrued at 12-16 patients per month. It is reasonable to expect this study to accrue at the high end of RTOG’s experience due to the expanded
eligibility criteria. The monthly accrual is expected to be 12 patients with the study completing the accrual phase within 18 months.

13.4 Randomization

The stratified treatment allocation scheme as described by Zelen\textsuperscript{99} will be used. The treatment arms will be balanced by institution. There will be stratification by total lung irradiated (25-37\% vs. 37\%), prior surgery (\textit{no} vs. \textit{yes}), and chemotherapy (\textit{no} vs. \textit{yes}).
13.5 **Analysis Plans (5/15/06)**

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

13.5.1 **Interim Analyses of Accrual and Toxicity Data**

Interim reports with statistical analyses will be prepared every six months until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about:

a) The patient accrual rate with projected completion date for the accrual phase;
b) the distribution of patients with respect to pretreatment characteristics;
c) compliance rate of treatment delivery with respect to the protocol prescription;
d) the frequency and severity of the toxicities not separated by treatment arm.

13.5.2 **Analysis and Reporting of Initial Treatment Results**

The major analysis will be undertaken when each patient has been potentially followed for a minimum of twelve months. The usual components of this analysis are:

a) Tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;
b) reporting institutional accrual;
c) distribution of the important prognostic factors by assigned treatment;
d) observed results with respect to the study endpoints.

1. Comparison of treatment results by radiation-induced lung toxicity will be performed using a Fisher’s exact test. The worst lung toxicity observed will be the primary endpoint.
2. A univariate logistic regression will be performed for each biomarker. In addition a recursive partitioning tree will be employed to determine the best predictive model for late lung toxicity that will examine interactions between biomarkers.
3. The QLQ C30 and QLQ LC-13 will be assessed at one-year and compared to baseline and the proportion of patients that have deteriorated at one year will be used to determine whether patients with lung damage have different QOL than patients without damage.

13.6 **Gender and Minorities**

There is no expectation of an interaction between the incidence of pulmonary fibrosis and gender or race. Based upon prior RTOG lung cancer trials, 35% of the sample should be female. It is estimated that at least 66 women will be accrued to this project. This project will have at least 58% statistical power to detect an absolute 25% difference in pulmonary fibrosis rate between genders. Evaluation of differences in baseline quality of life and follow-up serum markers between genders will also be performed. Differences in changes over time in QOL between men and women will also be performed. These analyses will be exploratory because no a priori hypothesis has been designed, because there is no differences expected.
### GENDER/MINORITY ACCRUAL ESTIMATES

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<td>134</td>
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</tr>
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</table>

### Racial Category

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<td>134</td>
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REFERENCES (5/15/06)


8. Ondetti MA. Squibb Institute for Medical Research. Personal communication. 1/16/90.


60. Germon PA and Brady LW. Physiologic changes before and after radiation treatment for carcinoma of the lung. *JAMA.* 206:808; 1968


APPENDIX 1A
RTOG 0123

SAMPLE CONSENT FOR RESEARCH STUDY

A PHASE II RANDOMIZED TRIAL WITH CAPTOPRIL IN PATIENTS WHO HAVE RECEIVED RADIATION THERAPY +/- CHEMOTHERAPY FOR STAGE II-IIIB NON-SMALL CELL LUNG CANCER, STAGE I CENTRAL NON-SMALL CELL LUNG CANCER, OR LIMITED-STAGE SMALL-CELL LUNG CANCER

RESEARCH STUDY (11/23/04)

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know”, is available from your doctor.

You are being asked to take part in this study because you have lung cancer and will be receiving radiation therapy.

PURPOSE OF THE STUDY

The purpose of this study is to find out what effects (good and bad) captopril, a heart medication, has on you and your lung cancer. This research is being done because currently, there is no effective treatment for side effects of lung radiation. It is not clear at the present time whether or not captopril effectively reduces the side effects of radiation. This study also will attempt to see how you view the quality of your life before treatment, during treatment, at the end of treatment, and at intervals afterward.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 205 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (5/15/06)

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. You will be assigned to a treatment group by a computer; neither you nor the researcher will
choose the group to which you are assigned. Your chance of receiving Treatment 1 (no captopril, observation only) is equally as likely as that of receiving Treatment 2 (captopril). You will have one of the following treatments:

**Treatment 1:**
You will not be asked to take captopril, but your health will be closely observed. You will have a CT scan within 2-3 weeks of starting radiation therapy. Depending upon when you agree to participate in this study, you will have a physical examination, blood tests, and a urinalysis within 2-3 weeks of starting radiation therapy and/or near the completion of radiation therapy.

You will have a physical examination at 2, 4, 6, 12, and 18 weeks, then at 6, 9, and 12 months, then every 6 months for the next 2 years, and then annually. In addition, you will have a CT scan at 3 and 6 months, every 6 months for 2 years, then annually.

One of the purposes of this study is to look at the side effects of your treatment and how the side effects and your cancer affect you. You will be asked to complete a questionnaire that describes your day-to-day activities and overall sense of well being. The questionnaire will take 15-20 minutes to complete. Depending upon when you agree to participate in this study, you will be asked to complete the questionnaire within 2-3 weeks of starting radiation therapy and/or near the completion of radiation therapy.

**Treatment 2:**
You will be asked to take captopril. You will have a CT scan within 2-3 weeks of starting radiation therapy. Depending upon when you agree to participate in this study, you will have a physical examination, blood tests, and a urinalysis within 2-3 weeks of starting radiation therapy and/or near the completion of radiation therapy.

Then within 2 days of beginning captopril, you will have a physical examination, blood tests, and a urinalysis. Following these tests, if it is determined that you are still a candidate for treatment, you will be asked to spend two hours in your doctor’s office after taking the first dose of captopril. During this time, your blood pressure and overall physical condition will be monitored. If it is determined that you tolerated captopril well, you will receive a second dose of medication the next day and will be asked to remain for one hour when a single blood pressure measurement and symptom check will be made.

If you are taking a diuretic (water pill), your doctor may ask you temporarily stop taking and/or adjust the dose you take before and after the first dose of captopril.

If you tolerate the second dose of captopril, you will be given two weeks worth of captopril to take at home. You will take one pill three times a day. You will take captopril one hour before your meals. At the end of the two weeks, a repeat physical examination, blood tests, and urinalysis will be performed. If these tests show that no problems have been encountered, you will be given a higher dose of
captopril. The same process will occur after an additional two weeks. Each time the dose of captopril is increased, an initial one-hour stay for a single blood pressure measurement and symptom check will be necessary. If it is determined that you tolerated captopril well, you will be asked to take captopril for one year. You will take one pill three times a day.

The physical examination, blood tests, and urinalysis will be repeated at 2, 4, 6, 12, and 18 weeks, then at 6, 9, and 12 months, then every 6 months for the next 2 years, and then annually. In addition, you will have a CT scan during the study at 3 and 6 months, then every 6 months for 2 years, then annually.

One of the purposes of this study is to look at the side effects of your treatment and how the side effects and your cancer affect you. You will be asked to complete a questionnaire that describes your day-to-day activities, and overall sense of well being. The questionnaire will take 15-20 minutes to complete. Depending upon when you agree to participate in this study, you will be asked to complete the questionnaire within 2-3 weeks of starting radiation therapy and/or near the completion of radiation therapy, then at 3, 6, 12, and 18 months.

**HOW LONG WILL I BE IN THE STUDY?**

If you are randomized to Treatment 2, you will take captopril for one year. All patients (Treatment 1 and 2) will be seen as outlined above. Follow up will continue every 6 months for 3 years, then annually.

Your doctor may decide to take you off this study if it is in your medical best interest, drug supply is insufficient, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

**WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the captopril is stopped, but in some cases side effects can be serious or long lasting or permanent.
Captopril

Very Likely
Loss of taste
Cough
Allergic reactions, such as rash, wheezing, shortness of breath
Skin rashes
Reduced blood pressure
Reduced blood counts
Protein in the urine, which could be a sign of kidney damage

Less Likely but Serious
Allergic reactions, which in rare cases could involve life threatening breathing problems or heart attack.
Increased blood potassium, which could lead to serious abnormal heart rate or other serious heart complications
Fast or abnormal heart rate
Reduced blood flow to the hands
Swelling of legs, face, mucous membranes, tongue, and throat
Chest pain
Congestive heart failure
Heart attack
Kidney damage
Liver damage

The risks of reduced blood counts and kidney damage may be increased as a result of previous radiation treatments or chemotherapy.

A fatal side effect may occur but would be considered extremely rare. There is always the risk that very uncommon or previously unknown side effects may occur.

Blood Draws

Risks and side effects include bruising and a small chance of infection.

Reproductive Risks

Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.
ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with lung cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include no treatment except medications to make you feel better.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

WHAT ARE MY RIGHTS AS A PARTICIPANT? (11/23/04)

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A group of experts from the Symptom Management Committee, the study chairs, and the study statistician will be reviewing the data periodically throughout the study.
We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHAT ABOUT CONFIDENTIALITY? (12/16/03)

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.
Organizations that may inspect and/or copy your research records for quality assurance and data analysis include the Radiation Therapy Oncology Group (RTOG) and groups such as the Food and Drug Administration (FDA) and the National Cancer Institute (NCI).

**WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

**WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS? (5/15/06)**

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [name(s)] at __________________ [telephone number].

For questions about your rights while taking part in this study, call the ___________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at __________________ (telephone number).

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]*

**WHERE CAN I GET MORE INFORMATION? (5/15/06)**

You may call the NCI’s Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/
SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

_____________________  _________________  ___________
Patient’s Name                               Signature             Date

_____________________                         __________________   ___________
Name of Person Obtaining Consent         Signature             Date
ABOUT USING BLOOD FOR RESEARCH (5/15/06)

You are being asked for permission to send a small amount of your blood to a central office for research into ways to detect lung injury as early as possible. Your blood will be drawn within 2-3 weeks of beginning radiation therapy and/or near the completion of radiation therapy, at 6 weeks, then at 3, 6, 9, and 12 months during the study. These samples of your blood will be sent to the central office to learn more about cancer and other diseases.

The research that may be done with your blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

All possible methods will be used to ensure your privacy and confidentiality. Identifying information will be taken off anything associated with your blood before it is given to a researcher. Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

THINGS TO THINK ABOUT

The choice to let us use your blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood and then any blood that remains will no longer be used for research; or, you may request that we dispose of your blood.

In the future, people who do research may need to know more about your health. While _________ (doctor/institution) may give researchers reports about your health, your doctor/institution will not give researchers your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health records.

Your blood will be used only for research. However, the research done with your blood may help to develop new products in the future. If this occurs, you will not be financially compensated.

BENEFITS

The benefits of research using blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.
RISKS
Physical Risks
If your blood is drawn, you may experience some discomfort, bruising, and/or bleeding at the site of the needle insertion. Occasionally, some people experience dizziness or feel faint. In rare instances, infection may develop at the site of the needle insertion.

Social-Economic Risks
There is a very small chance that information from your health records could be incorrectly released. All possible methods will be used to protect your privacy and ensure confidentiality. Unless you have given your specific permission, your _______ (doctor/institution) will not release your personal results or information to third parties such as employers or insurers.

In the case of injury or illness resulting from participating in this research, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

MAKING YOUR CHOICE
If you have any questions about the research involving blood or about this form, please talk to your doctor or nurse, or call the institution’s research review board at _________ (IRB’s phone number).

Please read each sentence below and think about your choice. After reading each sentence, circle “Yes” or “No”. No matter what you decide to do, it will not affect your care.

1. My blood may be used for the research in the current study.
   Yes                No

2. My blood may be kept for use in research to learn about, prevent, or treat cancer.
   Yes                No

3. My blood may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease).
   Yes                No

4. Someone from (doctor’s office/institution) may contact me in the future to ask me to take part in more research.
   Yes                No
**Participant statement:**
I have read and received a copy of this consent form. I have been given an opportunity discuss the information with my doctor/nurse, and all of my questions/concerns have been answered to my satisfaction. My answers above and my signature below indicate my voluntary participation in this research.

<table>
<thead>
<tr>
<th>Patient’s Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

**Witness statement:**
I have explained the information in this consent form to the patient and have answered any questions raised. I have witnessed the patient’s signature.

<table>
<thead>
<tr>
<th>Name of Person Obtaining Consent</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

0    Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1    Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2    Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3    Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4    Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
APPENDIX III

ANATOMICAL STAGING FOR LUNG CANCER

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 non-bloody 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).
**APPENDIX III (cont'd)**

**ANATOMICAL STAGING FOR LUNG CANCER**


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**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)*

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**STAGE GROUPING**

<table>
<thead>
<tr>
<th>Occult Carcinoma</th>
<th>T</th>
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</tr>
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<tr>
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<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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</table>
BLOOD COLLECTION KIT AND INSTRUCTIONS

The kit for serum, plasma, or buffy coat collection includes the following:
- Ten (10) 1ml cryovials
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)

INSTRUCTIONS for use of serum, plasma, or buffy coat collection kit:

Serum:
- Using four (4) or more 1ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “serum”.

Process:
- Allow one 5ml red top tube (or SST tube) to clot for 30 minutes at room temperature.
- Spin in a standard clinical centrifuge at ~2500 RPM at 4°Celsius for 10 minutes.
- Aliquot a minimum of 0.2-0.5 ml serum into each of the 1ml cryovials labeled with the RTOG study and case numbers, collection date and time, and clearly mark specimens as “serum”.
- Place cryovials into biohazard bag.
- Store serum at –80°Celsius until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma:
- Using three (3) or more 1ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “plasma”.

Process:
- After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
- Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4°Celsius for 10 minutes.
- If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
- Carefully pipette and aliquot a minimum of 0.2-0.5ml plasma into each of the 1ml cryovials labeled with the RTOG study and case numbers, collection date and time, and clearly mark specimens as “plasma”.
- Place cryovials into biohazard bag.
- Store plasma at a minimum –80°Celsius until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.
APPENDIX IV (Continued)

Buffy coat:
For a visual explanation of buffy coat, please refer to diagram below.

- Using one (1) or more 1ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) “buffy coat”.

Process:
- Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes.
- If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
- Carefully remove plasma close to the buffy coat and set plasma aside (can be used to send plasma samples – see above instructions).
- Remove the buffy coat cells carefully and place into the 1ml cryovials labeled “buffy coat” (it is okay if a few packed red cells are inadvertently collected in the process). Clearly mark the tubes with date and time of collection.
- Place cryovials into biohazard bag.
- Store buffy coat samples frozen until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Shipping/Mailing:
- Include all RTOG paperwork in pocket of biohazard bag.
- Ship specimens overnight Monday-Thursday. Avoid shipping on a weekend or around a holiday.
- Place frozen specimens and the absorbent shipping material in the Styrofoam cooler and fill with dry ice (if appropriate; double-check temperature sample shipping temperature). Ship ambient specimens in a separate envelope/cooler. Place Styrofoam coolers into outer cardboard box, and attach shipping label to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.

For questions regarding collection/shipping, contact the RTOG Tissue Bank:

(801) 408-5626 or (801) 408-2035
Fax (801) 408-5020
holly.goold@intermountainmail.org or justin.bryner@intermountainmail.org