RADIATION THERAPY ONCOLOGY GROUP

RTOG 98-01

A PHASE III STUDY OF AMIFOSTINE MUCOSAL PROTECTION FOR PATIENTS WITH FAVORABLE PROGNOSIS INOPERABLE STAGE II-IIIA/B NON-SMALL CELL LUNG CANCER (NSCLC) RECEIVING SEQUENTIAL INDUCTION AND CONCURRENT HYPERFRACTIONATED RADIOTHERAPY WITH PACLITAXEL AND CARBOPLATIN

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**AGE**

1. ≤ 70
2. > 70

Induction Paclitaxel/Carboplatin (q 3 wks for 2 cycles) followed by concurrent weekly P/C and HFX RT starting day 43 (69.6 Gy/6weeks/1.2 Gy bid) +/- Amifostine (A) 4X/week

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<th>Day</th>
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(P# = Paclitaxel 225 mg/m²/3hr I.V. on days 1, 22; 50 mg/m²/L.V./1 hr on days 43, 50, 57, 64, 71, 78*)
| C = Carboplatin AUC 6.0, days 1 & 22; AUC 2 on days 43, 50, 57, 64, 71, 78* |
| A = For patients randomized to amifostine arm only, amifostine 500 mg IV over 5 minutes prior to all PM treatments 4X/week (Mon-Thurs) see Section 7.4.8. |

**Note**: Cone-down volume is treated every Friday and the last 3 days of treatment.

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C | AAAA | AAAA | AAAA | AAAA | AAAA | AAAA | AAAA | AAAA |
A | XXXx | XXXx | XXXx | XXXx | XXXx | Xxxx | Xxxx | Xxxx |

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(R | XXXx | XXXx | XXXx | XXXx | XXXx | Xxxx | Xxxx | Xxxx |
PM | XXXx | XXXx | XXXx | XXXx | XXXx | X xxx | X xxx | X xxx |

(X | 1.2 Gy to initial volume) |
(x | 1.2 Gy to cone down volume)

*On days 43-78, chemotherapy will be administered prior to the PM radiation treatment.

**ELIGIBILITY** *(See Section 3.0 for details)*

- Medically inoperable stages II & IIIA or unresectable stages IIIA & IIIB non-small cell lung cancer.
- KPS ≥ 70, age ≥ 18
- Weight loss ≤ 5% in 3 months prior to diagnosis
- No distant metastasis, prior chemo- or thoracic or neck radiation therapy
- Serum creatinine ≤ 1.5, Hgb ≥ 8.0, absolute granulocyte count (AGC) ≥ 2000, platelets ≥ 100,000,
- Bilirubin ≤ 1.5 mg/dl; SGOT ≤ 1.5 x institutional upper limit
- No recurrent disease or prior complete tumor resection
- No prior invasive malignancy unless ≥ 3 years and currently disease-free
- Study-specific consent form
- Patients with pleural effusion *(on chest x-ray)* appearing only after thoracotomy or other invasive thoracic procedure are eligible
- Ineligible for RTOG 93-09 *(refer to Eligibility checklist [Q20] and Section 3.1.9)*

**Required Sample Size**: 244

**CASE CREDIT**: 2

1/8/99, 4/1/99, 9/28/01
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<tr>
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<th>Question</th>
<th>Answer</th>
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<td>1</td>
<td>Does the patient have histologic proof of non-small cell lung cancer documented by biopsy or cytology?</td>
<td>(Y)</td>
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<td>2</td>
<td>What is the patient's age?</td>
<td>(&gt;18)</td>
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<tr>
<td>3</td>
<td>What is the tumor stage?</td>
<td>(II-IIIB)</td>
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<tr>
<td>4</td>
<td>Has the patient had a weight loss of &gt; 5% in the 3 months prior to diagnosis?</td>
<td>(N)</td>
</tr>
<tr>
<td>5</td>
<td>Is there evidence of metastatic disease?</td>
<td>(N)</td>
</tr>
<tr>
<td>6</td>
<td>Prior total or subtotal surgical resection of the lung tumor?</td>
<td>(N)</td>
</tr>
<tr>
<td>7</td>
<td>Has the patient had any prior invasive malignancy within the past 3 years other than non-melanomatous skin cancer?</td>
<td>(N)</td>
</tr>
<tr>
<td>8</td>
<td>Has the patient received any prior chemotherapy or radiation to the thorax or neck?</td>
<td>(N)</td>
</tr>
<tr>
<td>9</td>
<td>Does the patient have a post-resection intrathoracic tumor recurrence?</td>
<td>(Y/N)</td>
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<tr>
<td>10</td>
<td>Is there evidence of pleural effusion on chest x-ray?</td>
<td>(Y/N)</td>
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<td>If yes, did it appear only after a thoracotomy or other invasive thoracic procedure was attempted?</td>
<td>(Y)</td>
</tr>
<tr>
<td>11</td>
<td>Has the patient had a myocardial infarction within the last 6 months or symptomatic heart disease, including angina, CHF or uncontrolled arrhythmia?</td>
<td>(&lt;1.5)</td>
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<td>12</td>
<td>Report the serum creatinine (mg/dl).</td>
<td>(≥8)</td>
</tr>
<tr>
<td>13</td>
<td>Report the hemoglobin (mg%).</td>
<td>(≥2000)</td>
</tr>
<tr>
<td>14</td>
<td>State the absolute granulocyte count (AGC).</td>
<td>(≥100)</td>
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<tr>
<td>15</td>
<td>Report the platelet count (x 1000).</td>
<td>(Y/N)</td>
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<td></td>
<td>Is the bilirubin ≤ 1.5 mg/dl and SGOT ≤ 1.5 times the institutional upper limits of normal?</td>
<td>(Y/N)</td>
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<td>If no, is the serum bilirubin and/or SGOT abnormality caused by documented benign disease?</td>
<td>(Y/NA)</td>
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<tr>
<td>17</td>
<td>If female, is the patient pregnant or lactating?</td>
<td>(Y/NA)</td>
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<tr>
<td>18</td>
<td>If the patient has reproductive capability, has the patient agreed to utilize effective contraception?</td>
<td>(Y/NA)</td>
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(cont’d on next page)
19. Reason for not entering this patient to RTOG 93-09?
   1. Does not meet eligibility criteria
   2. Deemed ineligible by thoracic surgeon
   3. Medically ineligible
   4. Patient refusal
   5. Institution not participating
   6. Other reason, specify ____________________________

20. What is the Karnofsky Performance Status?

The following questions will be asked at Study Registration:

1. Has the Eligibility Checklist (above) been completed?
2. Is the patient eligible for this study?
3. Date the study-specific Consent Form was signed? (must be prior to study entry)

____________________ Patient’s Name
____________________ Verifying Physician
____________________ Patient ID #
____________________ Referring Institution # (if different)
____________________ Stage (II vs. IIIA vs. IIIB)
____________________ KPS (90-100 vs. 70-80)
____________________ Age (≤70 vs. > 70)
____________________ Medical Oncologist
____________________ Birthdate
____________________ Sex
____________________ Race
____________________ Social Security Number
____________________ Zip Code (9 digit if available)
____________________ Method of Payment
____________________ Will any component of the patient’s care be given at a military or VA facility?
____________________ Treatment Start Date
____________________ Treatment Assignment

1.0 INTRODUCTION

1.1 Combined Chemoradiotherapy Regimens
Of at least 11 large published randomized trials comparing RT alone to RT and chemotherapy, six studies have demonstrated superiority of combined treatment. In the Cancer and Leukemia Group (CALGB) trial 84-33, 155 patients were randomized to two cycles of induction chemotherapy (vinblastine and cisplatin) prior to RT versus RT alone. In addition to a significant improvement in the median survival time from 9.6 months to 13.7 months, a recent update corroborated the long-term survival benefit at 5 years of 19% versus 7%, favoring the chemoradiotherapy arm \( (p = 0.01) \). RT0G 88-08 replicated CALGB 8433, randomizing patients to radiotherapy alone (60 Gy) or to induction chemotherapy with cisplatin plus vinblastine followed by standard radiotherapy; it also included a third randomized arm: hyperfractionated radiotherapy to a total dose of 69.6 Gy, which in phase II studies appeared promising. This study confirms a statistically significant improvement in median survival for the induction chemotherapy arm \( (13.7 \text{ months}) \) compared with radiotherapy alone \( (11.6 \text{ months}) \), with hyperfractionated radiotherapy demonstrating intermediate results. At 2 years of follow-up, combined-modality therapy produced a survival rate of 32%, compared with 25% for hyperfractionated radiotherapy and 19% for standard radiotherapy alone. At 3 years of follow-up, the survivals are 15%, 14%, and 9%, respectively. Although the study has not matured sufficiently to assess long-term survival, RT0G 88-08 has essentially confirmed the results of CALGB 8433, making induction therapy with cisplatin and vinblastine followed by standard radiotherapy the reference arm for subsequent phase III studies of locally advanced NSCLC in the RT0G. Another trial, the French Multicenter Trial CEBI 138, used a “sandwich” regimen of induction and post-RT chemotherapy (vindeisine, lomustine, cisplatin and cyclophosphamide). In this study, a 2-year survival advantage of 20% versus 12% \( (p = 0.02) \) favored the combined modality arm.

Rather than using induction chemotherapy, the trial by the European Organization Research in the Treatment of Cancer (EORTC 08844) compared radiotherapy alone to radiotherapy and concomitant cisplatin chemotherapy. This study demonstrated a significant survival advantage for low dose daily cisplatin/RT compared with weekly cisplatin/RT or RT alone \( (3-year \text{ survival rates of 32% versus 17% versus 14%, respectively}) \). A three-arm randomized study comparing hyperfractionated radiotherapy \( (1.2 \text{ Gy twice daily to a total dose of 64.8 Gy}) \) alone to a combination of hyperfractionated radiotherapy and carboplatin plus etoposide \( (\text{administered weekly or every other week}) \) generated median survival times of 8 months, 18 months, and 13 months, respectively, and 3-year survivals of 6.6%, 23% and 16%, respectively \( (p = 0.0027) \). Similarly, in another phase III study by Jeremic et al., the combination of hyperfractionated \( (\text{HFX}) \) RT and low-dose daily carboplatin plus VP-16 was superior to HFX RT alone to 69.6 Gy \( (\text{median survivals of 22 vs. 14 months and 4-year survivals of 23% vs. 9%, respectively, } p = 0.021) \).

A close analysis of these positive randomized trials favoring chemoradiation over radiation alone suggests a difference in the patterns of failure that relates to the method used to combine chemotherapy with thoracic RT. In the three trials employing induction chemotherapy (CALBG 84-33, CEBI 138, and RTOG 88-08), the improvement in survival rates over RT alone appear to be linked to a decrease in detectable distant metastases. In the CEBI 138 study, there was a reduction in the distant metastasis rate from 65% to 45% with the addition of chemotherapy \( (p < 0.001) \). In RTOG 88-08, the pattern of first failure showed that patients on the CT + RT arm had statistically significantly fewer distant metastases \( (\text{other than brain}) \) than patients on the RT alone arm \( (p = 0.04) \). These differences were most marked in patients with squamous cell histology \( (p = 0.0015) \). However, in the three studies employing concurrent chemoradiation, the survival advantage was associated with an improvement in local-regional control. In the EORTC study, which employed low dose daily cisplatin and concomitant thoracic RT, survival without local recurrence at 2 years was 30% for the chemoradiotherapy groups versus 19% for the radiotherapy only group. Similarly, in the context of HFX RT, concurrent chemotherapy improved local control rather than the rate of distant metastases. Jeremic et al. found that patients receiving HFX RT and daily concurrent chemotherapy had a significant improvement in local recurrence-free survival \( (42\% \text{ vs. } 19\% \text{ at 4 years, } p = 0.015) \), but not in distant metastasis-free survival \( (p = .33) \).

One hypothesis is that the simultaneous delivery of chemotherapy \( (\text{cisplatin or carboplatin}) \) with RT might be necessary to yield improvement in local tumor control. Such a construct fits well with the prior observations that platin-based chemotherapy can act as a radiosensitizer. The importance of
local failure, in addition to distant metastases, has been further highlighted by a recent patterns of failure analysis of RTOG chemo-radiation (CT/RT) trials demonstrating that persistent/recurrent local disease remains an important mode of failure.\textsuperscript{11}

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<th>Non-squamous</th>
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<td>Failure in primary tumor</td>
<td>34%</td>
<td>23%</td>
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<tr>
<td>Brain</td>
<td>8%</td>
<td>16%</td>
<td>0.017</td>
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<tr>
<td>Distant metastases (other than brain)</td>
<td>14%</td>
<td>26%</td>
<td>(&lt;0.001)</td>
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A recent phase III study has reported, for the first time, an advantage of concurrent vs. sequential chemoradiation. Furuse\textsuperscript{12} and colleagues from Osaka, Japan evaluated mitomycin, vindesine, and cisplatin (MVP) either concurrent with or prior to thoracic radiation, in unresectable stage III NSCLC. The doses of chemotherapy were identical in both arms and given over two cycles. In the sequential arm, after completion of MVP, TRT was administered to a total dose of 56 Gy. In the concurrent arm, split course TRT 2 Gy/Fx X 14 days followed by a 10 day rest, then more RT (another 28 Gy), was employed. The overall response rate was superior for concurrent therapy (84% vs. 66.4%) with a commensurate improvement in median survival (16.5 vs. 13.3 months) and in two and three year survival rates (37% vs. 26%; 27% vs. 12.5%, respectively). Similarly, in a phase II trial, RTOG 91-06, 76 patients were treated with hyperfractionated radiotherapy and concomitant cisplatin and oral etoposide.\textsuperscript{13} Preliminary results showed a one year survival rate of 67% and a median survival estimated at 19.7 months. This promising trial is being further evaluated as part of a three-arm phase III trial, RTOG 94-10. The other two arms evaluate the issue of chemotherapy-radiation sequencing. Two cycles of cisplatin and vinblastine are given as pre-RT induction therapy in the control arm and concurrently with RT in arm 2.

As high-dose induction chemotherapy has been associated with a decrease in distant metastases, while concurrent chemoradiation has improved loco-regional control, the current regimen will combine both of these strategies. RTOG has previously acquired its own experience with sequential induction and concurrent chemoradiation therapy regimens in NSCLC. In RTOG 88-04, a phase II trial was completed utilizing pre-irradiation Vinblastine (5 mg/m\textsuperscript{2} weekly X 5) and cisplatin (100 mg/m\textsuperscript{2} days 1 and 29 prior to radiation) and on days 50, 71 and 92 during radiation. The radiation began on day 50 and consisted of 63 Gy in 7 weeks. In general, the treatment regimen was tolerable. One hematologic death occurred. The majority of patients experienced grade 2 or greater hematologic toxicity, which required a reduction in the treatment dose. Despite this occurrence, 83% of patients received at least 4 courses of Vinblastine and 59% of the patients received at least 4 courses of cisplatin. Twenty-three of 29 patients received at least 95% of the prescribed dose of irradiation following cytotoxic chemotherapy. The median survival with a minimum follow-up of 12 months was 13.9 months. This represented an increase in the median survival of approximately 3-4 months compared to similar groups of patients in previously conducted RTOG trials. The results of RTOG 88-04 suggest that induction followed by concurrent chemoradiation is a promising treatment schema.\textsuperscript{14}

While we are awaiting the results of RTOG 94-10 to mature, the current study will build on the previous experience of the RTOG while incorporating novel chemotherapy (paclitaxel and carboplatin) which in phase II studies has been shown to be promising therapy (Section 1.2). Because hyperfractionated radiotherapy has been shown to be promising in the experience of RTOG\textsuperscript{4,13} as well as others\textsuperscript{5}, this regimen will employ hyperfractionated radiotherapy concomitant with chemotherapy in this setting. However, because this strategy has been associated with increased toxicity (particularly grade 3/4 esophagitis), this study will randomize patients to the radio-protector amifostine in order to determine the ability of this agent to reduce the toxicity associated with concurrent hyperfractionated radiotherapy and chemotherapy (see Sections 1.3 and 1.4). The basic outline of this regimen is as follows:

**Induction high-dose “systemic” paclitaxel (225 mg/m\textsuperscript{2}/3hr IV) and carboplatin (AUC 6.0) q 3 weeks X 2 cycles followed by weekly concurrent “radio-sensitizing” paclitaxel (50 mg/m\textsuperscript{2}/1hr**
Several other cooperative groups are also in the process of studying or proposing protocols involving chemoradiation with carboplatin and paclitaxel for locally advanced/unresectable NSCLC. In CALGB study 9534, patients with inoperable stage IIIA or IIIB NSCLC are treated with 2 cycles of induction paclitaxel (200 mg/m²/3 hrs IV) and carboplatin (AUC = 6) followed by concurrent chemoradiation (weekly paclitaxel 50 mg/m²/1 hr I.V. and carboplatin AUC = 2 and standard RT to 66 Gy). In the Hoosier Oncology Group (HOG) study, patients with stage III NSCLC are treated with 2 cycles of induction paclitaxel (225 mg/m²/3 hrs I.V.) and carboplatin (AUC = 6) followed by standard radiotherapy alone to 60 Gy. Patients without progression then receive another 2 cycles of post-radiation chemotherapy. The Eastern Cooperative Oncology Group (ECOG) has proposed a phase II randomized study in which patients receive 2 cycles of induction paclitaxel (225 mg/m²/3 hours I.V.) and carboplatin (AUC=6) followed by a randomization to either standard daily RT (64 Gy in 32 fractions) versus CHART radiotherapy (57.6 Gy in 36 fractions over 2.5 weeks). As well, the Southwest Oncology Group (SWOG) has proposed a study for patients with stage IIIB NSCLC with 2 cycles of induction paclitaxel (225 mg/m²/3 hours I.V.) and carboplatin (AUC=6) followed by concurrent chemoradiation with weekly paclitaxel (50 mg/m²) and carboplatin (AUC=2) with standard radiotherapy (60 Gy in 32 fractions over 6 weeks). The current study is unique for a number of reasons. First of all, it is the only regimen which employs hyperfractionated radiotherapy concurrently with paclitaxel and carboplatin. More importantly, this is the only study attempting to reduce the toxicity of such aggressive chemoradiation regimens by studying the role of amifostine. As treatment regimens become more and more aggressive, the risk of normal tissue injury, particularly esophagitis, also increases. The current study will not only attempt to improve the survival in patients with locally advanced NSCLC, but also focus on quality of life issues in an attempt to reduce the toxicity of the therapy and thereby improve quality-adjusted survival as well. (Sections 1.3 to 1.5)

1.2 Novel Chemotherapy and RT

The optimal chemotherapy regimen to combine with radiotherapy in patients with locally advanced disease is not known at this time. In a recent five arm ECOG study of multiple cisplatin analogs in combinations, initial therapy with carboplatin produced the best long-term survival with a p value of < 0.0115 and the least grade 4 toxicity. Moreover, with the exception of myelosuppression, carboplatin yields significantly less non-hematologic toxicity compared with cisplatin. Paclitaxel-based platinol combinations have proven superior to other regimens in advanced NSCLC (Giaccone). In an ECOG trial, for patients with advanced, previously untreated NSCLC, paclitaxel by 24 hour infusion was the most active single agent, with a response rate of 25%,16 and a one-year survival rate of 41%. This finding was corroborated by an MD Anderson study that reported a major response rate of 24%.17 A number of investigators have demonstrated comparable activity and survival for 3-hour paclitaxel infusion in advanced NSCLC.18,19 (Table 1). In a phase II study at Fox Chase Cancer Center and its network affiliates (FCCC 93024) in 54 patients with metastatic and recurrent NSCLC, carboplatin at a dose based on a targeted AUC of 7.5 and escalating doses of paclitaxel (135 mg/m² - 215 mg/m²) yielded response rates of 62%, a 1-year survival rate of 54%, and a 2-year survival rate of 15%. At a median potential follow-up of two years, the median response duration was 6 months and the median survival time was 12.5 months.20 Other investigators have generated similar results (Table 2).

Table 1. Activity and Survival for 3-hour paclitaxel infusion in NSCLC

IV) and carboplatin (AUC 2) with hyperfractionated radiotherapy (1.2 Gy BID to 69.6 Gy) with a randomization to +/- amifostine (1/8/99).

While the primary objective of this study will be to assess the protective effect of amifostine in this intense regimen known to be associated with high rates of Grade 3/4 esophagitis, this regimen also builds on the prior conceptual framework of the RTOG and incorporates novel chemotherapy to create a timely regimen that will be important when the results of RTOG 94-10 become available.
<table>
<thead>
<tr>
<th>Study (1st Author)</th>
<th>Dose (mg/m²)</th>
<th>Duration (hr)</th>
<th>N</th>
<th>OR</th>
<th>1 Y OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG (Chang)</td>
<td>250</td>
<td>24</td>
<td>24</td>
<td>23%</td>
<td>40</td>
</tr>
<tr>
<td>MDA (Murphy)</td>
<td>200</td>
<td>24</td>
<td>24</td>
<td>24%</td>
<td>38.5</td>
</tr>
<tr>
<td>Gatzemeier</td>
<td>225</td>
<td>3</td>
<td>43</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>AEMC (Tester)</td>
<td>200</td>
<td>3</td>
<td>20</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>CANNON (Greco)</td>
<td>135→200</td>
<td>1</td>
<td>56</td>
<td>26%</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Taxol and CBDCA combination for the treatment of NSCLC

<table>
<thead>
<tr>
<th>Study (1st Author)</th>
<th>Phase</th>
<th>Taxol*</th>
<th>Duration (hr) (interval [wk])</th>
<th>CBDCA</th>
<th>G-CSF</th>
<th>N (@MTD)</th>
<th>RR (%) at MTD</th>
<th>MS (wk)</th>
<th>1 YS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCCC (Langer)</td>
<td>II</td>
<td>135→225</td>
<td>24 (3)</td>
<td>AUC 7.5</td>
<td>+</td>
<td>54</td>
<td>62%</td>
<td>54</td>
<td>54%</td>
</tr>
<tr>
<td>Vanderbilt (Johnon)</td>
<td>I/II</td>
<td>135→175</td>
<td>24 (4)</td>
<td>300/m²</td>
<td>–</td>
<td>51 (23)</td>
<td>39%</td>
<td>38</td>
<td>41%</td>
</tr>
<tr>
<td>Maryland (Belani)</td>
<td>I/II</td>
<td>135→200</td>
<td>24 (3)</td>
<td>AUC 5→7→9→11</td>
<td>(±)</td>
<td>30 (16)</td>
<td>56%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Maximal tolerated doses are italic.
** Intrapatient dose toleration (other studies escalated doses across separate patient cohorts).

CBDCA, carboplatin; GS-CSF, granulocyte colony-stimulating factor; N, total number; @MTD, number treated at MTD; MTD, maximally tolerated dose; RR, response rate; MS, median survival; 1YS, 1 year survival rate; +, yes; -, no; AUC, area under the concentration time curve.

More recently, Fox Chase Cancer Center and other centers, have accumulated considerable experience using carboplatin and paclitaxel with radiotherapy in patients with good prognosis locally advanced non-small cell lung cancer. At FCCC, induction therapy consisted of 2 cycles of paclitaxel (175-225 mg/m²/3 hrs) and carboplatin (targeted AUC of 7.5) on days 1 and 22 with G-CSF support. On day 43, thoracic radiotherapy (60 Gy/30 Fx/5 d q wk) was initiated with escalating doses of paclitaxel and carboplatin in the absence of hematopoietic growth factors. Initially, patients received carboplatin (targeted AUC 3.75) and paclitaxel (67.5 mg/m²/3 hrs) on days 43 and 64 during radiotherapy. In the absence of dose-limiting toxicity, a phase I escalation in 3-patient cohorts during RT proceeded to maximum doses (thus far) of carboplatin (AUC of 5.0) and paclitaxel (175 mg/m²). So far, 37 patients (78% stage IIIB) have received induction therapy. Three are too early to evaluate and 34 are evaluable for response. Myelosuppression and neurosensory toxicity have been mild during induction treatment prompting a paclitaxel dose increase to 225 mg/m² on days 1 and 22 after the first 7 patients were accrued.

Seventeen patients have received concurrent thoracic radiation and chemotherapy, 15 of whom are evaluable for response and toxicity. There has been one episode each of grade 4 granulocytopenia and grade 3 anemia. Severity of esophagitis has corresponded to length of the esophagus in the radiation treatment field: grade 1 in 5 of 6 patients with esophageal exposure ≤ 16 cm; grade ≥ 2 in 8 of 9 patients with length of esophagus irradiated ≥ 16 cm. There have been only 2 of 15 evaluable patients with grade 3 esophagitis (13%), neither at the top chemo doses obtained. Five episodes of grade ≥ 2 steroid-responsive pulmonary toxicity have occurred 2-6 months after conclusion of the thoracic radiation and chemotherapy. The major response rate to induction therapy is 39%, and to combined modality 59%. The 1-year survival rate of the first 21 patients accrued is 62%, and the
median survival to date for those patients formally enrolled on the phase I chemo-radiation dose escalation study is 17 months.\textsuperscript{24}

In another study by Belani et al.\textsuperscript{25} employing weekly paclitaxel (45 mg/m\(^2\)/3hr infusion) and carboplatin (100 mg/m\(^2\)) with simultaneous thoracic RT (60-65 Gy) in locally advanced NSCLC, the 3 year actuarial survival rate is 54\% (95 CI 35-70\%). Similarly, Choy et al. reported excellent response rates with regimens involving weekly paclitaxel and carboplatin with concurrent thoracic RT. In one study, Choy et al. delivered paclitaxel (50 mg/m\(^2\)/1hr) plus carboplatin (AUC 2) weekly with standard radiotherapy (66 Gy in 2 Gy fractions) followed by two cycles of chemotherapy. They reported an excellent response rate of 77\% with this regimen. Using the same chemotherapy regimen (weekly paclitaxel/carboplatin), but this time with hyperfractionated radiotherapy (1.2 Gy BID to 69.6 Gy), Choy et al. similarly found an excellent response rate (79\%), and an estimated 1 year survival rate of 63\% (Hak Choy, personal communication). These studies indicate that chemoradiation with paclitaxel and carboplatin is active in locally advanced NSCLC, and merits further exploration.

1.3 Reducing the Toxic Effects of Therapy on Normal Tissue

While concomitant delivery of chemotherapy and thoracic radiotherapy appear to have a synergistic effect on tumor control, there are also potential disadvantages to such a strategy. As treatment regimens become more and more aggressive, the risk of normal tissue injury also increases, potentially resulting in treatment breaks or dose reductions that may limit the success of therapy. Cox et al.\textsuperscript{26} reviewed data from three RTOG randomized trials to determine if prolonged treatment time adversely affected outcome for patients with inoperable NSCLC. The investigators found that for “favorable” patients (i.e., high Karnofsky performance status, little weight loss, and less than N3 nodal disease), interruptions in the completion of the planned radiotherapy reduced survival. Although the analysis of overall treatment time is confounded by other factors, such as performance status, tumor burden, and total radiotherapy dose, the consensus opinion is that the outcome is optimized by maintaining the shortest treatment time feasible.

The toxic effects of greatest concern from thoracic radiotherapy are acute esophageal toxicity and subacute or late lung toxicity. In RTOG 91-06, in which patients received hyperfractionated radiotherapy and concomitant chemotherapy with cisplatin and oral etoposide, the risk of grade 3 or higher esophageal injury was 53\% and late lung toxicity (grade 3) was 18\% (3\% grade 5).\textsuperscript{27} Similarly, in the context of concurrent weekly paclitaxel (50 mg/m\(^2\)/1 hr) and carboplatin (AUC 2) and concomitant hyperfractionated radiotherapy (1.2 Gy BID to 69.6 Gy), Choy et al. found an RTOG Grade 3-4 esophagitis rate of 26\% and a Grade 3-4 pulmonary toxicity rate of 16\% (Hak Choy, personal communication). Of note, the corresponding rate of esophageal injury for induction cisplatin plus vinblastine followed by radiotherapy in RTOG 88-08 was only 1\%.\textsuperscript{4}

Recently, Scott et al. performed a quality adjusted survival analysis of the Radiation Therapy Oncology Group (RTOG) chemoradiation lung studies.\textsuperscript{28} This analysis included patients with locally advanced NSCLC who were treated on various phase II or III RTOG studies employing either standard RT alone (SRT), hyperfractionated RT to 69.6 Gy (HRT), induction chemotherapy (ICT) of cisplatin and vinblastine followed by SRT, ICT plus concurrent CT (CCT) and SRT, or CCT plus HRT. Quality adjusted survival was calculated by weighting the time spent with a specific toxicity, or local or distant tumor progression. Although patients receiving concomitant chemoradiation (ICT plus CCT and SRT or CCT plus HRT) had the best overall survival, patients receiving induction chemotherapy (ICT plus SRT) had nearly equivalent Q-Time (quality adjusted time) survival. For example, patients receiving CCT plus HRT (with etoposide or vinblastine plus cisplatin) had a median survival time (MST) of 15.8 months, exceeding the MST of the induction regimen by more than 2 months. However, the median quality adjusted time (Q-Time) in the concurrent chemoradiation study reduced to 13.7 months, essentially the same as that in the induction chemotherapy plus radiation arm (13.2 months). This analysis suggests that while the concurrent chemoradiation may have increased overall survival, this apparent benefit came at the price of increased toxicity that adversely affected the quality of the survival increment. In a subsequent analysis, Mowsas et al. found that reduction in
esophageal, lung and upper GI toxicities led to the greatest improvement of Q-Time. Thus, if one can reduce the toxicity of the more intense (concurrent) regimen, one may be able to improve not only the median survival time, but also the quality adjusted survival time (Q-Time). This analysis underlies the rationale to employ the radioprotector, amifostine, to attempt to reduce the high rate of esophagitis encountered in the promising, yet toxic weekly concurrent chemoradiation regimens with paclitaxel and carboplatin.

1.4 Amifostine (4/1/99)

Amifostine (Ethyol; WR-2721), is an organic thiophosphate which was selected from over 4400 compounds screened by the U.S. Army as the best radioprotective compound. It has been shown to protect experimental animals from lethal doses of radiation. Amifostine is a product that is dephosphorylated at the tissue site to its active metabolite (WR-1065) by alkaline phosphatase. Differences in the alkaline phosphatase concentration of normal versus tumor tissues result in greater conversion of amifostine to WR-1065 in normal tissues. Similarly, differences in the pH of normal versus tumor tissues lead to preferential uptake of WR-1065 by normal tissues. Once inside the cell, WR-1065, the free thiol, acts as a potent scavenger of the oxygen free radicals induced by ionizing radiation and also provides an alternative target to DNA and RNA for the reactive molecules of alkylating or platinum agents. The normal tissues which are reported to be protected from radiation toxicity include bone marrow, skin, oral mucosa, esophagus, kidney, and testes. Thus, these preclinical data provide the rationale for amifostine’s ability to improve the therapeutic index for radiotherapy in the clinical setting.

There have been several studies of amifostine as a radioprotectant. A randomized trial for patients with inoperable or recurrent rectal cancer conducted in China showed protection against the moderate or severe acute and late radiation toxicities (p=0.026) in the pelvis, with amifostine administered daily (340 mg/m²) prior to each radiation dose. At the same time, there was no evidence of tumor protection, with the median survival for the amifostine plus RT group of 15.0 months versus 12.3 months for the RT alone group.

Clinical trials of amifostine have demonstrated that this agent can provide protection from cisplatin-induced nephrotoxicity in patients with ovarian and lung carcinoma. In addition, the results of studies performed to date support a role for amifostine in protection against the hematologic toxicities seen with cyclophosphamide, carboplatin, and mitomycin C, as well as against the neurologic and otologic toxicity seen with cisplatin.

A promising venue is the investigation of amifostine’s role in combined chemoradiation regimens, which, as discussed above, are associated with enhanced toxicity to the normal tissues, particularly acute esophagitis. The optimal schedule of amifostine administration during combined chemoradiation regimens has not been established. In a German study reported by Buntzel et al., 28 patients with squamous cell carcinomas of the head and neck, treated with a combination of radiation therapy (daily to 60.0 Gy) and concurrent carboplatin (70 mg/m² days 1-5 and days 21-25) were randomized to receive either amifostine (500 mg prior to each carboplatin dose), or placebo. Toxicities graded by WHO score were significantly reduced with amifostine, including a significant decrease in dysphagia (5 Grade 3 and 9 Grade 2 dysphagia in placebo group versus 1 Grade 3, 7 Grade 2 and 6 Grade 1 in the amifostine group; p=0.005), as well as significant decreases in the hematologic toxicity and mucositis (p=0.002 and <0.001, respectively). The rationale for amifostine use in the current study is to demonstrate its efficacy in reducing esophagitis, which occurs in a high percentage of patients treated with aggressive concurrent chemotherapy and hyperfractionated thoracic irradiation.

The amifostine dose/scheduling employed in the current study is a modified version of Buntzel et al.’s approach. A flat dose of 500 mg has been chosen as having the advantage of simple dosing (one vial), a proven record of efficacy in a randomized trial (Buntzel), as well as less toxicity than higher doses (decreased nausea or vomiting; blood pressure drop of 20 mm Hg in only 2/25 patients, not requiring interruption or discontinuation of infusion). The dosing of amifostine has been modified here to suit a different chemoradiation schedule. Amifostine will precede each administration of
concurrent carboplatin/paclitaxel/RT, but will also be given three more times per week, before the afternoon RT fractions, for a total of four infusions weekly (Monday - Thursday). As amifostine will not be administered on Fridays, the smaller cone down field will be treated on each Friday (to minimize the length of esophagus treated on days without amifostine). Thus, a total of 40% of all RT fractions will be "protected" by amifostine. This is higher than in Buntzel's study, where 33% of all RT fractions were preceded by amifostine. Since paclitaxel infusion will last 1 hour in the concurrent portion of the treatment regimen, enough time will be provided between amifostine administration and the delivery of RT, assuring selectivity of cytoprotection.

Recently, pilot data became available from Thomas Jefferson University Hospital (Maria Werner-Wasik, personal communication). In a phase II study, 22 patients with locally advanced non-small cell lung cancer were treated with two cycles of induction chemotherapy with carboplatin (AUC 6) and paclitaxel (225 mg/m²) every 3 weeks, followed by concurrent standard thoracic irradiation to 62.4 Gy, with weekly paclitaxel (60 mg/m²). Since a high rate of Grade 3 esophagitis was noted in first 11 patients, amifostine, 500 mg i.v. twice weekly was added to the regimen. The incidence of Grade 3 esophagitis was 18% in the initial 11 patients versus 0% in the amifostine-treated pts (p=0.03, for distribution of maximum grade). Those results suggest that amifostine reduces severe esophagitis resulting from concurrent chemotherapy with weekly paclitaxel and thoracic irradiation. The current phase III study will be able to answer this important question in a randomized fashion in a cooperative group setting.

Before amifostine can be applied widely in combined modality regimens, it is important to establish that no adverse interactions exist between it and the cytotoxic agents.

Theoretically, drug interactions between amifostine and chemotherapeutic agents are not likely to occur, due to amifostine’s rapid clearance from plasma (90% of the drug is cleared within 6 minutes). The effect of amifostine on the pharmacokinetics of cisplatin (120 mg/m²) has been investigated, and no decrease in cisplatin’s pharmacokinetic parameters was observed. However, a recent abstract reported that paclitaxel's area under the curve was decreased by 29% in 10 tested patients, in whom the 3 hour infusion of paclitaxel was preceded by a 15 minute infusion of amifostine (910 mg/m²). Whether this leads to higher tissue distribution of the lipophilic drug remains unknown. On the other hand, animal experiments with ovarian carcinoma xenografts, in which mice were administered paclitaxel with or without amifostine (200 mg/kg ip), demonstrated the same tumor growth delay and survival rates whether or not the mice received amifostine. This argues against a clinically significant interaction between paclitaxel and amifostine. In both in vitro and in vivo animal models, amifostine did not interfere with paclitaxel anti-tumor activity even after prolonged exposure (24 hours) to high concentrations. Rather, the cytotoxicity of paclitaxel against human tumor cell lines may be actually increased by pretreatment with amifostine.

Amifostine has been administered prior to chemotherapy or radiotherapy in over 1000 patients in the clinical studies sponsored by the National Cancer Institute or US Bioscience. There have been no treatment-related deaths or life-threatening toxicities associated with the administration of amifostine at doses of up to 1300 mg/m².

1.5 Quality of Life

Quality of Life (QOL) is a critical outcome for this study. We hypothesize that amifostine will positively affect patient's overall assessment of QOL during and after treatment.

A multidimensional core questionnaire addressing physical, emotional and social functioning and global quality of life, the QLQ-30 (version 3), and a lung cancer-specific symptom module, the QLQ-LC-13, developed and refined by the European Organization for Research and Treatment of Cancer (EORTC) study group on quality of life are proposed as the measures of QOL, for this project. The current core survey, modified from previous questionnaires, includes a patient rated 30-item self-report covering a range of health-related QOL domains developed specifically for use in cancer clinical trials. An advantage of this instrument over other QOL tools is that it addresses therapy-related side effects. Questions related to physical functioning (5 items), role functioning (2 items),...
emotional functioning (4 items), cognitive functioning (2 items), social functioning (2 items), and pain (2 items) are rated on a 4-point Likert type scale as 1 (not at all) to 4 (very much). The presence and absence of dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact also are rated on a 4-point scale. Lower scores indicate better quality of life and less symptoms. Two additional questions, overall physical health and QOL within the past week are rated on a numerical analogue scale from 1 (very poor) to 7 (excellent), thus higher scores in these items indicate better quality of life for these two items. Subscale scores of the QLQ-30 as well as individual items are available for analysis.

The 13-item lung cancer module, EORTC QLQ-LC-13, accompanies the core survey. It includes an assessment of important relevant symptoms of lung cancer experienced during the previous week: cough (1 item), hemoptysis (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 has a 4-point response (1, “not at all” to 4, “very much”). Higher scores indicate more problems. Scores on individual items are available for this analysis. Of importance to this study, the item “trouble swallowing” will be able to be analyzed as an individual item. As the primary endpoint in this study is the rate of esophagitis, a patient swallowing diary and physicians’ dysphagia log have also been included.

The EORTC QLQ-30 has undergone extensive international testing in many cultures and in 17 languages.54 Both the QLQ-30 (version 3) and the QLQ-LC-13 have proven validity and reliability.52-56 The QLQ-LC-13 testing has been specifically evaluated in patients with unresectable lung cancer (2/3 of 305 with non-small cell lung cancer, 52% receiving radiation therapy) pre and during treatment.53 The version 2 of the QLQ-30 was recently substantially improved from previous versions according to recent testing of 1,181 patients over three points in time.52 Internal consistency with alpha’s ranging from .78-.88 for role function to .89 and .81 -.92 for the global QOL scale. The QLQ-LC-13 pain subscale has not been reliable and analysis of individual items rather than the scale is recommended. The QLQ-30 has been used to assess QOL over a course of palliative radiotherapy treatment (32% of 247 with lung cancer) and was found to be easy to use and responsive to treatment benefits.55 Of importance for this study, the QLQ-30 and QLQ-LC-13 have proven ability to detect significant changes over time and discriminate between patients by performance status, presence of weight loss, and by treatment toxicity and response to treatment.53,55

The average time to complete both the EORTC-30 and the QLQ-LC-13 is 11-12 minutes. The frequency of assessment during this study are projected to capture QOL prior to, during and post-treatment for both arms.

On-going tobacco use during radiation therapy has been associated with increased morbidity and can be an important cofounder of clinical outcomes.57-61 Both tobacco and alcohol use may increase the toxicity of esophagitis and impact the benefit of the mucosal protection of amifostine. A self-report survey will thus assess tobacco and alcohol history.

2.0 OBJECTIVES

2.1 **Primary**: To evaluate whether the addition of the radioprotector amifostine can reduce the incidence and severity of non-hematologic toxicity, specifically esophagitis and pneumonitis during concurrent hyperfractionated RT and chemotherapy (with paclitaxel and carboplatin).

2.2 **Secondary**: To evaluate the differences in quality of life (QOL) and symptom distress (especially dysphagia) between the two groups using the EORTC-QLQ-30 and QLQ-LC-13 forms.

2.3 **Secondary**: To evaluate the relationship of tobacco use and alcohol use during treatment to appraisals of QOL and symptom distress, specifically esophagitis in the two groups.

2.4 **Secondary**: To evaluate the efficacy of induction therapy with paclitaxel and carboplatin (q 3 weeks X 2) followed by concurrent CT/RT using weekly Paclitaxel/Carboplatin with hyperfractionated radiation.
3.0 **PATIENT SELECTION**

3.1 **ELIGIBILITY**

3.1.1 Patients with unresected loco-regionally advanced non-small cell lung cancer without evidence of hematogenous metastases, Stages II, IIIA, or IIIB *(See Appendix III)*.

3.1.2 **Age ≥ 18.**

3.1.3 Karnofsky performance status ≥ 70 *(Appendix II)*.

3.1.4 Weight loss < 5% in three months prior to diagnosis.

3.1.5 No pleural effusion on CXR unless it appeared only after a thoracotomy or other invasive thoracic procedure was attempted.

3.1.6 Serum creatinine ≤ 1.5 mg/dl, hemoglobin ≥ 8.0 gm%, absolute granulocyte count ≥ 2000/ul, platelets ≥ 100,000/ul.

3.1.7 Serum bilirubin ≤ 1.5 mg/dl; SGOT must be ≤ 1.5 times the institutional upper limits of normal unless the abnormality is caused by documented benign disease.

3.1.8 Patients must sign a study-specific consent form prior to randomization.

3.1.9 Patients cannot be eligible for RTOG 93-09 *(confirmed N2 involvement)*. At institutions participating in RTOG 93-09, patients with clinical or pathologic stage IIIA (N2) disease must either a) have been evaluated by a thoracic surgeon and deemed ineligible for 93-09, b) must be medically ineligible for 93-09, or c) must have refused participation in RTOG 93-09.

3.2 **Conditions for Patient Ineligibility**

3.2.1 Evidence of small cell histology.

3.2.2 Stage I or stage IV non-small cell cancer.

3.2.3 Patients who have undergone complete *(or subtotal)* tumor resection.

3.2.4 Patients with post-resection intrathoracic tumor recurrence.

3.2.5 Patients with a synchronous *(except for non-melanomatous skin cancer)* or prior invasive malignancy, unless disease-free for ≥ 3 years.

3.2.6 Patients with prior chemotherapy or thoracic or neck RT.

3.2.7 Patients with myocardial infarction within the preceding six months or symptomatic heart disease, including angina, congestive heart failure, uncontrolled arrhythmias.

3.2.8 Pregnant women are ineligible as the treatment involves unforeseeable risks to the participant and to the embryo or fetus. Patients with childbearing potential must practice appropriate contraception.

4.0 **PRETREATMENT EVALUATIONS**

4.1 A complete medical history & physical examination to include Karnofsky performance status, neurologic assessment, recent weight loss, usual weight, concurrent non-malignant disease and therapy.

4.2 CBC with differential, platelet count, SMA-12, electrolytes and Mg++ *within 14 days* prior to randomization.

4.2.1 SMA-12: Total protein, Albumin, Calcium, Glucose, BUN, Creatinine, Alkaline Phosphatase, LDH, Total Bilirubin, SGOT and SGPT *within 14 days* prior to randomization.

4.3 Chest x-ray; CT scan of the chest, liver, and adrenal glands *within 4 weeks* prior to randomization.

4.4 CT scan or MRI of the brain and radionuclide bone scan *within 6 weeks* prior to randomization.

4.5 EKG and pulmonary function tests including FVC, FEV-1 and DLCO *(within 2 months prior to randomization)*.

4.6 Location, type, and size of measurable lesion prior to treatment must be recorded.

4.7 Pregnancy test as applicable *(within 14 days)* prior to randomization.

4.8 Baseline QOL assessment with the EORTC QLQ-C30 and QLQ-LC-13 prior to start of treatment.

4.8.1 Request forms pack from HQ in advance.

4.9 Smoking history and current smoking assessment; alcohol history and current use assessment.

4.10 Physician's Dysphagia Log and Patient Swallowing Diary.

5.0 **REGISTRATION PROCEDURES**

5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered *prior* to any protocol therapy by calling RTOG headquarters at *(215)* 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a
treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:
- Institution Name & Number
- Patient’s Name & ID Number
- Verifying Physician’s Name
- Medical Oncologist’s Name
- Eligibility Criteria Information
- Stratification Information
- Demographic Data
- Treatment Start Date

### RADIATION THERAPY

#### 6.1 Radiation Dose (1/8/99, 4/1/99)

**6.1.1 Radiation Therapy** Radiation therapy will commence on day 43 of the chemotherapy dose schedule. Total dose to the involved areas will be 69.6 Gy. This will be administered at 1.2 Gy twice daily at least 5 hours apart (time of each treatment to be recorded in daily treatment record) 5 days a week. A total of 42 fractions (of 50.4 Gy) will be delivered to the primary and mediastinum plus a boost to the primary and involved nodes (and nodes measuring > 2 cm) of 19.2 Gy in 16 fractions. It is important to note that the cone-down volume is to be treated every Friday (on days without amifostine) in both arms, as well as the last 3 treatments. In this way, less of the esophagus will be treated with radiation on the days without amifostine. For this reason, the radiation therapy simulation and planning for the large fields and the cone-down fields must be done from the beginning of the radiation treatments. The total dose will be 69.6 Gy in 58 fractions in 29 treatment days in 6 weeks.

**6.1.2 Cord Dose** The initial treatment volume must be treated with fields that keep the maximum spinal cord dose ≤ 48 Gy. This typically involves a field arrangement sparing the spinal cord beginning at approximately 40.8 Gy (34 fractions). (4/1/99)

When the prescribed dose to the initial AP-PA large (CTV) fields (which are treated on Monday through Thursday) is completed (e.g., at approximately 40.8 Gy), the remainder of the Monday through Thursday treatments will be delivered to the off-cord CTV (large) fields (to bring the dose up to 50.4 Gy). Only on the last 3 days of treatment will the small off-cord GTV (cone down) fields be utilized (on Tuesday through Thursday). This off-cord GTV field will be the only field utilized on Fridays. Please review this scheduling with your dosimetrists and therapists who will be administering treatment to the patient. If the incorrect field is treated on a particular day, this will represent only a minor protocol deviation as long as the total doses to the proper fields are correct (50.4 Gy to the CTV and 19.2 Gy to the GTV). As always, document the field number that is treated on each day. If there are any questions, please call either Dr. Movsas, or in his absence, Dr. Werner-Wasik.

#### 6.2 Treatment Techniques

**6.2.1 All doses are to be prescribed and calculated assuming a homogeneous patient, that is there will be no heterogeneity corrections used in the definitions of these doses.** The doses shall be prescribed and calculated according to the following ICRU recommendations for external beam treatment, using photons and electrons.

**6.2.1.1 At the center of the target area on the central ray for a single beam.**

**6.2.1.2 At mid-separation on the central ray for two opposed coaxial equally weighted beams.**

**6.2.1.3 At the center of the target area on the central ray for two opposed coaxial unequally weighted beams.**

**6.2.1.4 At the point of intersection of the central rays for two or more intersecting beams which are not coaxial.**

**6.2.1.5 At the center of the rotation in the plane of rotation containing the central axis of rotation for arc therapy.**

**6.2.1.6 At the center of the target area for complex treatment arrangements which are not covered above.**

**6.2.1.7 At the depth of maximum dose for a single electron beam with electron beam energy chosen such that the depth of the distal 90% depth dose is at 3 cm depth.**

#### 6.3 Target Volumes (4/1/99)
6.3.1 Two distinct target volumes shall be considered. The initial large field target volume includes the known extent of primary tumor and nodal involvement as well as the nodal region(s) receiving elective nodal RT (see below). The boost target volume includes the known extent of the primary, pathologically involved nodes, and nodes ≥ 2.0 cm in diameter only. A minimum 2.0 cm margin and a maximum 2.5 margin should be maintained on clinical and radiologic tumor involvement in both treatment volumes. In treating these volumes, various sets of fields may be used.

6.3.2 In all regimens, no part of the primary lesion and ipsilateral hilar and mediastinal lymph nodes (within a 2 cm margin) will receive a dose less than 50.4 Gy from the initial large fields. In cases where the central rays of the large fields do not coincide the center of the boost target volume, it will be necessary to calculate the contribution from the initial sets of fields to the center of the boost target volume. The maximum dose in any part of either target volume should not exceed the prescribed dose more than 9%.

6.3.3 Deviations of the daily dose of up to 5% are allowed. In patients where the difference in dose between the initial large field target volume and boost target volume is such that a 5% change in the boost dose would not result in the proper final dose being delivered by the prescribed number of fractions, then additional fraction(s) can be added to reach the prescribed total dose. This patient could then receive one extra fraction of 1.2 Gy to the boost field.

6.4 **Irradiation Portals**

The irradiation target volume must be defined by the individual shaped ports with secondary lead blocking or tailor-made blocks.

6.4.1 **Target Volume of Primary Tumor**

6.4.1.1 Includes complete extent of visible primary tumor as defined radiographically with a minimum of 2 cm and the maximum of 2.5 cm around the mass. The extent of tumor prior to induction chemotherapy should be used to define the RT treatment volume with two exceptions: 1) in the case of primary tumor or nodal progression during chemotherapy, the extent of disease at day 43 should define the treatment volume. 2) if post-obstructive atelectasis is present at initial presentation and a chemotherapy-induced response results in better tumor/uninvolved lung definition, then this information should be used to define the RT treatment volume.

6.4.1.2 The entire lung may be included for extensive lesions if complicated by atelectasis or pneumonitis.

6.4.2 **Regional Nodal RT (1/8/99)**

The following lymph node regions must be included even in the absence of clinical or radiological involvement (to 50.4 Gy).

6.4.2.1 Supraclavicular lymph nodes - if primary is in upper lobes and main stem bronchus lesions. It is acceptable to treat the ipsilateral supraclavicular nodes only.

6.4.2.2 Ipsilateral hilar lymph nodes - always (2 cm margin)

6.4.2.3 Superior mediastinal lymph nodes (above carina) - always (ipsilateral 2 cm margin).

6.4.2.4 Subcarinal lymph nodes (include the contralateral main stem bronchus and extend field at least to 5 cm below the carina) - always.

6.4.2.5 Inferior mediastinal nodes to the diaphragm (to bottom of T10) for patients with lower lobe lesions or inferior mediastinal involvement.

6.4.2.6 Contralateral hilar lymph nodes - for patients with contralateral mediastinal, subcarinal, or contralateral hilar involvement - (1 cm margin).

6.5 **Technical Factors**

6.5.1 **Beam Energy**

Megavoltage equipment is required with minimum peak photon energies of 6 MeV. Electrons with at least 90% dose at 3 cm depth may be used to boost supraclavicular lymph nodes and should be specified to Dmax.

6.5.2 **Treatment Distance**

Minimal treatment distance to skin should be ≥ 100 cm for SSD technique and minimum isocenter distance should be 100 cm for SAD techniques.

6.5.3 **Blocking**

In the case of x-ray beams, the primary collimation may be used, and blocking will be required only for shaping of the ports to exclude volume of tissues that are not to be irradiated.

6.5.4 **Compensating Filters or Wedges**
In the case of a large sloping contour, such as usually encountered when treating upper lobe tumors in large patients, compensating filters are recommended. A wedge may also be used as a 2 dimensional tissue compensator. If necessary, appropriate reduction in field size must be done to avoid excessive irradiation to critical structures.

6.5.5 Fractionation (9/28/01)
Each field is to be treated every session. There should be at least 5 hours between daily fractions (actual time to be recorded in daily record. Adherence to the fractionation schemes is required although slight deviations in the daily dose fraction are allowed (± 5%).

6.5.6 Therapy Interruptions
6.5.6.1 If interruptions of therapy up to one week become necessary, irradiation should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported.

6.5.6.2 If more than one week interruption is required, resumption of the treatment is at the discretion of the radiation oncologist.

6.5.6.3 Radiotherapy interruptions or delays will be permitted only for febrile neutropenia or grade ≥ 3 esophagitis/mucositis. Interruptions longer than 3 days should be discussed with Dr. Movsas, or, in his absence, Dr. Werner-Wasik.

6.5.6.4 If neutropenic fever occurs and radiation is withheld, G-CSF may be initiated to expedite neutrophil recovery. However, G-CSF may not be used on days that radiation is being administered.

6.5.7 Treatment Planning (1/8/99)
6.5.7.1 Treatment planning should be performed in accordance with the prescribed doses (Section 6.1) to each target volume, together with restrictions in dose to normal tissues as given Section 6.6. Treatment planning simulation is required. It is recommended that CT-based treatment planning be utilized whenever possible. As the cone-down field is treated every Friday (and the last 3 treatments), the simulation and planning for the cone-down must be done up-front (at the same time as for the large fields).

6.5.7.2 One set of isodose distributions at the midplane transverse plane of the boost target volume should be submitted. Sagittal dose distributions are encouraged.

6.5.7.3 In addition to the isodose distribution, the following specific points of dose calculation should be included:

1) Spinal Cord Dose. If compensating filters are not used, the point at which the spinal cord dose is to be calculated is 2 cm below the superior margin of the posterior field. If compensating filters or wedges are used then the point of maximum dose to the spinal cord must be determined. Maximal spinal cord dose should not exceed 48 Gy at any level.

2) Subcarinal Nodes. Which are assumed to be at mid-plane.

3) Ipsilateral Normal Lung Dose. This is to be calculated at the level of the central rays of the boost fields at the point of maximum dose in the lung which lies at least 2cm outside of the projected border of the initial fields in the ipsilateral lung.

4) Contralateral Normal Lung Dose. This is to be calculated at the level of the central rays of the boost field at the point of maximum dose in the lung which lies at least 2 cm outside of the projected border of the initial treatment fields in the contralateral lung.

5) Maximum Normal Tissue Dose. This is to be calculated at level of the central rays of the boost fields as the maximum total dose at least 2 cm outside of the target volume.

6.5.8 Localization Films
All fields treated require filming on simulator units. Portal verification must be done for all treated fields. Copies of both simulator and portal fields must be submitted to RTOG Headquarters as specified in Section 12.0.

6.5.9 Dosimetry Monitoring
The American Association of Physicists in Medicine (Radiological Physics Center, Houston, TX) may conduct a field survey of equipment.

6.6 Compliance Criteria
6.6.1 Total Dose Criteria
≤ 4% Per Protocol
> 4% to ≤ 9% Variation Acceptable
> 9% Deviation Unacceptable
6.6.2 **HFX Fractionation Criteria**

- ≤ 2 Days of non HFX Per Protocol
- 3-5 Days of non HFX Variation Acceptable
- > 5 Days of non HFX Deviation Unacceptable

6.6.3 **Fields Borders**

- 2 cm to < 2.5 cm Per Protocol
- 1 to < 2 cm OR 2.5 to 3.5 cm Variation Acceptable
- < 1 cm OR > 3.5 cm Deviation Unacceptable

6.7 **Anticipated Side Effects or Toxicities**

6.7.1 **Suggested Maximum Doses to Critically Sensitive Normal Structures**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Lung</td>
<td>25 Gy</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>25 Gy</td>
</tr>
<tr>
<td>Contralateral (only if necessary)</td>
<td>20 Gy</td>
</tr>
<tr>
<td>Spinal Cord (maximum dose)</td>
<td>45 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>45 Gy</td>
</tr>
<tr>
<td>Entire Organ</td>
<td>50 Gy</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>60 Gy</td>
</tr>
</tbody>
</table>

6.7.2 The dose to spinal cord must be limited to 48 Gy. A posterior spinal cord shield will not be an acceptable technique. Oblique or lateral field arrangements with custom shielding are recommended to limit spinal cord dose. The use of a spinal cord shield (black) will result in a variation score in the RT Quality Assurance review.

6.7.3 Reversible alopecia, bone marrow toxicity, skin pigmentation and esophagitis are expected side effects of radiation therapy, while radiation induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiation pneumonitis and subsequent fibrosis of the lung will occur in 100% of all patients receiving ≥ 40 Gy to the lung, usually within the first 6 months after initiation of treatment so it is essential to spare all normal lung possible.

6.7.4 Radiation therapy may be interrupted for periods of up to one week for significant (≥ grade 3) esophagus toxicity: i.e., inability to tolerate liquids, whenever weight loss occurs and/or supplemental feedings are necessary. Sucralfate slurries may provide symptomatic relief of mucositis and esophagitis.

6.7.5 Post-treatment pneumonitis thought due to radiation should be treated with prednisone after excluding microbial causes.

6.7.6 Adverse reactions will be reported as described in Appendix V.

6.8 **Criteria for Removal from Protocol Treatment**

6.8.1 Disease progression at any time during therapy or the follow-up period. The patient should be restaged and sites of recurrence and/or progression documented. Re-biopsy is strongly encouraged.

6.8.2 Unacceptable toxicity.

6.8.3 The patient may elect to withdraw from study treatment at any time for any reason.

6.8.4 Development of intercurrent, non-cancer related illnesses that prevent either continuation of therapy or regular follow-up.

6.8.5 All reasons for discontinuation of treatment must be documented.

6.8.6 All patients will be followed until death.

7.0 **DRUG THERAPY**

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

7.1 **Paclitaxel (Taxol)**

7.1.1 **Formulation:** Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. Vials will be labeled with shelf-life. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.
7.1.2 **Preparation:** A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. Paclitaxel, at the appropriate dose, will be diluted in 1000 ml of D5W, USP, in 5% polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution (NOTE: acceptable limits established by the USP Particular Matter Test for LVP's) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

7.1.3 **Administration:** Paclitaxel, at the appropriate dose and dilution, will be given as a 3-hour infusion during induction therapy and by 1 hour infusion during concurrent CT/RT. The paclitaxel is mixed in 500 or 1000 cc of D5W in non-PVC containers and infused via polyolefin-lined nitroglycerin tubing or low absorption AVI‰ with 0.22 m in-line filter. In order to maximize radiosensitization of paclitaxel, patients will proceed with afternoon thoracic radiation 1/2 to 1-1/2 hours after paclitaxel infusion has been completed. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the i.v. administration sets (polyethylene or polyolefin) which are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered. (4/1/99)

7.1.4 **Storage:** Paclitaxel vials should be stored between 2°-25°C (36°-77°F).

7.1.5 **Adverse Effects:**
- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase) hepatic failure, hepatic necrosis.
- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness.
- Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights, blurred vision, scintillating scotoma.
- Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritis.
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration), radiation recall reaction.

7.1.6 **Supplier:** Commercially available.

7.2 **Carboplatin (Paraplatin)**

7.2.1 **Formulation:** is supplied as a sterile lyophilized powder available in a single-dose vial containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

7.2.2 **Preparation:** Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

<table>
<thead>
<tr>
<th>Vial Strength</th>
<th>Diluent Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>5 ml</td>
</tr>
<tr>
<td>150 mg</td>
<td>15 ml</td>
</tr>
<tr>
<td>450 mg</td>
<td>45 ml</td>
</tr>
</tbody>
</table>

These dilutions all produce a carboplatin concentration of 10 mg/ml. When prepared as directed, Paraplatin solutions are stable for eight hours at room temperature; since no antibacterial preservative is contained in the formulation, it is recommended that Paraplatin solutions be discarded eight hours after dilution.

7.2.3 **Administration:** Carboplatin, at the appropriate dose and dilution, will be given over 30 minutes, immediately after paclitaxel. Dose of carboplatin (mg) = target AUC x (GFR + 25) with a creatinine clearance calculated by the Cockroft-Gault Formula substituted for GFR,
i.e. \[ \text{GFR} = \frac{(140 - \text{age})(\text{kg wt})}{(\text{serum creatinine} (72))}; \] with 15% reduction for women

For example, a 60-year-old man with a serum creatinine of 1.0 and a weight of 72 kg will have a calculated GFR of 80 mg/min. On day 22 \((\text{AUC} = 6.0)\), his dose of carboplatin would be 630 mg.

NOTE: Aluminum reacts with Paraplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of Paraplatin.

### 7.2.4 Storage
Unopened vials of Paraplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

### 7.2.5 Adverse Effects
Myelosuppression, nausea, vomiting, peripheral neuropathy, ototoxicity, hepatic toxicity, electrolyte imbalance, hypomagnesemia, hypercalcemia and allergic reaction.

### 7.2.6 Supplier
Commercially available.

### 7.3 G-CSF

#### 7.3.1 Formulation
G-CSF is available in 1.6 cc single-use glass vials containing 300 mcg/cc. It is formulated as a sterile, clear, colorless liquid in a 10 mm sodium acetate buffer at pH 4.0. The quantitative composition \((\text{per ml})\) is:

- G-CSF: 300 mcg
- Acetate: 0.59 mg
- Mannitol: 0.50 mg
- Tween \(_{80}^{TM}\): 0.004%
- Sodium: 0.035 mg
- Water for injection \((\text{gs ad})\): to 1 ml

#### 7.3.2 Preparation
If given, filgrastim will be administered subcutaneously. It can be used directly from the vial.

#### 7.3.3 Administration
G-CSF will not be used routinely but will be implemented according to American Society of Clinical Oncology guidelines. The appropriate volume of G-CSF should be withdrawn and injected subcutaneously daily. Injection sites should be rotated. If the volume to be injected is greater than 1.5 ml, the dose should be divided in half and both doses should be given at the same time in two sites. G-CSF should not be administered during the radiation portion of the protocol.

#### 7.3.4 Storage
The intact vial of filgrastim should be stored under refrigeration (2 to 8°C).

#### 7.3.5 Adverse Effects
The adverse effects associated with G-CSF are usually mild and include bone pain and, rarely, splenomegaly. Laboratory effects include increases in alkaline phosphatase, LDH, WBC and uric acid.

#### 7.3.6 Supplier
Commercially available.

### 7.4 Amifostine

#### 7.4.1 Formulation
Amifostine \((\text{Ethylol})\) is an organic thiophosphate cytoprotective agent known chemically as ethanethiol, 2-[-3-aminopropyl]amino]-, dihydrogen phosphate (ester).

#### 7.4.2 Preparation
Amifostine is a white crystalline powder that is freely soluble in water. It is supplied as a sterile lyophilized powder mixture that requires reconstitution for intravenous infusion. Each single-use 10 mL vial contains 500 mg of amifostine \((\text{anhydrous basis})\). Prior to intravenous injection, amifostine for injection must be reconstituted with 9.7 mL of sterile Sodium Chloride for injection, USP, 0.9%. The reconstituted solution \((500 \text{ mg amifostine/10mL})\) is chemically stable for up to 5 hours at room temperature \((\text{approximately } 25 \degree \text{C})\) or up to 24 hours under refrigeration \((2 \degree \text{ to } 8 \degree \text{C})\). Amifostine solution prepared in polyvinylchloride (PCV) bags at concentrations ranging from 5 mg/mL to mg/mL is chemically stable for up to 5 hours when it is stored at room temperature or up to 24 hours when it is stored under refrigeration.

#### 7.4.3 Administration
Before the infusion of amifostine is initiated, the intravenous tubing must be primed. Administer the solution i.v. over 5-7 minutes. After the amifostine infusion is complete, flush the mini-bag with normal saline.

#### 7.4.4 Storage
See Section 7.4.2.

#### 7.4.5 Adverse Effects

1. **Hemodynamic:** Amifostine administration has been associated with hypotension in patients who are dehydrated or otherwise indisposed. Predisposing factors include the use of antihypertensive medications or diuretics.

2. **Hematologic:** none.

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7.4.5.3 Gastrointestinal: nausea, vomiting.
7.4.5.4 Heart: none.
7.4.5.5 Neurologic drowsiness.
7.4.5.6 Allergy: sneezing, flushing, allergic reaction.
7.4.5.8 Other: hypocalcemia.

7.4.6 Supplier: ALZA Pharmaceuticals/US Bioscience will supply amifostine to Livingston, Inc. for distribution. RTG members must submit the Amifostine Shipping Form (Appendix VI) to RTG Headquarters prior to the randomization of the institution’s first patient to this study but after institutional IRB approval has been obtained. After each randomization to Arm 1, RTG will notify Livingston who will send 28 vials of amifostine to the institution. Livingston will fax a confirmation of drug shipment to RTG and Alza. The supply will not be patient-specific and may be used as needed for study patients on Arm 1. Drug inventory logs must be kept by the institution for review by RTG upon request. At the completion of the study, remaining amifostine supplies will be inventoried and destroyed on site.

7.4.7 Precautions: 1) Amifostine should be administered in a supine position. 2) Patients will be instructed to drink 2 cups of fluids 30 minutes before amifostine infusion (on RT-only days) or will receive i.v. hydration (on carboplatin/paclitaxel-RT days). 3) Anti-hypertensive/diuretic medications should not be taken until after the amifostine infusion is completed.

7.4.8 Premedication and Amifostine Infusion Schema: (1/8/99, 4/1/99)
Amifostine will be administered on the first and subsequent 3 days of each RT week before the second daily (i.e., the PM) fraction of RT. The schedule of therapy can be compared to a “sandwich” technique, with AM RT first, followed by amifostine/chemotherapy and completed with PM RT fraction. Amifostine must always be infused before the chemotherapy infusion when given. Since amifostine infusion has been associated with nausea and vomiting at doses of 340 mg/m² or higher, patients should receive premedication prior to infusion. The antiemetic schedule below is to be done before the PM RT fraction (starting approximately 60 minutes before PM RT on “RT days” and 2 to 2 1/2 hours before PM RT on “chemo/RT” days).

- 1 hour (on chemo/RT days) or 30 to 60 minutes (on RT days): Ondansetron (32 mg i.v.) or granisetron (1 mg) in 50 ml D5W i.v. over 15 minutes; dexamethasone (20 mg i.v.) and cimetidine (300 mg i.v.) on chemo/RT days only

Note: Dexamethasone should not be administered as premedication on RT-only days.

If desired, diphenhydramine (50 mg i.v.) or lorazepam (1 mg i.v.) may be incorporated into the premedication regimen.

- 15 to 30 minutes (on RT days): 2 cups of oral fluids.

- 0: Amifostine (500 mg i.v.) infusion over 5-7 minutes. Patient should remain supine during the infusion and for 30 minutes after amifostine administration.

+ 10 minutes (on chemo/RT days): Start paclitaxel 50 mg/m² i.v., to be infused over 1 hour.

+ 70 minutes (on chemo/RT days): Start carboplatin (AUC 2) i.v., to be infused over 30 minutes, immediately after paclitaxel infusion.

+ 100 minutes (on chemo/RT days): Thoracic RT, second daily dose (on days without chemotherapy, thoracic RT should be delivered 30-60 minutes from the beginning of amifostine infusion).

7.4.9 Please note that timing of RT in relationship to amifostine is crucial. On chemo/RT days, RT should start as soon as possible and not later than 180 minutes after amifostine infusion. On RT only days, RT should be given 15-30 minutes (maximum of 60) from the start of amifostine infusion. All RT times must be recorded in the treatment record. (4/1/99, 9/28/01)
7.4.10 **Guidelines for Interrupting Amifostine Infusion:**

Blood pressure and pulse will be monitored every 2 minutes using a Dynamap (or equivalent) automatic blood pressure monitoring system during the entire amifostine infusion. The amifostine infusion should be interrupted if the patient’s systolic blood pressure decreases significantly from baseline (see table below) or if the patient develops symptoms of decreased cerebral or cardiovascular perfusion.

<table>
<thead>
<tr>
<th>Baseline systolic blood pressure (mm Hg)</th>
<th>&lt; 100</th>
<th>100-119</th>
<th>120-139</th>
<th>140-179</th>
<th>&gt;180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in systolic BP (mm Hg) during amifostine infusion</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>

Should a significant decrease in blood pressure occur, patients should be treated with a rapid infusion of normal saline and should be placed in the Trendelenburg position. The amifostine infusion may be restarted if the blood pressure returns to a level above the threshold (baseline minus significant decrease) within 5 minutes of the interruption of the infusion. If the blood pressure does not return to a level greater than the threshold within 5 minutes, the dose of amifostine should be decreased by 25% for the next infusion. Any amifostine infusion which is interrupted will not be made up.

7.5 **Chemotherapy Plan (4/1/99)**

Induction paclitaxel/carboplatin (q 3 weeks for 2 cycles) followed by concurrent weekly P/C and HFX RT starting day 43 (69.6 Gy/6 weeks/1.2 Gy bid) +/- Amifostine (A) 4X/week

<table>
<thead>
<tr>
<th>Day</th>
<th>P#1</th>
<th>P#2</th>
<th>P#3</th>
<th>P#4</th>
<th>P#5</th>
<th>P#6</th>
<th>P#7</th>
<th>P#8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Day 22</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Day 43</td>
<td>C#1</td>
<td>C#2</td>
<td>C#3</td>
<td>C#4</td>
<td>C#5</td>
<td>C#6</td>
<td>C#7</td>
<td>C#8</td>
</tr>
<tr>
<td>Day 50</td>
<td>(RT AM)</td>
<td>XXXx</td>
<td>XXXx</td>
<td>XXXx</td>
<td>XXXx</td>
<td>XXXx</td>
<td>XXXx</td>
<td>XXXx</td>
</tr>
<tr>
<td>Day 57</td>
<td>(PM)</td>
<td>AAAA</td>
<td>AAAA</td>
<td>AAAA</td>
<td>AAAA</td>
<td>AAAA</td>
<td>AAAA</td>
<td></td>
</tr>
<tr>
<td>Day 64</td>
<td>(RT PM)</td>
<td>XXXx</td>
<td>XXXx</td>
<td>XXXx</td>
<td>XXXx</td>
<td>XXXx</td>
<td>XXXx</td>
<td>XXXx</td>
</tr>
</tbody>
</table>

(X = 1.2 Gy to initial volume)

(* = 1.2 Gy to cone down volume)

Note: Cone-down volume is treated every Friday and the last 3 days of treatments.

P = Paclitaxel 225 mg/m²/3hr I.V. on days 1, 22; 50 mg/m²/I.V. / 1 hr. on days 43, 50, 57, 64, 71, 78*

C = Carboplatin AUC 6.0, days 1 & 22; AUC 2 on days 43, 50, 57, 64, 71, 78 *

A = For patients randomized to amifostine arm only, amifostine 500 mg IV over 5 minutes prior to all PM treatments 4 X/week (Mon-Thurs) see Section 7.4.8.

G-CSF will not be used routinely but will be implemented according to the American Society of Clinical Oncology guidelines.

* On days 43-78, chemotherapy will be administered prior to the PM radiation treatment.

7.5.1 **Initial Treatment Arm 1**

7.5.1.1 **Initial Treatment**

Paclitaxel 225 mg/m² i.v. by 3-hour continuous infusion (on an outpatient basis) days 1 and 22; 50 mg/m² i.v. by 1-hour infusion on days 43, 50, 57, 64, 71 and 78 (prior to second daily dose of radiotherapy). Note: The treating medical oncologist has the option of delivering the weekly chemotherapy on Tuesdays, i.e., days 44, 51, 58, 65, 72, and 79. Similarly, when there is Monday holiday, the weekly chemotherapy will be administered on Tuesdays. A one-day shift in the
weekly chemotherapy will thus be allowed, as needed. The paclitaxel is mixed in 500 or 1000 cc of D5W in plastic containers and infused over 1 hour via polyolefin-lined nitroglycerin tubing or low absorption AVITM with a 0.22 m in-line filter i.v. All patients will be pre-dosed with steroids, H-1 and H-2 blockers. See Section 7.5.2 for premedication.

7.5.1.2 Carboplatin, AUC 6.0, days 1 and 22 (1/8/99)
(Use AUC of 2.0 on days 43, 50, 57, 64, 71 & 78 prior to second daily dose of XRT). (Note: the treating medical oncologist has the option of delivering the weekly chemotherapy on Tuesdays, i.e., days 44, 51, 58, 65, 72, and 79). Similarly, when there is a Monday holiday, the weekly chemotherapy will be administered on Tuesdays. A one-day shift in the weekly chemotherapy will thus be allowed, as needed. Carboplatin will be given over 1/2 hour immediately after paclitaxel.

Calculated dose of carboplatin (mg) = target AUC x (GFR + 25) with GFR as per the Cockroft-Gault formula: GFR = [(140 - age)(kg wt*)] divided by [(serum creatinine) x (72)].

*Note: Multiply the GFR by 0.85 for females (represents a 15% reduction. For example, a 60-year-old man with a serum creatinine of 1.0 and a Wt of 72 kg will have a calculated GFR of 80 mg/min. On day 1 or 22, his dose of carboplatin would be 630 mg. Repeat treatment at 3 week intervals. Patients will not receive the next cycle of therapy until ANC (absolute neutrophil count) is greater than or equal to 1500/cc3 and platelets are greater than or equal to 100,000/cc3.

7.5.1.3 G-CSF 5 mcg/kg SQ G-CSF will not be used routinely but will be implemented according to the American Society of Clinical Oncology guidelines.

7.5.2 Premedications
The patient will be premedicated 30 minutes prior to paclitaxel with 1) dexamethasone-20 mg i.v. immediately (or dexamethasone 20 mg orally 12 and 6 hours pre paclitaxel) in conjunction with 2) diphenhydramine-50mg i.v. and 3) ranitidine-50mg i.v. or cimetidine-300 mg i.v. or Pepcid at investigator's discretion. Patients may receive Compazine 10 mg i.v. or po q 4 hr prn during paclitaxel infusion, or other antiemetic regimens at treating physician's discretion. Prior to carboplatin administration, the choice of antiemetics will be left to individual physician's discretion.

7.5.3 Anti-Emetic
The choice of anti-emetic regimen will be left to the discretion of individual investigators except as specified before each amifostine infusion. Ondansetron at a dose of 32 mg i.v. prior to carboplatin is recommended. Alternatively, a combination of lorazepam 1 mg; metoclopromide 1mg/kg; dexamethasone 10-20 mg; diphenhydramine 25-50 mg, repeated at reasonable intervals is appropriate. Prophylaxis against delayed nausea and vomiting is a consideration; e.g., a tapering dose of dexamethasone, with or without lorazepam, metoclopromide, or diphenhydramine.

7.5.4 Dosage Modifications for Toxicity During Induction Chemotherapy

7.5.4.1 Hematologic Toxicity (9/28/01)
If platelets drop below 25,000/cc3 for more than 5 days, if the patient develops neutropenic fever, or if the subsequent course of chemotherapy is delayed > 7 days, the doses of carboplatin and paclitaxel during cycle 2 will be reduced by 20% to paclitaxel 180 mg/m2 and carboplatin AUC 5. G-CSF should not be administered during the radiation portion of this protocol but can be given during cycles 1 and 2 of the pre-radiation chemotherapy as above. G-CSF will not be used routinely but will be implemented according to the American Society of Clinical Oncology guidelines.64

<table>
<thead>
<tr>
<th>Platelets</th>
<th>*Other Toxicity</th>
<th>Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 25,000</td>
<td>------</td>
<td>No modification</td>
</tr>
<tr>
<td>&lt; 25,000 for &gt; 5 days</td>
<td>Neutropenic Fever or Subsequent Course</td>
<td>180 mg/M2</td>
</tr>
</tbody>
</table>

Drug Modifications for Induction Phase Hematologic Toxicity
7.5.4.2  **Non-Hematologic Toxicity**  
For non-hematologic, grade 3 or 4 toxicity, excluding nausea, vomiting, and alopecia, the dose of the implicated agent(s) will be reduced by 20% for the next administration once the non-hematologic toxicity resolves to grade ≤ 1. If a patient loses > 10% of his/her onstudy weight at any given time during treatment, the patient should be considered for a nutrition *(and/or GI)* consultation. Doses of all chemotherapeutic agents will be based on the patient’s weight on the day of treatment.

7.5.5  **Dosage Modifications for Toxicity During Concurrent Chemoradiation**

<table>
<thead>
<tr>
<th>Hematologic Toxicity</th>
<th>Neurpathic Pain*/myalgia, arthralgia</th>
<th>Dysphagia (esophageal) related to RT</th>
<th>Paclitaxel Dose</th>
<th>Carboplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &gt; 1000</td>
<td>Grade 0-1</td>
<td>Grade 0-2</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>ANC 500-999</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>ANC &lt; 500</td>
<td>Grade 3</td>
<td>Grade 4**</td>
<td>Hold</td>
<td>Hold</td>
</tr>
<tr>
<td>PLTS &gt; 80</td>
<td></td>
<td></td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>PLTS 50 - 79</td>
<td></td>
<td></td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>PLTS &lt; 50</td>
<td></td>
<td></td>
<td>Hold</td>
<td>Hold</td>
</tr>
<tr>
<td>Neutropenia Fever</td>
<td></td>
<td></td>
<td>Hold**</td>
<td>Hold**</td>
</tr>
</tbody>
</table>

* For other neuropathy, see CTC-Neuropathy.  
** Radiotherapy must also be discontinued in these situations. Interruptions in RT > 3 days should be discussed with Dr. Movsas, or, in his absence, Dr. Werner-Wasik.

**Dysphagia**
Grade 1 - mild dysphagia, but can eat regular diet  
Grade 2 - dysphagia, requires predominately pureed, soft, or liquid diet  
Grade 3 - dysphagia, requiring feeding tube, IV hydration or hyperalimentation  
Grade 4 - complete obstruction *(cannot swallow saliva)*; ulceration with bleeding not induced by minor trauma or abrasion or perforation

**Neuropathic Pain, Myalgia, Arthralgia**
Grade 1 – mild pain not interfering with function  
Grade 2 – moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living  
Grade 3 – severe pain: pain or analgesics severely interfering with activities of daily living

7.5.6  **Dosage Modifications for Cardiac Toxicities**
In the event of a grade 3 or 4 cardiac toxicity, Dr. Langer must be notified (215) 928-2985. Dr. Langer will make the decision regarding a dose modification.

7.6  **Toxicity Reporting**
7.6.1 This study will utilize the Common Toxicity Criteria *(CTC)* version 2.0 for toxicity and Adverse Event Reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP Home page *(http://ctep.info.nih.gov)*. All appropriate treatment areas should have access to a copy of the CTC version 2.0.  
This study will be monitored by the Clinical Data Update System *(CDUS)* version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.
The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational drug Branch, Cancer Therapy Evaluation Program, within 10 working days.

7.6.2.1 Any ADR which is both serious (life threatening, fatal) and unexpected.
7.6.2.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
7.6.2.3 Any death on study if clearly related to the commercial agent(s).
7.6.2.4 Acute myeloid leukemia (AML). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.

7.6.3 The ADR report should be documented on Form FDA 3500 (Appendix V) and mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824
Telephone: (301) 230-2330 (24 hours)
fax (301) 230-0159

7.6.4 Special Reporting for this Study (fax 215/928-0153)
7.6.4.1 All grade ≥3 non-hematologic toxicities must be reported to RTOG within 24 hours.
7.6.4.2 All grade ≥4 hematologic toxicities must be reported to RTOG within 24 hours.
7.6.4.3 Data submission must adhere to the timetable specified by the patient calendar and Section 12.0.

7.6.5 Investigator Reporting Responsibilities
7.6.5.1 All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator will record this information on Form FDA 3500 and will provide reports of adverse experiences on a regular basis during the study conduct. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and “unexpected” as defined above are present.

7.6.5.2 ADVERSE EXPERIENCES THAT ARE BOTH SERIOUS AND UNEXPECTED, REGARDLESS OF CAUSES OR RELATIONSHIP TO STUDY DRUG, OCCURRING UP TO 30 DAYS FOLLOWING THE END OF TREATMENT, SHOULD BE REPORTED IMMEDIATELY TO ALZA CORPORATION BY TELEPHONE AT (650) 237-2500 OR BY FAX AT (650) 237-2992.

7.6.5.3 The investigator should send a written follow-up report (Form 3500) to Alza with copies to RTOG, within three (3) working days of the original telephone report. The investigator should also provide additional information, including a copy of the following documents:
- Narrative summary of the adverse experience by the investigator
- Copies of all test results
- Pertinent medical record program notes/study record
- Hospital discharge summary (as soon as it is available to the investigator)
- Autopsy report (as soon as it is available to the investigator).

8.0 SURGERY
Not applicable to this study.

9.0 OTHER THERAPY
Not applicable to this study.

10.0 BLOOD SAMPLE COLLECTION (4/1/99)
The OPTION of collecting blood for cytokine analysis has been added. Please see Appendix VII for the background information as well as the instructions regarding the collection and shipping of the blood work. This is not required, but for the first 90 patients that are enrolled on this optional component, the participating institution will be reimbursed $100 per patient. The goal of this blood work is to correlate an extensive cytokine analysis to be done at the University of Rochester with treatment and toxicity endpoints,
particularly pneumonitis. Blood work will be collected at 4 time points: pre-treatment, pre-chemoradiation (post 2 cycles of induction chemotherapy), at the end of the chemoradiation (week 6), and at the 6-week follow-up visit (the exact time points as the QOL forms). This optional project has been funded by a grant from the RTOG translational research group.

11.0 PATIENT ASSESSMENTS (4/1/99)

11.1 Study Parameters

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pretreatment (see Section 4.0 for timing)</th>
<th>Within 3 Days of Chemo cycle 2 and chemo cycle 3</th>
<th>Weekly During Chemo/RT</th>
<th>After RXa</th>
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</thead>
<tbody>
<tr>
<td>History &amp; Physical</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Neurological Assessment</td>
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<td>X</td>
<td>X</td>
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<td>Height, Weight &amp; KPS</td>
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<td>Tumor Measurement</td>
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<td></td>
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<td>Patient Swallowing Diary</td>
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</tr>
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<td>Quality of Life (QOL)</td>
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<tr>
<td>Smoking/ETOH Questionnaire</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Chest x-ray, PA &amp; LAT</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest CT scan (liver &amp; adrenals)</td>
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<td>Xg</td>
<td>Xb</td>
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</tr>
<tr>
<td>CBC, diff, platelets, creatinine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>SMA-12f, electrolytes, Mg++</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>FVC,FEV-1,DLCO, EKG</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test (as applicable)</td>
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<td></td>
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</tr>
<tr>
<td>Metastatic Evaluation (bone, brain)</td>
<td>X</td>
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<tr>
<td>Toxicity Evaluation</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Blood for Cytokine Study (optional)</td>
<td>Xj</td>
<td>Xj</td>
<td>Xj</td>
<td>Xj</td>
</tr>
</tbody>
</table>

a. After completing radiation therapy, patients will be seen 6 weeks later, then every 3 months for one year, then every six months for 2 years, then annually. The followup intervals are calculated from start of RT.
b. Every 6 months for 2 years from start of RT, then annually. Note: When a chest CT scan is ordered, the chest x-ray can be omitted.
c. When appropriate for new symptoms or findings.
d. Prior to start of treatment, weekly during RT, and at 6 weeks following RT.
e. Prior to the start of all treatment, prior to start of concurrent chemo/RT, week 6 of chemo/RT and at the six week followup visit. Note: The full EORTC QLQ-30 and QLQ-LC-13 questionnaires of 43 questions will be required only pretreatment and at the 6 week followup visit. At the two other timepoints (prior to start of concurrent chemo/RT and week 6 of chemo/RT), only the 13 questions of the EORTC questionnaire lung cancer module (QLQ-LC-13) will be required.
f. SMA-12: Total protein, Albumin, Calcium, Glucose, BUN, Creatinine, Alkaline Phosphatase, LDH, Total Bilirubin, SGOT and SGPT.
g. Chest CT (for response to induction chemotherapy) to be done within 1 week prior to chemo cycle 3 only.
h. Daily during RT and at 6 weeks following completion of RT, i.e, at 13 weeks from start of RT.
i. See Section 12.0 for acute effects reporting on the FS form. Late effects will be reported on each Followup Form (F1). A LENT (Late Effects of Normal Tissues) evaluation will be collected with each Followup Form beginning at 6 months and continuing thereafter.
j. Prior to the start of all treatment, prior to start of concurrent chemo/RT, week 6 of chemo/RT and at the six week followup visit.

2.0.0 21
11.2 Evaluation During Study
11.2.1 An interval history and physical examination with particular attention to drug-induced side effects along with documentation of the patient's weight and performance status on each visit.
11.2.2 Weekly CBC, platelet count, differential AGC count, and serum creatinine.
11.2.3 An SMA-12, electrolytes, and MG++ shall be performed at least every 4 weeks or as frequently as needed to define drug toxicity.
11.2.4 Tumor measurements, response of each lesion, site and overall response shall be evaluated with every chest CT obtained within one week prior to chemo cycle 3 and every 6 months for 2 years, then annually. Followup timing is based on the start of RT.
11.2.5 All relevant information regarding drug dosage, tumor response, laboratory examinations, and treatment-related toxicities must be recorded before each treatment is given.
11.2.6 Patient Swallowing Diary is done prior to start of treatment, daily during RT, and at 6 weeks following RT. Physician Dysphagia Log is done prior to treatment, weekly during RT and at the three-month followup visit. It is important that the patients are asked regarding their smoking and alcohol use. It is also important to fill out the Physician's Dysphagia Log and Patient Swallowing Diary since the incidence of esophagitis is one of the study's major endpoints.
11.2.7 The radiation oncologist should document on the T1 form the estimated length of the esophagus in the initial (large) field and the cone-down field. The length of the esophagus is estimated to be the length of the radiation field minus the length of any central blocks over the region of the esophagus (such as a vocal cord block).
11.2.8 EORTC QLQ-C30 & QLQ-LC-13 pretreatment and at the 6-week follow-up. EORTC QLQ-LC-13 (13 questions) subscale will be done just prior to concurrent chemo/RT and at week 6 of chemo/RT. These data will enhance the information about esophagitis obtained from the Physician Dysphagia Log. (4/1/99)
11.2.9 Smoking history and current use and alcohol questionnaire at pre-treatment.
11.2.10 After completing radiation therapy, patients will be seen according to the schedule in Section 11.0. Required studies for follow-up are listed in Section 11.0.
11.2.11 Assessment of late radiation effects will be made on all patients receiving any radiation therapy. This evaluation will be scored on the Follow-up Forms using the RTOG/EORTC Late Radiation Morbidity Scheme. In addition, a LENT Evaluation will be completed on the appropriate SOMA pages that are applicable for patients receiving irradiation to the lung. The applicable SOMA sites for this protocol are: Lung, Heart, Vessels, Spinal Cord, Bone Marrow, Mature Bone, Muscle/Soft Tissue, Peripheral Nerve, Skin/Subcutaneous, Esophagus, Mucosa-oral/pharyngeal, and Thyroid. Instructions for completing this instrument are found on the LENT Form. The Analytic portion of the SOMA scales may be omitted. The LENT Evaluation is completed by the investigator or his/her designee, i.e., not by the patient.

11.3 Criteria for Response
A measurable lesion is defined as a lesion with clearly defined perpendicular diameters seen on physical examination, chest x-ray, CT scan, or ultrasonic examination. The longest diameter and its perpendicular will be measured. All measurable lesions will be measured in centimeters prior to each course of therapy. Measurements should be made and recorded by the physician or the oncology research nurse under his or her supervision. An evaluable lesion is defined as a lesion that is clinically apparent but not bidimensionally measurable. An estimate of overall objective and subjective response will be made and recorded at each visit. Quality of Life (QOL), symptom distress, smoking and alcohol status will be recorded before, during, and after treatment.

11.3.1 Response Definitions
Patients with measurable indicator lesions:

11.3.1.1 Complete Response (CR): Disappearance of all clinical evidence of tumor persisting for a minimum of 4 weeks. The patient must be free of all symptoms of cancer.

11.3.1.2 Partial Response (PR): 50% or greater decrease in the sum of the products of diameters of all measured lesions persisting for a minimum of 4 weeks. No lesions may increase in size and no new lesions may appear.

11.3.1.3 No Change (NC): Any regression of indicator lesions not fulfilling the criteria of partial remission and no evidence of progression as defined below. NC is considered a failure, but should be noted as a possible signal of biologic activity.
11.3.1.4 **Progressive Disease (PD):** An increase of ≥ 25% in the sum of the products of diameters of any measurable lesion or appearance of an unequivocal new lesion.

Patients with evaluable (non-measurable) indicator lesions:

11.3.1.5 **Complete Remission:** Disappearance of all clinical evidence of disease on physical examination, x-rays, and CT scans for a minimum of 4 weeks.

11.3.1.6 **Improved:** Definite decrease (≥50%) in the size of the evaluable lesions for a minimum of four weeks; this must be concurred in by at least 3 observers, including the referee radiologist if the evaluable lesion is assessed by its x-ray appearance. No simultaneous increase in the size of other lesions or the appearance of new lesions may occur.

11.3.1.7 **No Change:** Any regression of indicator lesions not fulfilling the criteria of complete remission or improved and no evidence of progression as defined below.

11.3.1.8 **Progression:** Unequivocal worsening of any evaluable lesions or the appearance of new lesion.

11.3.1.9 **Response Duration:** Response durations are measured from the time of response (not the beginning of treatment) until there is evidence of progressive disease.

11.3.1.10 **Survival Duration:** The survival of patients will be measured from the date of randomization.

11.3.1.11 **Improvement in QOL:** Decrease in EORTC QLQ-C30 scores (lower scores indicate better quality of life for items 1-28; for items 29 & 30 the direction is reversed (higher scores indicate better overall quality of life and physical condition during the past week).

11.3.1.12 **Improvement in Symptoms:** Decrease in the overall score on the QLQ-LC-13, specifically item #6 (sore mouth) and item #7 (trouble swallowing). Items #13 (lacked appetite), and #14 (felt nauseated), and #16 (vomited) also will be examined (lower scores indicate less distress).

11.3.1.13 **Smoker:** Positive response on Smoking Assessment.

11.3.1.14 **Non-smoker:** Negative response on Smoking Assessment.

11.3.1.15 **Alcohol User:** Positive response on alcohol assessment.

11.3.1.16 **Non-alcohol User:** Negative response of alcohol assessment.

11.4 **Criteria for Discontinuing Therapy**

11.4.1 1) Progressive disease after a minimum of one course chemotherapy.

2) The development of unacceptable toxicity defined as unpredictable, irreversible, or grade 4.

3) Intercurrent illness that precludes further protocol treatment.

4) Patient refusal.

5) All patients will be followed.

---

**DATA COLLECTION (4/1/99)**

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 **Summary of Data Submission**

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td></td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pretreatment Swallowing Diary (DP) *</td>
<td></td>
</tr>
<tr>
<td>Physician Dysphagia Log (DL)</td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-C30 &amp; QLQ-LC –13 (QL) * (one questionnaire)</td>
<td></td>
</tr>
<tr>
<td>Smoking and ETOH Questionnaire (PQ)</td>
<td></td>
</tr>
<tr>
<td>Study-Specific Flowsheets (SF) (must include pretx lab values,ht, wt, calculated BSA, and 1st dose of chemo)</td>
<td></td>
</tr>
</tbody>
</table>

* must be completed prior to the start of RX

<table>
<thead>
<tr>
<th>Post Induction Treatment Form (F0)</th>
<th>Within 1 week after completion of induction chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Dosimetry Information:</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>RT prescription (Protocol Treatment Form) (T2)</td>
<td></td>
</tr>
</tbody>
</table>
Initial Large Field Films (*simulation and portal*) (T3)
Calculations (T4)
Boost Films (*simulation and portal*) (T8)

Radiotherapy Form (T1)

*Final Dosimetry Information:*

Treatment Record (T5)
Isodose Distribution (T6)

Patient Swallowing Diary (DP) Within 1 week of RT end

EORTC QLQ-C30 & QLQ-LC -13 (SS) Prior to start of, and at the end of, chemo/RT; at 3 months from start of RT

Physician Dysphagia Log (DL) Within 1 week of RT end and at 3 months from start of RT.

Initial Followup Form (FS) ** At 3 months (90 days) from RT start

Study Specific Flowsheet (SF) At 4, 8, and 14 weeks.

Follow-Up Form (F1) At 6 months from start of RT, q 3 months for one year, then q 6 months x 2 years, then annually. Also at progression/relapse, onset of severe or unusual toxicity and at death.

LENT Evaluation (LE)

Autopsy Report, final/microscopic (D3) As applicable.

** This form collects the acute effects following completion of treatment. Submit at 90 days from RT start regardless of duration of RT. The FS is required on all patients who receive any RT and at progression/relapse/death if these events occur within 90 days of RT start.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints (9/28/01)

13.1.1 The primary endpoint is the frequency of severe (> grade 3) non-hematologic toxicities will be examined, with emphasis on esophageal toxicity.

13.1.2 Quality of life (QOL) and symptom distress will be assessed.

13.1.3 Correlation between toxicity and QOL and tobacco and alcohol use.

13.2 Sample Size

13.2.1 The treatment arm containing hyperfractionated radiotherapy (HRT) and carboplatin and paclitaxel (CT) has been shown to have a 26-35% grade 3 and 4 acute esophagitis rate which will be the historical control. The alternative hypothesis for the HRT+CT and amifostine (A) arm is a relative 50% reduction in grade 3 and 4 acute esophagitis. The required sample size for 90% statistical power and a two-sided 0.05 type I error, is 73 patients per arm. This assumes the HRT+CT arm will have 35% grade 3 and 4 acute esophagitis. If the rate is 26%, then the required sample size, by Whitehead's formula, is 93 patients per arm.

According to King, the expected average QOL score is 53 and the clinically important difference is 10 points on the EORTC QLQ-C30. The estimated standard deviation is 27, so 116 patients per arm are required for a two-sided 0.05 type I error and 80% statistical power. This is examining the QOL difference at three months follow-up.

Correlation between toxicity and tobacco and alcohol use or QOL and tobacco and alcohol use will be assumed to be zero. The alternative hypothesis of at least moderate correlation, defined as 0.30 or higher, will be tested at the two-sided 0.05 level with 90% statistical power.
The HRT+CT arm is expected to have a median survival time (MST) of at least 13.8 months. With 288 evaluable patients then this study will have at least 80% statistical power to find a 50% difference in MST between HRT+CT and HRT+CT+A. This is using a two-sided test at the 0.05 significance level.

Assuming 5% of the patients are either retrospectively ineligible or inevaluable due to never starting any therapy, then a total of 152 patients per arm or **304 randomized patients will be required.**

13.2.2 *(added 9/28/01)* The RTOG Data Monitoring Committee determined that due to lower than expected monthly accrual rate and new information from external studies, the survival endpoint could be removed. Results from Komaki et al. and Leong et al. indicated that amifostine had no relationship with survival in non-small cell lung cancer patients. Based upon the DMC’s review the sample size has been reduced to 244 total patients in order to keep the other endpoint intact.

13.3 **Patient Accrual**

The patient accrual is projected to be 8 patients per month, which is less than the 12 patients per month based upon the accrual of this patient group to RTOG 94-10. This trial should complete the accrual phase in 38 months. If the monthly accrual is less than 6 cases per month, the study will be re-evaluated with respect to feasibility.

13.4 **Randomization Scheme**

The treatment allocation will be one using a randomized a permuted block within strata to balance for patient factors other than institution. The stratifying variables are Age ≤ 70 versus Age >70, Stage II versus Stage IIIa versus Stage IIIb and KPS 70-80 versus 90-100.

13.5 **Analyses Plans**

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 have 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) the frequency and severity of the toxicities, not split by treatment.

13.5.2 **Interim Analyses of Study Endpoints**

There will be one interim analysis of survival and toxicity when 152 patients have been accrued and followed for a minimum of 3 months. If the test of the difference in survival is less than 0.001, the accrual will be suspended. The results of these interim analyses will only be reported, in a blinded fashion, the RTOG data monitoring committee as privileged communications. A report with recommendations will be given to the study chairman. Any problems or recommendations identified by the data monitoring committee, not results, will be reported to the lung committee, which responsible for this study and, if necessary, the RTOG executive committee, so that corrective action can be taken.

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

This major analysis will be undertaken after all patients have been potentially followed for a minimum of 12 months. The usual components of this analysis are:

1) tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;
2) reporting institutional accrual;
3) distribution of the important prognostic factors by assigned treatment;
4) observed results with respect to the study endpoints.
13.6 **Inclusion of Women and Minorities (9-28-01)**

Some investigators have shown gender to be a prognostic factor in non-small cell lung cancer. However, the RTOG did not show this to be the case in a recent analysis. Furthermore, an analysis of race did not indicate an association with outcome. In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between gender/to race and treatments. The participation rates of men and women will be examined according to Section 13.5.1. The projected gender and minority accruals are shown below:

<table>
<thead>
<tr>
<th></th>
<th>American Indian or Alaskan Native</th>
<th>Asian or Pacific Islander</th>
<th>Black, not of Hispanic Origin</th>
<th>Hispanic</th>
<th>White, not of Hispanic Origin</th>
<th>Other or Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td>8</td>
<td>4</td>
<td>70</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>16</td>
<td>6</td>
<td>140</td>
<td></td>
<td>162</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>24</td>
<td>10</td>
<td>210</td>
<td></td>
<td>244</td>
</tr>
</tbody>
</table>
REFERENCES


42. Delaflor-Weiss E, Blommaert F, Gilli, Muggia FM, Cortes V, den Engelse L. Amifostine (WR-2721) protects from bone marrow toxicity of combinations of cisplatin (P) and carboplatin (C) without decreasing platinum-DNA adduct formation. 8th NCI/EORTC Symposium on New Drugs and Cancer Therapy. 1994;214. Abstract.


52. Osoba D, Aaronson NK, Zee B, Sprangers M, te Velde A. Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer. The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committees of the NCI of Canada Clinical Trials. Quality of Life Research, 6 (2), 103-108, 1997.


APPENDIX I

RTOG 98-01

A PHASE III STUDY OF AMIFOSTINE MUCOSAL PROTECTION FOR PATIENTS WITH FAVORABLE PROGNOSIS INOPERABLE STAGE II-III/A/B NON-SMALL CELL LUNG CANCER (NSCLC) RECEIVING SEQUENTIAL INDUCTION AND CONCURRENT HYPERFRACTIONATED RADIOTHERAPY WITH PACLITAXEL AND CARBOPLATIN

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks, benefits, and alternatives. This disclosure is an effort to make me better informed so that I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I have been diagnosed with a lung cancer that cannot be completely removed. Further treatment is recommended. There is some evidence that the best treatment for my condition involves both radiation therapy and chemotherapy. Radiation therapy is a form of cancer treatment using high energy x-rays. Chemotherapy is a form of cancer treatment using special medications. Previous studies have shown that chemotherapy given prior to radiation therapy or at the same time as radiation is more effective for patients with lung tumors such as mine when compared to radiation treatments alone. This study uses two cycles of chemotherapy (paclitaxel and carboplatin) every 3 weeks followed by weekly chemotherapy combined with twice daily radiation given five days a week for approximately 6 weeks. Since this treatment combination has been associated with difficulty, pain, or a burning sensation upon swallowing, the purpose of this study is to investigate whether the addition of another drug, amifostine, can reduce the side-effects of the treatment. In addition, this study will evaluate whether giving chemotherapy before the combination radiation/chemotherapy portion improves the effectiveness of treatment. Another purpose in doing this research will be to evaluate the differences in quality of life and symptoms and the relationship of tobacco and alcohol use during treatment, as applicable.

DESCRIPTION OF PROCEDURES (4/1/99)

This study involves a random (by chance) assignment to the addition of the drug amifostine or not. It is not clear at the present time whether or not amifostine effectively reduces the side effects of the chemotherapy and radiation. There is no evidence that amifostine will protect the tumor itself. The therapy that is to be offered to me will be based upon the method of selection called randomization. Randomization means that my physician will call a statistical office which will assign me one of the treatments by computer. The chance of receiving Arm 1 (with amifostine) is equally likely as that of receiving Arm 2 (no amifostine). I will be treated with one of following:

Arm 1

On days 1 & 22, I will receive chemotherapy (on an out-patient basis) consisting of paclitaxel by i.v. infusion (in my vein) over a 3-hour period, followed by carboplatin (by i.v. infusion) over one half hour. G-CSF may be given by an injection under the skin (to improve my blood counts) for approximately 10-14 days. Starting on day 43, I will begin twice daily radiation treatments (separated by at least 5 hours), 5 days per week, for approximately 6 weeks. During the radiation, I will also receive weekly chemotherapy infusions with paclitaxel & carboplatin (prior to the second daily radiation treatment). G-CSF will not be given during the radiation period.

If I am randomized to Arm 1, I will also receive amifostine as a 5 minute intravenous infusion prior to my afternoon radiation treatment 4 days a week (Monday through Thursday) for a total of 24 treatments over 6 weeks. My blood pressure will be checked frequently before and after the amifostine injections.
**Arm 2**

On days 1 & 22, I will receive chemotherapy (*on an out-patient basis*) consisting of paclitaxel by i.v. infusion (*in my vein*) over a 3-hour period, followed by carboplatin (*by i.v. infusion*) over one half hour. G-CSF may be given by an injection under the skin (*to improve my blood counts*) for approximately 10-14 days. Starting on day 43, I will begin twice daily radiation treatments (*separated by at least 5 hours*), 5 days per week, for approximately 6 weeks. During the radiation, I will also receive weekly chemotherapy infusions with paclitaxel & carboplatin (*before the second daily radiation treatment*). G-CSF will not be given during the radiation period.

The study treatment calendar for both treatment arms is summarized below:

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 22</th>
<th>Day 43</th>
<th>Day 50</th>
<th>Day 57</th>
<th>Day 64</th>
<th>Day 71</th>
<th>Day 78</th>
</tr>
</thead>
<tbody>
<tr>
<td>P#1</td>
<td>P #2</td>
<td>P #3</td>
<td>P #4</td>
<td>P #5</td>
<td>P #6</td>
<td>P #7</td>
<td>P #8</td>
</tr>
<tr>
<td>------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>C#1*</td>
<td>C#2*</td>
<td>C#3</td>
<td>C#4</td>
<td>C#5</td>
<td>C#6</td>
<td>C#7</td>
<td>C#8</td>
</tr>
</tbody>
</table>

*(RT AM) XXXX XXXX XXXX XXXX XXXX XXXX XXXX
(AM) AAAA AAAA AAAA AAAA AAAA AAAA
(RT PM) XXXX XXXX XXXX XXXX XXXX XXXX

* P = Paclitaxel on days 1, 22, 43, 57, 64, 71, 78**
* C = Carboplatin on days 1, 22, 43, 57, 64, 71, 78**
* A = For patients randomized to amifostine arm, amifostine will be given 4 days a week prior to afternoon radiation treatments.
* * G-CSF for 10-14 days, if given.
* ** On days 43-78, chemotherapy will be administered prior to the afternoon radiation treatment.

Since the purpose of this study is to reduce the side effects of treatment, I will be asked to fill out a questionnaire which describes my symptoms, my day-to-day activities, and my overall sense of well-being before treatment starts, just before the start and at the end of chemoradiation, and at my first follow-up appointment. The average time to complete this questionnaire is 12 minutes.

Since both tobacco and alcohol use may increase the side effects of treatment I have been advised to stop both, I will be asked to complete a questionnaire about my smoking and drinking habits before and after treatment. The average time to complete this questionnaire is two minutes.

After completion of my treatment, I will be followed one month later, then every 3 months for one year, then every six months for two years and then annually. A CT scan of the chest and pulmonary (*lung*) function studies will be obtained every 6 months for two years after the chemoradiation and then annually. On visits when I do not have a CT scan done, I will have a chest x-ray. At every visit, I will also have blood work done. Other tests will be done as needed.

With my permission, additional small samples of my blood will be collected and stored for future studies that might be helpful to better understand and treat future patients with a similar kind of tumor. Blood samples would be collected at the start of any treatment, at the start of combined chemoradiation, at the end of the chemoradiation, and at my first followup appointment.

**RISKS AND DISCOMFORTS**

Cancer treatments often have side effects. The treatment used in this program may cause all, or some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

*Amifostine* may cause lowering of blood pressure, nausea, vomiting, a warm or flushed feeling, tiredness, chills or feeling cold, sneezing, dizziness, sleepiness, hiccups, a metallic taste in my mouth, allergic reactions (*rare*), and a temporary decrease in calcium levels in the blood. This drug is given to help decrease the risk of side effects from the radiation therapy and chemotherapy, particularly to decrease esophagitis (*or painful and difficult swallowing*).
**Carboplatin (Paraplatin)** can lower the blood counts, which could cause an increased risk of infection, bleeding or tiredness. I might need antibiotics, hospitalization, and/or transfusions if the blood counts are severely lowered. It may cause nausea and vomiting, diarrhea, weight loss, fever, and hair loss. It rarely causes damage to the liver and kidney. The damage is usually detected by blood tests and usually reverts to normal when the drug is stopped. Also ringing in the ears, numbness of the fingers and toes, cessation of menstrual periods, allergic reactions, and decrease in calcium or magnesium levels may occur.

**G-CSF** may produce bone pain, muscle aches, headaches, an increase in the level of liver enzymes in the blood and a possible increase in uric acid in the blood. This may increase the risk of kidney stones. G-CSF may also cause an enlarged spleen and worsening of any pre-existing inflammatory disease such as psoriasis or vasculitis. Rarely seen side effects of G-CSF include allergic reactions, chest pain, diarrhea and decrease in blood pressure with the first injection. I will take Benadryl and acetaminophen (Tylenol) prior to the G-CSF injections in an attempt to minimize these side effects.

**Paclitaxel** can commonly cause a decrease in the white blood cell count, leading to an increased risk of fever and infection; a decrease in the red blood cell count leading to anemia, a weak and tired feeling; and a decrease in the platelet count which may lead to easy bruising and/or bleeding. It can also cause sores in the mouth, nausea and vomiting, muscle and/or joint aches, and hair loss. Paclitaxel can cause numbness and tingling in the hands and feet that may lead to difficulty walking, or manipulating fine objects. Paclitaxel could infiltrate outside of the vein to the skin or adjacent tissues leading to redness, tenderness, induration and rarely ulceration. Rare side effects include allergic reactions with hives, wheezing, and low or high blood pressure; pleurisy (chest pain when breathing deeply or coughing) with or without fluid build-up in the pleural space between the lung(s) and chest wall; abnormalities in heart rate, which may cause lightheadedness but are generally of little concern, and disappear when drug treatment has finished; bowel inflammation and/or damage (colitis); mental status changes; radiation-recall (whereby the side effects of the radiation can recur); the sensation of flashing lights, blurred vision or blind spots; an increase in liver enzyme tests or rarely, liver damage. There is also the unlikely possibility that Taxol may result in blood in my urine.

**Radiation Therapy** may cause: 1) difficulty, pain or burning sensation on swallowing. This effect usually begins after the second week of radiotherapy and goes away within a month of completion of radiation therapy; 2) fatigue - tiredness for no apparent reason, which is a temporary effect, resolving within a month of completion of treatment; 3) skin damage within the area of radiation; the skin may develop a sunburn-like appearance which may itch, feel dry, or burn slightly. Although this resolves within 2-6 weeks after treatment, the skin will be permanently more dry than other skin, and chest hair (if any) may not regrow; 4) decrease in white blood cells and platelets. Decrease in platelet cell production may result in bleeding and bruising easily; 5) cough and some difficulty in breathing due to lung damage (radiation pneumonitis and subsequent scarring of the lung). In addition, although uncommon, pericarditis (irritation of the heart sac), myocarditis (irritation of the heart muscle), transverse myelitis (irritation of spinal cord), or esophageal narrowing may occur long after radiation therapy.

My physician will be checking me closely to see if any of these side effects are occurring. Routine tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor will prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects (such as antiemetics prior to amifostine for nausea) will result in added costs. This institution is not financially responsible for treatment of side effects caused by the study treatments.

This study may be harmful to an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to pregnant women causes significant risks to the fetus. If I am a woman of childbearing age and have not been surgically sterilized (tubal ligation or hysterectomy), I must have a pregnancy test before enrolling in this study. I must use adequate birth control measures to prevent pregnancy while participating in this study. If I am unwilling to use adequate birth control measures to prevent pregnancy, I should not participate in this study. If I should become pregnant while on this study, I must tell my doctor immediately.

**CONTACT PERSONS**

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I
receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr._________ the investigator in charge at ________. In addition, I may contact _____________ at ________ for information regarding patients’ rights in research studies.

**BENEFITS**

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

**ALTERNATIVES**

Although combined modality treatment with chemotherapy and radiotherapy have been associated with a modest improvement in survival compared to radiotherapy alone, alternatives which could be considered in my case include radiation therapy and chemotherapy either alone or together or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

**VOLUNTARY PARTICIPATION**

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care.

**CONFIDENTIALITY**

Records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representative of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

_________________________  ________________________
Patient Signature (or Legal Representative)  Date
BLOOD TESTING (4/1/99)

I agree to the use of my four blood samples for additional research studies.

☐ Yes  ☐ No

______________________________  _______________________
Patient Signature (or Legal Representative)  Date
### APPENDIX II

**KARNOFSKY PERFORMANCE SCALE**

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

ANATOMICAL STAGING FOR LUNG CANCER
(AJCC, 1997)

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
(AJCC, 1997)

Distant Metastasis (M)

MX  Distant metastasis cannot be assessed

M0  No distant metastasis

M1  Distant metastasis present

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

STAGE GROUPING

Occult Carcinoma  TX  N0  M0
Stage 0  Tis  N0  M0
Stage IA  T1  N0  M0
Stage IB  T2  N0  M0
Stage IIA  T1  N1  M0
Stage IIB  T2  N1  M0
          T3  N0  M0
Stage IIIA  T1  N2  M0
           T2  N2  M0
           T3  N1  M0
           T3  N2  M0
Stage IIIB  Any T  N3  M0
           T4  Any N  M0
Stage IV  Any T  Any N  M1
<table>
<thead>
<tr>
<th>ORGAN TISSUE</th>
<th>0</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN</td>
<td>None</td>
<td>Slight atrophy; Pigmentation change; Some hair loss</td>
<td>Patch atrophy; Moderate telangiectasia; Total hair loss</td>
<td>Marked atrophy; Gross telangiectasia</td>
<td>Ulceration</td>
<td>D</td>
</tr>
<tr>
<td>SUBCUTANEOUS TISSUE</td>
<td>None</td>
<td>Slight induration (fibrosis) and loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymptomatic; Slight field contracture; &lt;10% linear reduction</td>
<td>Severe induration and loss of subcutaneous tissue; Field contracture &gt; 10% linear measurement</td>
<td>Necrosis</td>
<td>E</td>
</tr>
<tr>
<td>MUCOUS MEMBRANE</td>
<td>None</td>
<td>Slight atrophy and dryness</td>
<td>Moderate atrophy and telangiectasia; Little mucus</td>
<td>Marked atrophy with complete dryness; Severe telangiectasia</td>
<td>Ulceration</td>
<td>U</td>
</tr>
<tr>
<td>SALIVARY GLANDS</td>
<td>None</td>
<td>Slight dryness of mouth; Good response on stimulation</td>
<td>Moderate dryness of mouth; Poor response on stimulation</td>
<td>Complete dryness of mouth; No response on stimulation</td>
<td>Fibrosis</td>
<td>F</td>
</tr>
<tr>
<td>SPINAL CORD</td>
<td>None</td>
<td>Mild L’Hermitte’s syndrome</td>
<td>Severe L’Hermitte’s syndrome</td>
<td>Objective neurological findings at or below cord level treated</td>
<td>Mono, para quadriplegia</td>
<td>Q</td>
</tr>
<tr>
<td>BRAIN</td>
<td>None</td>
<td>Mild headache; Slight lethargy</td>
<td>Moderate headache; Great lethargy</td>
<td>Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)</td>
<td>Seizures or paralysis; Coma</td>
<td>C</td>
</tr>
<tr>
<td>EYE</td>
<td>None</td>
<td>Asymptomatic cataract; Minor corneal ulceration or keratitis</td>
<td>Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma</td>
<td>Severe keratitis; Severe retinopathy or detachment Severe glaucoma</td>
<td>Panophthalmitis/Blindness</td>
<td>P</td>
</tr>
<tr>
<td>LARYNX</td>
<td>None</td>
<td>Hoarseness; Slight arytenoid edema</td>
<td>Moderate arytenoid edema; Chondritis</td>
<td>Severe edema; Severe chondritis</td>
<td>Necrosis</td>
<td>N</td>
</tr>
<tr>
<td>LUNG</td>
<td>None</td>
<td>Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances</td>
<td>Moderate symptoms; Some abnormal liver function tests; Serum albumin normal</td>
<td>Severe symptoms of fibrosis or pneumonitis; Dense radiographic changes</td>
<td>Severe respiratory insufficiency/continuous 02/Assisted ventilation</td>
<td>T</td>
</tr>
<tr>
<td>HEART</td>
<td>None</td>
<td>Asymptomatic or mild symptoms; Transient T wave inversion &amp; ST Changes; Sinus tachycardia &gt;110 (at rest)</td>
<td>Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes ; Low ORS</td>
<td>Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities</td>
<td>Tamponade/Severe heart failure/Severe constrictive pericarditis</td>
<td>R</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>None</td>
<td>Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing</td>
<td>Unable to take solid food normally; Swallowing semi-solid food; Dilatation may be indicated</td>
<td>Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilatation required</td>
<td>Necrosis/Perforation Fistula</td>
<td>X</td>
</tr>
<tr>
<td>SMALL/LARGE INTESTINE</td>
<td>None</td>
<td>Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colic; Bowel movement &gt;5 times daily; Excessive rectal mucus or intermittent bleeding</td>
<td>Obstruction or bleeding, requiring surgery</td>
<td>Necrosis/Perforation Fistula</td>
<td>F</td>
</tr>
<tr>
<td>LIVER</td>
<td>None</td>
<td>Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function</td>
<td>Moderate symptoms; Some abnormal liver function tests; Serum albumin normal</td>
<td>Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites</td>
<td>Necrosis/Hepatic coma or encephalopathy</td>
<td>Y</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>None</td>
<td>Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%;Creatinine 1.5-2.0 mg%; Creatinine clearance &gt; 75%</td>
<td>Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea &gt;36-60mg% Creatinine clearance (50-74%)</td>
<td>Severe albuminuria; Severe hypertension Persistent anemia (&lt; 10%); Severe renal failure; Urea &gt;60 mg% Creatinine &gt;4.0 mg% Creatinine clearance &lt; 50%</td>
<td>Malignant hypotension; Uremic coma/Urea &gt; 100%</td>
<td>O</td>
</tr>
<tr>
<td>BLADDER</td>
<td>None</td>
<td>Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)</td>
<td>Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria</td>
<td>Severe frequency &amp; dysuria Severe generalized Telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (~ &lt; 150 cc)</td>
<td>Necrosis/Contracted bladder (capacity &lt; 100 cc); Severe hemorrhagic cystitis</td>
<td>I</td>
</tr>
<tr>
<td>BONE</td>
<td>None</td>
<td>Asymptomatic; No growth retardation; Reduced bone Density</td>
<td>Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis</td>
<td>Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis</td>
<td>Necrosis/Spontaneous fracture</td>
<td>A</td>
</tr>
<tr>
<td>JOINT</td>
<td>None</td>
<td>Mild joint stiffness; Slight limitation of movement</td>
<td>Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement</td>
<td>Severe joint stiffness; Pain with severe limitation of movement</td>
<td>Necrosis/Complete fixation</td>
<td>R</td>
</tr>
</tbody>
</table>
APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supercede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.

   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment **regardless of cause** requires telephone notification within 24 hours of discovery.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

   A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated Intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. **All fatal toxicities (grade 5)** resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. **All life-threatening (grade 4)** toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

i. Any fatal (grade 5) or life threatening (grade 4) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters’ Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions (> grade 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters’ Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities (> grade 3) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (IDB)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent. Report by phone within 24 hours to IDB and RTOG Headquarters.
A written report to follow within 10 working days.

- All deaths within 30 days of termination of the agent.
  As above

- All life threatening (grade 4) events which may be due to agent.
  As above

- First occurrence of any toxicity (regardless of grade).
  Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters.
  **A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent.
  Report by phone to RTOG Headquarters and the Study Chairman within 24 hours
  **A written report must be sent to RTOG within working days with a copy to IDB.
  (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.
  Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours.
  **A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.
  **Report in writing to RTOG Headquarters and IDB within 10 working days.

** See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form
APPENDIX VI (4/1/99)

RTOG 98-01

AMIFOSTINE SHIPMENT FORM

Livingston, Inc. will ship amifostine only to institutions who have identified a single individual associated with the investigational drug unit of the institution. This form must be completed and returned to RTOG Headquarters prior to registering any patients on study. Documentation of IRB approval must be enclosed. Allow adequate processing time (7-10 days) at Headquarters before calling to randomize your first patient. Twenty eight vials of amifostine will be shipped for each patient randomized to Arm 1.

SHIP TO:

Name: ____________________________________________________________

Address: _________________________________________________________

(No P.O. Box numbers)

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

Telephone:________________________________________________________

Fax#: ___________________________________________________________

RTOG Institution#: ________________________________

Institution Name: ________________________________________________

IRB Approval Date: ___________________________________________________________________(attach copies of IRB approval and sample consent form)

Investigator (PI) Signature __________________________________________ Date: ___________

Investigator Name (Print) ____________________________________________

Investigator NCI # (Required) _________________________________________

Return to:

RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107

ATTN: ELAINE PAKURIS
FAX# 215/574-0300

RTOG Headquarters Approval _________________________________________ Date: ___________

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APPENDIX VII

STUDY FOR THE EVALUATION OF CIRCULATING CYTOKINES AS BIOMARKERS OF THERAPY-INDUCED LATE EFFECTS.

1. BLOOD SAMPLE COLLECTION INSTRUCTIONS

1.1 The majority of studies performed to date have established a correlation between either pre-treatment, intra-treatment or immediately post-treatment serum cytokine values. Therefore, blood samples taken at the following timepoints will be analyzed:

1) Pretreatment
2) Pre-chemoradiation (post-induction chemotherapy)
3) Week 6 of chemoradiation
4) Post-treatment: 6-week follow-up visit

(Note: These are the same timepoints as the required QOL forms).

1.2 At each of these 4 timepoints, two 10 ml tubes must be drawn (1 red top serum tube and 1 green top (Na) plasma tube), in addition to other blood work as required per protocol. The red top tube is allowed to stand for 20 minutes at room temperature; the green top tube is placed on ice. Following this time period, the tubes must be spun for serum and plasma collection at 1200 r.p.m. for 10 minutes in a refrigerated centrifuge at 0°C.

1.3 Please be sure to clearly label all tubes (with a method that will not scrape off or fall off the tube) with the patient ID #, date, and "P" for plasma (for the blood collected in the green top tube) versus "S" for serum (for the blood collected in the red top tube). The samples must then be stored aseptically at -80°C. Please do not use capped tubes.

1.4 Mail specimens on sufficient dry ice. We recommend that the four blood specimens from each patient be mailed together to save cost. Send specimens by Federal Express and address specimens to:

Radiation Oncology Laboratory
Strong Memorial Hospital
Room G6628
601 Elmwood Avenue
Rochester, NY 14642
(716) 275-1687
Attention: Dr. Jacqueline Williams
Label package: Freeze on arrival. RTOG 98-01.

DO NOT MAIL SPECIMENS WITH A WEEKEND OR HOLIDAY ARRIVAL DATE.

1.5 Note: For the first 90 patients accrued to this companion study, the accruing institution will be reimbursed $100 per patient.

2. BACKGROUND

The pathological sequence of events leading to the development of therapeutic side effects in the upper GI tract, i.e. the esophagus, has been well described, both for radiation and chemotherapy. For instance, following irradiation, a recent review by Coia et al. noted that the target cells producing the majority of acute effects are those of the basal epithelial layer of the esophagus. Biomarkers, which could identify activation of cells or pathway(s) in a patient leading to these adverse effects, either pre- or during the course of treatment, would allow for amelioration and/or prevention and could, therefore, greatly improve the therapeutic ratio.

One of the most basic tenets of radiation biology describes the indirect action of radiation in biologic material, producing an array of free radicals. These entities are highly diffusible and reactive, capable of reaching and damaging critical cellular targets. There is now increasing evidence implicating the involvement of free radicals, particularly those derived from molecular oxygen, in radiation-induced damage leading to
late effects. The major forms of active oxygen are superoxide \((O_2^-)\), singlet oxygen \((^1O_2)\), the hydroxyl radical \((\cdot OH)\) and hydrogen peroxide \((H_2O_2)\). These can all transiently or permanently damage nucleic acids, lipids and proteins. Active oxygen and the ensuing lipid peroxidations may affect tissues in two ways: (1) by causing DNA damage and chromosomal rearrangement, or (2) by modulating and/or activating genes that regulate cell repair mechanisms and pathways.

Nonetheless, a primary focus of many laboratories looking at radiation late effects has been to define the cytokine induction pathways following irradiation. In recent years, our group, along with other investigators, has focused strongly on the inflammatory component of this process and we have studied, in particular, two primary proinflammatory cytokines, tumor necrosis factor-α (TNFα) and interleukin-1 (IL-1) in radiation lung late effects.\(^4\sim6\) Tumor necrosis factor-α in particular has been shown to be of primary importance in pulmonary fibrosis following injury and has been demonstrated to coordinate and network secondary, downstream cytokines and chemokines, recruiting and amplifying inflammatory cells and components.\(^7\sim8\) This network ultimately leads to the expression of radiation-induced late effects. In addition, our group in conjunction with RTOG and Dr. William Hartsell has previously investigated the role played by IL-1, IL-6 and TNFα in the promotion or causation of pulmonary toxicity following irradiation.

However, the cytokine pathways and the free radical components of radiation-induced injury are not separate issues and these two entities may have an interwoven effect; as with all cytokine-driven mechanisms, there is a pleuripotentiality and cell-specific or organ-specific mechanism. It has been shown that reactive oxygen intermediates and radicals induce elevated expression of proinflammatory cytokines: TNFα, IL-1α, IL-6, G-MCSF and MIP-2 in skin\(^9\) and in blood vessels,\(^10\) leading to recruitment of inflammatory cells.\(^11\) Multiple oxygen radical generating systems also have been shown to contribute to TNFα-stimulated transcriptional activation of VCAM-1 in endothelial cells.\(^12\) However, the presence of TNFα and IL-1α have been shown to both increase superoxide production by neutrophils\(^13\) and decrease free radical generation in cancer cell lines.\(^14\) In addition, elevated levels of primary proinflammatory cytokines have correlated with enhanced mitochondrial radical production in rheumatoid arthritis patients. Of major importance is that cytokines such as IL-1 and TNFα induce specific cellular responses through the activation of the transcriptional factor, NF kappa B. This activation requires the phosphorylation of an inhibitory subunit which relies upon intracellular production of reactive oxygen intermediates. This then begs the question, which came first: the reactive oxygen species or the primary proinflammatory cytokines? In all probability, the answer is both, with a cyclical pathway inducing and maintaining the process. Radiation may initiate and/or promote this self-sustaining process.

Of note, other inflammatory cytokines, notably IL-8, have been shown to reduce free radical production systemically\(^15\) and IL-8’s production by endothelial and epithelial cells is mediated by reactive oxygen species. Interleukin-8 has been hypothesized as a major chemokine in airway epithelium response to injury\(^16\sim17\) and would therefore be a primary marker for epithelial cell damage as described by Coia et al.\(^1\) In addition, studies using transforming growth factor-β (TGFβ) as a serum biomarker have shown good correlation with late radiation injury.\(^18\sim19\)

**Preliminary Data**

Our group has previously functioned as the reference laboratory for RTOG 91-03 and is therefore equipped to receive, manage and analyze both plasma and serum samples. In addition, using an in-house protocol, we have analyzed circulating cytokines as predictors of lung radiation injury in patients receiving thoracic irradiation. The cytokines examined included the interleukins IL-1α, IL-1β and IL-6, and TNFα. Preliminary results have been previously reported.\(^20\) Circulating levels of cytokines were correlated to clinical late effects as defined by chest X-rays and CT scans. Patients were independently assessed for the development of pneumonitis. The strongest correlation was found with IL-6 (Figure 1).
The mean pretreatment plasma levels of IL-6 were significantly higher for those patients who subsequently developed pneumonitis than those who did not (76 pg/ml vs. 0.5 ng/ml, p=0.01). Figure 1 illustrates the differences in circulating levels of IL-6 according to pneumonitis grading. It is interesting to note that there was a comparable elevation of IL-6 in those patients who demonstrated radiographic infiltrates up to the 12 week timepoint, at which time their levels returned to baseline. This corresponded with the mean time of onset of clinical symptoms.

**Figure 1.**

With respect to TNFα, no apparent correlation was found between circulating levels and the induction of radiation pneumonitis in our protocol (see Table 1). This may be a function of the short half-life of TNFα or the endpoint used. For instance, Dr. Hartsell has reported at a recent RTOG meeting a correlation between pretreatment TNFα values and the endpoint used on RTOG 91-03, i.e., dyspnea scores.

**Table 1. Patients demonstrating detectable vs. non-detectable plasma levels of TNFα in relation to incidence of symptomatic pneumonitis vs. no clinical symptoms of pneumonitis.**

<table>
<thead>
<tr>
<th></th>
<th>Pneumonitis (Grade 2A &amp; 2B)</th>
<th>No Pneumonitis (Grade 0 &amp; 1)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=0.63 by 2 tail Fisher Exact Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNFα+</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>TNFα-</td>
<td>11</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td><strong>During Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=0.22 by 2 tail Fisher Exact Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNFα+</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>TNFα-</td>
<td>11</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>10</td>
<td>25</td>
</tr>
</tbody>
</table>

3. **OBJECTIVES**

**Objective 1:** To assess the value of analyzing oxidative stress markers to predict for radiation late effects.

Much attention has been focused on the effects of reactive oxygen species (ROS) on DNA, and various types of oxidative lesions have been identified. One conventional biomarker for oxidative stress is 8-hydroxy-2-deoxyguanosine, an oxidative DNA adduct which can now be assayed using a newly developed ELISA kit. Analysis of oxidative stress, when taken in conjunction with cytokine levels, should provide a powerful indicator of induced tissue damage. This would be especially true during the course of treatment. Since amifostine (WR 2721) has proved to be protective against free radical-induced damage by acting as a radical scavenger, use of this oxidative stress marker could act as a direct measure of scavenger success. If measurements prove correlative, real time adjustments in drug administration levels could be made.
Objective 2: To assess the value of analyzing circulating cytokine levels to predict for radiation late effects.

To date, a number of circulating cytokine levels have been measured in patient serum and appear to have clinical relevance: TNFα, IL-1, TGFβ, IL-6, and IL-8. Tumor necrosis factor-α could well provide a marker for both tissue damage and the induction of inflammatory processes. However, the poor specificity of presently available capture antibodies and its pleuripotential nature offsets its advantages. However, good (specific) ELISA capture antibodies are available for both IL-1α and IL-1β; circulating levels of these cytokines will be used as a measure of primary damage and activation. Correlation may be found between these values and oxidative stress that would further enhance the use of amifostine. More useful tools with respect to late effects, however, may well prove to be more down-stream indicators: TGFβ, IL-6 and IL-8. Interleukin-6 will indicate activation of the inflammatory mechanisms as demonstrated by preliminary data from our group, while TGFβ is a potent inflammatory and fibrogenic cytokine, known from clinical studies to be involved in thoracic fibrosis. The latter cytokine (IL-8) has a more direct chemokine effect, is implicated in free radical response and is highly correlatative both with endothelial and epithelial cell damage. The latter is the primary radiation target leading to esophagitis.

4. DATA ANALYSIS

At the University of Rochester, the specimens will be thawed, aliquoted and then analyzed in batches containing a minimum of a complete batch of samples per patient (where applicable). Sample concentrations of 8-hydroxy-2-deoxyguanosine, IL-1β, IL-1α, TGFβ1, IL-6 and IL-8 will be determined by ELISA. The resulting serum/plasma levels of the markers for each patient will be determined in two separate trials.

These samples, collected prospectively, will allow correlation of cytokine/chemokine concentrations with the defined endpoint of pulmonary injury following chemoradiotherapy and use of amifostine.

Levels of cytokines in patient samples will be determined by ELISA. These assays will be performed in 96 well micro-titer plates. The wells are coated with the appropriate human anti-cytokine, washed with PBS/Tween, and then blocked with PBS/10% FBS (fetal bovine serum)/0.1% azide. Standards and patient samples are then applied and incubated overnight at 4°C and washed. Wells are incubated for 1 hour with biotinylated rat-anti-human and then washed; this is followed by a 1 hour incubation with streptavidin-AP at 37°C. The wells are washed and a 1 mg/ml PNPP solution (p-nitrophenyl phosphate) is added and color is allowed to develop for 10 to 20 minutes; the reaction is stopped with 3N NaOH. The absorbency between 490-410 nm per well is determined spectrophotometrically.

5. REFERENCES


