02-014

TRIMODALITY PROTOCOL FOR THE TREATMENT OF LOCALLY ADVANCED, POTENTIALLY RESECTABLE NON-SMALL CELL LUNG CANCER TARGETING

- **Pancoast tumors**
- **T_4N_X primary lesions invading mediastinum**
- **Chest wall lesions**
- **Potentially resectable N_2 NSCLC**

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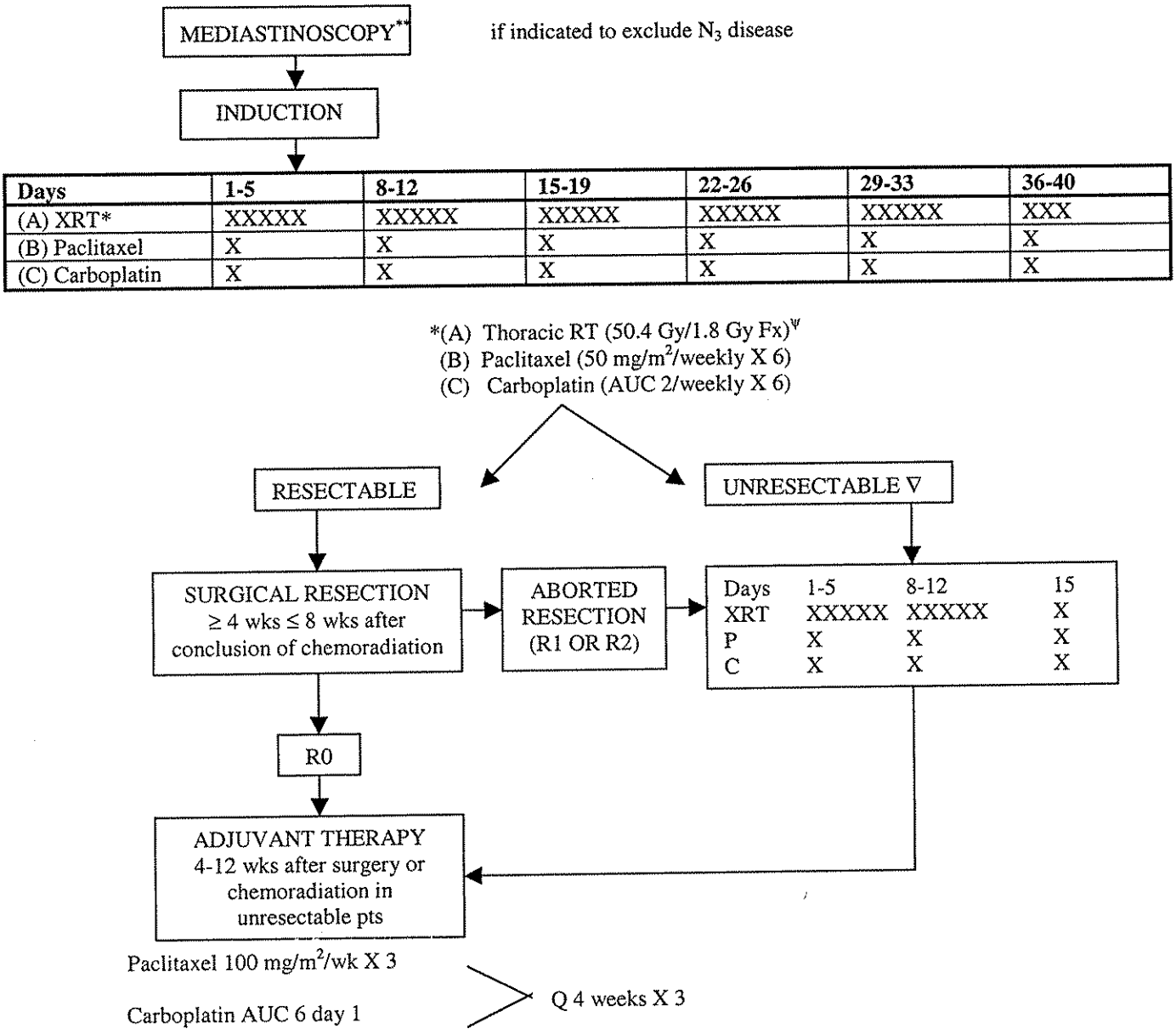
(1) SCHEMA



Days	1-5	8-12	15-19	22-26	29-33	36-40
(A) XRT*	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXX
(B) Paclitaxel	X	X	X	X	X	X
(C) Carboplatin	X	X	X	X	X	X

*If mediastinoscopy and CT (-) or PET scan (-) for nodal involvement, then can treat "involved field" (primary +/- hilum)

∇Mediastinoscopy or Chamberlain procedure mandatory in patients with T_3N_x chest wall disease; Pancoast tumors and those with potentially resectable N_2 involvement

ΨΨ5940cGy/180c Gy Fx to chest wall region only for patients with chest wall disease.

****Patients who prove unresectable or who undergo thoracotomy or aborted R0 resection will receive additional XRT (up to a maximum of 1980cGy/180cGy per fraction) plus concurrent chemotherapy as stipulated above (during induction) followed by adjuvant therapy after hematologic recovery.**

2.0 INTRODUCTION/RATIONALE

Locally advanced, potentially resectable NSCLC remains a therapeutic challenge. Multiple studies have investigated the role of induction chemotherapy, either alone or in conjunction with radiation with or without subsequent surgical resection, with promising results (1-9). Pathologic complete remissions have been observed, and when chemotherapy is given concurrently with radiation in the induction setting, the rate of pCR has been as high as 15-25% (5-8).

Three separate phase III randomized trials have investigated the utility of induction chemotherapy followed by surgery vs. surgery alone in resectable stage III-A NSCLC. Two of these studies, albeit relatively small efforts, were positive, with improvements in median and long-term survival (2, 3). The third, the largest, from France, using MIC chemotherapy followed by surgery, demonstrated a trend toward improved survival at three years (52% vs. 41%, $p = 0.09$), which did not meet statistical significance. Of note, the combined modality arm included a higher proportion of N_2 patients compared to the surgery only arm, leading to potential selection bias favoring the control group (4).

Some of the most promising results in marginally or initially unresectable III-A and III-B disease has been observed with induction concurrent chemoradiation followed by surgical resection (5-9a). Fleck et al. reported therapeutic superiority for induction chemoradiation vs chemotherapy alone prior to surgical resection in the setting of resectable, locally advanced NSCLC (LA-NSCLC) with significant improvement in resection rates, freedom from progression, median and 2-year survival rates for the trimodality approach (5). The Southwest Oncology Group reported an update of their trial with induction etoposide and cisplatin given for two cycles concurrently with thoracic RT (45 Gy) followed by surgical resection, and additional "adjuvant" chemotherapy. This was the largest trial ever mounted in the setting of LA-NSCLC. The R0 resection rate (negative margins; highest node (-)) was 60% for IIIB lesions and 75% for IIIA patients. Twenty of 122 evaluable patients died in the induction period or peri-operative period. Despite these observations, the long-term six year survival rate was 20% and 22%, respectively, for pathologically documented III-A and III-B disease (9). Outcome was best in those who had pathologic complete remissions, downstaging from N_2 or N_3 to N_0 or N_1, and in T_4N_X patients (6). An intergroup study (RTOG 9309) is currently evaluating the role of bi-modality therapy (chemoradiation alone) vs. tri-modality therapy (chemoradiation followed by surgery) in potentially resectable N_2 NSCLC; this study completed accrual in January of 2002.

In addition, an intergroup phase II study has used the same concept (concurrent chemoradiation with etoposide and cisplatin followed by surgery) in potentially resectable, mediastinoscopy (-) Pancoast tumors. Historically, in this group, *standard* treatment has featured radiation upfront followed by surgical resection (10, 11), but local and distant recurrence rates are generally high and long-term survival is 20-30% at best in selected good prognosis patients, indicating a need for more aggressive local and systemic control.

Standard treatment in resectable T_3 NSCLC (chest wall invasion) has generally been surgery, either alone or followed by local XRT to the tumor bed (12-13). Five year survival

rates in this group approach 25-40%, but these patients also have a relatively high incidence of local and systemic recurrence.

There is major need to introduce newer, more effective, less toxic agents into the induction setting. Taxane-based systemic chemotherapy has yielded improvements in response rate and improved survival compared to platinum alone or etoposide/cisplatin in advanced, stage IV NSCLC (14-15). Most induction regimens have employed cisplatin. However, toxicity is a major concern. Carboplatin, an analog of cisplatin, is a far safer platinating agent, with much less, non-hematologic toxicity, specifically a marked reduction in nephrotoxicity, neurotoxicity, ototoxicity, and GI toxicity. Its tendency toward enhanced myelosuppression has been offset, in part, by pharmacokinetic (AUC) based dosing. In combination with etoposide, it has proven equivalent to "standard" etoposide/cisplatin (16). In addition, as a single agent, despite somewhat lower response rates (9%) vs. cisplatin combinations (14-21%), initial therapy with carboplatin has yielded improvements in median survival (31 weeks vs. $\leq$ 26 weeks), with substantially lower toxicity (3% grade 4 vs. 13% or higher grade 4 toxicity with cisplatin combinations) (17). Newer combinations of paclitaxel and carboplatin have demonstrated promising activity in advanced NSCLC and have proven equivalent to other new, more toxic combinations (e.g., vinorelbine and cisplatin) (18-24).

Hence, it is reasonable to introduce paclitaxel and carboplatin into induction therapy in potentially resectable patients. Fledgling attempts have been mounted. Rice and colleagues (Proc IASLC 1997 A-245) evaluated the role of concurrent chemoradiation with paclitaxel, in combination with cisplatin in stage III-A and III-B disease, demonstrating a complete resection rate of 71% and a promising two-year survival rate of 65% (25). The regimen employed, however, was not user-friendly: paclitaxel was given at a dose of 175 mg/m^2 over 24 hours, in combination with cisplatin 20 mg/m^2 daily X 4, with concurrent XRT (30 Gy total; 1.5 Gy bid X 2 weeks). This resulted in substantial toxicity, including an 89% incidence of esophagitis, 40% incidence of neutropenic fever, and 20% incidence of grade III esophagitis.

In locally advanced, unresectable NSCLC, multiple studies have demonstrated the feasibility and potential benefit of combination weekly taxol/carboplatin or q 3 week paclitaxel/carboplatin, given concurrently with radical thoracic RT (both daily and BID regimens), with acceptable rates of esophagitis, minimal myelosuppression, and promising activity/survival outcome (Semin Oncol 24: S23,89-95, 1997; S12-21-26, 1997) (26-29). Given the safety record of concurrent chemo/radiation with paclitaxel and carboplatin in locally advanced, unresectable disease, using relatively higher doses of XRT, it appears reasonable to test this combination with attenuated RT dose in the induction setting prior to surgical resection. In this manner, we can specifically determine the safety and feasibility of induction therapy and gauge post induction surgical morbidity and mortality. Presumably, unlike advanced metastatic disease, survival benefits may be enhanced. Moreover, if this regimen proves feasible, it may set the stage for phase III trials of induction chemoradiation comparing newer combinations vs. older, established systemic combinations.

In addition, we will test the utility of weekly paclitaxel and q 4 week carboplatin in the postoperative adjuvant setting. In patients with stage IIIB NSCLC, SWOG 9504 applied

concurrent etoposide/cisplatin/full dose RT followed by three cycles of "consolidation" docetaxel after definitive local therapy. This effort yielded a 2-year survival rate of 50% and 3-year survival rate of 40% (30). These results are quite promising. In a randomized phase II study in advanced NSCLC, weekly paclitaxel and bolus carboplatin Q 4 weeks resulted in a median survival of 49 weeks and appeared superior to weekly carboplatin and paclitaxel (p=0.05) as well as high dose weekly paclitaxel (p=0.45) which yielded median survivals of 30 weeks and 40 weeks, respectively (31). Analogous to the SWOG effort, we will give this regimen in the postop setting once definitive local therapy has been completed.

Because this is a feasibility trial, we will target a grade 5 toxicity rate of $\leq 16\%$ as our primary objective. An R0 resection rate of $\geq 60\%$ will be our leading secondary objective; both criteria have been established by the largest trial to date in potentially resectable LA-NSCLC (6). Because no established reference standards exist, other endpoints, including the RT-treatment disruption rate, peri-operative morbidities, etc., will be tabulated after successful completion of the study, but will not constitute a priori the basis of statistical analysis.

Once we've demonstrated feasibility of this approach in an initial pilot trial, we will conduct separate, but concurrent, phase II trials in each cohort:

- Pancoast tumors NSCLC (T_{3-4}), with (-) pretreatment mediastinoscopy or mediastinotomy
- Mediastinoscopy (-) T_3 chest wall lesions
- T_4 locally advanced, marginally resectable, central NSCLC, indistinguishable from mediastinal adenopathy and currently ineligible for RTOG 9309
- Mediastinoscopy (+) or histologically documented N_2 NSCLC.

However, the successful conduct of this trial will require an extensive protocol infra-structure, which is not yet in place.

3.0 OBJECTIVES

3.1 Primary:
Toxic death rate and complete resection rates (RO) will be the primary endpoints.

3.2 Secondary:
To assess survival, event-free survival, incidence of pathologic complete remission (pCR); and protocol completion rate in patients undergoing trimodality therapy for Pancoast tumors, resectable mediastinoscopy (-) chest wall tumors, marginally resectable central T4N1-0 NSCLC, and IIIA N_2 NSCLC.

3.3 Tertiary:

3.3.1 Induction chemoradiation feasibility and tolerance
3.3.2 Pathologic near CR rate
3.3.3 Pathologic response rate/downstaging
3.3.4 Freedom from distant metastasis rate
3.3.5 Freedom from local regional failure rate
3.3.6 Toxicity

4.0 ELIGIBILITY

4.1 Histologic or cytologic proof of newly diagnosed, unilateral, primary NSCLC with involvement of either the superior sulcus, chest wall, or mediastinum (tissue or nodes).

4.2 Patients must fit ≥ one of the following categories:

4.2.1 Locally advanced Pancoast tumors with no documented mediastinal or supraclavicular nodal involvement (T3-T4, N0-1).

4.2.2 Patients with resectable chest wall disease (T3N0-1).

4.2.3 Marginally resectable T4N0-1 or NX central NSCLC.

4.2.4 N_2 patients who are potentially resectable after induction chemoradiation.

4.3 No evidence of supraclavicular nodes, malignant pleural or pericardial effusions, SVC syndrome and/or distant metastases.

4.4 KPS ≥ 70

4.5 Adequate physiologic parameters:

4.5.1 ANC ≥ 2,000/μl
4.5.2 Platelets ≥ 100,000/μl
4.5.3 Bilirubin ≤ 1.5 mg/dl
4.5.4 Serum creatinine ≤ 2.0 mg/dl
4.5.5 SGOT (AST) ≤ 3 X upper limit of normal

4.6 Age 18 years or older

4.7 No evidence of extra-thoracic spread by CT of liver and adrenals; brain scan (either CT or MRI), or bone scan. Questionable findings will require additional radiographic studies and explicit explanation in chart records/source

documentation. (PET scan can be substituted for bone scan, and if necessary, for CT of the liber and adrenal, if the latter study has "timed out" for eligibility).

4.8 Projected postoperative FEV1 of ≥ 800 cc's as documented by pulmonologist or thoracic surgeon

4.9 No prior history of MI within the past six months or active, uncontrolled congestive heart failure or active uncontrolled arrhythmia within the previous six months. (Patients on beta blockers, digitalis derivatives, and channel blocking agents are allowed, if cardiac conditions are stable)

4.10 No prior thoracic radiotherapy for this diagnosis and no prior pelvic radiotherapy.

4.11 No other active invasive malignancies requiring therapy in the preceding two years. No ongoing need for adjuvant therapy.

4.12 Evaluation and sign-off by each member of the institution-specific multidisciplinary thoracic team, including pulmonologist, medical oncologist, radiation oncologist, and surgical oncologist (See Appendix C)

4.13 Informed consent in accordance with the FCCC Institutional Review Board.

4.14 Negative HCG in women of childbearing potential

4.16 Patients of childbearing potential must use acceptable form of contraception.

5.0 PRETREATMENT EVALUATION

5.1 Baseline history and physical exam

5.2 Hgb/Hct, WBC/differential/platelets

5.3 Sodium, potassium, chloride, HCO_3, glucose, BUN and creat, bilirubin, alkaline phosphatase, SGOT, albumin, calcium

5.4 Chest x-ray and ECG

5.5 CT scan of the chest, liver and adrenals

5.6 MRI or CT scan of brain

5.7 Bone scan (with correlative plain films, CT, +/or MRIs to rule out metastases if (+)). PET scan may substitute for bone scan at baseline.

5.8 HCG (if child-bearing potential)

5.9 Pulmonary function studies, with calculation of projected postop FEV1 (split function VQ scan in questionable or borderline cases, at treating team's discretion)

6.0 TREATMENT PROGRAM

Registration, once eligibility checklist is satisfied, will occur through the FCCC Protocol Office, Tracy Tisone at 215-214-1451. Eligibility checklist will be faxed to 215-728-2687.

6.1 Treatment will be administered on an outpatient basis

6.2 Preoperative (induction or neoadjuvant) Radiotherapy

6.2.1 Total dose 50.4 Gy/1.8 Gy per fraction daily, 5 days a week (minus holidays) for 5-1/2 weeks (28 Fx). Patients with chest wall tumors can receive a boost for an additional 900cGy in 5 fractions to the chest wall region to a total dose of 5940cGy. The mediastinum and hilum should not be treated above 5040cGy preoperatively

6.2.2 Equipment/Simulation: All treatment fields must be simulated. All treatment must be given with high energy photons (peak energy $\geq$ 6 MV).

6.2.3 Treatment Planning: There will be no dose inhomogeneity corrections for the lung or other anatomy. All fields will be treated each day. For AP-PA treatment, the daily dose will be prescribed to the point of intersection of the central rays at the midplane; this will be considered the 100% isodose. The dose to the spinal cord must be calculated at a minimum of three levels, with the maximal spinal cord dose not exceeding 105% of the prescription dose. A compensator or wedge may be used to minimize the dose inhomogeneity within the spinal cord. For field arrangements other than AP-PA, the prescription dose may be "renormalized" to an isodose that adequately covers the target volume, but may not be more than 5% less than the dose at the isocenter. On such plans, the maximal dose may not exceed 110% of the isocenter dose. 3D CT-planning is strongly recommended for field arrangements other than AP-PA.

6.2.4 **Normal Tissue Considerations: Spinal cord dose may not exceed 48 Gy at any point.** This likely means that it often may not be acceptable to treat AP-PA to a nominal dose of 45 Gy, since the cord will receive slightly more than that dose at several points.

6.2.5 Initial Target Volume: With the exception of patients with chest wall lesions with (-) pre-treatment mediastinoscopy, in whom Tx can

encompass GTV only (avoiding hilum and mediastinum), the preoperative target volume will include the primary tumor + 1.5 cm margin, ipsilateral hilar lymph nodes, and bilateral mediastinal lymph nodes. For upper lobe lesions without gross subcarinal adenopathy, the inferior aspect of the field should be set 5 cm below the carina. For gross subcarinal adenopathy or middle/lower lobe tumors, the inferior aspect of the field should be set low enough to cover the Level 8 and 9 lymph nodes. Coverage of the ipsilateral supraclavicular fossa is optional. Coverage of the contralateral supraclavicular fossa or contralateral hilar lymph node regions is not allowed.

6.2.6 **Dose Fractionation: Once daily fractionation at 180 cGy per day will be used, five days per week X 5-1/2 weeks (28 Tx days) to a dose of 5040cGy. Patients with chest wall disease will receive a boost of an additional 900cGy in 5 fractions to a total dose of 5940cGy to the chest wall region only**

6.2.7 Dose Modifications and Interruptions: Radiation interruptions are strongly discouraged. Radiation should be withheld in the face of neutropenic fever, ANC < 500, platelets < 50,000 or Grade 3 esophagitis causing severe dehydration. Radiation will also be withheld for grade 4 esophagitis or pneumonitis.

6.3 Paclitaxel will be administered at a dose of 50 mg/m^2 over one hour weekly X 6; it will begin either before or after the first or second fraction of XRT.

6.4 Carboplatin will be administered at an AUC of 2.0 weekly for six weeks, immediately following the day's paclitaxel dose.

6.5 Other agents to be used in protocol:

6.5.1 Hypersensitivity prophylaxis 30 minutes prior to paclitaxel will consist of:

6.5.1.1 Dexamethasone 10-20 mg IV
6.5.1.2 Diphenhydramine 25-50 mg IV
6.5.1.3 Cimetidine 300 mg IV (or Ranitidine 50 mg IV pre-paclitaxel)

6.6 Surgical assessment

6.6.1 Patients will undergo restaging 7-21 days after completion of chemoradiation to establish response status, and to make certain extra-thoracic progression has not occurred.

6.7 Patients who prove unresectable and undergo an abortive resection (R1, R2) will receive additional RT ranging from 1620 cGy in 9 fractions (for cumulative dose of 6660 cGy to the gross target volume) up to a maximum of

1980 cGy in 11 fractions to a total dose of 7020 cGy to the gross target volume. The radiation will be given in conjunction with weekly paclitaxel and carboplatin. Patients should be referred back for consideration of further chemoradiation as soon as possible after their surgical re-evaluation (if the patient is found to be unresectable or had undergone an abortive resection).

6.8 Systemic therapy post chemoradiation +/- surgical resection

6.8.1 Adjuvant therapy (see schema) will start four to twelve weeks after resection or completion of chemoradiation in patients who prove unresectable. Any delays beyond 8 weeks will need clearance from study P.I. Delays beyond 12 weeks will result in patient's removal from formal protocol, but continued follow-up with respect to delayed toxicity, progression, and survival.

6.8.2 Surgical resection will be performed between four and eight weeks after chemoradiation concludes, with an allowance up to 12 weeks if clinical circumstances dictate.

7.0 TREATMENT PLAN/DOSE MODIFICATIONS

7.1 The doses for each patient enrolled will not be raised

7.2 Dose Modifications

7.2.1 During initial chemoradiation and, if indicated, post-resection chemoradiation. These criteria will apply to blood counts on either the day of Tx or the day prior to Tx

(% Target Dose During Chemoradiation)

	Carboplatin	Paclitaxel		Carboplatin	Paclitaxel
ANC ≥ 1250	100%	100%	Plts ≥ 75K	100%	100%
750-1249	50%	50%	50-74K	50%	100%
< 750	0%	0%	< 50K	0%	0%

If radiation is omitted or delayed, then omitted chemotherapy doses will be made up on the day radiation is resumed.

7.2.2 Chemoradiation Dose Modification

Dose Modifications During Chemoradiation for Interval Events Occurring During Tx

The doses of both carboplatin and paclitaxel will be reduced permanently by 25% during the second or subsequent week of chemoradiation for any of the following:

7.2.2.1 Interval neutropenic fever (fever of ≥ 100.6 and grade 3 or 4 neutropenia requiring hospitalization and intravenous antibiotics).

7.2.2.2 Delay in resuming radiation by more than one week (during chemoradiation only).

7.2.2.3 Thrombocytopenia requiring platelet transfusion.

7.2.2.4 Grade 3 or 4 esophagitis requiring TPN and/or hospitalization.

7.2.2.5 Grade 3 or 4 fatigue, which at the treating physician's discretion, precludes full dose therapy.

7.2.2.6 Grade 3 peripheral sensory neuropathy (reduce paclitaxel only)

7.2.3 Doses omitted will not be made up, unless radiation has also been omitted and schedule permits. If dose is omitted, but counts fully recover by the time of next scheduled Tx, full dose will be given.

7.2.4 Non-hematologic grade 4 toxicity (excluding nausea and vomiting): The dose of the implicated agent(s) will be reduced by 25% once patient has recovered to grade ≤ 1 level, and will not be raised back to the original dose, even in the absence of subsequent grade 3 or 4 toxicity. Osteoarthralgias or myalgias attributed to paclitaxel will be controlled by analgesics and will not mandate dose reduction.

7.2.5 Criteria for treatment delays: Chemotherapy treatment may be delayed up to two weeks for any of the following toxicities:

7.2.5.1 Ongoing esophagitis that precludes adequate hydration or intake and requires hospitalization (not applicable to patients with gastrostomy tubes who can be treated through severe esophagitis).

7.2.5.2 Grade 2 or 3 neurotoxicity (paclitaxel only), (resume paclitaxel once grade ≤ 1)

7.2.5.3 Other, ongoing, grade ≥ 3 non-hematologic toxicities at the time treatment is due to resume (except for alopecia).

7.2.5.4 If delay > 2 weeks, call study chair(s). If delay exceeds 3 weeks, patient will be removed from protocol.

7.3 Adjuvant Treatment Dose Modifications

Dose modifications during full dose systemic therapy (3 cycles post surgery)

7.3.1 Criteria for resumption of systemic therapy

7.3.1.1 ANC ≥ 1500/μl

7.3.1.2 Platelets ≥ 100,000/μl

7.3.1.3 PS 0-2

7.3.2 Hematologic dose adjustment criteria for day 8, day 15 paclitaxel:

	Paclitaxel Dose		
	100%	75%	Hold
ANC	≥ 1000	500-999	< 500
Platelets	≥ 75 K	50-74 K	< 50 K

7.3.3 The doses of both carboplatin and paclitaxel will be reduced permanently by 25%:

7.3.3.1 Interval neutropenic fever (fever of ≥ 100.6 and grade 3 or 4 neutropenic requiring hospitalization and intravenous antibiotics)

7.3.3.2 Thrombocytopenia requiring platelet transfusion.

7.3.3.3 Non-hematologic grade 4 toxicity (excluding nausea and vomiting): The dose of the implicated agent(s) will be reduced by 25% once patient has recovered to grade ≤ 1 level, and will not be raised back to the original dose, even in the absence of subsequent grade 3 or 4 toxicity. Osteoarthralgias or myalgias attributed to paclitaxel will be controlled by analgesics and will not mandate dose reduction.

7.3.3.4 Grade 3 fatigue, which at the treating physician's discretion, precludes full dose therapy.

7.3.3.5 Grade 3 peripheral sensory neuropathy (reduce paclitaxel only)

7.3.4 Criteria for treatment delays: Chemotherapy treatment may be delayed up to two weeks for any of the following toxicities at the time chemotherapy is due to resume:

7.3.4.1 Grade 2 or 3 neurotoxicity (resume dose once grade ≤ 1).

7.3.4.2 Failure to recover ANC to ≥ 1500/ml or platelets to $\geq 75{,}000$/ml during adjuvant Tx.

7.3.4.3 Other, ongoing, grade ≥ 3 non-hematologic toxicities at the time treatment is due to resume.

7.3.4.4 If delay > 2 weeks, call study chair(s). If delay exceeds 3 weeks, patient will be removed from protocol.

7.4 Hypersensitivity reactions

7.4.1 Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, transient back pain, dyspnea requiring bronchodilators, or tachycardia do not require interruption of therapy. However, severe reactions such as hypotension requiring pressors, angioedema or generalized urticaria require immediate discontinuation of Taxol and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with Taxol, but can still receive carboplatin.

7.4.2 If hypersensitivity reaction occurs during paclitaxel infusion, infusion will be halted for 5-30 minutes. Patients will receive hydrocortisone 150 mg IV and diphenhydramine 25-50 mg IV, and paclitaxel will then be resumed initially at a slower rate, then gradually accelerated. If, despite slowing the infusion rate, allergic reaction recurs, patients will receive a full 24 hours of oral steroid prophylaxis (e.g., dexamethasone 6-10 mg po q 6) prior to the next dose. If allergic reaction again occurs, further Tx with paclitaxel will be halted, but patients can still receive carboplatin.

7.5 Premedications

Patients will be premedicated 30 minutes prior to paclitaxel with dexamethasone 10-20 mg IV, in conjunction with diphenhydramine 25-50 mg IV, and cimetidine 300 mg IV or ranitidine 50 mg IV. Higher dose premedications are recommended during adjuvant treatment; lower doses are recommended during concurrent lower dose chemoradiation.

7.6 Anti-emetics

7.6.1 Anti-emetic prophylaxis will be left up to individual physician discretion.

7.6.2 Recommended regimen: prochlorperazine 10 mg IV or, alternatively, ondansetron 8-16 mg IV, or granisetron 1 mg IV.

7.7 Supportive Measures

G-CSF or GM-CSF or other colony stimulating factors during radiotherapy is discouraged. If it is necessary to administer G-CSF (e.g., for neutropenic fever), it is recommended that radiotherapy be withheld for at least 24 hours before the start of G-CSF and for at least 24 hours after the last dose of G-CSF. If colony stimulating factor is necessary during full dose pre-op chemotherapy or full dose adjuvant post-op, its administration will be governed by ASCO guidelines.

7.8 Esophagitis

7.8.1 Iced Carafate 1 gm prior to XRT and p.m. will be instituted routinely.

7.8.2 GI prophylaxis using Prilosec 20 mg po QD, Pepcid 20 mg po BID or Prevacid 30 mg QD is strongly recommended.

7.9 Adverse Events

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

7.9.1 Definitions of adverse events

7.9.1.1 Adverse event (AE)

Any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

7.9.1.2 Serious adverse event (SAE)

An adverse event occurring at any dose that results in any of the following outcomes (CFR 312.32):

-death

-a life-threatening adverse drug experience

-inpatient hospitalization or prolongation of existing hospitalization excluding those for study drug administration, transfusional support, disease staging/re-staging procedures, concomitant radiotherapy,

thoracentesis/paracentesis, or placement of an indwelling catheter, unless associated with other serious events.

-persistent or significant disability/incapacity,

or

-congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug experiences when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Death, regardless of cause, which occurs within 30 days of the last dose of study drug or after 30 days and is a result of delayed toxicity due to administration of the study drug, should be reported as a serious adverse event.

7.9.1.3 Unexpected adverse event

An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's brochure or package insert.

7.9.1.4 Life-threatening

Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

7.9.2 Reporting adverse events

7.9.2.1 Adverse events

Adverse events will be recorded for the duration of a patient's participation in the trial. All adverse events (except grade 1 and 2 laboratory abnormalities unless a dose treatment modification, delay or therapeutic intervention is required), regardless of causal relationship, are to be recorded in the case report form and source documentation. Pre-existing conditions at baseline will be recorded. If a pre-existing condition does not change, it does not have to be reported on subsequent cycles.

The investigator must determine the toxicity of adverse events according to the Cancer Therapy Evaluation Program Common Toxicity Criteria (CTC) Version 2.0 for toxicity and Adverse Event reporting and their causal relationship. A copy of the CTC Version 2.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

7.9.2.2 Serious adverse events

7.9.2.3 Reporting of All Second Primary Cancers

	NCI/CTEP Secondary AML/MDS Report Form[1]	Second Primary Form[2] (Form #630)
AML/MDS	X	
All other secondary cancers		X

1. To be completed within 30 days of diagnosis of AML/MDS that has occurred during or after protocol treatment. A copy is to be sent to BMS/NCI accompanied by copies of the pathology report (and when available, a copy of the cytogenic report).
2. To be submitted to BMS/NCI within 30 days of diagnosis of a new primary cancer during or after protocol treatment, regardless of relationship to protocol treatment. Not for use for reporting recurrence of metastatic disease. A copy of pathology report should be sent, if available.

Telephone reports to the Investigational Drug Branch of the NCI at (301) 230-2330 available 24 hours daily (recorder between 5 pm and 9 am EST).

7.9.2.4 SAE Reporting: The following table should be used to determine which events require submission of expedited reports via Medwatch. All reports submitted via Medwatch must also be submitted simultaneously (via email or fax) to BMS.

Unexpected Event		Expected Event	
GRADES 2-3 Attribution of Possible Probable or Definite	GRADES 4 and 5 Regardless of Attribution	GRADES 1-3	GRADES 4 and 5 Regardless of Attribution (except for asymptomatic myelosuppression)
GRADES 2-3 Initial IRB report within 24 hours	Report by phone to IDB within 24 hours. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.

	Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.		**Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.**

1. **For Hospitalization only – Any medical event equivalent to CTC 3, 4, 5, that precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of expected or unexpected and attribution.**

MedWatch forms should be sent to the FDA online to:
http://www.accessdata.fda.gov/scripts/MedWatch

Or Fax to:

MEDWATCH
Fax: 1-800-FDA-0178

All SAE's should simultaneously be faxed to Bristol-Myers Squibb at:
Bristol-Myers Squibb
Worldwide Safety and Surveillance
311 Pennington/Rocky Hill Road
Pennington, NJ 08534
Fax: 609-818-7205

7.10 Criteria for study removal

7.10.1 Disease progression during treatment within the irradiated volume

7.10.2 Intractable toxicity which, in the opinion of the investigator, precludes further therapy

7.10.3 Repeated non-compliance which potentially threatens patient safety or compromises efficacy of therapy

7.10.4 Patient choice

8.0 SURGERY

8.1 Surgery will be performed no sooner than 4 weeks following the completion of chemoradiotherapy. Surgery ideally should not be delayed longer than eight

weeks after the first full systemic dose of chemotherapy after chemoradiation unless necessary for recovery of the acute toxicity of induction chemoradiotherapy. Delays beyond 12 weeks will obligate withdrawal from study.

8.2 Surgery will consist of thoracotomy with tumor resection, preferably lobectomy. Lesions with direct extension into parietal pleura or chest wall should be resected with an en bloc chest wall resection. Lesions with direct extension into the pericardium or diaphragm should have an en bloc resection with an attempt to achieve a minimum of 1 cm margins around tumor cells. Lesions with limited extension to a vertebral body should be resected with the assistance of a neurosurgeon. Ipsilateral hilar and mediastinal lymph nodes should be resected and labeled as per the standard lymph node mapping (AJCC 1997).

8.3 Patients not felt to be candidates for surgery or whose tumors are found to be unresectable at the time of surgery will be considered "off-study," although they will be treated with additional adjuvant therapy and will be followed with toxicity, survival and progression data collected and analyzed using the schedule outlined in section 9.0. Further treatment will be at physician's discretion; this treatment will be recorded.

8.4 Adjuvant therapy will commence 4-12 weeks post-resection. If delays beyond 8 weeks are necessary, medical oncology P.I. must be contacted.

9.0 PROTOCOL SCHEDULE/STUDY PARAMETERS

9.1 Chest CT $\leq$ 3 weeks before registration (radiation planning CT is acceptable)

9.2 All other scans and x-rays should be done $\leq$ 6 weeks before registration.

9.3 Scans or x-rays used to document measurable or evaluable disease should be obtained within 3 weeks of registration to study.

9.4 CBC with differential and platelets should be done $\leq$ 2 weeks before registration and again $\leq$ 2 weeks prior to initiation of adjuvant therapy. If abnormal, they must be repeated < 48 hours prior to treatment initiation.

9.5 All chemistries should be done $\leq$ 2 weeks before registration unless specifically required on Day 1 per protocol. If abnormal, they must be repeated within 48 hours of treatment initiation to document eligibility.

9.6 Study will be coordinated and monitored through the FCCC Protocol Office. All study files and central regulatory files will be maintained in the FCCC Protocol Office.

9.7 Follow-up schema delineated in the following table applies to patients who are free from disease progression. If and when disease progression is documented, those patients will be followed for survival only. Their survival status will be updated using the regular follow-up schedule delineated.

9.8 Patients who do not comply with the follow-up schedule delineated will not be removed from study unless they formally withdraw their consent. Every attempt will be made to document their disease and survival status.

9.9 Study withdrawl criteria:

9.9.1 Patient refusal
9.9.2 Untoward toxicity
9.9.3 Disease progression (cite location)

	Prior to Regis-tration	Weekly during chemo-radiation	7-35 d after conclusion of chemo-radiation	4-8 wk after surgery[6]	Q wk during adjuvant Tx	Q 4 wk X 3 during systemic adjuvant therapy	Follow-Up[4]
History[7] & Physical Exam	X		X	X		X	X
Weight & Height[8]	X		X	X		X	X
Vital Signs (**HR, BP, RR**)	X	X[3]	X	X		X[3]	X
Performance Status	X	X	X	X		X	X
Tumor Measurement	X		X	X			X
WBC	X	X	X	X	X	X	X
Differential	X	X	X	X	X	X	X
Hgb, Hct, Platelet Count	X	X	X	X	X	X	X
BUN/Creatinine, Na, K+, Cl, CO_2	X	X	X	X		X	X
Bilirubin, SGOT, Alk, Phos, Calcium, Albumin, Blood sugar	X		X	X		X	X
Chest X-ray	X		X[1]	X			X[1]
Bone Scan[9]	X		X[1]				X[2]
Bone X-ray, if indicated	X[2]		X[1]				X[2]
CT chest/liver/Adrenals	X		X	X			X
CT or MRI brain	X		X				X[2]
ECG	X		X				
Toxicity Assessment		X	X	X		X	X
HCG	X[5]		X[5]				

[1] Optional, as clinically indicated.
[2] As clinically indicated.
[3] The patient's blood pressure and heart rate will be monitored every 15 minutes x 4 during paclitaxel infusion.
[4] Q 3 mo X 2 yrs, then Q 6 mo X 3 yrs. After 5 years NED patients should be followed Q year. Follow-up can be performed more frequently if necessary. This schedule of follow-up will be operative in patients who have not manifested disease progression, whether they have completed protocol therapy or stopped treatment because of toxicity.
[5] Only in women of child-bearing potential (within 2 weeks of registration) and 7 to 35 days after conclusion of chemoradiation.
[6] Within **four** weeks prior to initiation of systemic adjuvant chemotherapy
[7] Interval history after initial H&P
[8] Height must be verified baseline; it need not be repeated regularly thereafter
[9] PET scan may be substituted for bone scan

10.0 MEASUREMENT OF EFFECT

10.1 Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference

10.1.1 Eligibility

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter (<20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascities, pleural/pericardial effusion, inflammatory breast disease, lymphangitis, cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

10.1.2 Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

10.1.3 Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.1.4 Response Criteria

Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions.

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

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of non-target lesions

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

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

10.1.5 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	Evaluation of Non-Target Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

10.1.6 Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

10.1.7 Duration of overall response

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

10.1.8 Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the

protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

10.1.9 Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

10.1.10 Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data).

- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

- All conclusions should be based on all eligible patients.

- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

- The 95% confidence intervals should be provided.

10.2 Evaluation of Patient's Total Response

10.2.1 Organ Site Evaluation

10.2.1.1 Record responses as complete (CR), partial (PR), stable (S), progression (P), or (NED) no evidence of disease under appropriate methods of evaluation.

10.2.1.2 If more than one type of evaluation methods exists for a given organ site, each must be recorded separately.

10.2.1.3 If there is more than one measurable lesion per organ site, an organ site PR occurs if there is a greater than 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions.

10.2.1.4 Stabilization of evaluable disease will not detract from a PR of measurable disease by organ site, but will reduce a CR to a PR.

10.2.1.5 Progression in any classification of measurability or evaluability in an organ site shall prevail as the response for that organ site.

10.2.2 Objective Total Patient Response

10.2.2.1 Progression occurs if any previously measurable or evaluable malignant lesions fulfill progression criteria or new malignant lesions **not known** to be present at the start of therapy develop. Questionable lesions, that may or may not represent disease progression, will be re-evaluated 4-6 weeks after their first appearance.

10.2.2.2 Organ site stabilizations will not detract from a total patient PR in the presence of other organ site PR's and CR's.

10.2.2.3 Stabilization of evaluable disease does not detract from CR's or *PR's* in measurable sites, but the patient's overall response should be a PR.

10.2.2.4 Patients with a deterioration in ECOG performance status of greater than or equal to 1 level due to malignant disease are considered to have progressive disease.

10.2.3 Onset of Response

The time between initiation of therapy and the onset of PR or CR as established by follow-up scans +/- surgical findings.

10.2.4 Duration of Response

Time from onset of PR (even if patient later has a CR) until objective evidence of progression.

10.2.5 Subjective Patient Response
In order to evaluate the quality of life during therapy, the investigator must summarize the changes in performance status and evaluate whether these changes are due to malignant disease, treatment, or to unrelated factors.

10.2.6 Freedom from Progression
Defined as time from protocol enrollment to time of disease progression. Differentiation will be made between local regional progression and distant progression.

10.3 Pathologic complete response (pCR): No evidence of disease in the surgical specimen.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Endpoint

Toxic death and resectability are the primary endpoints of this phase II study.

11.1.1 We will test the null hypothesis that the chance of this endpoint (toxic death) is not over 5% versus the alternative that it exceeds 16%, the aggregate induction mortality rate and peri-operative mortality (30 day) rate observed in the SWOG trial prior (5) that forms the basis of the recently completed intergroup phase III trial. With 48 evaluable patients we will be able to make this distinction with 82% power and 4.9% type I error. In addition, we will introduce an **EARLY STOPPING RULE**; we will terminate the study if, at any time during the evaluation of the first 24 patients, four or more toxic deaths have occurred. If the study accrues its target goal of 48 evaluable patients, the null hypothesis will be rejected if at least six toxic deaths occur. Again, the study will be terminated if at any point, six toxic deaths have occurred. If the true rate of toxic death is at least 16%, then the study has a 55% chance of stopping after evaluating only the first 24 patients. The chance of early stopping under the null hypothesis is only 2.9%. The table below lists the several outcome probabilities, where n1, r1, n2, a2 are respectively:

n1: number of patients evaluated to determine if the study will be terminated early.

r1: number of deaths at or before n1 patients have been evaluated that will result in study termination and rejection of the null hypothesis.

n2 maximum number of patients to be evaluated

a2: maximum number of deaths after all n2 patients are evaluated that will result in acceptance of the null hypothesis. Exceedance of a2 deaths at any point in the sequence of patient evaluations will lead to study termination and rejection of the null.

n2	a2	n1	r1
48	5	24	4

p1 = 0.05 p2 = 0.16

p(S.ge.r1|n1): 0.0298 p(S.ge.r1|n1): 0.5496
p(S.gt.a2|n2): 0.0191 p(S.gt.a2|n2): 0.2724
p(early stop): 0.0298 p(early stop): 0.5496

overall type I error: 0.0489
overall power: 0.8220

11.1.2 Fraction of patients determined to be resectable (R0).

With 48 evaluable patients we will be able to distinguish a null hypothesis that only 36% of patients will be resectable versus the alternative that at least 60% of them will prove resectable. This distinction can be made with 86% power and 2.6% type I error. Here the null hypothesis is that at least 60% of patients will be resectable. The study may be terminated if, at any point, 15 of the first 24 patients are not resectable; or if accrual continues beyond 24 patients, it may be terminated if, at any point, ≥ 28 patients are found not resectable.

Below n1 and n2 are as above. r1 is the number of non-resectable patients in the first group of 24 mandating early termination of the study. a2+1 are the number of non-resectable patients requiring rejection of the null hypothesis and study termination within the second group of 24 patients. The study will be terminated early with probability 65% if only 36% of patients are resectable.

n2	a2	n1	r1
48	27	24	15

p(not resectable)
0.40 0.64

p(S.ge.r1|n1): 0.0217 p(S.ge.r1|n1): 0.6488
p(S.gt.a2|n2): 0.0042 p(S.gt.a2|n2): 0.2161
p(early stop): 0.0217 p(early stop): 0.6488

overall type I error: 0.0258
overall power: 0.8648

11.1.3 Composite endpoint:

Two composite conditions are of interest. The first composite condition: if toxicity is in fact as low as 5%, and the fraction of resectable patients is in fact as great as 60%, i.e. the overall treatment is acceptable. Assuming, as a first approximation, that toxicity and ultimate resectability are independent events, the chance that the study will be stopped early even though both above conditions are true is:

p(stop|tox<5%)+p(stop|R0>60%) - p(stop|tox<5%)*p(stop|R0>60%)

= 0.0298 + 0.0217 - 0.0298*0.0217 = 0.0508. Similarly, the chance of

ultimate rejection of the treatment, in error, but not necessarily early, is 0.0743, not far from 5%.

The second condition of interest is the opposite of the first. We suppose that either toxicity exceeds 16% OR at most 36% of patients will be resectable. We consider three situations:

1. Both toxicity exceeds 16% and resectability is at most 36%: p(stop|tox>16%)+p(stop|R0<36%) - p(stop|tox>16%)*p(stop|R0<36%) = 0.5496 + 0.6488 - 0.5496*0.6488 = 0.8418. Similarly, the chance of ultimate rejection of the treatment, correctly, but not necessarily early is 0.9759.

2. Toxicity is less than 5% but resectability is at most 36%: p(stop|tox<5%)+p(stop|R0<36%) - p(stop|tox<5%)*p(stop|R0<36%) = 0.0298 + 0.6488 - 0.0298*0.6488 = 0.6592. The chance of ultimate rejection of the treatment, correctly, but not necessarily early is 0.8714.

3. Toxicity exceeds 16% but resectability is at least 60%: p(stop|tox<5%)+p(stop|R0<36%) - p(stop|tox<5%)*p(stop|R0<36%) = 0.5496 + 0.0217 - 0.5496*0.0217 = 0.559. The chance of ultimate rejection of the treatment, correctly, but not necessarily early is 0.8265.

Under all four composite conditions the power of the study is adequate, type I error minimal.

11.2 Secondary endpoints:

11.2.1 Survival:

We will test the null hypothesis that median survival is 16 months versus the alternative that it is at least 24 months. With 48 valuable patients on study we will be able to make this distinction with 81% power and 5% type I error. e will accrue patients for at least three years and follow them for an additional three years.

11.2.2 Event-free survival:

We test the null hypothesis that median event-free survival is 8 months versus the alternative that it is at least 12 months. With 48 evaluable patients on study we will be able to make this distinction with 87% power and 5% type I error.

11.2.3 Pathologic complete remission (pCR):

If 60% of patients are resectable then approximately 29 patients will be available to estimate the rate of pCR. The pCR rate is reported to be between 15% and 25%. An improvement of 20% can be detected over this range as indicated below. We will be able to estimate the pCR rate to within 14% with 95% confidence.

With 27 resected patients we will be able to distinguish a pCR rate of 0.15 from one of 0.34 with 80% power and 5% type I error.

With 29 resected patients we will be able to distinguish a pCR rate of 0.2 from one of 0.40 with 80% power and 5% type I error.

With 27 resected patients we will be able to distinguish a pCR rate of 0.25 from one of 0.47 with 80% power and 5% type I error.

11.2.4 Completion rates:

This refers to all patients who complete the study, including scheduled "adjuvant" therapy after definitive local treatment, whether or not they are resected. All 48 evaluable patients will be used unless the study is terminated early, in which case completion is not at issue. We will be able to distinguish a (null hypothesis) completion rate of 32.5% from one of 50% (alternative hypothesis) with 80% power and 5% type I error.

11.3 Tertiary Endpoints will be reported, but not tested for statistical significance.

11.3.1 Induction chemoradiotherapy feasibility/tolerance: % of patients who complete induction chemoradiotherapy without interruption for toxicity or other reasons of > 3 days or > 5 days.

11.3.2 Pathologic Near-Complete Response Rate: % of patients who have minimal residual disease at the time of surgical resection (microscopic residua or ≥ 80% reduction in viable tumor volume).

11.3.3 Pathologic Response Rate: % of patients whose tumor is "downstaged" to AJCC Stage I or II with negative margins (applies only to Cohort #1).

11.3.4 Freedom from Distant Metastases Rate: % of patients free of distant metastases at one, two, three, and five years after the start of treatment.

11.3.5 Freedom from Local-Regional Failure Rate: % of patients free of local-regional failure/progression at one, two, three, and five years after the start of treatment.

11.3.6 Toxicity: RTOG and Common Cooperative Group Grade 3 or greater esophageal, pulmonary (pre and post-op) toxicity. In addition, neuropathy, myalgias/arthralgias of any grade will be recorded.

11.4 Sample size and accrual period:
We expect 15% of accrued patients to be inevaluable, thus we need to accrue a total of approximately 57 patients. These patients will be accrued in approximately four years.

11.5 The Data Safety Monitoring Board (DSMB)
The DSMB will convene at least twice yearly; monitor toxicities prospectively and retain the power to suspend or close the study if untoward toxicity occurs. The DSMB plan is attached (Appendix F).

12.0 DRUG FORMULATION

12.1 Taxol® (paclitaxel)

Taxol® is a natural product obtained via a semi-synthetic process from *Taxus baccata* and will be supplied commercially.

12.1.1 Formulation
Taxol is supplied as a nonaqueous solution that must be diluted prior to its use. It is available in 5 mL (30 mg) single-dose, 16.7 mL (100 mg), and and 50 mL (300 mg) multi-dose vials multi-dose vials. Each mL contains 6 mg of paclitaxel, 527 mg of Cremophor EL (polyuoxyethylated castor oil) and 49% (v/v) dehydrated alcohol, USP. Commercial supplies of Taxol will be used for this trial.

12.1.2 Preparation

Taxol should be diluted to a final concentration of 0.3 to 1.2 mg/mL in either 0.9% sodium chloride or 5% dextrose. The diluted Taxol solution will show a slight haziness that is proportional to the concentration of drug and the time elapsed since preparation. A solution that exhibits excessive particulate formation should be discarded.

The Taxol solution must be prepared in glass, polypropylene, or polyolefin due to the leaching of diethylhexylphthalate (DEHP) plasticizer when polyvinyl chloride bags are used. Non-PVC tubing and connectors, such as those which are polyethylene lined, must be used during administration of Taxol. In-line filtration should be done using a hydrophilic, microporous filter of pore size not greater that 0.22 microns (e.g., IVEX-HP and IVEX-II, Abbot).

12.1.3 Storage and stability

Intact vials of Taxol are stable until the date indicated on the package if stored at temperatures ranging from 2-25°C (36-77°F) and protected from light. The product can be refrigerated or frozen without impact on quality; any precipitates that form upon refrigeration will redissolve upon reaching room temperature. If the solution remains cloudy after agitation, it should be discarded.

When prepared as described above, 0.3-1.2 mg/mL solutions of Taxol are stable for 27 hours.

12.1.4 Adverse events associated with Taxol

Incidence rates of adverse events associated with Taxol are provided in the product package insert. The following events are expected with the administration of Taxol:

12.1.4.1 Hematologic: Myelosuppression is the major dose-limiting toxicity. Neutropenia is both dose-and schedule-dependent and typically resolves rapidly. Fever is common and infectious episodes are seen in about 1/3 of the patients receiving Taxol. Thrombocytopenia is uncommon and the cases that occur are usually mild to moderate. Bleeding episodes may occur. While anemia is common, it is severe only in 16% of the cases.

12.1.4.2 Allergic reactions: Although patients are premedicated, hypersensitivity reactions still occur in approximately 40% of patients receiving Taxol (20% of cycles). Severe reactions are rare and generally occur within the first hour of administration; no severe reactions have been reported after the third cycle.

The most common symptoms observed in severe reactions include dyspnea, flushing, chest pain, and tachycardia. Minor hypersensitivity reactions include flushing, rash, hypotension, dyspnea, tachycardia, and hypertension.

12.1.4.3 Cardiovascular: Cardiovascular events observed with Taxol therapy include hypotension and bradycardia; typically, neither discontinuation of Taxol nor specific therapy for the event is required. Cardiovascular events which are possibly related to Taxol therapy occur in approximately 1% of patients and include syncope, rhythm abnormalities (asymptomatic ventricular tachycardia, bigeminy, and complete AV block requiring a pacemaker), hypertension, and venous thrombosis.

12.1.4.4 Neurologic: The frequency and severity of neurologic events are dose-dependent. Peripheral neuropathy is rarely severe and may be the cause of Taxol discontinuation in 1% of patients. Sensory symptoms usually improve or resolve within several months of Taxol discontinuation. Serious neurologic events, such as grand mal seizures, syncope, ataxia, and neuroencephalopathy, are rare. Pre-existing neuropathies from previous therapies are not a contraindication to treatment with Taxol.

12.1.4.5 Gastrointestinal: The most common GI toxicities, which include nausea, vomiting, diarrhea, and mucositis, are typically mild or moderate in severity. Mucositis is schedule-dependent and occurs more frequently with a 24-hour infusion than a 3-hour infusion of Taxol.

12.1.4.6 Other: Although 60% of all patients experience arthralgia and myalgia, there is no consistent relationship between the dose or schedule of Taxol and the frequency of these events. The symptoms, which usually begin 2 or 3 days after Taxol treatment, are generally transient. Injection site reactions are more common with the 24-hour infusion of Taxol and are typically mild, consisting of erythema, tenderness, skin discoloration, or swelling at the injection site. Almost all of the patients receiving Taxol experience alopecia, but nail changes are uncommon. Edema may occur, but it is rarely severe enough to lead to discontinuation of treatment.

12.2 Paraplatin® (carboplatin)

Paraplatin® (carboplatin for injection or platinum diamine [1,1-cyclobutane-decarbozxylate (2—0,0')-,(SP-4-2)]) is a platinum compound used as a chemotherapeutic agent. It will be supplied commercially.

12.2.1 Formulation

Paraplatin is available as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Commercial supplies of Paraplatin will be used in this trial.

12.2.2 Preparation

Immediately before use, the contents of a Paraplatin vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP. The following shows the proper diluent volumes to be used to obtain a carboplatin concentration of 10 mg/mL:

Vial size	Diluent volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

Carboplatin reacts with aluminum to form a precipitate and cause a 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.

12.2.3 Storage and stability

Intact vials of Paraplatin are stable for the period indicated on the package when stored at room temperature (15-30°C or 59-86°F) and protected from light.

When prepared as described above, Paraplatin solutions are stable for 8 hours at room temperature if protected from light. The solution should be discarded after 8 hours since no antibacterial preservative is contained in the formulation.

12.2.4 Adverse events associated with Paraplatin

Incidence rates of adverse events associated with Paraplatin are provided in the product package insert. Some of the adverse events expected with Paraplatin treatment are listed below.

12.2.4.1 Hematologic: Myelosuppression is the major dose-limiting toxicity. Thrombocytopenia, neutropenia, leukopenia, and anemia are common, but typically resolve by Day 28 when Paraplatin is given as a single agent.

12.2.4.2 Allergic reactions: Hypersensitivity to Paraplatin has been reported in 2% of patients receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

12.2.4.3 Neurologic: Peripheral neuropathies have been observed in 4% of patients receiving Paraplatin with mild paresthesia being the most common.

12.2.4.4 Gastrointestinal: Nausea and vomiting are the most common GI events; both usually resolve within 24 hours and respond to antiemetics. Other GI events include diarrhea, weight loss, constipation, and gastrointestinal pain.

12.2.4.5 Hepatic toxicity: Elevated alkaline phosphatase, total bilirubin, and SGOT have been observed.

12.2.4.6 Other: Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the patients taking Paraplatin.

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APPENDIX A

CASE REPORT FORMS

APPENDIX B

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) OR ZUBROD PERFORMANCE STATUS SCORE

Performance Status Scale

(Zubrod)	ECOG Karnofsky	Definitions
0	100	Asymptomatic
1	80 – 90	Symptomatic, fully ambulatory
2	60 – 70	Symptomatic, in bed < 50% of day
3	40 – 50	Symptomatic, in bed > 50% of day but not bedridden
4	20 - 30	Bedridden

APPENDIX C

PHYSICIAN PARTICIPANT SIGN OFF SHEET

I certify that I am familiar with the contents and objectives of FCCC 02-014 and that I believe _____ MR#_____ is a reasonable participant on this study.

_____ _____

Pulmonologist Signature Print

_____ _____

Thoracic Surgical Oncologist Signature Print

_____ _____

Medical Oncologist Signature Print

_____ _____

Radiation Oncologist Signature Print

APPENDIX D

ANATOMICAL STAGING FOR LUNG CANCER
(IUCC-AJCC, 1997)
Chest 111; 1710-17
Mountain CF

TNM CATEGORIES

DEFINITIONS
Primary Tumor (T)

Tx Primary tumor cannot be assessed, or tumor proven by 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 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 of 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 tumor), 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; separate tumor nodule(s) in the same lobe; or tumor with a malignant pleural effusion**

*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.

***Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is nonbloody and is not an exudate. When these elements and clinical judgement 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 node metastasis

N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the primary tumor

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

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

MX Distant metastasis cannot be assessed

MO No distant metastasis

M1 Distant metastasis present (includes synchronous separate nodule(s) in a different lobe)

Stage Grouping

Occult 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	T3	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stave IV	Any T	Any N	M1

APPENDIX E

Data Safety and Monitoring Plan for the Trimodality Protocol for the Treatment of Locally Advanced, Potentially Resectable Non-small Cell Lung Cancer

This document specifies procedures for monitoring the conduct of this phase II feasibility study in accordance with the FCCC Data and Safety Monitoring Plan (10/08/01).

Authority

The Phase I-II Program Committee will monitor this trial. In this capacity it will serve as an advisory committee to the PMEC. The Phase I-II Program Committee will review those aspects of this trial that are outlined in the Responsibilities section below. If the phase I-II committee decides that changes should be made to this trial, it will make recommendations to the PMEC, which, in turn, has the authority to approve or disapprove these recommendations according to the procedures discussed in the FCCC Data and Safety Monitoring Plan. These changes will be discussed with the protocol chair before they are implemented.

Responsibilities

The Phase I-II Program Committee will be responsible for:

1. Reviewing interim toxicity for the trial and proposing corrective actions when side effects are unexpectedly severe in accordance with the statistical considerations and thresholds outlined in section 11.1. Corrective actions may include modification to the treatment, early closing or suspension of the trial, or changes to the eligibility criteria for future patients. This review of toxicity by the Phase I-II Committee is in addition to ongoing reviews by the study chair and study team who have primary responsibility for monitoring toxicity on a continual basis.

2. Reviewing any interim analyses of outcome data prepared by the study statistician and recommending changes in the study status on the basis of these analyses. These changes may include early termination of accrual consistent with any sequential stopping rules built into the design of the study (section 11). Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

3. Assess the impact of other scientific investigations, especially other clinical trials for the same disease and stage, on the present protocol and recommend any changes, including protocol termination, based upon these external results.

4. When it becomes appropriate and feasible, develop with the PI a means for monitoring accrual, toxicity, and other events at satellite study sites.

Membership

The DSMC for this study will consist of the Phase I-II Committee. No member of the Phase I-II Committee is a member of the study team for this trial.

Procedures

The Phase I-II Committee meets biweekly and reviews all toxicity and other events for all of the in-house phase I and II trials, including this study, which are not otherwise peer-reviewed or monitored by NCI, a drug company or the equivalent. The Committee will review this particular trial not less than twice per year. The structure of DSMC deliberations for this trial will follow the procedures outlined in the Data and Safety Monitoring Plan for the FCCC.

Recommendations

A written copy of the Phase I-II Committee recommendations will be given on a semi-annual basis to the PI, PMEC, and Chairs of the RRC and IRB. The PMEC will then make a recommendation for study continuation, modification, or closure according to the procedures outlined in the Data and Safety Monitoring Plan for the FCCC.

12/13/2001

Consent Form
Trimodality Protocol for The Treatment of
Locally Advanced, Potentially Resectable Non-Small Cell Lung Cancer

You are being asked to take part in a research study for the treatment of locally advanced non-small cell lung cancer (LA-NSCLC). Taking part in the study is entirely voluntary. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are explained below. You are urged to discuss any questions you have about this study with your doctor and the staff members.

Why is this study being done?

The purpose of this study is to determine the safety and effectiveness of combined modality treatment of locally advanced non-small cell lung cancer, which is confined to chest, but not amenable to initial surgery. Multiple clinical researchers in the past have shown that patients like you, with LA-NSCLC, can benefit from combination chemotherapy and radiation as induction therapy (initial treatment), followed by surgical removal of tumor. However, the vast majority of these studies employed outmoded chemotherapy or insufficient doses of radiation. In this study, we will gauge the side effects and benefits of employing newer chemotherapy (paclitaxel and carboplatin administered initially on a once a week basis), given concurrently with modern radiation for five to six weeks. At that point, you will be reassessed, and if the tumor is surgically resectable (removable), you will proceed to surgical resection (thoracotomy and either lobectomy (removal of a lobe) or pneumonectomy (removal of a lung). Once you have recovered from surgery, you will go on to receive three additional cycles of chemotherapy with carboplatin administered once every month, and paclitaxel administered weekly, three weeks in a row every month. You will be monitored closely throughout this process. You will be seen weekly during the

induction period, daily in the postoperative setting, and once a month while you receive adjuvant (additional) chemotherapy.

The goal of this study is to determine if newer chemotherapy and radiation can be administered more safely than older regimens, and also to determine the success rate of newer chemotherapy and radiation followed by surgical removal.

In addition, we will look closely at the resected specimens to determine if chemoradiation can eradicate viable tumor, and we will follow all participants closely to determine if there is early indication of recurrence, either within the chest or outside the chest (metastatic). We will also follow all participants closely for any late toxicities (side effects).

FUTURE RESEARCH: (Use of specimens beyond this study):
You understand that in signing this consent form you also consent to the use of any of your specimens for future research. You understand that your identity will be carefully guarded and no information by which you can be identified will be released or published in connection with future use of your specimens and that there will be no financial benefit to you for allowing your specimens to be studied.

What is involved In the Study?

All participants will receive radiation once a day to the primary tumor and draining lymph node structures for 5.5 weeks minimum. This may extend to six or even seven weeks. In addition, paclitaxel will be administered by one hour infusion once a week for six weeks during radiation. Carboplatin will be administered on the same day of

the week as paclitaxel over one-half hour for six weeks through the course of radiation.

At the conclusion of chemoradiation, you will undergo reassessment to determine if the tumor is resectable (removable). If it is, you will undergo surgical resection from four to eight weeks after conclusion of chemoradiation, and once you have recovered from surgery, you will receive adjuvant (additional) chemotherapy consisting of carboplatin given once every four weeks, and paclitaxel given weekly X 3 every four weeks.

If, however, the tumor proves unresectable, or if at the time of surgery, the tumor cannot be removed, you will receive additional radiation for up to three weeks plus three additional courses of weekly paclitaxel and carboplatin during radiation. Four to 12 weeks after the conclusion of chemoradiation, you will receive three adjuvant (additional) cycles of paclitaxel and carboplatin as outlined above.

Participation will absolutely require close monitoring, weekly blood tests to make certain there are no severe side effects, and repeated x-rays and CT scans to gauge tumor status.

If you take part in this study, you will have the following tests and procedures:

History and physical exam with a record of your height, weight and vital signs; measure of functional or performance status; tumor measurements; blood work, including CBC, electrolytes, liver and kidney function tests; chest x-ray; bone scan or

PET scan; CT scan of the chest, liver and adrenals; CT scan or MRI of the brain; electrocardiogram; HCG if woman of childbearing age; and coagulation tests (PT/PTT) to make sure there is no significant risk of bleeding.

These tests, with virtually no exceptions, are considered standard in the routine combined modality treatment of patients with LA-NSCLC.

If you do not already have one, you may be asked to undergo a surgical procedure to place an indwelling catheter port into a large vein in your chest through which medication can be administered and blood may be drawn. You will be asked to sign a separate consent form for this procedure.

How long will you be on this study?

The course of treatment, including induction chemoradiation, surgery, and additional chemotherapy will take up to six months. In addition, after treatment is completed, you will be followed regularly: every three months for two years, then every six months for three years, and then once a year after five years have elapsed.

What are the risks of the study?

While on the study, you are at risk for side effects. You should discuss these with your doctor. There also may be other side effects we cannot predict. Other drugs will be given to make side effects less serious and less uncomfortable. Most side effects go away weeks to months after chemotherapy and radiation are stopped. But, in some cases, side effects can be serious or long lasting, though only rarely permanent.

Risks and side effects related to the use of chemotherapy include:

Common:

- Drop in white blood count, which can increase your risk of fever and infection
- Drop in hemoglobin and hematocrit, which can result in anemia and make you feel weak, tired or short of breath
- Drop in platelet count, which rarely can lead to bleeding
- Numbness and tingling in the fingers or toes, which rarely can advance up the arms and legs, but which is seldom severe or bothersome
- Aches and pains in the muscles and joints which tend to be short-lasting, but can be severe
- Fatigue
- Nausea, less commonly, vomiting
- Diarrhea
- Mouth sores

Less Common:

- Allergic reactions, including wheezing, rash, swelling, for which you will standardly receive prophylactic (preventative) medications before each dose of chemotherapy. These medications include steroids, antihistamines, and an H2 blocker (i.e., cimetidine or ranitidine).
- Acceleration or reduction in pulse rate
- Decline in appetite

Rare:

- Lightheadedness or syncope (passing out)
- Electrocardiogram rhythm abnormalities
- Elevated blood pressure
- Blood clots
- Liver enzyme changes
- Kidney function abnormalities

Risks and side effects related to radiation include:

Common:

- Skin rash that looks like a sunburn within the radiation field
- Trouble swallowing, including odynophagia (pain upon swallowing), which, if it occurs, will tend to be worse toward the end of chemoradiation, and will generally improve within 1-2 weeks after radiation is stopped.
- Pneumonitis (inflammation of the lung), which can lead to coughing or shortness of breath, and which can, rarely, prove severe

Less Common:

- Damage to muscle or ribs within the chest wall which, if it occurs, will generally be delayed months, if not years.

- Esophageal stricture (narrowing of the swallowing tube) which is generally amenable to balloon dilatation (dilation); if it occurs, it is generally delayed until months or years after treatment.

The risks of frequent blood sampling include bruising and bleeding around the site, discomfort, fainting and rarely infection.

Your doctor will check you closely to see if any of these side effects are occurring. Routine blood and possibly urine tests will be done to monitor the effects of treatment. Most side effects disappear after the treatment is stopped. In the meantime, your doctor will prescribe medication to keep these side effects under control. Schedules and dosages may be altered to reduce the side effects.

Reproductive Risks

Because the drugs of this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask about counseling and more information on preventing pregnancy.

If you are a woman of childbearing potential, you must use an adequate form of contraception once you are entering the study, during the study, and for at least three (3) months after the end of drug administration. If you are pregnant or breast feeding, you may not participate in this study, and if you become pregnant, you will be removed from the study.

If you are a man, you must use an effective method of birth control while you are participating in this study and for three (3) months after the end of drug administration.

Are there benefits to taking part in the study?

If you agree to take part in this study, there may or may not be direct medical benefit to you. Regardless, we hope the information learned from this study will benefit other patients with locally advanced, non-small cell lung cancer in the future. From your personal standpoint, we hope this treatment will both eradicate and help delay or prevent recurrence of your cancer.

It is not possible to predict whether any personal benefit will result from your participation in this study. However, it is possible that your condition will improve. Also, what is learned from this study may benefit others with the same disease.

What other options are there?

Instead of being in this study, you have these options:

(1) No treatment, which will very likely result in rapid, local progression (tumor growth) or metastasis (spread beyond the chest), and will likely cause your demise within six to 12 months.

(2) Radiation alone, which has proven ineffective compared to combined modality therapy.

(3) Chemotherapy given even before or during radiation, off study, using the same agents or similar agents.

(4) Chemotherapy alone, which is not likely to benefit you in the long-term

(5) Chemotherapy followed by surgical resection, which has been shown in at least one study to be less effective than chemoradiation given prior to surgery.

Surgery alone, without initial treatment using chemotherapy and radiation, is not likely to prove feasible for you.

Alternatives, which could be considered in your case, include treatment with different drugs, or perhaps participation in another study. An additional alternative is no therapy. You understand that your doctor can provide detailed information about your disease and the possible benefits of the various treatments available.

You may get the same treatment even if you do not take part in this study, although we cannot guarantee that everything will be given on appropriate schedule; nor can be guarantee that the same care or diligence will be applied.
Please talk to your doctor about these and other options.

What about confidentiality?

Efforts will be made to keep your personal information confidential. The confidentiality of any central computer record will be carefully guarded and no information by which you can be identified will be released or published. We cannot

guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Representatives of the Food and Drug Administration (FDA), the study's sponsor, Fox Chase Cancer Center, and other organizations may inspect and/or copy your research records for quality assurance and data analysis.

What are the costs?

You will receive no pay for taking part in this study. Procedures such as x-rays and laboratory tests purely related to the research will be explained, although this is not anticipated. Some of these procedures or tests may result in added costs which may not be covered by insurance, and for which you may then be personally responsible. These possible additional costs will be discussed with you prior to the beginning of the study.

In the event of physical injury resulting from this study, medical treatment to the extent that it is available will be provided. The financial burden for this treatment may be your personal responsibility. No monetary compensation will be provided for wages lost or for any other reason because of injury resulting from this study.

Both paclitaxel and carboplatin are commercially available and will be billed to you in the customary manner. These agents have been covered by most insurance companies outside of the study setting.

Medications used to control side effects may result in costs that may not be covered by insurance. You understand that you will be responsible for these costs if your insurance does not cover them.

Whom do you call if you have questions or problems?

You are free to ask questions at any time about these procedures and to ask for additional information from your doctor or his designated representatives or other doctors involved in your care. If you have questions, you can reach your doctor at (215) 728-4300.

Can you withdraw from the study? What are your rights as a participant?

Participation in this study is voluntary. You understand that you are free to withdraw your consent to participate in this treatment program at anytime without affecting your future care. Refusing to participate will involve no penalty or loss of benefits. You are free to seek care from a physician of your choice at anytime. If you withdraw from the study, you will continue to be followed and clinical data will continue to be collected form your medical records.

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

Can you be removed from the study?

Your participation in the project may be removed by your doctor without your consent if you are not benefiting from the treatment or if it develops that the treatment is not appropriate to your case or for reasons at his/her discretion.

Where can you get more information about this study?

If you have questions about the research, or in the event of a research-related injury, you may contact the Institutional Review Board, which is concerned with protection of participants in research projects. You may reach the Institution Review Board office by calling (215) 728-2518 from 9:00 a.m. to 5:00 p.m., Monday through Friday, or by writing to the Institutional Review Board, Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111.

As the research progresses, any significant new finds beneficial or otherwise, will be told to you and explained as related to your case.

By signing below, you indicate that you have read this form, received acceptable answers to any questions, and willingly consent to participate.

You will receive a copy of this form. You may also request a copy of the protocol.

_____ _____

Signature of Participant Date

_____

Signature of Physician

Revised 04/24/01