



DEPARTMENT OF THE AIR FORCE
HEADQUARTERS UNITED STATES AIR FORCE



4 Nov 94

MEMORANDUM FOR 375th Medical Group/SGGT
ATTN: Mr. Deltgen
310 W Losey Street
Scott AFB IL 62225-5252

AIR1.941108.003

FROM: HQ AFMOA/SGPT
170 Luke Avenue, Suite 400
Bolling AFB DC 20332-5113

SUBJECT: Clinical Investigation Protocols SGO 93-203 (Your
Telefax Msg, 4 Nov 94)

The Surgeon General's Clinical Investigation Committee approved the following protocol action via the expedited review process on this date:

93-203, Scott, "CALGB 9130, A Phase III Trial of Vinblastine/ Cisplatin/ Radiation Therapy with or without Carboplatin (NSC# 241240) for Inoperable Stage IIIA and Stage IIIB Non-Small Cell Lung Cancer," Revised Informed Consent Document, 31 Oct 93

Mrs. Darlene Casto, Clinical Investigation Program Manager, DSN 297-5078, is our point of contact for clinical investigation issues.

DANIEL R. BROWN, Lt Col, USAF, BSC
Acting Chief, Clinical Investigations and
Life Sciences Division
Air Force Medical Operations Agency
Office of the Surgeon General

SGO 93-203

AFR 169-6
 Attachment 3

SCOTT AIR FORCE BASE
 INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES

Participant _____

Principal Investigator Joanne Mortimer, M.D. Human Studies Committee
Dennis Costa, M.D. Approval number _____

Title of Project: CALGB 9130 - A phase III Trial of Vinblastine/Cisplatin/ Radiation
 Therapy with or without Carboplatin for Inoperable Stage IIIA and
 Stage IIIB Non-Small Cell Lung Cancer

1. I have been asked to participate in a research project conducted by Dr. Dennis Costa
 and/or assistants. The overall purpose of this research is:

The purpose of this project is to attempt: 1) to slow or stop the growth of my disease
 or, if possible, to reduce the activity of my disease; 2) to gain information
 about my type of lung cancer; and 3) to compare the usefulness and side effects of
 these different treatments. Approximately 270 people will be registered to this study
 over 4 years, approximately 10 of those will be from Scott Air Force Base.

2. My participation will involve the following:

Before beginning treatment and at specified intervals, I will have the following tests
 performed: routine blood tests (2-3 teaspoons), chest x-rays, CT scans of the chest
 and abdomen (computer-assisted x-rays), bone scans (scan using a radioactive dye), EKGs
 (heart function test), urinalysis, pulmonary function tests, and bronchoscopy before
 beginning treatment, after completion of radiation therapy and as indicated by my
 disease throughout the study. A bronchoscopy is a procedure in which a flexible,
 lighted instrument is passed through the mouth and throat into the windpipe so that
 areas of the lungs can be seen.

I will be randomized (chosen by chance, much like the drawing of a card) to receive
 treatment with one of the following. My chances of being assigned to either of the
 treatment arms is approximately equal.

1) The anti-cancer drug vinblastine will be given in my vein over 30 minutes for once
 per week for five weeks in a row. In addition, cisplatin will be given in my vein over
 30-60 minutes on days 1 and 29. To reduce the side effects of cisplatin, it will be
 necessary for intravenous fluids to be given approximately twenty four hours before and
 two hours after the cisplatin is administered. Due to the nature of the cisplatin
 chemotherapy administration, it will be necessary for me to be hospitalized for those
 treatments. After a three week rest period, I will receive radiation therapy to my
 tumor five days per week for six weeks.

OR

2) Treatment will be identical as in #1 above but during the time period while I am
 receiving radiation therapy, I will also receive the anti-cancer drug carboplatin in
 my vein over 30 minutes once per week for six weeks.

APPROVED 31 Oct 93
 SCOTT MED CTR IRB 

D. 11/10/94

3. I understand there are certain risks and discomforts that might be associated with this research:

The treatment of lung cancer requires the use of powerful drugs (chemotherapy) that have side effects, some potentially very serious. It may be necessary for me to be admitted to the hospital if these side effects are severe.

The specific side effects for each drug are listed below; the most common side effects are underlined.

Bone marrow suppression: The drugs used to kill cancer cells also kill some normal body cells, especially those that grow rapidly (blood cells, hair, and cells that line the mouth, stomach, and intestines). A reduction in the number of these blood cells (bone marrow suppression) can lead to an increased risk of bleeding and infection.

Nausea and vomiting: Anti-nausea medication will be prescribed before and after therapy.

Constipation: Severe constipation may occur; laxatives may prevent this from occurring.

Hair loss: Hair will fall out about three weeks after the first dose of chemotherapy but will grow back when chemotherapy is discontinued. Hair color may change and hair is sometimes curlier.

Neurologic abnormalities: I may experience temporary unsteadiness when walking, fatigue, headache, tingling of the fingers and toes, jaw pain, muscle weakness, loss of reflexes, blurred vision, slight depression and confusion, agitation, and hallucinations. More severe side effects are rare but have occurred including: cranial nerve paralysis (slurred speech, facial paralysis, difficulty hearing).

Kidney damage: Potential damage is minimized by giving fluids by vein and by drinking plenty of fluids. Kidney function will be monitored with blood tests. Damage is usually reversible.

Liver irritation: This is temporary, usually mild, and does not usually lead to any long-term damage.

Hearing loss of high tones (higher than human speech) is possible.

Skin rash: A few patients who receive high doses develop a rash, particularly on the hands and feet. Later, the skin on the palms and soles may peel. A variety of creams may lessen the symptoms significantly.

Skin ulcer: can be irritating to the tissue if it leaks out of the vein. In the unlikely event of a severe reaction, irreversible tissue damage may result, and a skin graft may be required.

Severe allergic reactions: Severe allergic reactions may occur. These symptoms include a fast heart rate, wheezing, low blood pressure, sweating, and face rash. If a severe allergic reaction occurs, the drug will not be given again.

In addition the the side effects of mentioned above, additional side effects carboplatin include:

APPROVED 31 Oct 93
SCUIT McD CTR IRB

Liver toxicity: When given at higher doses than used in this study, there may rarely be narrowing or blockage of the small veins in the liver resulting in liver tenderness, pain, and jaundice (yellowing the skin and eyes). This may lead to liver failure and, very rarely, death.

Blood in the urine: Carboplatin may, on rare occasions, cause bloody urine. **Low sodium:** Carboplatin may cause a lowering of the sodium level in the blood which could lead to confusion and/or coma. Frequent blood tests will monitor this side effect. Should low sodium occur, it can be easily corrected.

Side effects of radiation therapy may include: temporary irritation of the throat and esophagus may cause a sore throat, difficult and painful swallowing, and dry cough. Scarring of the lungs due radiation therapy may occur. This may cause shortness of breath and a dry cough.

The large amount of intravenous fluids that are administered could result in an overload of fluid in the body. Side effects from the overload may include swelling in the hands, arms, feet, or legs; shortness of breath; congestive heart failure; and fluid accumulation in body organs.

Some of the side effects mentioned above, if severe, may cause death.

4. I understand that the possible benefits to myself or society from this research are:

It is possible that the treatment will cause my tumor to shrink or disappear, lessen or eliminate my symptoms, and thus increase my life expectancy. The information learned in this study may be beneficial to other cancer patients in the future.

5. I may chose not to participate in this research; My choice will not at any time affect the commitment of health care providers to administer optimal care.

6. I understand that the following alternative(s) is/are available:

Treatment with other chemotherapy drugs and/or radiation therapy may be of advantage to me.

7. To the best of my knowledge I am not pregnant. If I do become pregnant, I understand that I should notify the principal investigator immediately.

8. Records of my participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5U. S.C. 552a, and its implementing regulations. DD Form 2005 contains the Privacy Act Statement for the records. I understand that records of the study may be inspected by the US Food and Drug Administration (FDA), as well as the group sponsoring the research known as the Cancer and Leukemia Group B (CALGB).

9. I Understand that my entitlements to medical and dental care and/or compensation in the event of injury are governed by federal laws and regulations, and if I desire further information, I may contact Rodney Deltgen, Administrator of the Institutional Review Committee (IRC).

10. In the event that an unanticipated event (clinical or medical misadventure) occurs during my participation in this study, I will be informed. If I am not competent at the time to understand the nature of the event, such information will be brought to the attention of my guardian or next of kin.

APPROVED 31 Oct 93
SCOTT MED CTR IRB [Signature]

11. The decision to participate in this study is completely voluntary on my part. No one has coerced or intimidated me into participating in this program. I am participating because I want to. Dr. Dennis Costa and or his assistants have adequately answered any and all questions I have about this study, my participation, and the procedures involved.

I understand that Dr. Costa will be available to answer any questions concerning procedures throughout this study. I understand that if significant new findings develop during the course of this study which may relate to my decision to continue participation, I will be informed. I further understand that I may withdraw this consent at any time and discontinue further participation in this study without prejudice to my entitlements to care. I also understand that the investigator of this study may terminate my participation in this study if he or she feels this to be in my best interest.

Subject's Signature and Social Security Number

Date

Sponsor's Signature and Social Security Number
(When Appropriate)

Date

Witness Signature

Date

Responsible Investigator's Signature

Date

Distribution:

1. IRC (Attention: Mr. Deltgen)
2. Subject's Medical Record (to be maintained permanently)
3. Principal Investigator (Dr. Costa)
4. Subject
5. Washington Univ. (Attention: Janet)

APPROVED 31 Oct 93
SCOTT MED CTR IRB [Signature]

4 Nov 94

MEMORANDUM FOR THE RECORD

SUBJECT: Protocol 93-203

Upon telephone request, Mr. Deltgen, Scott telefaxed the attached preliminary "progress report." He will prepare one in the proper format and submit for review by the Scott Institutional Review Board and the Commander.

Additionally, he will send other outstanding CALGB progress reports and informed consent documents.

DARLENE G. CASTO
Clinical Investigation Program Manager
and Human Use Program Manager
Air Force Medical Operations Agency
Office of the Surgeon General

SCOTT AIR FORCE BASE MEDICAL CENTER

REQUEST FOR REVISION OR AMENDMENT TO AN APPROVED PROTOCOL

Responsible Investigator Thomas Johnson IRC 93-203 Date 9/22/94

Title of Project CALGB 9130 A Phase III Trial of Vinblastine/Cisplatin/Radiation Therapy with or Without Carboplatin (NSC #241240) for Inoperable Stage IIIA and Stage IIIB Non Small Cell Lung Cancer

	SAFB	Cooperative Group
Number of Subjects Accrued	<u>1</u>	<u>232</u>
Over What Period of Time	<u>14 months</u>	<u>35 months</u>

Attached please see update numbers 6 & 7 both dated 2/23/94 to the approved referenced, previously approved protocol.

There have been several changes to the protocol as noted on the summary pages, including changes made to the model consent.

Please note: that these changes were not submitted at the time they were issued because Protocol activity was temporarily suspended due to data management restraints and no new patients were to be entered onto the protocol. The changes did not affect the one patient who was already registered. The protocol has subsequently closed, and the changes will not be made. The updates are provided for your records only.

No untoward events have occurred involving the single patient entered onto this protocol.

Please let me know if additional paperwork is required.

The information above affects the consent document

Yes No

Tom Johnson, MD
Signature of Responsible Investigator

9/22/94
Date



DEPARTMENT OF THE AIR FORCE
HEADQUARTERS UNITED STATES AIR FORCE
WASHINGTON DC

12 Apr 94

MEMORANDUM FOR 375th Medical Group/SGE
ATTN: Mr. Deltgen
310 W Losey Street
Scott AFB IL 62225-5252

FROM: HQ AFMOA/SGPT
170 Luke Avenue, Suite 400
Bolling AFB DC 20332-5113

SUBJECT: Clinical Investigation Protocols - ACTION MEMORANDUM

A review of the clinical investigation records indicates that a status/final report or other documentation is required to bring our files up to date on the following protocols:

89-247, "Placebo Controlled Study of Antibiotic Treatment of Chronic Sinusitis and Allergic Rhinitis" -- Transferred from Yakota AFB, Japan"

90-095, "CALGB 9194 (SWOG 8814), Phase III Comparison of Adjuvant Chemoendocrine Therapy with CAF and Concurrent or Delayed Tamoxifen to Tamoxifen Alone in Postmenopausal Patients with Involved Axillary Lymph Nodes and Positive Receptors"

90-112, "A Jet Nebulizer Comparison in Treating Acute Asthma Phase 2" - Transfer from WHMC Pending

90-330, "Efficacy of Sustained Release Diltiazem in Treating Hypertensives"

91-131, "CALGB 9193 (SWOG 8931), Phase III Comparison of Cyclophosphamide, Doxorubicin, and 5-Fluorouracil (CAF) and a 16-Week Multi-Drug Regimen as Adjuvant Therapy for Patients with Hormone Receptor Negative"

91-160, "Changes in Neuromuscular Performance of Weightlifters with the Use of Hypnosis"

91-169, "Use of Fluoxetine in the Treatment of Premenstrual Syndrome"

91-229, "A Cooperative Study of Chlorhexidine Versus Povidone-Iodine Cutaneous Antisepsis for the Prevention of Central Total Parental Nutrition Catheter Related Infections"

92-196, "CALGB 9190, SWOG 9111, Intergroup Post-Operative Adjuvant Interferon Alfa-2b (Intron A) In Resected High-Risk Primary and Regionally Metastatic Melanoma"

92-202, "Safety, Tolerability and Immunogenicity of Tetravalent Pneumococcal Conjugate Vaccine "

92-267, "Meeting Consumer Demands: Satisfaction and Cost Effectiveness of Interdisciplinary Group and Individual Lifestyle Counseling for Clients with Hyperlipidemia"

93-200, "CALGB 9192, Phase III Comparison of Combination Chemotherapy (CAF) and Chemohormonal Therapy (CAF + Zoladex or CAF+ Zoladex + Tamoxifen) in Premenopausal Women with Axillary Node-Positive Receptor-Positive Breast Cancer"

93-201, "CALGB 9033, Oral Versus Intravenous Etoposide in Combination with Intravenous Cisplatin in Extensive Small Cell Lung Cancer: Phase III Includes Pharmacology Companion Protocol CALGB 9062"

93-202, "CALGB 8971, A Dose Response Trial of Megestrol Acetate for the Treatment of Cachexia in Patients with Advanced Lung or Colorectal Cancer"

93-203, "CALGB 9130, A Phase III Trial of Vinblastine/ Cisplatin/ Radiation Therapy with or without Carboplatin (NSC# 241240) for Inoperable Stage IIIA and Stage IIIB Non-Small Cell Lung Cancer"

94-046, "Thrombolysis and Thrombin Inhibition in Acute Myocardial Infarction"

You are encouraged to submit the requested documentation as soon as possible, but no later than 27 May 94. We appreciate your cooperation in this matter. If I can be of assistance, please contact me at DSN 297-5078 or commercial (202) 767-5078. Our telefax number is DSN 297-5302.



DARLENE G. CASTO
Clinical Investigation Program Manager
Air Force Medical Operations Agency
Office of the Surgeon General



DEPARTMENT OF THE AIR FORCE
HEADQUARTERS UNITED STATES AIR FORCE



FROM: HQ AFMOA/SGPT
170 Luke Ave, Suite 400
Bolling AFB DC 20332-5113

12 Jul 93

SUBJ: Clinical Investigation Protocols

TO: Scott Medical Center/SGE (Mr. Rodney Deltgen)

1. For record-keeping purposes, we have assigned SGO file numbers to the clinical investigation protocols as listed below. Please refer to these numbers in future correspondence regarding the studies:

a. 93-200, "CALGB 9192, Phase III Comparison of Combination Chemotherapy (CAF) and Chemohormonal Therapy (CAF + Zoladex or CAF+ Zoladex + Tamoxifen) in Premenopausal Women with Axillary Node-Positive Receptor-Positive Breast Cancer"

b. 93-201, "CALGB 9033, Oral Versus Intravenous Etoposide in Combination with Intravenous Cisplatin in Extensive Small Cell Lung Cancer: Phase III Includes Pharmacology Companion Protocol CALGB 9062"

c. 93-202, "CALGB 8971, A Dose Response Trial of Megestrol Acetate for the Treatment of Cachexia in Patients with Advanced Lung or Colorectal Cancer"

d. 93-203, "CALGB 9130, A Phase III Trial of Vinblastine/ Cisplatin/ Radiation Therapy with or without Carboplatin (NSC# 241240) for Inoperable Stage IIIA and Stage IIIB Non-Small Cell Lung Cancer"

2. The Surgeon General's Clinical Investigation Committee concurred with your participation in the studies, in accordance with AFR 169-6, Clinical Investigation and Human Test Subjects in the Medical Service, and HQ USAF/SG letter dated 20 Apr 93, Subject: Blanket Approval for Participation in National Cancer Institute Sponsored Groups. However, the informed consent documents (ICD) should be revised as follows:

a. Include the number of patients to be enrolled in the study, (both nationally and locally), and the duration of the study.

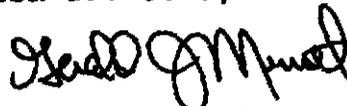
b. Explain the randomization chances. ("The chances of my receiving any of the 3 drug treatment plans offered are approximately equal," or appropriate language.)

c. Reference the pregnancy para. If pregnancy is an exclusion criteria, than a pregnancy test should be offered and it should be stated in the ICD and the potential harm to the fetus should be addressed. We recommend you add the following language: "If I am a female of childbearing potential, my physician will do a pregnancy test before I participate in the study. I agree to take precautions to avoid becoming pregnant during the course of this study due to the potentially catastrophic harm the drug(s) may cause the fetus."

3. Please provide this office a copy of the revised ICDs by 26 Aug 93 to complete our records. Also, in future National Cancer Institute sponsored protocol submissions, you should include the medical law consultant's letter of approval for the ICD, and the personnel and manpower data.

4. To assist in the proper accomplishment of these protocols you should assure compliance with AFR 169-6 as it pertains to annual progress reports, final reports, proper maintenance of records, and the application of written informed consent to all study participants.

5. Mrs. Darlene Casto, Clinical Investigation Program Manager, DSN 297-5078, is our point of contact for NCI-sponsored protocols.


GERALD J. MERRITT, Col, USAF, BSC
Chief, Clin Investigations & Life Sci Div
Air Force Medical Operations Agency
Office of the Surgeon General

cc: HQ AMC/SG
SMC/SGJ

92-213

DEPARTMENT OF THE AIR FORCE
USAF MEDICAL CENTER SCOTT (AMC)



FROM: USAF Medical Center Scott/SGE
310 W Losey St
Scott AFB IL 62225-5252

SUBJ: Clinical Investigation Protocol- Cancer/Leukemia Group B-9130

TO: HQ AFMOA/SGPT

1. The attached CALGB Protocol #9130, entitled - A Phase III Trial of Vinblastin/Cisplatin/Radiation Therapy with or without Carboplatin (NSC#241240) for Inoperable Stage IIIA and Stage IIIB Non-Small Cell Lung Cancer, is forwarded for your review and approval.
2. The protocol and informed consent form was reviewed and approved by our Institutional Review Committee on 23 Dec 93. As the Medical Center Commander I have reviewed the protocol and consent form, accepted the recommendation of the IRC and approved the implementation of the proposed study at USAF Medical Center Scott.
3. Please contact Mr Rodney Deltgen, DSN 576-7342/7535 if you have any questions.

JOHN G. JERNIGAN, Colonel, USAF, MC, CFS
Commander

Atch
CALGB Protocol #9130 Package

Approved 12 Jul 93

AMC--GLOBAL REACH FOR AMERICA

77 JUL 93

SCOTT AIR FORCE BASE
 INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES

Participant _____

Principal Investigator Joanne Mortimer, M.D. Human Studies Committee
Dennis Costa, M.D. Approval number _____

Title of Project: CALGB 9130 - A phase III Trial of Vinblastine/Cisplatin/
 Radiation Therapy with or without Carboplatin for Inoperable
 Stage IIIA and Stage IIIB Non-Small Cell Lung Cancer

1. I have been asked to participate in a research project conducted by Dr. Dennis Costa and/or assistants. The overall purpose of this research is:

The purpose of this project is to attempt: 1) to slow or stop the growth of my disease or, if possible, to reduce the activity of my disease; 2) to gain information about my type of lung cancer; and 3) to compare the usefulness and side effects of these different treatments.

2. My participation will involve the following:

Before beginning treatment and at specified intervals, I will have the following tests performed: routine blood tests (2-3 teaspoons), chest x-rays, CT scans of the chest and abdomen (computer-assisted x-rays), bone scans (scan using a radioactive dye), EKGs (heart function test), urinalysis, pulmonary function tests, and bronchoscopy (prestudy only). A bronchoscopy is a procedure in which a flexible, lighted instrument is passed through the mouth and throat into the windpipe so that areas of the lungs can be seen.

I will be randomized (chosen by chance, much like the drawing of a card) to receive treatment with one of the following:

1) The anti-cancer drug vinblastine will be given in my vein over 30 minutes for once per week for five weeks in a row. In addition, cisplatin will be given in my vein over 30-60 minutes on days 1 and 29. To reduce the side effects of cisplatin, it will be necessary for intravenous fluids to be given approximately twenty four hours before and two hours after the cisplatin is administered. Due to the nature of the cisplatin chemotherapy administration, it will be necessary for me to be hospitalized for those treatments. After a three week rest period, I will receive radiation therapy to my tumor five days per week for six weeks.

or

2) Treatment will be identical as in #1 above but during the time period while I am receiving radiation therapy, I will also receive the anti-cancer drug carboplatin in my vein over 30 minutes once per week for six weeks.

APPROVED
 SCOTT MED CTR IRB

9 Apr 93 *Dcd*

3. I understand there are certain risks and discomforts that might be associated with this research:

The treatment of lung cancer requires the use of powerful drugs (chemotherapy) that have side effects, some potentially very serious. It may be necessary for me to be admitted to the hospital if these side effects are severe.

The specific side effects for each drug are listed below; the most common side effects are underlined.

Bone marrow suppression: The drugs used to kill cancer cells also kill some normal body cells, especially those that grow rapidly (blood cells, hair, and cells that line the mouth, stomach, and intestines). A reduction in the number of these blood cells (bone marrow suppression) can lead to an increased risk of bleeding and infection.

Nausea and vomiting: Anti-nausea medication will be prescribed before and after therapy.

Constipation: Severe constipation may occur; laxatives may prevent this from occurring.

Hair loss: Hair will fall out about three weeks after the first dose of chemotherapy but will grow back when chemotherapy is discontinued. Hair color may change and hair is sometimes curlier.

Neurologic abnormalities: I may experience temporary unsteadiness when walking, fatigue, headache, tingling of the fingers and toes, jaw pain, muscle weakness, loss of reflexes, blurred vision, slight depression and confusion, agitation, and hallucinations. More severe side effects are rare but have occurred including: cranial nerve paralysis (slurred speech, facial paralysis, difficulty hearing).

Kidney damage: Potential damage is minimized by giving fluids by vein and by drinking plenty of fluids. Kidney function will be monitored with blood tests. Damage is usually reversible.

Liver irritation: This is temporary, usually mild, and does not usually lead to any long-term damage.

Hearing loss of high tones (higher than human speech) is possible.

Skin rash: A few patients who receive high doses develop a rash, particularly on the hands and feet. Later, the skin on the palms and soles may peel. A variety of creams may lessen the symptoms significantly.

Skin ulcer: can be irritating to the tissue if it leaks out of the vein. In the unlikely event of a severe reaction, irreversible tissue damage may result, and a skin graft may be required.

Severe allergic reactions: Severe allergic reactions may occur. These symptoms include a fast heart rate, wheezing, low blood pressure, sweating, and face rash. If a severe allergic reaction occurs, the drug will not be given again.

In addition to the side effects of mentioned above, additional side effects carboplatin include:

Liver toxicity: When given at higher doses than used in this study, there may rarely be narrowing or blockage of the small veins in the liver resulting in liver tenderness, pain, and jaundice (yellowing the skin and eyes). This may lead to liver failure and, very rarely, death.

Blood in the urine: Carboplatin may, on rare occasions, cause bloody urine.

Low sodium: Carboplatin may cause a lowering of the sodium level in the blood which could lead to confusion and/or coma. Frequent blood tests will monitor this side effect. Should low sodium occur, it can be easily corrected.

Side effects of radiation therapy may include: temporary irritation of the throat and esophagus may cause a sore throat, difficult and painful swallowing, and dry cough. Scarring of the lungs due radiation therapy may occur. This may cause shortness of breath and a dry cough.

The large amount of intravenous fluids that are administered could result in an overload of fluid in the body. Side effects from the overload may include swelling in the hands, arms, feet, or legs; shortness of breath; congestive heart failure; and fluid accumulation in body organs.

Some of the side effects mentioned above, if severe, may cause death.

4. I understand that the possible benefits to myself or society from this research are:

It is possible that the treatment will cause my tumor to shrink or disappear, lessen or eliminate my symptoms, and thus increase my life expectancy. The information learned in this study may be beneficial to other cancer patients in the future.

5. I may chose not to participate in this research; My choice will not at any time affect the commitment of health care providers to administer optimal care.

6. I understand that the following alternative(s) is/are available:

Treatment with other chemotherapy drugs and/or radiation therapy may be of advantage to me.

7. To the best of my knowledge I am not pregnant. If I do become pregnant, I understand that I should notify the principal investigator immediately.

8. Records of my participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5U. S.C. 552a, and its implementing regulations. DD Form 2005 contains the Privacy Act Statement for the records. I understand that records of the study may be inspected by the US Food and Drug Administration (FDA), as well as the group sponsoring the research known as the Cancer and Leukemia Group B (CALGB).
9. I Understand that my entitlements to medical and dental care and/or compensation in the event of injury are governed by federal laws and regulations, and if I desire further information, I may contact Rodney Deltgen, Administrator of the Institutional Review Committee (IRC).
10. In the event that an unanticipated event (clinical or medical misadventure) occurs during my participation in this study, I will be informed. If I am not competent at the time to understand the nature of the event, such information will be brought to the attention of my guardian or next of kin.
11. The decision to participate in this study is completely voluntary on my part. No one has coerced or intimidated me into participating in this program. I am participating because I want to. Dr. Dennis Costa and or his assistants have adequately answered any and all questions I have about this study, my participation, and the procedures involved. I understand that Dr. Costa will be available to answer any questions concerning procedures throughout this study. I understand that if significant new findings develop during the course of this study which may relate to my decision to continue participation, I will be informed. I further understand that I may withdraw this consent at any time and discontinue further participation in this study without prejudice to my entitlements to care. I also understand that the investigator of this study may terminate my participation in this study if he or she feels this to be in my best interest.

Subject's Signature and Social Security Number

Date

Sponsor's Signature and Social Security Number
(When Appropriate)

Date

Witness Signature

Date

Distribution:

1. IRC (Attention: Mr. Deltgen)
2. Subject's Medical Record (to be maintained permanently)
3. Principal Investigator (Dr. Costa)
4. Subject
5. Washington Univ. (Attention: Janet)

PROTOCOL SUMMARY

TITLE: CALGB Protocol #9130 - A Phase III Trial of Vinblastine/Cisplatin/Radiation Therapy with or without Carboplatin for Inoperable Stage IIIA and Stage IIIB Non-Small Cell Lung Cancer

Principal Investigator: Major (Dr) Dennis Costa, USAF, MC
Dr Joanne Mortimer, MD

FACILITY: USAF Medical Center Scott
Barnard Cancer Center, Washington University Medical Center

1. SUMMARY: Patients will be randomized to receive IV vinblastine weekly for five consecutive weeks and IV cisplatin on days 1 and 29 followed by six weeks of radiation therapy to the tumor site with or without weekly IV carboplatin chemotherapy. Subjects for this protocol must have a histologically proven diagnosis of non-small cell lung cancer. Approximately 270 patients will be enrolled in the study. All patients must be able to give voluntary informed consent to the proposed study. No remuneration is given to the participants. Potential risks to the cancer patient include: bone marrow suppression, neurologic abnormalities, nausea and vomiting, constipation, alopecia, nephrotoxicity, renal toxicity, hearing loss of high tones, skin rash, skin ulcer, mild or severe allergic reactions, hematocrit, hyponatremia, esophagitis, radiation pneumonitis, edema, and congestive heart failure. The potential risks are minimized by review of laboratory data, frequent examinations and contact with the oncologist, and careful education of patients and family. Emergency medical care is always available by contacting the oncologist or USAF Medical Center Scott's Emergency Medicine Department. Alternative options for patients include treatment with other experimental agents or commercially available agents, radiotherapy where appropriate, or observation and supportive care alone. The potential benefits for patients participating in this protocol include the possibility of slowing or stopping their disease, decreasing or eliminating their symptoms and, hopefully, extending their life span. The knowledge gained from cancer research protocols, such as the one proposed here, will hopefully one day lead to a cure.

2. ADDITIONAL INFORMATION:

a. No investigational drugs used.

b. Patient Selection: Subjects for this protocol must have a histologically proven diagnosis of non-small cell lung cancer. Patients must be greater than 18 years of age. Inclusion criteria in addition to the above stated diagnosis include: prior radiotherapy consultation, measurable or evaluable disease, performance status 0-1. Criteria for exclusion include: history of previous malignancy other than carcinoma in situ of the cervix or basal cell carcinoma of the skin, other serious physical or psychiatric illnesses, malignant pleural effusion, less than two weeks since exploratory thorcotomy, prior chemotherapy, radiation therapy or total resection.

c. Schedule of patient evaluation study: see summary

93-203

CANCER AND LEUKEMIA GROUP B

PROTOCOL UPDATE TO CALGB 9130

A PHASE III TRIAL OF VINBLASTINE / CISPLATIN / RADIATION THERAPY WITH OR WITHOUT CARBOPLATIN (NSC# 241240) FOR INOPERABLE STAGE IIIA AND STAGE IIIB NON-SMALL CELL LUNG CANCER

EDITORIAL CORRECTIONS

Cover page:

The telephone and fax numbers for the Protocol Editor have been updated and the new Data Coordinator's name and corresponding telephone and fax numbers have been included. Also, Dr. Green's fax number has been updated.

Section 8.1:

The column header which references time of restaging has been revised to "1 month post-RT...". This corresponds with the change in section 8.2.

Section 8.2:

The first sentence has been modified to, "At approximately 30 days after completion of radiation therapy, patients will be....." in order to clarify the timing of restaging. This change is reflected in the column header in section 8.1.

Replacement pages are enclosed: Cover page, pages 15

*Blank sheets
are not included
in this document.*

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

cc: Dr. J. Rosenman

CANCER AND LEUKEMIA GROUP B

PROTOCOL UPDATE TO CALGB 9130

**A PHASE III TRIAL OF VINBLASTINE / CISPLATIN / RADIATION THERAPY WITH OR
WITHOUT CARBOPLATIN (NSC# 24 1240) FOR INOPERABLE STAGE IIIA AND STAGE IIIB
NON-SMALL CELL LUNG CANCER**

EDITORIAL CORRECTION:

Section 8.1:

The single asterisk note has been changed to correspond with the Data Submission schedule. The following changes are highlighted in bold for easier identification, "At least every 2 months for 2 years, then every 4 months x 2 years, then q year."

Replacement pages are enclosed: pages 15-16.

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NON-SMALL CELL LUNG CANCER**

EDITORIAL CORRECTIONS

Section 8.0:

A typographical error has been corrected in the Required Data section. The correction is in the second column from the right, "Day 155 Restaging" has been changed to "Day 125 Restaging".

Replacement pages are enclosed: pages 15-16.

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cc: Dr. J. Rosenman

CANCER AND LEUKEMIA GROUP

MEMORANDUM

To: Principal Investigators, CCOP Responsible Investigators, Disease and Modality
Chairs, Executive Committee

From: Moira Lawlor, Protocol Editor

Subject:

ATTN: DATA MANAGERS

ACTIVATION OF PROTOCOL 9130

**A PHASE III TRIAL OF VINBLASTINE / CISPLATIN / RADIATION THERAPY WITH OR
WITHOUT CARBOPLATIN (NSC# 241240) FOR INOPERABLE STAGE IIIA AND STAGE IIIB
NON-SMALL CELL LUNG CANCER**

Dr. Gerald Clamon

ACTIVATED JULY 4, 1991

cc: Dr. J. Rosenman

CANCER AND LEUKEMIA GROUP B

CALGB 9130

**A PHASE III TRIAL OF
VINBLASTINE / CISPLATIN / RADIATION THERAPY
WITH OR WITHOUT CARBOPLATIN (NSC# 241240) FOR INOPERABLE STAGE IIIA AND STAGE IIIB NON-
SMALL CELL LUNG CANCER**

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A PHASE III TRIAL OF VINBLASTINE/CISPLATIN/RADIATION THERAPY WITH OR WITHOUT CARBOPLATIN FOR INOPERABLE STAGE IIIA & STAGE IIIB NON-SMALL CELL LUNG CANCER

ELIGIBILITY CRITERIA

Histologically documented NSCLC
 Measurable or evaluable disease
 Disease Stage: IIIA and selected IIIB (See 3.22)
 No malignant pleural effusion*
 No prior CT, RT or total resection
 > 2 weeks since formal exploratory thoracotomy
 No previous or concomitant malignancy
 No other serious medical or psychiatric condition
 Radiotherapy consult
 CALGB Performance status 0-1
 Age ≥ 18
 Signed Informed consent; IRB approval
 Weight loss < 5% over past 3 months

REQUIRED LABORATORY DATA

Granulocytes	≥ 1,8000/μl
Platelets	≥ 100,000/μl
Hemoglobin	> 10mg/dl
BUN	< 1.5 x normal
Creatinine	≤ 1.5 x mg/dl or
Creatinine Clearance	≥ 60ml/min
Billrubin	< 1.5 x normal
ABG	pO ₂ > 50, pCO ₂ < 50
Fev ₁	>800cc

* A non-malignant pleural effusion must be a transudate, cytologically negative and non-bloody

SCHEMA

Regimen I

	DDP				DDP						
	<u>VBL</u>	<u>VBL</u>	<u>VBL</u>	<u>VBL</u>	<u>VBL</u>	<u>RT1</u>	<u>RT1</u>	<u>RT1</u>	<u>RT1</u>	<u>RT2</u>	<u>RT2</u>
Day:	1	8	15	22	29	50	57	64	71	78	85

VBL: Vinblastine 5 mg/m², IV bolus weekly x 5

DDP: Cisplatin 100 mg/m² IV, over 30-60 minutes, days 1 & 29

RT1: Radiation Therapy; original volume = 200 cGy/day, 5 days/week; weeks 1-4 of Radiation

RT2: Radiation Therapy; boost volume = 200 cGy/day, 5 days/week; weeks 5 & 6 of Radiation

RANDOMIZE*

Regimen II

	DDP				DDP	CBDCA	CBDCA	CBDCA	CBDCA	CBDCA	CBDCA
	<u>VBL</u>	<u>VBL</u>	<u>VBL</u>	<u>VBL</u>	<u>VBL</u>	<u>RT1</u>	<u>RT1</u>	<u>RT1</u>	<u>RT1</u>	<u>RT2</u>	<u>RT2</u>
Day:	1	8	15	22	29	50	57	64	71	78	85

VBL: Vinblastine 5 mg/m², IV bolus weekly x 5

DDP: Cisplatin 100 mg/m² IV, over 30-60 minutes, days 1 & 29

CBDCA: Carboplatin 100 mg/m² IV bolus weekly X 6

RT1: Radiation Therapy; original volume = 200 cGy/day, 5 days/week; weeks 1-4 of Radiation

RT2: Radiation Therapy; boost volume = 200 cGy/day, 5 days/week; weeks 5 & 6 of Radiation

Patients with extra thoracic disease progression are removed from protocol therapy.

* Patients will be stratified by stage 3A or 3B disease.

To Register: Confirm all eligibility criteria listed in Section 3.0. Main Institutions call the Central Office (603-646-6701) 9AM - 5PM Eastern Time with the information contained in Section 4.0.

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APPENDIX 1: CALGB Expanded Common Toxicity Criteria

1.0 INTRODUCTION

At the time of diagnosis, approximately 20% of patients with non-small cell lung cancer have disease confined to the chest by standard staging techniques but are inoperable. Although some patients with Stage IIIA disease may be made operable by combined modality therapy (1), most patients with Stage IIIA and IIIB disease are inoperable. The standard therapy for IIIA and IIIB disease has been radiation therapy. Although 5 year disease free survival is obtainable with radiation therapy (2-6), this is only in a small proportion of patients and median survival remains in the range of 6-12 months (2,3,4).

Chemotherapy for non-small cell lung cancer has not made a dramatic impact on survival to date. However, using Cisplatin based regimens, response rates of 20%-45% are obtained in patients with metastatic disease (7-11). Prior trials combining single agent chemotherapy with radiation therapy have not shown improvement over radiation alone (12). Uncontrolled trials combining combination chemotherapy with radiation therapy have suggested benefit in some cases, (13,14) but not in another (15).

The CALGB recently completed an important controlled trial (CALGB 8433) in which patients with inoperable Stage IIIA or IIIB disease received Vinblastine and Cisplatin for 5 weeks followed by radiation therapy to 6000 cGy or radiation therapy to 6000 cGy without the chemotherapy. Results to date show a significant survival advantage for the combined modality therapy arm. Most significantly, there is an approximately 20% disease free survival at 3 years in the combined modality therapy arm vs 10% in the radiation therapy alone arm (16).

In order to try to build on this promising result, the Respiratory Core Committee of CALGB considered a wide variety of ways to improve therapy. However, the median age for patients with lung cancer is between 60-65 in these trials and the capacity to tolerate prolonged aggressive chemotherapy had to be taken into consideration. In CALGB 8831, a randomized phase II trial was carried out to assess the toxicity of two new combined modality programs for Stage IIIA and IIIB disease. In arm 1, patients received Vinblastine and Cisplatin for 5 weeks and then 6000 cGy of radiation therapy in exactly the same fashion as the combined modality arm of 8433. This was then followed by 4 cycles of further Vinblastine and Cisplatin chemotherapy. In arm 2, patients received Vinblastine and Cisplatin for 5 weeks and then 6000 cGy of XRT but this time weekly Carboplatin was given with the radiation therapy based on preclinical data demonstrating the radiosensitizing effects of Carboplatin (17).

To date 91 patients were entered onto 8831 and accrual is complete. Five patients are still completing therapy. To date, there is no survival difference between the two treatment arms. However, there does appear to be decreased ability to tolerate arm 1 of the therapy. Of 46 patients randomized to receive the extra four doses of Vinblastine and Platinum (arm 1), only 23 will receive that therapy. Fourteen patients have progressed prior to the point at which those 4 cycles of therapy would have been given, 3 patients refused the 4 cycles of therapy due after the radiation, 2 had toxicity which precluded giving the 4 cycles, and 3 patients still have data pending. At the present time only 17 of the 45 patients have been able to complete the entire therapy and at the most, 20 patients will have completed the therapy once all data is in. An analysis of the dose received for the 4 cycles of "posterior" chemotherapy is as follows:

	Cycle 1	Cycle 2	Cycle 3	Cycle 4
VLB*	100% (16)	90% (13)	80% (8)	73% (6)
CPPD**	100% (16)	86% (13)	89% (7)	81% (6)

* % of protocol dose able to be given of Vinblastine to all patients who actually received a dose (# patients).

** % of protocol dose able to be given of Cisplatin to all patients who actually received a dose (# patients).

By contrast, in arm 2 in which concurrent CBDCA was given during the radiation therapy, a larger proportion of patients will finish the intended therapy. Of 46 patients entered onto this arm of therapy, 41 will have received at least some of the CBDCA and at least 34 will have received the entire therapy. Of the original 46 patients, 1 patient died a septic death during the induction therapy with Vinblastine and Cisplatin, 2 patients had rapid disease progression prior to CBDCA and radiation. Two patients have data pending. The percentage of the intended dose which was able to be administered was high until the last two doses of therapy. The doses of Carboplatin received were as follows:

	week 1	week 2	week 3	week 4	week 5	week 6
% dose (mean)	98.1	85.1	94.7	91	67.9	67.9
(# pts)	(39)	(37)	(38)	(36)	(35)	(34)

This data suggest that the combined modality arm of 8831 which is best tolerated by the patient population to be served is arm2. In CALGB 9130, we propose a randomized trial of the best arm of 8433: Vinblastine/Cisplatin and XRT vs the best arm of 8831: Vinblastine/Cisplatin and XRT with concurrent Carboplatin. The fundamental question being sought is whether the addition of the Carboplatin either prolongs survival or improves disease control within the chest.

In an analysis of 8433, stage (3A vs 3B) was found to be an important prognostic factor for survival. Therefore stage will be stratified for prior to randomization in this study (9130). However, in 8433, cell type (adeno vs squamous vs large cell) was not of prognostic significance. Cell type will not be stratified for in 9130.

2.0 OBJECTIVES

- 2.1 To determine if the concurrent addition of CBDCA during radiation therapy for Stage IIIA and IIIB inoperable non-small cell lung cancer will prolong survival and improve local disease control.
- 2.2 To determine if the improvement in survival, if any, is related to disease stage: tumor (T) status and nodal status.
- 2.3 To determine if the improvement in survival, if any, is related to tumor size.

3.0 ELIGIBILITY CRITERIA Patients must fulfill all of the following criteria.

- 3.1 Histologically or cytologically documented NSCLC including squamous cell carcinoma, adenocarcinoma (including bronchoalveolar cell), and large cell anaplastic carcinoma (including giant and clear cell carcinomas).
- 3.2 Eligible disease stages
 - 3.21 Patients must be MO.
 - 3.22 Patients with T1 or T2 disease and N2 disease are eligible. Patients with T3 or T4 disease and N0-N2 disease are eligible (if this is on the basis of closeness to the carina, invasion of the mediastinum or invasion of the chest wall).

Patients with vertebral body direct invasion are ineligible.

Patients with N3 disease are eligible unless they have scalene, supraclavicular, or contralateral hilar node involvement.

Patients with a pleural effusion which is a transudate, cytologically negative and non-bloody are eligible if the radiation oncologists feel the tumor can still be encompassed within a reasonable field of radiotherapy.

3.3 Measurable or Evaluable Disease

3.31 Measurable Disease: Any mass reproducibly measurable in two perpendicular diameters by CXR scan or Computerized Tomography (CT).

3.311 A solid tumor mass or a hilar lesion surrounded by aerated lung.

3.312 Pleural-based masses.

3.32 Evaluable Disease: Lesions apparent on CXR or CT which do not fit the criteria for measurability. Patients with both measurable and evaluable disease will be evaluated by criteria for measurable disease.

3.321 Ill-defined masses associated with post-obstructive changes.

3.322 Mediastinal or hilar adenopathy measurable in one dimension.

3.33 PLEURAL EFFUSIONS are neither measurable nor evaluable (and are excluded from entry if malignant). Nonmalignant effusions have negative cytology, are non-bloody and must be a transudate.

3.4 Radiotherapy Consultation deems patient suitable for radiotherapy. The boost volume must be limited to < 50% of the ipsilateral lung volume (see 5.43).

3.5 Performance 0-1
Weight loss < 5% in 3 months prior to diagnosis.
Age ≥ 18 years.

3.6 Prior Therapy
No prior chemotherapy or radiation therapy.
≥ 2 weeks since formal exploratory thoracotomy.
Totally resected tumors are excluded.

3.7 Required initial laboratory values:

Granulocytes	≥ 1,800/μl
Platelet count	≥ 100,000/μl
Hemoglobin	> 10 gm/dl
BUN	< 1.5 x normal
Bilirubin	< 1.5 x normal
Creatinine	≤ 1.5 mg/dl
or Creatinine Clearance	≥ 60 ml/min
Arterial blood gases	pO ₂ >50, pCO ₂ <50
FEV ₁	>800 cc

3.8 Informed Consent: Each patient must be aware of the neoplastic nature of his/her disease process and must willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. (Human protection committee approval of this protocol and consent form is required.)

- 3.9 No previous or concurrent malignancy is allowed, except inactive non-melanoma skin cancer, in situ carcinoma of the cervix, or other cancer if the patient has been disease-free for > 5 years.
- 3.10 No serious medical or psychiatric illness which would prevent informed consent or limit survival to <2 years. Patients with postobstructive pneumonia remain eligible.

4.0 RANDOMIZATION, DATA SUBMISSION, AND QUALITY ASSURANCE DOCUMENTATION

4.1 Randomization will be accepted: Through the Main Institution only.

4.11 Randomization

Prior to initiation of therapy.

Confirm eligibility criteria (see 3.0). Call the Central Office (603-646-6701, Monday-Friday, 9 a.m. 5 p.m. Eastern Time) with the following information:

- Your name
- Study #
- Institution #
- Treating Physician
- Patient's Name, I.D. #
- Signed Informed Consent (yes, no)
- Race, Sex, Date of Birth
- Diagnosis, Date of Diagnosis
- *TNM Status, Stage:
- Eligibility Criteria met (Sec. 3.0) (yes, no)
- Disease: Evaluable or Measurable
- Date of Institutional Review Board approval for first patient registered/institution
- Name of Radiation Therapist who approved the patient

* As we are stratifying by stage, please have data manager call Dr. Clamon if questions arise regarding stage of disease.

The Main Institution will receive a Confirmation of Randomization. Please check for errors. Submit corrections in writing to CALGB, Frontier Science, 4033 Maple Road, Amherst, NY 14226.

4.2 **DATA SUBMISSION:** Submit Forms to CALGB-Frontier Science at the following intervals:

FORMS

SUBMISSION SCHEDULE

Chemotherapy

C-074 Respiratory On-Study Form	}	Within 1 week of Registration
C-076 Respiratory Measurement Form		
ST-3 Solid Tumor Flow Sheet		
C-109 Respiratory Follow-up Form	}	Day 50 (Start of RT 1), Day 85 (end of RT 2), Day 125 (at restaging).After therapy q 2 months x 2 years. Then q 4 months x 2 years, then q year, at progression and death
C-090 Toxicity Reporting Form		
C-076 Respiratory Measurement Form		
ST-4 Solid Tumor Flow Sheet		
C-113 CALGB Notification of Death Form	}	Within 4 weeks of death.

FORMS

SUBMISSION SCHEDULE

Radiation Therapy

RT1 and RT2

See Section 4.3; copy to FSTRF

C-052 Radiotherapy Follow-up Form

At Completion of RT (Day 85)

4.3 **QUALITY ASSURANCE DOCUMENTATION:**

4.31 On Treatment Review: Forward the following data to:

Arvin S. Glicksman, M.D.
 Quality Assurance Review Center
 Roger Williams General Hospital
 825 Chalkstone Avenue
 Providence, Rhode Island 02908

Within three days of the onset of radiotherapy to each treatment volume:

- 4.311 Copies of the localization films. * Radiotherapist should draw on localization film the intended tumor volume.
- 4.312 Copies of the verification (portal) films.* ("Double exposure" technique showing surrounding anatomical landmarks is preferred.)
- 4.313 Polaroid pictures of the patient in the treatment position with fields appropriately marked.
- 4.314 Radiotherapy daily dose calculation check form (RT-1).
- 4.315 Copies of central axis dose calculations worksheet.
- 4.316 Copies of pre-treatment x-rays, CAT scans, surgical findings, and other diagnostic determinations used in defining the primary treatment volume shall be submitted.
- 4.317 Calculation of dose reference points. See section 5.26.

*NOTE: If Polaroid or other photographic process for duplication of localizations and verification films is employed, it is important to ensure that these images are of sufficiently good quality for review. It is recommended that photographs of these films be taken at a distance close enough to allow portal (or verification) film to fill up the entire Polaroid print.

4.32 Within one week of completion of radiotherapy, the following data should be forwarded to Dr. Glickman for post-treatment review:

- 4.321 Copies of localization and verification films for the boost volume and films of any field modifications made subsequent to initial "on treatment" submission.
- 4.322 Radiotherapy Total Dose Record (RT-2).
- 4.323 Copies of any dose calculation worksheet for central axis calculations.

- 4.324 Copies of all off-axis dose calculations and isodose maps showing tumor, lung and spinal cord volumes. (see sections 5.26 and 5.293.)
- 4.325 Copies of chest x-ray (PA and lateral) after 3,000 cGy if needed to document peripheral clearing.
- 4.326 Treatment Record (show daily doses and all dose calculations).
- 4.33 Direct any questions regarding completion of RT-1 and RT-2 data forms, required dose calculations and other documentation to:

Bengt Bjarngard, Ph. D., Chief Physicist
 Quality Assurance Review Center
 Roger Williams General Hospital
 825 Chalkstone Avenue
 Providence, Rhode Island 02908
 (401) 456-6500

5.0 TREATMENT PLAN

- 5.1 Chemotherapy: Patients will be randomized to regimen I or II.

Regimen I: Vinblastine and Platinum followed by radiation therapy.

Regimen II: Vinblastine and Platinum followed by radiation therapy with concurrent Carboplatin.

Treatment plan: All patients entered on study will receive initial chemotherapy and regional radiation therapy. Patients randomized to Regimen II will receive weekly concurrent CBDCA during the radiation therapy.

- 5.11 Initial chemotherapy:
 Begin on day 1 for all patients on study (both regimen I and II).

Vinblastine (VBL) 5 mg/m² IV bolus weekly x 5 doses (days 1, 8, 15, 22, 29).

VBL is a vesicant and should be administered through a running IV with good blood return or a central line.

Cisplatin (DDP) 100 mg/m² IV over 30-60 minutes days 1 and 29 only.

Calculate all doses on patients' actual body weight.

Hydration for DDP

1. Over 24 hours prior to giving DDP, hydrate with 3 L. po ± IV.
2. Over 3-4 hours prior to giving DDP give 1 liter D₅.1/2NS with 8mEq MgSO₄.
3. Immediately prior to DDP, give 12.5 gm Mannitol IV over 10 minutes.
4. Administer DDP in 250 ml of D₅.1/2NS over 60 minutes.

5. Then over 2 hours give 500 ml of D₅.1/2NS with:
 - 10 mEq KCL
 - 8 mEq MG SO₄
 - 12.5 gm mannitol
6. Replace urine output with an equal volume of D₅.1/2NS until p.o. intake adequate.

5.12 Concurrent Chemotherapy (Regimen II only)

- 5.121 Carboplatin (CBDCA) administration is to be concurrent with radiation therapy. CBDCA should begin on day 50 along with radiotherapy following the two cycles of Vinblastine and DDP. The CBDCA should be started only after the radiotherapy field has been planned so that the CBDCA can be given once weekly, on the first day of radiotherapy each week prior to that day's radiotherapy for 6 consecutive weeks.
- 5.122 CBDCA 100 mg/m² should be administered as an IV bolus. Hydration for CBDCA is not necessary and it can be given in 250 mg of D5W (or saline) over 15 minutes.

There will be no dose escalation.

- 5.2 Radiation therapy:** All patients without evidence of progressive disease outside the planned radiation field (either regional or distant) during the neoadjuvant chemotherapy should begin chest irradiation on day 50 (week 8, 21 days following last dose of chemotherapy) if granulocytes >1800/μl and platelets >100,000/μl.

If counts are below these values, repeat counts twice weekly and start when granulocytes >1,800/μl and platelets >100,000/μl.

During RT check counts weekly and if granulocytes <1000 or platelets <75,000, hold XRT until counts, measured twice weekly, are again above that level.

Any patient with rapid disease progression outside of the chest should be removed from study (See Sec. 10.12).

Patients with progression of intrathoracic disease within the potential radiation field during anterior chemotherapy may be considered for accelerated initiation of thoracic irradiation after discussion with the Study Chair.

5.21 Equipment

Modality - Use external beam photon irradiation.

Energy - Use radiation of megavoltage quality, i.e., Cobalt-60 or x-ray beams with accelerating potential of between 4-25 MV. For Cobalt-60, beam trimmers or secondary blocking must be used.

Geometry - Use isocentric teletherapy with a source to axis distance (SAD) ≥ 80 cm.

Dose Rate - The dose rate must be > 50 cGy per minute at d max (1cGy=1 rad).

Radiotherapy equipment must have its calibration check by the Radiologic Physics Center (RPC).

- 5.22 **Treatment Volume** consists of two parts which are radiated sequentially: the original and the boost volumes.

Original Volume: based upon conventional CXR and CT taken before any cytotoxic therapy is delivered, generally this volume will include the volume of the primary lesion and the ipsilateral pulmonary hilum, mediastinal lymph node, and both supraclavicular fossae.

Boost Volume: include the entire original (pre-therapy) radiologically defined primary tumor volume and clinically involved regional hilar and/or mediastinal nodes. Do not include pulmonary infiltrates which clear with chemotherapy and/or radiation to the original tumor volume if judged to be secondary to obstruction (infiltrate, atelectasis) (see 5.291).

- 5.23 **Physical Extent of Irradiated Volume**

Original Volume: include the primary disease site within the portal with a margin of 2 cm around the mass and the ipsilateral hilum. Include the whole width of the mediastinum with a margin of 2 cm around the radiographically visible involvement (pre-treatment chest film and CT scan).

Spare the contralateral lung as much as possible by allowing the portal to extend no more than 1 cm lateral to the soft tissue of the involved mediastinum, but at least 2 cm beyond radiographically demonstrated tumor. There should be no intention to cover the contralateral hilum. (Tumor volume takes precedence over normal lung sparing.) Extend the inferior margin of the mediastinal portion of the portal 3 - 3.5 vertebrae below the carina or 2 cm below the radiographically demonstrated tumor mass (chest film and CT scan), whichever dimension is greater.

Include both supraclavicular fossae within the original treatment volume which follows minimum volume margin.

- Laterally - intersection of clavicle and 1st rib anteriorly
- Inferiorly - a line approximately mid-contour of 1st rib
- Superiorly - larynx immediately below vocal cords
- no larynx blocks shall be used

Even if the primary tumor is in the lung periphery, only one radiation field should be used to cover it in the mediastinum.

Boost Volume: base the boost portal on the radiographically visible original tumor volume with a margin of 2 cm. The boost volume must be limited to < 50% of ipsilateral lung volume. Since patients with clinically evident supraclavicular adenopathy are excluded from the protocol, the boost volume will include the supraclavicular fossa only in patients with apical lesions.

- 5.24 **Treatment Dose**

- 5.241 **Prescription Point** (original and boost volume)

Parallel Opposed Portals (Equal Weight): For equally weighted parallel opposed portals, the prescription point is defined as a point along the central axis of the opposed beams which is midway between the entrance points of those beams.

Parallel Opposed Portals (Unequal Weight): For unequally weighted parallel opposed portals, the prescription point is defined as a point along the central axis of the opposed beams which is midway between the entrance and exit points of the tumor volume.

Multiple Convergent Beams: For these complex techniques (wedge pairs, three fields, rotation) the prescription point is defined as a point which is at the intersection of the central axes of the multiple beams (i.e. the isocenter). When these techniques are used, isodose distributions must be calculated, plotted and submitted as part of the quality assurance documentation (section 4.31).

5.242 Doses:

Absorbed dose is described in cGy to water tissue (1cGy = 1 rad).

Original Volume: deliver 4,000 cGy in 20 fractions of 200 cGy/fraction to the prescription point.

Boost Volume: deliver 2,000 cGy in 10 fractions of 200 cGy/fraction to the prescription point.

5.25 Time-Dose Considerations

5.251 Daily Dose for original and boost treatments

The dose/fraction: 200 cGy to the prescription point.
Treat with one fraction/day, five days/week.
Treat all fields each day.

5.252 TDF: The TDF of the original volume (4000 cGy) = 66. The TDF of the boost volume (2000 cGy) = 33. TDF for the entire course = 99.

If significant, unscheduled interruptions occur, the total dose should be modified to approximate the appropriate TDF for that phase of therapy. Add adjusted doses due to interruptions occurring during the treatment of the original volume to the original volume treatment phase; add those occurring during the treatment of the boost volume to the boost volume phase. (See Orton and Ellis, BJR 46: 529-537, 1973).

5.26 Dose Homogeneity and Off-Axis Reference Points

5.261 Original Volume: the dose will be 4,000 cGy \pm 5 % throughout the treatment volume. Tissue compensators are preferred to achieve uniformity, but blocking supraclavicular areas early when they have reached this dose or boosting the lower mediastinum are acceptable techniques.

5.262 Off-Axis Points: to insure dose uniformity and observe normal tissue tolerance, calculate the original field dose at 2 off-axis points.

5.2621 Supraclavicular Fossa (Reference Point "A") - The mid-plane of the supraclavicular fossa defined as a point 6 cm to the right (or left, as appropriate) of midline at the superior border of the clavicle.

5.2622 Lower Mediastinum (Reference Point "B") - The mid-plane of the lower mediastinum defined as 2 cm superior to the inferior field margin.

- 5.2623 **Boost Volume Homogeneity:** design a plan for the boost volume so that the dose throughout the target volume for the boost is within 5% of the dose to the prescription point.
- 5.2624 **Inhomogeneity Corrections:** For the purposes of this study, no inhomogeneity corrections are applied for bone or lung attenuation.
- 5.27 **Spinal Cord Sparing** (Reference Point "C") The maximum dose to any point in the spinal cord will be 4,600 cGy.
- 5.271 Since the spinal cord will receive > 4,000 cGy in the original volume, it must receive no more than 600 cGy in the boost. Choose a suitable treatment plan to achieve this dose distribution. This plan will depend on tumor volume and can be AP/PA opposed only if no midline structures are clinically involved. When tumor volume in the midline must be boosted, possible plans include oblique opposed, lateral opposed, converging or rotational portals.
- 5.272 Midline spinal cord blocks for the boost phase of therapy are not acceptable.
- 5.28 **Treatment Technique**
- 5.281 **Patient Position:** generally treat supine. Since isocentric technique is used, treatment position will be the same for AP+PA fields. Generally, the patient's position will be the same for boost.
- 5.282 **Field Arrangement**
- 5.2821 **Original Field:** Equally weighted AP/PA parallel opposed portals will be used. Other treatment techniques which achieve the homogeneity requirement of this study may be used when appropriate.
- 5.283 **Blocks:** Individually shape field with divergent blocks whenever possible, as determined by tumor volume. Use of shadow blocks is permitted.
- 5.29 **Calculations and Treatment Planning**
- 5.291 **Special Diagnostic Information**
- Before therapy begins, computed tomography through the tumor volume in the chest is required for tumor volume determination, in addition to standard PA and lateral CXRs.
- Subsequent CXR for shadows on Original CXR judged to be infiltrate or atelectasis: obtain a CXR required after chemotherapy and/or after 3,000 cGy. If infiltrates have cleared, the volume from the original and/or boost judged to be atelectasis or infiltrate may be excluded in the boost volume (see 5.22).
- 5.292 **Timing of Planning:** If there is no question of pulmonary infiltrates or atelectasis, plan the boost therapy at the same time as the original

volume. If peripheral lung shadows on roentgenogram are clear, plan the boost following 3,000 cGy. There should be no delay between the original and the boost courses.

5.293 **Documentation of Treatment Planning (See sec 4.2 and 4.3)**

Original Field

Reference Points - Submit calculated doses to the prescription point, (point "T"), supraclavicular (ipsilateral) (point "A") and lower mediastinum (point "B") on RT-1 reporting forms to Quality Assurance Review Center (QARC).

Document position of blocks and use of compensators.

Boost Volume

Submit isodose maps for all plans other than equally-weighted parallel opposed portals. Calculate composite isodose curves in the central plane of the tumor volume and include dose contributions from all treatment fields as well as the effects of blocks.

Isodoses must be clearly labeled with the normalization point and dose levels indicated. Include an outline of the target volume, lung volume and spinal cord location. For treatment planning, there is no correction for lung densities.

Spinal Cord Calculation

Record the spinal cord calculation (point "C") on the RT-1 reporting form.

6.0 DOSE MODIFICATION, TOXICITY & MANAGEMENT

6.1 **Chemotherapy (Treatment Regimens I and II)**

6.11 **Hematologic Toxicity:** based on counts on the day of treatment:

			Give the following dose:		
Granulocytes/ μ	and/or Platelet/ μ	VBL mg/m^2	DDP mg/m^2	CBDCA mg/m^2	
$\geq 1,800$	$\geq 100,000$	5	100	100	
1,000 - 1,799	75,000 - 99,999	3	100	75	
$< 1,000$	$< 75,000$	0	0	0	

At any time Vinblastine is due to be given but Platinum is not, if the counts turn out to be too low to give the Vinblastine, simple omit that dose. Do not delay and try to make up that dose of Vinblastine.

If counts are too low to treat with either drug on day 29 of anterior chemotherapy, hold both drugs 1 week and deliver on day 36. If day 36 counts are still too low, delete further pre-radiation drugs, check counts weekly, and begin RT in day 50 or thereafter when counts permit. If counts are too low while on CBDCA and XRT for treatment, skip the week's dose of CBDCA and restart XRT per section 5.2.

6.12 Nephrotoxicity: may arise despite vigorous hydration. Adjust the dose of DDP or CBDCA for nephrotoxicity as follows:

<u>Serum Creatinine mg/dl is:</u>	Give the following % of full dose DDP or CBDCA
< 1.5	100
1.5 - 2.0	50
> 2.0	•

• Delay DDP and CBDCA until serum creatinine is < 1.5 mg/dl. Restart DDP at 75% and CBDCA at 100% dose. If the creatinine again is > 2.0 mg/dl, remove the patient from study. If the subsequent cycles at 75% result in a creatinine of 1.5 - 2.0 mg/dl, reduce DDP and CBDCA to 50%.

6.13 Hepatic Dysfunction: Disease or treatment related to hepatocellular and obstructive jaundice dose adjustments are identical.

<u>Bilirubin (mg/dl)</u>	Give the following % of full dose:	
< 1.5	<u>VBL</u>	<u>DDP</u>
1.5 - 3.0	100	100
> 3.0	50	100
	25	100

6.14 Gastrointestinal Toxicity:

6.141 Antiemetics are required. Steroids may be utilized as antiemetic therapy.

6.142 VBL may produce G.I. hypomotility with constipation or ileus. Start stool softeners (e.g. colace 100 mg, p.o., tid) prior to VBL administration. Use milk of magnesia, metamucil, etc., to reestablish regular bowel function. Decrease VBL dose 50% for severe constipation with ileus despite aggressive medical management. Discontinue VBL for severe persistent G.I. hypomotility following dose adjustment.

6.15 Hypomagnesemia is not an indication for stopping therapy. Oral or parenteral MgSO₄ supplementation is indicated for serum Mg levels < 1.4 mEq/l.

6.16 Hyponatremia: This has been seen in approximately 5% of patients (particularly in patients with other risk factors such as concurrent diuretic therapy). Should this be observed, contact the Study Chair and the Central Office.

6.17 Neurologic Toxicity Secondary to DDP, VBL or CBDCA:

6.171 An audiogram is recommended prior to treatment. If tinnitus or clinically significant hearing loss develops, discontinue DDP or CBDCA.

6.172 For neurologic toxicity reduce chemotherapy doses as follows:

<u>Toxicity Level</u>	<u>Description</u>	<u>%DDP, CBDCA, VBL Given</u>
mild	mild paresthesias; diminished or absent DTR's	100%
moderate	severe paresthesias; mild decrease in muscle strength; inability to handle fine objects (e.g. pick up coin or shirt button); severe constipation *	50%
severe	cranial nerve dysfunction (not tumor related); ileus; orthostatic hypotension; seizures; cerebellar dysfunction or unexpected neurologic events.	0%

* give stool softeners (e.g. Colace 100 mg, p.o., tid), milk of magnesia, metamucil, or a high residue diet.

6.18 Hypersensitivity: Discontinue CBDCA and DDP for anaphylaxis. Call the Study Chair for management of mild to moderate hypersensitivity reaction.

6.2 During radiation therapy: As in section 5.2, if the weekly granulocyte count is under 600 or platelets less than 75,000, hold XRT until counts, measured twice weekly, are again above that level.

6.3 Special dose and treatment modifications:

IF a patient progresses outside the field of intended radiotherapy while on the initial vinblastine and platinum, the patient has progressed and should be removed from study. For rapid progression within the intended radiation field, call the Study Chair as per sec. 5.2.

IF a patient suffers a decline in performance score to a level of 3 or 4 while on study, the patient should complete radiotherapy with no further chemotherapy.

IF A PATIENT SUFFERS ESOPHAGITIS SO THAT IV FLUID SUPPORT IS NEEDED, radiation therapy is to be held until the patient can again swallow satisfactorily and then the XRT finished. If the patient is receiving CBDCA, no more should be given. Any patient having XRT held for severe esophagitis must be discussed with the study chairs prior to receiving further chemotherapy.

7.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

When prepared as directed, solutions are stable at room temperature and should be discarded after 8 hours. Needles and intravenous sets containing aluminum parts should not be used since they will cause a loss of potency of platinum compounds.

7.1 Vinblastine (VBL) is supplied commercially in 10 mg vials. The sterile powder should be refrigerated and reconstituted with 10 ml normal saline. It is not necessary to use preservative containing solvents if unused portions of the remaining solutions are discarded immediately. Unused preservative containing solutions should be refrigerated for future use.

- 7.2 **Cisplatin (DDP)** is supplied commercially for IV use as a lyophilized powder in vials containing 10 or 50 mg of drug. Unopened vials may be stored for 2 years Reconstitute with 10 ml or 50 ml of Sterile Water for Injection, USP, to yield a clear solution of 1 mg/ml. This solution is stable for 20 hours at room temperature, but precipitates when refrigerated.

The required dose is diluted in at least 100 ml of saline or D₅W.45NS for administration. Needles and intravenous sets containing aluminum parts should not be used since these will cause a loss of platinum potency.

- 7.3 **Carboplatin (CBDCA NSC# 241240)** is now commercially available in 50 mg, 150 mg and 450 mg vials. Each vial contains equal parts by weight of CBDCA and mannitol. Immediately before use each vial should be reconstituted with Sterile Water for Injection. Dilute 50 mg vial with 5 ml, 150 mg vial with 15 ml and 450 mg vial with 45 ml to yield a 10 mg/ml concentration.

Vials do not require refrigeration

Administer in 150 ml of fluid over 30 minutes.

8.0 REQUIRED DATA

8.1 Tests and Observations

	<u>Prior to Study</u>	<u>Day 1 & 29 of Neoadjuvant Chemotherapy</u>	<u>Prior to, or During Radiotherapy</u>	<u>1 month post-RT Restaging (Sec. 8.2)</u>	<u>Post Treatment Follow-up*</u>
Signed Informed Consent History	X				
Physical Examination	X	X	X	X	X
Pulse, Blood Pressure	X	X	X	X	X
Height/Weight Surface Area	X	X	X	X	X
Performance Status	X	X	X	X	X
Tumor Measurement	X	X	X	X	X

Laboratory

CBC, Platelet Count	X	q week	q week	X	X
BUN, Creatinine, Cr Cl***	X	X	X	X	X
Electrolytes, MG++	X	X	PRN	X	PRN
SGOT/Alk Phos/Bili	X	PRN	PRN	X	X
Uric Acid, CA++, PO ₄ , Glucose	X	PRN	PRN	X	X
Total Protein, Albumin	X	PRN	PRN	X	X
Urinalysis	X	PRN	PRN	PRN	PRN
Arterial Blood Gases	X				

Staging

CT Scan of Chest and upper abdomen (incl adrenals & liver)	A	PRN	A	C	PRN
Chest x-ray	X	PRN	B	X	X
Bone Scan	X	PRN	PRN	X	PRN
Bronchoscopy	X	PRN	PRN	(see 8.2)	(see 8.2)
Pulmonary Function Test **	X	PRN	PRN	PRN	PRN

* At least every 2 months for 2 years, then every 4 months x 2 years, then q year.

** PFT's to include FeV1, FVC, ABG's.

*** Creatine Clearance prior to study and then PRN (when clinically appropriate)

A Perform CT at 1 cm intervals with 1 cm slice thickness from the level of the adrenals and liver parenchyma through the lung apices. IV contrast is optional. Photograph images at both lung and mediastinal window settings. A repeat scan just prior to initiation of chest radiation is strongly recommended.

B At initiation of radiation and after completion of 3,600-4,000 rad.

C Repeat chest CT (to include upper abdomen) as required at d 125 and/or at relapse.

PRN When clinically appropriate.

- 8.2 At approximately 30 days after completion of radiation therapy, patients will be re-staged with a chest x-ray, chest CT (including upper abdomen to assess the liver and adrenals, a bone scan, and a bronchoscopy as needed to evaluate persistent abnormalities on chest x-ray). Patients who have received such radiation and chemotherapy may have changes of "radiation scarring or radiation pneumonitis" on chest x-ray which are difficult to tell from persistent tumor. If there are significant questions, a repeat bronchoscopy is suggested in those patients in whom the tumor could be visualized or cytologically demonstrated prior to the start of therapy on bronchoscopy. Patients with negative pretreatment bronchoscopies do not need to be rebronchoscoped.

9.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

- 9.1 **Complete response (CR):** Disappearance of all measurable or evaluable disease, signs, symptoms, and biochemical changes related to the tumor, for >4 weeks, during which no new lesions may appear.
- 9.2 **Partial response (PR) (Measurable Disease Only):** When compared with pretreatment measurements, a reduction of >50% in sum of the products of the perpendicular diameters of all measurable lesions lasting >4 weeks, during which no new lesions may appear, and no existing lesion may enlarge.
- 9.3 **Regression (Evaluable Disease Only):** Definite decrease in tumor size agreed upon by 2 independent investigators; no new lesions for >8 weeks.
- 9.4 **Stable Disease:** Must persist for >8 weeks.

9.41 Measurable: A <50% reduction and <25% increase in the sum of the products of two perpendicular diameters of all measured lesions, and the appearance of no new lesions.

9.42 Evaluable: No clear-cut change in tumor size; no new lesions.

9.5 **Objective Progression or Relapse:**

Obtain histologic confirmation, when feasible, of relapse/progression particularly:

- a) in patients who have had a CR
- b) for apparent relapse/progression limited to the irradiated field. Because of potential errors in CXR interpretation related to radiation change, a bronchoscopy may be indicated.

At the time of relapse/progression outside the chest, a bronchoscopy to determine whether relapse also occurred within the irradiated field is strongly encouraged if there is no other evidence of intrathoracic recurrence.

9.51 Measurable: An increase in the product of two perpendicular diameters of any measured lesion by $\geq 25\%$ over the size present at entry on study, or at the point of greatest response.

Evaluable: Definite increase in tumor size; the appearance of new lesions.

9.52 The appearance of new areas of malignant disease, excluding CNS metastases.

- 9.53 A 2-step deterioration in performance status, a 10% loss of pre-treatment weight, or increasing symptoms in and of themselves do not constitute progression. However, their appearance should initiate a new evaluation for extent of disease.

10.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

10.1 Duration of Treatment

- 10.11 **Response or Stable Disease:** Continue treatment or observation per protocol until the appearance of progressive disease.

- 10.12 **Disease Progression:** Any patient with rapid disease progression outside of the chest should be removed from study. Details and tumor measurements should be documented on flow sheets.

- 10.2 **Extraordinary Medical Circumstances or withdrawal of consent by the patient:** If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the patient shall be withdrawn from protocol therapy. In this event:

- 10.21 Notify the Study Chair.

- 10.22 Document the reason(s) for withdrawal on flow sheets. Follow the patient for survival and progressive disease with follow-up forms and flow sheets.

11.0 ADVERSE DRUG REACTION (ADR) REPORTING

Investigators are required by Federal Regulation to report possible adverse drug reactions. CALGB investigators are required to notify the IDB, the CALGB Central Office, and the Study Chair. As a tracking mechanism, CALGB requires investigators to route toxicity reports through the Central Office (see below).

- 11.1 Direct questions regarding drug therapy to the Study Chair.

- 11.2 Reporting requirements and procedures depend upon: (1) whether investigational agents are suspected of causing toxicity, (2) whether the possibility of such a toxicity was reported in the protocol, consent form, or manufacturer's literature (Expected toxicity), (3) the severity or grade of the toxicity, and (4) the Phase of the study. All reactions in a "reportable" category must be reported unless it is documented on flow sheets and/or follow-up forms that the treatment is definitely not responsible for the toxicity.

11.3 Types of Report

11.31 Telephone Report

- Call the Investigational Drug Branch (IDB) (301-496-7957), the Study Chair, and the Central Office (603-646-6701) within 24 hours.
- The Central Office will notify the Study Sponsor if other than NCI.
- Send written report (see Sec. 11.32)

11.32 Written Report

- Send the **original** copy of an NCI Adverse Drug Reaction (ADR) form and **copies** of all available and updated study data (on-study forms, flow sheets, follow-up forms, etc.) to date, within 5 days, to:

Toxicity Reports
CALGB Central Office
444 Mount Support Road, Suite 2
Lebanon, NH 03766

- Immediately upon receipt the Central Office will forward Adverse Drug Reaction (ADR) form to:
 - NCI
 - Study Sponsor (if different)
- The Central Office will forward Adverse Drug Reaction (ADR) form and all data sheets to:
 - Study Chair
 - FSTRF
 - CALGB Statistical Center
 - Pharmacology & Experimental Therapeutics Committee

Do not delay the report for information not yet available. (ie. pending test results)

- **Send a copy of all related follow-up reports to Central Office as they become available.**

11.4 **Reporting Requirements for Investigational Agents, Doses or combinations** (use the CALGB Expanded Common Toxicity Criteria, Appendix I)

11.41 Phase I Study

- All Grade 4 and 5 toxicities: Telephone Report and Written Report (Grade 5 regardless of cause)
- Unexpected* grade 1-3 Toxicities:
Telephone Report and Written Report
- Expected grade 3 Toxicities:
Written Report

11.42 Phase II and III Studies

11.421 Unexpected* toxicities:

- Grades 4 and 5:
Telephone Report and Written Report
- Grades 2 and 3:
Written Report

- * Unexpected toxicities are toxicities that are not listed in the toxicity management section of the protocol, the model consent form, the current clinical brochure or the manufacturer's package insert.

11.422 Expected toxicities:

- a. Grade 5 aplasia in leukemia patients:
Written report.
- b. All other expected Grade 5 toxicities:
Telephone Report and Written Report
- c. Grade 4 myelosuppression or aplasia:
Report only as part of regular data submission
- d. All other expected Grade 4 toxicities:
Written report
- e. All other expected toxicities, grades 1-3; Report only as part of regular data submission

- 11.5 **Reporting Requirements for Non-Investigational Agents:** For fatal or unexpected toxicities involving non-investigational agents at non-investigational doses, send an original FDA Adverse Drug Reaction (ADR) form (1639) with copies of the follow-up form and flow sheets to the Central Office within 5 days. The Central Office will forward as appropriate.
- 11.6 The Investigator is required by Federal regulation to notify the concerned Institutional Review Board (IRB) when an unexpected Adverse Drug Reaction occurs.
- 11.7 Where warranted, and at the recommendation of the Study Chair, The Central Office will notify all participating member institutions of such toxicities and any required dose modifications.

12.0 ANCILLARY THERAPY

- 12.1 Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets.
- 12.2 Treatment with hormones or other chemotherapeutic agents will result in the patient's removal from the study, except for steroids administered for documented CNS metastases, adrenal failure, septic shock, or hormones administered for non-disease-related conditions, e.g., insulin for diabetes. Glucocorticosteroids may be used as antiemetics.
- 12.3 If CNS relapse occurs prior to the end of therapy, the patient should be removed from treatment.

13.0 STATISTICAL CONSIDERATIONS

- 13.1 **Objectives and Study Design:** The primary objective of this trial is to determine if the addition of concurrent CBDCA to radiotherapy given after induction therapy improves survival in patients with Stage IIIA and IIIB inoperable non-small cell lung cancer. This study will have a 2-arm randomized Phase III design. Patients will be stratified by stage (stage 3A or 3B) and randomized in equal proportions to the two treatment programs.
- 13.2 **Sample Size Calculations:** The sample size considerations are based on survival, defined as the time from randomization to the time of death. The better arm of study 8433, which is the same as Regimen I of the current study, demonstrated a 3-year survival of over 20%. We would like to have 80% power to be able to detect a 15% increase in the 3-year survival from 20% to 35%, which corresponds approximately to a 50% increase in the median survival (assuming exponentiality).

Assuming survival comparisons will be performed using the logrank test at a two-sided significance level of $\alpha=0.05$, we will require 95 failures on each arm for a total of 190 failures (18). If we have at least 3 years of follow-up on all patients and a 3-year survival rate of 20%, approximately 244 patients will be required. The sample size will be increased to 265 to allow for a 5% ineligibility rate.

- 13.3 **Interim Analyses and Group Sequential Monitoring:** Interim analyses will be performed approximately every six months to correspond to the semiannual CALGB group meetings. At these analysis times, only results for the two treatment arms combined will be reported for endpoints such as disease-free survival and survival. However, toxicity will be evaluated separately for each treatment and protocol modifications considered if excessive toxicity is observed.

In order to allow early termination of the study if one of the treatment arms appears to be significantly inferior, comparisons of survival and disease-free survival will be made after approximately 20%, 40%, 60%, 80%, and 100% of the expected number of failures occur. The Lan and DeMets (19) analog to the O'Brien-Fleming (20) group sequential boundary will be used to calculate boundary significance levels at each of the five "looks" to maintain the overall significance level at $\alpha=0.05$. The O'Brien-Fleming boundary will be truncated at 3.0 standard deviations to adjust for its extreme conservativeness early in the follow-up period. Use of such a truncated O'Brien-Fleming boundary requires a 3% to 5% increase in the number of patients for a final required sample size of 270 patients or 135 patients per arm.

- 13.4 **Patient Accrual and Length of Follow-up:** The recently closed randomized Phase II protocol (CALGB 8831) for this group of patients demonstrated an accrual rate of 6.5 patients per month or approximately 78 patients per year. Therefore, accrual of 270 patients should require about 3 1/2 years. An additional year of follow-up will ensure 80% power for the above comparison (21).

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15.0 MODEL CONSENT FORM: A PHASE III TRIAL OF VINBLASTINE/CISPLATIN/RADIATION THERAPY WITH OR WITHOUT CARBOPLATIN FOR INOPERABLE STAGE IIIA AND STAGE IIIB NON-SMALL CELL LUNG CANCER

We invite you to take part in a research study for inoperable stage IIIA and stage IIIB non-small cell lung cancer. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) any significant new findings that relate to your treatment will be discussed with you; (d) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the staff members who explain it to you.

Objectives:

The purpose of this study is to attempt: 1) to slow, or stop the growth of your disease or if possible to reduce the activity of your disease; 2) to gain information about your disease; and 3) to compare the usefulness and side effects of these different treatments. It is not possible to predict whether your disease will respond to this treatment.

Study Description

Approximately 270 patients will participate in this research study. This program seeks to determine whether the addition of the drug carboplatin to radiation therapy, after a standard chemotherapy course of treatment, can prolong survival and improve disease control in inoperable lung cancer. If you agree to participate, you will be randomly assigned to receive one of two treatments. It is not clear at the present time which of the treatments in this program would be better for you. For this reason, the plan offered to you will be picked by a method called randomization. Randomization means that your physician will call a statistical office of CANCER AND LEUKEMIA GROUP B, which will assign one of the therapies to you. The chances of your receiving one of the treatments described above are approximately equal.

Treatment Arm I:

If randomized to the first treatment arm, you will receive the drug vinblastine by intravenous infusion, once each week for 5 consecutive weeks. On the first and last weeks, you will also receive the drug cisplatin over a period of 30-60 minutes by intravenous infusion. After 3 weeks of rest, a 6 week course of radiation therapy will be given. Monday through Friday of each week, radiotherapy will be administered to the site of the tumor.

Treatment Arm II:

If randomized to the second treatment arm, you will receive the drug vinblastine by intravenous infusion, once each week for 5 consecutive weeks. On the first and last weeks, you will also receive the drug cisplatin over a period of 30-60 minutes by intravenous infusion. After 3 weeks of rest, a 6 week course of radiation therapy will be given. Monday through Friday each week, radiotherapy will be administered to the site of the tumor. Additionally, on the first treatment day of each week of radiation therapy, the drug carboplatin will be given by intravenous infusion.

Risks:

The treatment of non-small cell lung cancer requires the use of powerful drugs (chemotherapy) that have side effects, some potentially very serious. The specific side effects for each drug are

listed below; the most common side effects are underlined. Unless otherwise specified, the side effects mentioned are reversible.

Bone Marrow Suppression: The drugs used to kill cancer cells also kill some normal body cells, especially those that grow rapidly (blood cells, hair, cells that line the mouth, stomach, and intestines). Blood cells are made in the bone marrow and are responsible for fighting infections (white blood cells), carrying oxygen (red blood cells), and causing blood to clot (platelets). A reduction in the number of these blood cells (marrow suppression) can lead to an increased risk of bleeding and infection. Should these effects occur, they can be treated with blood products (transfusions) and antibiotics.

Lung Toxicity: Temporary irritation of the trachea may be felt as an increase in non-productive cough and shortness of breath, resulting from a scarring of the irradiated lung. Scarring of the lungs due to lung irritation may occur. Report any cough or shortness of breath to your doctor.

Heart Damage: Rarely, scarring of the sac of the heart will occur as a result of radiation.

Liver Toxicity (CBDCA): Carboplatin, when given at higher doses than in this study, may rarely be associated with narrowing or blockage of small veins in the liver, resulting in liver tenderness, pain, and jaundice. This may lead to liver failure and, very rarely, death.

Kidney Damage: is uncommon. Kidney function will be monitored with blood tests. If necessary, the dose will be reduced. Kidney damage is usually reversible. Can occur with Cisplatin administration.

Neurologic Abnormalities: Patients may experience temporary unsteadiness when walking, fatigue, headache, tingling of the fingers and toes, jaw pain, muscle weakness, loss of reflexes, and blurred vision. These side effects occur more commonly in older patients, but are usually temporary and disappear after several days. More serious side effects are rare and have occurred with much higher doses: cranial nerve paralysis, convulsions, death. Other side effects include slight depression and confusion, hallucinations, and agitation.

Spinal Cord: Very rarely, damage to the spinal cord will result from radiation therapy. If it does occur paralysis may result.

Skin Itching at Irradiated Areas: If you have had radiation therapy, skin redness or itching in the irradiated areas may recur when drugs are given.

Skin Changes: Patients may develop a discoloration of the skin due to the radiation therapy.

Nausea and Vomiting: Cisplatin may cause severe nausea and vomiting and lead to dehydration. Anti-nausea medication will be prescribed before and during treatment as needed.

Mouth and Throat Sores: Temporary irritation to the mouth and difficulty in swallowing may result from the radiation therapy.

Blood in the Urine (CBDCA): Carboplatin may, on rare occasions, cause bloody urine. If this occurs, notify your physician immediately.

Low Sodium: Carboplatin may cause a lowering of the serum sodium which, if undetected or untreated, could cause confusion and/or coma. This is a correctable condition and is uncommon (less than 5%).

Allergic Reactions(CBDCA): Carboplatin may cause skin itching, tingling or rash. Rarely, severe reactions with low blood pressure and difficulty breathing have occurred.

Hair Loss: Radiation therapy may result in hair loss, which is usually reversible.

Constipation: With the use of vinblastine, severe constipation may occur; requiring admission. Laxatives may prevent this from happening.

Redness and Swelling of Vein (Vinblastine): may be painful; warm soaks may lessen pain.

Skin Ulcer: Vinblastine can be irritating to the skin if it leaks out of the vein. Tell the person administering the drug if you feel any burning, stinging, or pain while the drug is being given. If the area of injection becomes red and swollen after the injection, notify your doctor immediately. In the unlikely event of a severe reaction, irreversible tissue damage may result, and a skin graft may be required.

Unanticipated side effects may occur which have not been reported. If you have any unusual symptoms, report them immediately to your physician.

In an attempt to avoid side-effects, your physician will examine you and obtain laboratory tests (blood tests, chest x-rays, scans, etc.) to determine the effects of your treatment and alter the drug dosages if necessary.

Bone Marrow Aspirations and Biopsies: A bone marrow aspiration is a procedure in which an area of the hip is numbed and a small sample of bone marrow is withdrawn. A bone marrow biopsy is similar to a bone marrow aspiration except a sample of bone is removed through the needle. There may be some temporary pain or discomfort associated with these routine procedures.

Alternatives:

Other treatments for your disease include supportive care only or different drugs or drug combinations similar to those used in this study with similar side-effects.

There is no clear evidence that other treatments:

- 1) are significantly more effective than those used in this study.
and/or
- 2) are curative.

Your doctor feels that one of these treatments would be appropriate at this time.

Costs:

Any procedure related solely to research which would not otherwise be necessary will be explained. Some of these procedures may result in added costs and some of these costs may not be covered by insurance. Your doctor will discuss these with you.

In addition, the use of medications to help control side-effects could result in added costs.

Circumstances Under Which Your Participation May Be Terminated Without Your Consent

If health conditions occur which would make your participation possibly dangerous, or if other conditions occur that would make participation detrimental to you or your health, then your doctor may discontinue this treatment.

Patient Protection:

You may contact either the investigator in charge or a member of the human protection committee of _____ Hospital whose names and phone numbers are listed

at the end of this form, if at any point during the duration of this treatment you feel that you have been:

- a. inadequately informed of the risks, benefits, or alternative treatments.
- or
- b. encouraged to continue in this study beyond your wish to do so.

In the event that complications occur as a result of this treatment, you will be provided with the necessary care. However, you will not automatically be reimbursed for medical care or receive other compensation as a result of any complications.

Participation is voluntary. If you choose not to participate or wish to withdraw your consent to participate in this treatment at any time, it will in no way affect your regular treatments or medical care.

The results of this study may be published, but individual patients will not be identified in these publications.

A record of your progress will be kept in a confidential form at _____ Hospital and also in a computer file at the statistical headquarters of the Cancer and Leukemia Group B (CALGB).

Results of your tests, including blood samples and pathology slides, and confidential information contained in your medical record may not be furnished to anyone unaffiliated with the Hospital or CALGB without your written consent, except as required by Federal regulation. There is a possibility that your medical record, including identifying information, may be inspected and/or photocopied by the National Cancer Institute, the Food and Drug Administration, or other Federal or state government agencies in the ordinary course of carrying out their governmental functions. If your record is used or disseminated for government purposes, it will be done under conditions that will protect your privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

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.

(Patient's Signature)

(Date)

(Physician's Signature)

(Date)

(Witness's Signature)

(Date)

(Responsible Investigator)

(Phone #)

(IRB Representative)

(Phone #)

APPENDIX I

CALGB EXPANDED COMMON TOXICITY CRITERIA

1. Toxicity grade should reflect the most severe degree or most abnormal lab value occurring during the evaluated period.
2. Toxicity grade = 5 if that toxicity caused or contributed to the death of the patient.
3. Do not code if the symptoms are certainly or most likely due to disease or other non-treatment cause.
4. If patient at baseline has grade 1 or greater, do not code unless patient worsens due to toxicity. If there is worsening, code the level the patient increases to - DO NOT adjust for baseline.
5. Note that for some toxicities certain grades are not defined and may not be coded, e.g. no grade 3 or 4 Alopecia.
6. Granulocytes (mature cells) refers to segmented neutrophils (Segs, Polys, PMN, Polymorphonuclear leukocytes) plus bands (Staff cells, Stabs). To calculate granulocyte count multiply the white count by the % bands + % segmented neutrophils.
7. All coded toxicities must be documented and described on accompanying flowsheets.

September 11, 1989

CALGB EXPANDED COMMON TOXICITY CRITERIA
 (Adapted from Common Toxicity Criteria, SWOG Toxicity Criteria, CALGB Toxicity Grading) - 1 of 9-

TOXICITY	0	1	Grade 2	3	4
HEMATOLOGIC					
WBC	≥4.0	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0
PLT	WNL	75.0-normal	50.0-74.9	25.0-49.9	<25.0
Hgb	WNL	10.0-normal	8.0-10.0	6.5-7.9	< 6.5
Granulocytes/ Bands	≥2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
Lymphocytes	≥2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
Hematologic- Other		mild	moderate	severe	life-threatening
HEMORRHAGE (clinical)					
	none	mild, no transfusion	gross, 1-2 units transfusion per episode	gross, 3-4 units transfusion per episode	massive, >4 units transfusion per episode
INFECTION					
	none	mild no active treatment, (e.g., viral syndromes)	moderate requires outpatient PO antibiotic	severe requires IV antibiotic or antifungal or hospitalization	life-threatening e.g., septic shock
GASTROINTESTINAL					
Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	-
Vomiting	none	1 episode in 24 hrs	2-5 episodes in 24 hrs	6-10 episodes in 24 hrs	> 10 episodes in 24 hrs, or requiring parenteral support
Diarrhea	none	increase of 2-3 stools/day over pre-Rx	increase of 4-8 stools/day, or nocturnal stools, or moderate cramping	increase of 7-9 stools/day, or incontinence, or severe cramping	increase of ≥10 stools/day or grossly bloody diarrhea, or need for parenteral support
Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers, but can eat	painful erythema, edema, or ulcers, and cannot eat	requires parenteral or enteral support
Esophagitis/ Dysphagia	none	painless ulcers, ery- thema, mild soreness or mild dysphagia	painful ery- thema, edema or ulcers or moderate dysphagia but can eat without narcotics	cannot eat solids or requires narcotics to eat	requires paren- teral or enteral support or complete ob- struction or perforation
Anorexia	none	mild	moderate	severe	life-threatening

September 11, 1989

CALGB EXPANDED COMMON TOXICITY CRITERIA

-2 of 9-

TOXICITY	Grade				
	0	1	2	3	4
Other GI: Gastritis/ Ulcer	no	antacid	requires vigorous medical management or non-surgical treatment	uncontrolled by medical management; requires surgery for GI ulceration	perforation or bleeding
Small Bowel Obstruction	no	--	intermittent, no intervention	requires intervention	requires operation
Intestinal Fistula	no	--	--	yes	--
GI- other	--	mild	moderate	severe	life-threatening

OTHER MUCOSAL	none	erythema, or mild pain not re- quiring treatment	patchy & produces serosanguin- ous discharge or requires non-narcotic for pain	confluent fibrinous mucositis or requires narcotic for pain or ulceration	necrosis
---------------	------	--	--	---	----------

LIVER					
Bilirubin	WNL	--	<1.5 x N	1.5 - 3.0 x N	>3.0 x N
Transaminase (SGOT, SGPT)	WNL	≤2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	>20.0 x N
Alk Phos or 5' nucleotidase	WNL	≤2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	>20.0 x N
Liver- clinical	no change from baseline	--	--	precoma	hepatic coma
Liver - Other	--	mild	moderate	severe	life-threatening

KIDNEY, BLADDER					
Creatinine	WNL	<1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	>6.0 x N
Proteinuria	no change	1+ or <0.3 g% or <3 g/l	2 - 3+ or 0.3 - 1.0 g% or 3 - 10 g/l	4+ or >1.0 g% or >10 g/l	nephrotic syndrome
Hematuria	neg	micro only	gross, no clots	gross + clots	requires transfusion

CALGB EXPANDED COMMON TOXICITY CRITERIA

-3 of 9-

TOXICITY	0	1	Grade 2	3	4
BUN mg%	WNL, <20	21-30	31-50	>50	--
Hemorrhagic Cystitis	none	blood on microscopic exam	frank blood no treatment required	bladder irrigation required	requires cystectomy or transfusion
Renal failure	--	--	--	--	dialysis required
OTHER Kidney/Bladder:					
Incontinence	normal	with coughing sneezing, etc.	spontaneous some control	no control	--
Dysuria	none	mild pain	painful or burning urination, controlled by pyridium	not controlled by pyridium	--
Urinary Retention	none	urinary residual >100cc or occasionally requires catheter or difficulty initiating urinary stream	self catheterization always required for voiding	surgical procedure required (TUR or dilatation)	--
Increased Frequency/Urgency	no change	increase in frequency or nocturia up to 2x normal	increase >2x normal, but <hourly	with urgency and hourly or more or requires catheter	--
Bladder Cramps	none	--	yes	--	--
Ureteral Obstruction	none	unilateral, no surgery required	bilateral, no surgery required	not complete bilateral, but stents, nephrostomy tubes or surgery required	complete bilateral obstruction
GJ Fistula	none	--	--	yes	--
Kidney/Bladder-Other	--	mild	moderate	severe	Life-threatening

ALOPECIA	no loss	mild hair loss	pronounced or total hair loss	--	--
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PULMONARY					
Dyspnea	none or no change	asymptomatic, with abnormality in PFT's	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea at rest

CALGB EXPANDED COMMON TOXICITY CRITERIA

-4 of 9-

TOXICITY	0	1	Grade 2	3	4
pO ₂ /pCO ₂	no change or pO ₂ > 85 and pCO ₂ ≤ 40	pO ₂ > 70 and pCO ₂ ≤ 50, but not grade 0	pO ₂ > 60 and pCO ₂ ≤ 60, but not grade 0-1	pO ₂ > 50 and pCO ₂ ≤ 70 but not 0-2	pO ₂ ≤ 50 or pCO ₂ > 70
Carbon Monoxide Diffusion Capacity (DLCO)	> 90% of pretreatment value	decrease to 76 - 90% of pretreatment	decrease to 51 - 75% of pretreatment	decrease to 26 - 50% pretreatment	decrease to ≤ 25% of pretreatment
Pulmonary Fibrosis	normal	radiographic changes, no symptoms	--	changes with symptoms	--
Pulmonary Edema	none	--	--	radiographic changes and diuretics required	requires intubation
Pneumonitis (non-infectious)	normal	radiographic changes, symptoms do not require steroids	steroids required	oxygen required	requires assisted ventilation
Pleural effusion	none	present	--	--	--
Adult Respiratory Distress Syndrome (ARDS)	none	mild	moderate	severe	life-threatening
Other Pulmonary: Cough	no change	mild, relieved by OTC meds	requires narcotic antitussive	uncontrolled coughing spasms	--
Pulmonary-Other	--	mild	moderate	severe	life-threatening

HEART

Cardiac dysrhythmias	none	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring; or hypotension, or ventricular tachycardia, or fibrillation
Cardiac function	none	asymptomatic, decline of resting ejection fraction by less than 20% of baseline value	asymptomatic, decline of resting ejection fraction by more than 20% of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
Cardiac-ischemia	none	non-specific T-wave flattening	asymptomatic, ST and T wave changes suggesting ischemia	angina without evidence for infarction	acute myocardial infarction

CALGB EXPANDED COMMON TOXICITY CRITERIA

-5 of 9-

TOXICITY	0	1	Grade 2	3	4
Cardiac-pericardial	none	asymptomatic effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required
Heart-Other		mild	moderate	severe	life-threatening

CIRCULATORY

Hypertension	none or no change	asymptomatic, transient increase by greater than 20 mm Hg (D) or to >150/100 if previously WNL. No treatment required	recurrent or persistent increase by greater than 20 mm Hg (D) or to >150/100 if previously WNL. No treatment required	requires therapy	hypertensive crisis
Hypotension	none or no change	changes requiring no therapy (including transient orthostatic hypotension)	requires fluid replacement or other therapy but not hospitalization	requires therapy and hospitalization; resolves within 48 hrs of stopping the agent	requires therapy and hospitalization for >48 hrs after stopping the agent
Phlebitis/Thrombosis/Embolism	--	--	superficial phlebitis (not local)	Deep vein thrombosis	major event (cerebral/hepatic/pulmonary/other infarction) or pulmonary embolism
Edema	none	1+ or dependent in evening only	2+ or dependent throughout day	3+	4+, generalized anasarca

NEUROLOGIC

Neuro-sensory	none or no change	mild paresthesias, loss of deep tendon reflexes	mild or moderate objective sensory loss; moderate paresthesias	severe objective, sensory loss or paresthesias that interfere with function	--
Neuro-motor	none or no change	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis

CALGB EXPANDED COMMON TOXICITY CRITERIA

TOXICITY	Grade				
	0	1	2	3	4
Neuro-cortical	none	mild somnolence or agitation	moderate somnolence or agitation	severe: somnolence or agitation or confusion or disorientation, or hallucinations or aphasia, or severe difficulty communicating	coma, seizures, toxic psychosis
Neuro-cerebellar	none	slight incoordination, dysdiadokinesis	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
Neuro-mood	anxiety-none depression-none	mild anxiety mild depress.	moderate anxiety mod. depression	severe anxiety severe depression	severe agitation suicidal ideation
Neuro-headache	none	mild	moderate or severe but transient	unrelenting and severe	--
Neuro-constipation	none or no change	mild	moderate	severe	ileus >96 hrs
Neuro-hearing	none or change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
Neuro-vision	none or no change	--	--	symptomatic subtotal loss of vision	blindness
Pain	none	mild	moderate	severe	intolerable
Other Neuro: Behavioral Change	no change	change, not disruptive to pt. or family	disruptive to pt. or family	harmful to others or self	psychotic behavior
Dizziness/Vertigo	none	non-disabling	--	disabling	--
Taste	normal	slightly altered taste, metallic taste	markedly altered taste	--	--
Insomnia	normal	occasional difficulty sleeping, may require sleeping pills	--	difficulty sleeping despite medication	--
Neurologic Other	--	mild	moderate	severe	life-threatening

CALGB EXPANDED COMMON TOXICITY CRITERIA

TOXICITY	0	1	Grade 2	3	4
DERMATOLOGIC					
Skin	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symptoms	generalized symptomatic macular, papular, or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
Local	none	pain	pain and swelling with inflammation or phlebitis	ulceration	plastic surgery indicated
ALLERGY	none	transient rash, drug fever <38C, 100.4F	urticaria, drug fever ≥38C, 100.4F, mild bronchospasm	serum sickness, bronchospasm, req. parenteral meds	anaphylaxis
FLU-LIKE SYMPTOMS					
Fever in absence of infection	none	37.1 - 38.0C 98.7 - 100.4F	38.1 - 40.0C 100.5 - 104.0F	>40.0C >104.0F for less than 24 hours	>40.0C (104.0F) for more than 24 hrs. or fever accompanied by hypotension
Chills	none	mild or brief	pronounced and prolonged	--	--
Myalgia/ Arthralgia	normal	mild	decrease in ability to move	disabled	--
Sweats	normal	mild and occasional	frequent or drenching	--	--
Malaise/ Fatigue*	none	mild, able to continue normal activities (PS1)	impairment of normal daily activity or bed rest <50% of waking hours (PS2)	in bed or chair >50% of waking hrs. (PS3)	bed ridden or unable to care for self (PS4)
Flu-Like Symptoms- Other	--	mild	moderate	severe	life-threatening
WEIGHT GAIN	<5.0%	5.0-9.9%	10.0-19.9%	≥20.0%	--
WEIGHT LOSS	<5.0%	5.0-9.9%	10.0-19.9%	≥20.0%	--

CALGB EXPANDED COMMON TOXICITY CRITERIA

-8 of 9-

TOXICITY	0	1	Grade 2	3	4
METABOLIC					
Hyperglycemia	<116	116 - 160	161 - 250	251 - 500	>500 or keto-acidosis
Hypoglycemia	>64	55 - 64	40 - 54	30 - 39	<30
Amylase	WNL	<1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 x N	>5.1 x N
Hypercalcemia	<10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	≥13.5
Hypocalcemia	>8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	≤6.0
Hypomagnesemia	>1.6	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤0.5
Hyponatremia	no change or > 135	131 - 135	126 - 130	121 - 125	≤120
Hypokalemia	no change or > 3.5	3.1 - 3.5	2.6 - 3.0	2.1 - 2.5	≤2.0
Metabolic-Other	--	mild	moderate	severe	life-threatening

COAGULATION

Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	≤0.24 x N
Prothrombin Time	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	>2.00 x N
Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	>3.00 x N
Coagulation Other	--	mild	moderate	severe	life-threatening

ENDOCRINE

Impotence/Libido	normal	decrease in normal function	--	absence of function	--
Sterility	--	--	--	yes	--
Amenorrhea	no	yes	--	--	--
Other Endocrine:					
Gynecomastia	normal	mild	pronounced or painful	--	--
Hot flashes	none	mild or <1/day	moderate and ≥1/d	frequent and interferes with normal function	--
Cushingoid	normal	mild	pronounced	--	--
Endocrine Other	--	mild	moderate	severe	life-threatening

CALGB EXPANDED COMMON TOXICITY CRITERIA

-9 of 9-

TOXICITY	0	1	Grade 2	3	4
EYE					
Conjunctivitis/ Keratitis	none	erythema or chemosis not requiring steroids or antibiotics	requires treatment with steroids or antibiotics	corneal ulceration or visible opacification	
Dry eye	normal	--	requires artificial tears	--	requires enucleation
Glaucoma	no change	--	--	yes	--
Eye Other	--	mild	moderate	severe	life-threatening

***PERFORMANCE STATUS**

**CALGB
(ZUBROD)**

Performance Status	PS0 Normal	PS1 Fatigue without significant decrease in daily activities	PS2 Fatigue with significant im- pairment of daily activities or bedrest <50 percent of waking hours	PS3 Bedrest >50 percent of waking hours	PS4 Bedridden or unable to care for self
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KARNOFSKY

Performance Status %	100-90	80-70	60-50	40-30	20-10
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CONVERSIONS/FORMULAS

- | | |
|--|--|
| <p>a) Body Temperature</p> $F^{\circ} = C^{\circ} \times 9 \frac{5}{9} + 32$ $C^{\circ} = F^{\circ} - 32 \times 5 \frac{9}{5}$ | <p>c) Body surface area
(BSA (m²))</p> $\sqrt{\frac{Ht (cm) \times wt (kg)}{3600}}$ <p align="center">or</p> $\sqrt{\frac{Ht (in) \times wt (lbs.)}{3131}}$ |
| <p>b) Metric measures</p> <p>1 inch = 2.54 cm</p> <p>2.2 lbs. = 1 kg</p> | <p>d) Granulocyte Count</p> <p>WBC 2.2; Segs 61%; Bands 4%</p> <p>2200 x .65 = 1430</p> |

**INSTRUCTIONS FOR CALGB
RESPIRATORY ON-STUDY FORM
(FORM NO. C-074)**

A. Purpose - This form is used for respiratory studies that opened after November of 1987.

NOTE: Please note that studies which opened prior to November of 1987 may still require C-007.

B. Form Specific Instructions

Page 1

The heading of this form contains identification items and patient description, including a box to indicate how BSA was determined. The 3-digit diagnosis codes are now at the bottom right of the page.

Symptoms have been added, along with weight loss < or > 5%.

Please note the carcinogens section; comment on quantity/frequency where applicable.

Indicate the basis for diagnosis and assessment of disease (which should correlate with information provided on measurement form).

Use 'equivocal' for those sites suspicious for involvement, but without positive documentation.

Where two sites share one box, please circle applicable one. Specify left or right in cases such as adrenal, kidney, etc.

Nodal involvement is divided into hilar, mediastinal, supraclavicular and 'other', as opposed to regional/distant. Please specify location of lung disease as 'primary' and/or 'contralateral'.

Page 2

Staging work-up includes all tests/scans completed (or note required), along with their results. Use 'equivocal' where results are pending or ambiguous. Circle either aspirate or biopsy under bone marrow.

Lab data requires exact date test was performed.

Prior treatment section includes 'regression' as a response description.

Page 3

CALGB has adopted the new International Staging System for lung cancer, referenced at bottom of page 3.

We require that extent of disease be reported by tumor, nodal and metastatic involvement. Select code representing most advanced description for Tumor and Nodal; if distant Metastasis is present, be sure to indicate site(s) on page 1.

For those patients who have recurrent disease, please indicate with a '2-yes'; TNM status may be omitted for such cases, if recurrence is basis by which eligibility is determined.

INSTRUCTIONS: This form is to be completed and submitted within one week of the patient's entry into the study. Enter "-1" to indicate that an answer is "unknown", "unobtainable", or "not done".

Patient's Name _____ Patient Hospital No. _____
 CALGB Protocol Number _____ CALGB Patient No. _____
 in Member Institution _____ /Adjunct _____
 signed Treatment _____

Date Treatment Started
 M D Y

PATIENT DESCRIPTION

Birth Date
 M D Y
 Sex (1-male, 2-female)
 Race (1-white, 2-black, 3-other)

Height (cm)
 Weight (kg)
 Surface area (m²)
 Surface area(1-based on ideal weight, 2-based on actual weight)

DISEASE DESCRIPTION

Date of initial diagnosis
 M D Y
 Initial diagnosis
 (use codes at bottom of page)

CURRENT CLINICAL DATA

Performance status at time of randomization
 0-fully active
 1-ambulatory, capable of light work
 2-in bed <50% of time, capable of self-care but not of work activities
 3-in bed >50% of time, capable of only limited self-care
 4-completely bedridden
 SYMPTOMS (1-no, 2-yes)

Chest pain
 Respiratory infection
 Cough
 Dyspnea
 Hoarseness
 Hemoptysis
 Bone pain
 CNS symptoms
 Anorexia
 Other,specify _____
 Duration of initial symptom(s) prior to diagnosis
 1-less than 3 months
 2-3 to 6 months
 3-more than 6 months
 Weight loss in previous 6 months
 1-none or <5% of body weight
 2->5% of body weight

Exposure to Possible Carcinogens (1-no, 2-yes, 3-unknown)
 Tobacco
 Comment: _____
 Asbestos
 Comment: _____
 Radiation
 Comment: _____
 Alcohol
 Comment: _____
 Other,specify _____
 Comment: _____

BASIS FOR DIAGNOSIS
 1-Cytology (sputum, bronchial washings, pleural fluid)
 2-Biopsy (bronchial, lymph node, needle biopsy of lung)
 3-Resection (lobectomy, pneumonectomy, segmentectomy)
 4-Other,specify _____
 Assessment of Disease
 1-measurable
 2-evaluable

CURRENT SITES OF INVOLVEMENT

1-not involved
 2-involved
 3-equivocal
 Hilar nodes
 Mediastinal nodes
 Supraclavicular/Scalene nodes
 Other nodal,specify _____
 Primary lung
 Contralateral lung
 Pleura
 Liver
 Adrenal(s)
 Bone
 Bone Marrow
 Brain
 Skin
 Other,specify _____
 Other,specify _____

Diagnosis Codes
 551-Oat cell, undifferentiated small cell
 552-Adenocarcinoma, including alveolar cell or terminal bronchiolar carcinoma
 553-Squamous cell carcinoma (epidermoid)
 554-Undifferentiated large cell carcinoma
 556-Mesothelioma
 557-Undifferentiated non-small cell

Patient Name _____ CALGB Patient No. _____ CALGB Protocol No. _____

TAGGING WORK-UP AT PROTOCOL ENTRY

- 1-required but not done
- 2-required and done
- 3-not required

- *1-negative
- 2-positive
- 3-equivocal

*Results

<input type="checkbox"/>	Head CT scan	<input type="checkbox"/>
<input type="checkbox"/>	Chest film	<input type="checkbox"/>
<input type="checkbox"/>	Bronchoscopy	<input type="checkbox"/>
<input type="checkbox"/>	Chest CT scan	<input type="checkbox"/>
<input type="checkbox"/>	Mediastinoscopy	<input type="checkbox"/>
<input type="checkbox"/>	Abdominal CT scan	<input type="checkbox"/>
<input type="checkbox"/>	Tomogram	<input type="checkbox"/>
<input type="checkbox"/>	Liver/Spleen scan	<input type="checkbox"/>
<input type="checkbox"/>	Abdominal ultrasound	<input type="checkbox"/>
<input type="checkbox"/>	Bone scan	<input type="checkbox"/>
<input type="checkbox"/>	EKG	<input type="checkbox"/>
<input type="checkbox"/>	Pulmonary function tests	<input type="checkbox"/>
<input type="checkbox"/>	Bone marrow aspirate/Bx	<input type="checkbox"/>
<input type="checkbox"/>	Other,specify _____	<input type="checkbox"/>
<input type="checkbox"/>	Other,specify _____	<input type="checkbox"/>

LAB DATA AT PROTOCOL ENTRY

<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	WBC (x10 ³)	Date (m/d/y)
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Granulocytes (x10 ³)	___/___/___
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Platelet count (x10 ³)	___/___/___
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Hemoglobin (g/dl)	___/___/___
<input type="checkbox"/> <input type="checkbox"/>	BUN (mg/dl)	___/___/___
<input type="checkbox"/> <input type="checkbox"/>	Serum Creatinine (mg/dl)	___/___/___
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Creatinine clearance (ml/min), if required	___/___/___
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	SGOT (U/ml)	___/___/___
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Alkaline phosphatase (U/dl)	___/___/___
<input type="checkbox"/> <input type="checkbox"/>	Bilirubin (mg/dl)	___/___/___
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	LDH (units)	___/___/___

PREVIOUS TREATMENT

Previous radiotherapy (1-no, 2-yes, specify below)

SITE	INCLUSIVE DATES	TOTAL TUMOR DOSE (cGy)	TREATMENT DETAILS	BEST *RESPONSE	RESPONSE DURATION (MONTHS)

Previous chemotherapy (1-no, 2-yes, specify below)

AGENT OR COMBINATION	INCLUSIVE DATES	TREATMENT DETAILS	BEST *RESPONSE	RESPONSE DURATION (MOS.)	*Response:
					1-complete
					2-partial
					3-regression (of evaluable disease)
					4-stable
					5-progression
					6-not evaluable

Previous surgery (1-no, 2-yes, specify below)

<table border="1"> <tr><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td></tr> </table>													Date	<table border="1"> <tr><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td></tr> </table>													Procedure	<table border="1"> <tr><td> </td></tr> <tr><td> </td></tr> <tr><td> </td></tr> <tr><td> </td></tr> </table>					*Site	**Purpose	<p>*Site</p> <p>1-primary</p> <p>2-primary and other</p> <p>3-metastatic</p> <p>**Purpose</p> <p>1-diagnostic ONLY</p> <p>2-palliative</p> <p>3-tumor debulking</p> <p>4-curative</p>

Investigator's Comments:

Patient Name _____ CALGB Patient No. _____ CALGB Protocol No. _____

TNM STAGING - Indicate extent of disease at time of diagnosis.**Primary Tumor (T)** (select one)

- TX** Tumor proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically, or any tumor that cannot be assessed in a retreatment staging.
- T0** No evidence of primary tumor.
- TIS** Carcinoma in situ.
- T1*** A tumor that is 3.0 cm or less in greatest dimension, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy.
- T2** A tumor more than 3.0 cm in greatest dimension, or a tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung.
- T3** A tumor of any size with direct extension into the chest wall (including superior sulcus tumors), diaphragm, or the mediastinal pleura or pericardium without involving the heart, great vessels, trachea, esophagus or vertebral body, or a tumor in the main bronchus within 2 cm of the carina without involving the carina.
- T4**** A tumor of any size with invasion of the mediastinum or involving heart, great vessels, trachea, esophagus, vertebral body or carina or presence of malignant pleural effusion.

Nodal Involvement (N) (select one)

- N0** No demonstrable metastasis to regional lymph nodes.
- N1** Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension.
- N2** Metastasis to ipsilateral mediastinal lymph nodes and subcarinal lymph nodes.
- N3** Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene or supraclavicular lymph nodes.

Distant Metastasis (M) (select one)

- M0** No (known) distant metastasis.
- M1** Distant metastasis present - Specify Site(s) on page 1

Recurrent Disease (1-no, 2-yes)

Recurrent disease in the chest after radiation therapy, surgery, or both regardless of stage at recurrence, if all other eligibility criteria are met.

Histologic confirmation of recurrence desirable.

Footnotes to TNM Definitions

- 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 classified as T1.
- ** Most pleural effusions associated with lung cancer are due to tumor. There are, however, some few patients in whom cytopathological examination of pleural fluid (on more than one specimen) is negative for tumor, the fluid is non-bloody and is not an exudate. In such cases where these elements and clinical judgment dictate that the effusion is not related to the tumor, the patients should be staged T1, T2 or T3, excluding effusion as a staging element.

Ref: CHEST/89/4/April 1986/Supplement

Investigator's Comments:

Investigator (please print)

Date

Investigator: Keep a photocopy and send original to Frontier Science.

5/3/88 CM

**INSTRUCTIONS FOR CALGB
RESPIRATORY MEASUREMENT FORM
(FORM NO. C-076)**

- A. **Purpose** - This form will be requested along with the on-study at protocol entry, and as a supplement to follow-up form(s) and flow sheets as submission schedule dictates.

All disease sites should be reported in the same order each time the form is submitted. Include date of observation on top line, and response status at present on second line.

- B. **Form Specific Instruction**

List all parameters in boxes from 1-10. Measurable sites require bidimensional tumor measures, i.e. "right hilar mass, 3x3 cm"; evaluable sites require description of disease, i.e. "mediastinal adenopathy, decreased".

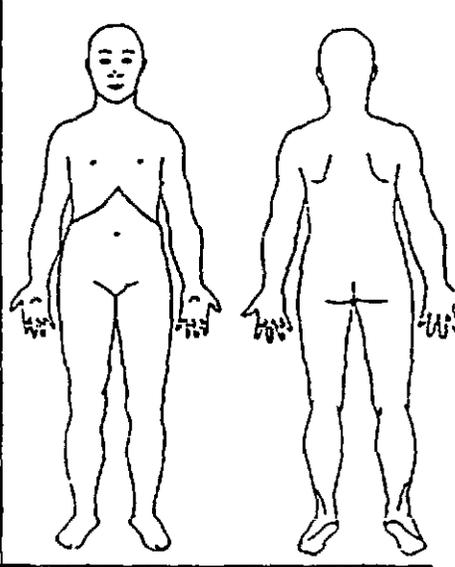
Distinct liver lesions should be treated as any other measurable site; if hepatomegaly is being used as a response determinant, provide liver size in cm. below right costal margin.

CM/rd 7/90

4-7-70

	I Date (mo/day/yr)	TUM	RX	DATA	SERIAL OBSERVATIONS					III MARKS Number & date		
											1. Est Survival	MORNING
STUDY Rx	2. Day on Study											
	3. Initials											
	4.											
	5.											
	6.											
	7.											
	8.											
	OTHER Rx	9. Analgesics										
10. Transfusions												
11. Radiation												
12. Antibiotics												
13.												
SYMPTOMS	14.											
	15. Pain											
	16. Performance											
	17. Food Intake											
	18. Vomiting											
	19. Diarrhea											
	20. Oral											
	21. Bleeding											
	22. Infection											
	23. Respiratory											
PHYSICAL FINDINGS	24. Urinary											
	25.											
	26. Reproductive											
	27.											
	28. Temp. (C° or F°)											
	29. Wt. (kg/lb)											
	30. Skin											
	31. Mouth											
	32. Lymphnodes											
	33. Chest											
	34. Breasts											
	35. Heart											
	36. Liver											
	37. Abdomen											
TUMOR MEASUREMENT	38. G.U.											
	39. Edema											
	40. Neurologic											
	41.											
	42.											
	43. Tumor 1											
	44. Tumor 2											
	45. Tumor 3											
	46. Tumor 4											
	47. Tumor 5											
LABORATORY	48. Hgb/Hct											
	49. Retic. (%)											
	50. WBC (x10 ³)											
	51. Diff. Neut/Eos.											
	52. Lymph/Monos											
	53. Plt (x10 ³)											
	54. Bone Marrow											
	55. BUN											
	56. Creatinine											
	57. Uric Acid											
	58. Alc. Phase											
	59. Bilirubin											
	60. SGOT											
	61. LDH											
	62. Calcium											
	63. Serum Prot.											
64. Serum Alb.												
65. Cytology												
66.												

SHOWS TUMORS 1, 2, 3, 4, 5



KEY: Non-measured items
IMPAIRMENT **PERFORMANCE**
 0 = None Normal
 1 = Mild Ambulatory
 2 = Moderate < 50% time in bed
 3 = Severe > 50% time in bed
 4 = Life-Threatening Bedridden

Patient _____
 Chart No. _____
 Institution _____
 Page _____ of _____ Pages

**INSTRUCTIONS FOR CALGB
RESPIRATORY FOLLOW-UP FORM
(FORM NO. C-109)**

- A. Purpose - Since the Expanded Common Toxicity Criteria and the Toxicity Reporting Form, C-090 have been approved for new studies, a new CALGB Respiratory Form (C-109) has been developed. This form differs from the previous one (C-075) in only one respect: the toxicity section has been deleted resulting in a larger area at the bottom for comments.

PLEASE NOTE: C-109 will eventually replace C-075 in all respiratory studies. It has been implemented for use in protocols 8931, 8934 and 8935 to date.

CM 7/90

CALGB RESPIRATORY FOLLOW-UP FORM

INSTRUCTIONS: Submit this form as required by protocol. If appropriate, send CALGB flow sheets for treatment period covered by this form. Enter '-1' to indicate that an answer is "unknown", "unobtainable", or "not done".

Patient's Name _____ Patient Hospital No. _____

CALGB Protocol No. _____ CALGB Patient No. _____

Main Member Institution _____ /Adjunct _____

_____ (Leave blank)

TIME PERIOD COVERED BY THIS FORM:

From To
M D Y M D Y

Survival status If patient has died:
1-alive Cause of death
2-dead 1-treatment related
3-lost to follow-up 2-disease related
3-other, specify

Date last known alive or date of death
M D Y

Performance Status for This Period:

Best Worst
0-fully active
1-ambulatory, capable of light work
2-in bed <50% of waking time, capable of self-care but not of work activities
3-in bed >50% of waking time, capable of only limited self-care
4-completely bedridden

No. of cycles given during this follow-up period (complete or partial cycles)

Was protocol treatment modified during this follow-up period? (1-no, 2-yes)

TREATMENT DATA

Treatment type
1-initial
2-consolidation
3-maintenance
4-crossover
5-follow-up off therapy
6-other, specify

Status of assigned treatment
1-therapy has been terminated permanently
2-therapy is being continued

Date treatment ended or date of last dose given
M D Y

If treatment has ended during this time period:

Reason for ending treatment
1-completed protocol requirements
2-progressive disease
3-excessive toxicity
4-death of patient
5-patient withdrawal of consent
6-other complicating disease, specify below
7-error, specify below
8-maximum dosage reached
9-other, specify below

Comments:

RESPONSE DATA

- Best overall objective response to date
- 1-complete remission
 - 2-partial remission
 - 3-regression (nonmeasurable disease)
 - 4-stable disease
 - 5-progression
 - 6-unevaluable

If response occurred:

- Current status of remission
- 1-continues in remission
 - 2-relapsed after response or improvement
 - 3-died with no evidence of relapse

Date last known in remission
M D Y

If any of the following have occurred during this report period, please give date(s):

Date of partial response/
M D Y regression onset

Date of complete response
M D Y onset

Date of disease progression/
M D Y relapse

Date of CNS Metastases
M D Y

Please indicate all sites of involvement during this report period:

- SITES OF INVOLVEMENT**
- 1-not involved
 - 2-involved
 - 3-equivocal

- ASSESSMENT METHOD**
- 1-clinical (palpation radiologic/scan)
 - 2-pathologic
 - 3-autopsy

<input type="checkbox"/> Hilar nodes	<input type="checkbox"/>
<input type="checkbox"/> Mediastinal nodes	<input type="checkbox"/>
<input type="checkbox"/> Supraclavicular/Scalene nodes	<input type="checkbox"/>
<input type="checkbox"/> Other nodal, specify _____	<input type="checkbox"/>
<input type="checkbox"/> Primary lung	<input type="checkbox"/>
<input type="checkbox"/> Contralateral lung	<input type="checkbox"/>
<input type="checkbox"/> Pleura	<input type="checkbox"/>
<input type="checkbox"/> Liver	<input type="checkbox"/>
<input type="checkbox"/> Adrenal(s)	<input type="checkbox"/>
<input type="checkbox"/> Bone	<input type="checkbox"/>
<input type="checkbox"/> Bone Marrow	<input type="checkbox"/>
<input type="checkbox"/> Brain	<input type="checkbox"/>
<input type="checkbox"/> Skin	<input type="checkbox"/>
<input type="checkbox"/> Other, specify _____	<input type="checkbox"/>
<input type="checkbox"/> Other, specify _____	<input type="checkbox"/>

RELAPSE DATA

If a relapse has occurred during this report period:

Symptoms of relapse (1-no, 2-yes)

Date onset

<input type="checkbox"/> Chest pain	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="checkbox"/> Respiratory infection	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="checkbox"/> Cough	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="checkbox"/> Dyspnea	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="checkbox"/> Hoarseness	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="checkbox"/> Hemoptysis	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="checkbox"/> Bone pain	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="checkbox"/> CNS symptoms	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="checkbox"/> Anorexia	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="checkbox"/> Other, specify: _____	<input type="text"/>	<input type="text"/>	<input type="text"/>
	M	D	Y

- How was relapse documented?
- 1-clinical exam
 - 2-radiologic scan
 - 3-laboratory tests
 - 4-biopsy

If radiotherapy was received as a part of protocol treatment:

Where did relapse occur?

- 1-within the boost volume
- 2-within other radiated volume, specify: Stat office use

Site _____

Site _____

Site _____

- 3-at margins of radiated volume, specify:

Site _____

Site _____

Site _____

- 4-at non-radiated site

Investigator (please print) _____

Date _____

**INSTRUCTIONS FOR CALGB
TOXICITY REPORTING FORM
(FORM NO. C-090)**

- A. **Purpose** - With the activation of the Common Toxicity Criteria from the NCI, it has become evident that CALGB follow-up forms do not adequately capture toxicity data that will comply with the NCI reporting requirements. Form C-090 (CALGB Toxicity Reporting Form) has been developed to provide toxicity reports that fully address the Common Toxicity Criteria.

- B. **Form Specific Instructions** - Submit form C-090 to FSTRF only when specified in the protocol. This form should reflect toxicity data for each follow-up period for which a follow-up form is required. The time periods covered by form C-090 and the follow-up form should correspond. Remember that all coded toxicities **MUST** be documented and described on accompanying flowsheets. Code **EVERY** box.

INSTRUCTIONS: Submit this form as specified in protocol together with corresponding flow sheets and follow-up forms. All coded toxicities should be documented on accompanying flow sheets. Enter '-1' to indicate an answer is 'unknown', 'unobtainable', 'not done', or 'not applicable'. Investigator. Copy form and send original to FSTRF.

Patient's Name _____ Patient Hospital No. _____
Participating Group Protocol No. _____ Participating Group Patient No. _____
CALGB Protocol No. _____ CALGB Patient No. _____
Main Member Institution _____ /Adjunct _____

TOXICITY AND COMPLICATIONS - DUE TO THERAPY
(Use CALGB Expanded Common Toxicity Criteria)

TIME PERIOD COVERED BY THIS FORM:

From: [] [] [] [] [] [] [] [] [] [] To: [] [] [] [] [] [] [] [] [] []
M D Y M D Y (Start Use Only)

HEMATOLOGIC

- [] WBC
[] Platelets
[] Hemoglobin
[] Granulocytes/Bands
[] Lymphocytes
[] Other Hematologic, specify _____
[] HEMORRHAGE
[] INFECTION specify site _____

GASTROINTESTINAL

- [] Nausea
[] Vomiting
[] Diarrhea
[] Stomatitis
[] Esophagitis/Dysphagia
[] Anorexia
[] Other GI, specify _____
[] OTHER MUCOSAL Specify site _____

LABORATORY

- [] Bilirubin
[] Transaminase (SGOT, SGPT)
[] AlkPhos or 5' nucleotidase
[] Liver-clinical
[] Other Liver, specify _____

KIDNEY/BLADDER

- [] Creatinine
[] Proteinuria
[] Hematuria
[] BUN
[] Hemorrhagic Cystitis
[] Renal Failure
[] Other Kidney/Bladder, specify _____
[] ALOPECIA

PULMONARY

- [] Dyspnea
[] pO2/pCO2
[] Carbon Monoxide Diffusion Capacity (DLCO)
[] Fibrosis
[] Pulmonary Edema
[] Non-infect. Pneumonitis
[] Pleural Effusion
[] Adult Respiratory Distress Syndrome (ARDS)
[] Other Pulmonary, specify _____

HEART

- [] Cardiac dysrhythmias
[] Cardiac function
[] Cardiac-ischemia
[] Cardiac-pericardial
[] Other Heart, specify _____

CIRCULATORY

- [] Hypertension
[] Hypotension
[] Phlebitis/Thrombosis/Embolism
[] Edema

NEUROLOGIC

- [] Neuro-sensory
[] Neuro-motor
[] Neuro-cortical
[] Neuro-cerebellar
[] Neuro-mood
[] Neuro-headache
[] Neuro-constipation
[] Neuro-hearing
[] Neuro-vision
[] Pain
[] Other Neurologic, specify _____

DERMATOLOGIC

- [] Skin
[] Local
[] ALLERGY

FLU-LIKE SYMPTOMS

- [] Fever in absence of infection
[] Chills
[] Myalgias/Arthraigias
[] Sweats
[] Malaise/Fatigue
[] Other Flu-like Symptoms, specify _____

[] WEIGHT GAIN

[] WEIGHT LOSS

METABOLIC

- [] Hyperglycemia
[] Hypoglycemia
[] Amylase
[] Hypercalcemia
[] Hypocalcemia
[] Hypomagnesemia
[] Hyponatremia
[] Hypokalemia
[] Other Metabolic, specify _____

COAGULATION

- [] Fibrinogen
[] Prothrombin time
[] Partial thromboplastin time
[] Other Coagulation, specify _____

ENDOCRINE

- [] Impotence/Libido
[] Sterility
[] Amenorrhea
[] Other Endocrine, specify _____
[] Eye

OTHER MISCELLANEOUS

- [] Specify _____
[] Specify _____

**INSTRUCTIONS FOR CALGB
ACUTE LEUKEMIA GROUP B SOLID TUMOR FORM
(FORM NO. ST-4)**

- A. Purpose - To document all data recorded on the onstudy form and follow-up form.
- B. Form Specific Instructions
1. The first flow sheet submitted with the on-study form should document all pre-study work-up and information including a brief history and any necessary expansion of physical findings.
 2. All current sites of involvement and measurements must be documented along with the method used to determine this, such as CT scan, x-ray or bone scan.
 3. Required information not specifically printed on flow sheets (example: lab data) must be added.
 4. It would be helpful to use a separate flow sheet for each cycle when alternating treatments are administered.
 5. Any toxicity or response coded on a follow-up form must be documented on flow sheets.
 6. Submit completed flow sheets along with follow-up forms at the time periods specified in "Protocol Submission Schedule".
 7. Remarks should detail reasons for modification or delay of treatment, administration of other medication, toxicities, etc.
 8. The month day and year should be clearly marked at the top of each column.

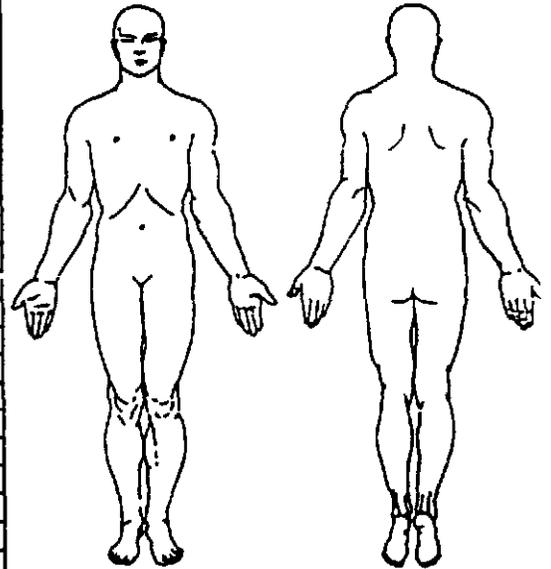
AC/rd 7/90

1985

SERIAL OBSERVATIONS

		REMARKS: Number & Date						
1 Date (Mo/Day)								
2 Day on Study								
3 Initials								
4								
5								
6								
7								
8								
9 Analgesics								
10 Transfusions								
11 Radiation								
12 Antibiotics								
13								
14								
15 Perform. Status								
16 Pain								
17 Food Intake								
18 Vomiting								
19 Diarrhea								
20 Constipation								
21 Bleeding								
22 Infection								
23 Respiratory								
24 Urinary								
25 Other								
26 Temp (C°)								
27 Wt (kg)								
28 Blood Pressure								
29 Pulse/Resp.		/	/	/	/	/	/	/
30 Skin/Alopecia		/	/	/	/	/	/	/
31 Mouth								
32 Lymph Nodes								
33 Chest								
34 Breasts								
35 Heart								
36 Liver								
37 Abdomen								
38 G.U.								
39 Edema								
40 Neurologic								
41 TUMOR 1								
42 TUMOR 2								
43 TUMOR 3								
44 TUMOR 4								
45 Markers								
46 Hgb/Hct		/	/	/	/	/	/	/
47 WBC (10 ⁹)								
48 Neut/Eos		/	/	/	/	/	/	/
49 Lymphs/Monos		/	/	/	/	/	/	/
50 Plts (10 ⁹)								
51 Calcium/Phos								
52 Uric Acid								
53 Protein								
54 Albumin								
55 Bilirubin								
56 LDH								
57 GOT/GPT		/	/	/	/	/	/	/
58 Alk Phos (<300)								
59 CPK								
60 BUN/Creat		/	/	/	/	/	/	/
61 Na/K		/	/	/	/	/	/	/
62 Cl/CO ₂		/	/	/	/	/	/	/
63 Glucose								
64 Cr. Cl. (ml/min)								
65 Bone Marrow								
66								
67								
68								

SHOW TUMORS 1,2,3,4



KEY

IMPAIRMENT	PERFORMANCE
0 = None	0 = Normal
1 = Mild	1 = Ambulatory
2 = Moderate	2 = < 50% in bed
3 = Severe	3 = > 50% in bed
4 = Life threat.	4 = Bedridden

PATIENT:
CHART NO. :
UNIV. OF MD. CANCER CENTER
FLOW SHEET PAGE # :

**INSTRUCTIONS FOR CALGB
NOTIFICATION OF DEATH FORM
(FORM NO. C-113)**

- A. **Purpose** - To collect information specific to events surrounding a patient's death, whether it occurred on or off-study. It will not replace any follow-up form required by protocol, but rather provide details regarding:

primary and secondary cause(s) of death
whether an ADR is required, and has been sent
any prior, or concurrent, Gr.3/Gr.4 toxicities
status of disease at time of death
whether a second malignancy occurred
source of death information

NOTE: The form is required within 4 weeks of the patient's death. It should be accompanied by any relevant documentation such as a death certificate or autopsy report if available. Protocol-specific follow-up forms and flowsheets should also be attached, if they have not already been submitted. If death has been reported via a survival listing, C-113 should still be forwarded to "close out" the case.

B. **Form Specific Instructions**

1. **Date of Death** - The minimum requirements for entering a date of death into the database are month and year.
2. **Cause of Death** - Code as "3" if death is attributable to something other than treatment or disease, but be sure to complete the 'specify' section.
3. **Prior or Concurrent Toxicities** - Please code only the prior toxicities **WHILE ON MOST RECENT PROTOCOL TREATMENT**, in the event a patient has been on more than one study. Code concurrent toxicities **WHETHER THE PATIENT IS ON OR OFF-STUDY**; the purpose of this question is to ascertain any latent complications induced by treatment.

4. **Recurrent Disease** - If this is coded "2", then "Cause of Death" (first column) is likely to be "disease related" and the subsequent two questions should be addressed regarding the submission of appropriate forms, and ...
5. **Primary Cause** - This information is of interest in assessing sites and patterns of relapse across disease types. If a second malignancy has occurred, please specify site and histology.
6. **Death Information Obtained From:** - Please note that, if autopsy/death certificate are available, they are to be submitted for verification and inclusion in patient's records.

NOTE: This form is to be implemented hereafter in the event of death for any patient enrolled on a CALGB treatment protocol. (Not applicable for those on non-treatment studies, such as in certain companions, psychiatric assessments, laboratory evaluations and cancer control protocols). It is the institution's responsibility to keep a supply of forms.

**INSTRUCTIONS FOR CALGB
RADIOTHERAPY FOLLOW-UP FORM
(FORM NO. C-052)**

- A. Purpose - To be completed by the radiotherapist of record; please refer to the individual protocol for submission requirements.
- B. Form Specific Instructions

Please specify dose and volume for RT administration each time period (not cumulative dose).

If modifications were made to radiotherapy, please code reason. Any additional remarks should be made on the flowsheets.

Response must be coded per protocol definition; therefore consult individual study document for guidelines regarding measurable vs. evaluable disease, longevity of response, etc.

The Complications section utilizes two grading criteria: the Acute Morbidity and the Late Morbidity Scoring Criteria. The former is used to reflect those toxicities directly attributable to radiotherapy while treatment is being received or shortly thereafter (≤ 90 days); the latter is used for complications which manifest at a later time (≥ 90 days).

NOTE: Both grading criteria should be attached to the protocol; please contact the FSTRF database manager to request additional copies.

CM/rd 7/90

CALGB
NOTIFICATION OF DEATH

INSTRUCTIONS: This form is to be submitted in the event of a patient's death due to any cause. It is to be submitted within four (4) weeks of event, along with copies of death certificate*/autopsy report* (if performed). If appropriate, include CALGB follow-up forms/flowsheets. Enter '-1' if an answer is "unknown", "unobtainable" or "not done".

Patient's Name _____ Patient Hospital No. _____
Coordinating Group Protocol No. _____ Coordinating Group Patient No. _____
CALGB Protocol No. _____ CALGB Patient No. _____
Main Member Institution _____ /Adjunct _____

Date of Death
M D Y

Did patient have evidence of recurrent disease?

1-no
2-yes

CAUSE OF DEATH

- 1-treatment related
- 2-disease related
- 3-not treatment or disease related, specify

If yes, have required follow-up forms and flowsheets been submitted?

1-no
2-yes

If death is disease related:

Primary Cause

- 1-original malignancy
- 2-metastatic from original malignancy
- 3-second malignancy, specify _____

4-non-malignant systemic disease, specify _____

Immediate Cause of Death:

Secondary to:

Death information obtained from:

- 1-autopsy*
- 2-medical records/death certificate*
- 3-physician
- 4-relative or friend
- 5-other, specify _____

If death is treatment related, has ADR been submitted?

1-no
2-yes

Any prior Grade 3 or Grade 4 toxicities while on most recent protocol treatment?

1-no
2-yes

Any concurrent Grade 3 or Grade 4 toxicities?

1-no
2-yes

Comments:

Date of last protocol treatment
M D Y

Investigator _____

Date _____

Investigator: Keep a photocopy and send original to Frontier Science.

CM 6/1/90

CALGB RADIOTHERAPY FOLLOW-UP FORM

INSTRUCTIONS: Submit this form (along with CALGB flowsheets if applicable) as required by protocol. Enter "-1" to indicate that an answer is unknown, "unobtainable" or "not done".

NOTE: For complications/toxicities which occur within 90 days after the start of radiotherapy, use the Acute Radiation Morbidity Scoring Criteria; complications/toxicities which occur more than 90 days after the completion of radiotherapy, use the Late Radiation Morbidity Scoring Scheme.

Patient's Name _____ Patient Hospital No. _____
CALGB Protocol No. _____ CALGB Patient No. _____
Coordinating Group Protocol No. _____ Coordinating Group Patient No. _____
Member Institution _____ /Adjunct _____

Time Period covered by this form: From: [][] [][] [][] To: [][] [][] [][]
M D Y M D Y

Date first dose, this time period: [][] [][] [][]
Date last dose, this time period: [][] [][] [][]
M D Y M D Y

COMPLICATIONS DUE TO RADIOTHERAPY

Did any complications occur during this period due to radiotherapy? (1-no, 2-yes)

If yes, complete the following:

(s) radiotherapy administered this reporting period:
cGy to _____ (site)
cGy to _____ (site)
cGy to _____ (site)
cGy to _____ (site)

Table with 2 columns: Site of Complication/Toxicity* and Grade**. Rows contain empty boxes for data entry.

Was protocol radiotherapy modified this reporting period? (1-no, 2-yes)

- Reason for modification
1-Excessive toxicity of radiotherapy
2-Excessive toxicity of other therapy (chemotherapy, surgery, immunotherapy)
3-Patient noncompliance
4-Scheduling difficulties
5-Other, specify _____

*Sites of Complication/Toxicity Codes:

- 1-skin 13-Esophagus
2-Subcutaneous 14-Upper GI
3-Mucous Membranes 15-Lower GI
4-Breast Edema 16-Liver
5-Arm Edema 17-Kidney
6-Salivary Glands 18-Bladder
7-Spinal Cord 19-Bone
8-Brain 20-Joint
9-Eye 21-Delayed Wound Healing
10-Larynx 22-Leukopenia
11-Lung 23-Anemia
12-Heart 24-Thrombocytopenia
25-Other, specify: _____

Radiotherapy has ended during this time period:

- Reason for ending radiotherapy
1-Completed protocol requirements
2-Progressive disease
3-Excessive toxicity
4-Death of patient
5-Patient withdrawal of consent
6-Other complicating disease
7-Other, specify _____

**For Grade, see Acute Radiation Morbidity Scoring Criteria (< 90 days) or Late Radiation Morbidity Scoring Scheme (>90 days).

Arm/Breast Edema Grading Scale

Best overall response to date (see protocol definition)
Onset occurred:
0-None 1-Minimal/Mild 2-Moderate 3-Severe 4-Life-threatening 5-Fatal

- Current status of remission
1-Continues in remission
2-relapsed after response or improvement
3-died with no evidence of relapse

Investigator (please print) _____ Date _____

PATIENT NAME _____

CALGB # _____

DATE OF BIRTH _____ SEX: M ___ F ___ RADIO THERAPY DEPT _____

RADIO THERAPIST _____

USE SEPARATE RT-1 FOR EACH TREATMENT AREA. AREAS SHOULD BE NUMBERED SEQUENTIALLY, AND MODIFICATIONS (e.g., "BOOST, "CONE DOWN", ETC.) IDENTIFIED BY ALPHABETICAL SUFFIX.

PHYSICIST/DOSIMETRIST _____

NAME OF TREATMENT AREA _____ DATE OF 1ST TREATMENT _____

DAILY DOSE CALCULATIONS
(PRESCRIPTION POINT
PER PROTOCOL)

FIELD I FIELD II FIELD III FIELD IV FIELD V

1. FIELD NAME (ANT, POST, RT LAT, ETC)					
2. TREATMENT MACHINE	MODEL				
	ENERGY				
3. DEPTH OF PRESCRIPTION POINT (INCLUDE THICKNESS OF BOLUS, IF ANY)					
4. SSD					
5. COLLIMATOR SETTING (W x L) (FIELD SIZE IN CM AT ISOCENTER)					
6. EQUIVALENT SQUARE ACCOUNT FOR BLOCKS/AIR <input type="checkbox"/> AT PRESCR PT <input type="checkbox"/> ON SURFACE					
7. <input type="checkbox"/> TOR <input type="checkbox"/> TMR <input type="checkbox"/> TPR <input type="checkbox"/> PDD					
8. OUTPUT FACTOR					
9. OTHER CORRECTION FACTOR PLEASE SPECIFY _____					
10. TRANSMISSION FACTOR	TRAY				
	WEDGE				
	OTHER				
11. OFF-AXIS PRESCRIPTION POINT	DISTANCE				
	OAR				
12. MONITOR SETTING (MINUTES IF COBALT-60)					
13. DOSE TO PRESCRIPTION POINT PER FRACTION					
14. INTENDED TOTAL DOSE TO PRESCRIPTION POINT					
15. TREATMENT POSITION					

This form to be submitted with films 3 days after starting radiotherapy.

TO: Quality Assurance Review Center
 Roger Williams Medical Center
 825 Chalkstone Avenue
 Providence, RI 02908



Rev:6/91

NO If yes, please complete the following section.
 YES

REFERENCE POINT CALCULATION (LABELS ARE ASSIGNED TO EACH POINT BY PROTOCOL)	POINT__	POINT__	POINT__	POINT__	POINT__
ANATOMICAL SITE					
CONTRIBUTING FIELD(S)					
OFF-AXIS REFERENCE POINT					
DISTANCE					
QAR					
DEPTH TO POINT	ANT / POST				
SSD (OFF-AXIS)	ANT / POST				
CALCULATED DAILY DOSE TO POINT					

Was an isodose distribution been generated?

NOT REQUIRED

NO
 YES If yes, please submit a copy indicating which isodose line the physician prescribed to.

Was a gap calculation performed?

NOT REQUIRED

NO
 YES If yes, please submit documentation

RELEVANT CLINICAL DATA

Clinical stage of disease: T N M

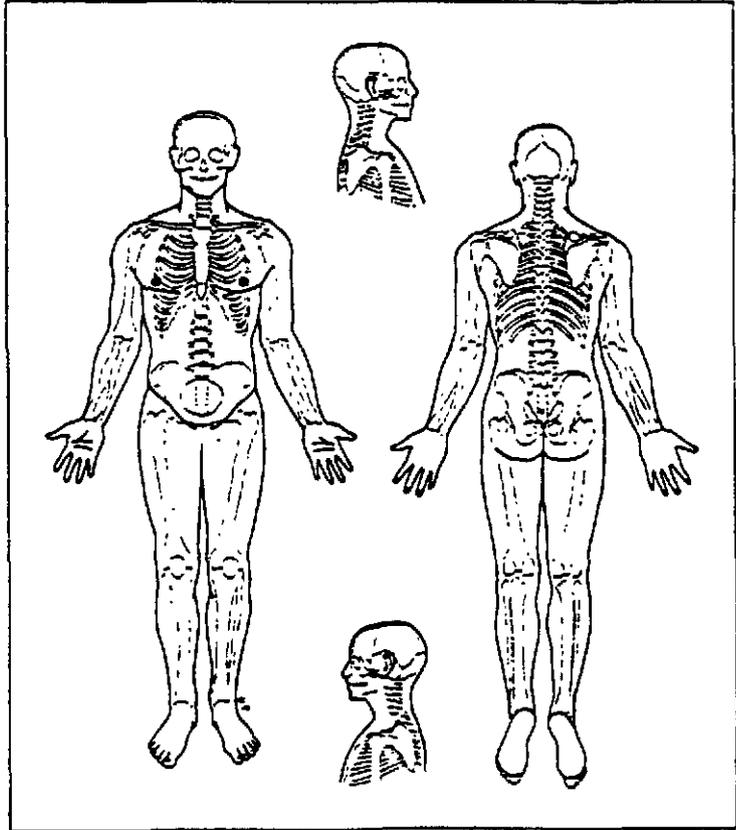
Histology _____

Was Patient had surgical excision? (y/n) Date: _____

- Complete resection
- Incomplete resection Microscopic Gross Residual
- Inoperable

Please indicate the original tumor location and size.

This form was completed by: _____



**QUALITY ASSURANCE REVIEW CENTER
RT-2 RADIOTHERAPY TOTAL DOSE RECORD**

PROTOCOL# _____
REGIMEN# _____

PATIENT NAME _____ PRINCIPAL INSTITUTION _____
 RADIO THERAPY DEPT. _____
 RADIO THERAPISTS _____
 PHYSICIST/ DOSIMETRIST _____

LIST AREA NUMBERS CORRESPONDING TO THOSE ON "RT-1" FORMS. RECORD BOOST AREAS SEPARATELY.

CENTRAL AXIS	AREA # _____	AREA # _____	AREA # _____	AREA # _____	AREA # _____	AREA # _____
ANATOMICAL AREA						
DATE OF FIRST Rx TO AREA						
NUMBER OF TREATMENTS						
DATE OF LAST Rx						
TOTAL DOSE TO Rx POINT (CENTRAL AXIS)						
OFF-AXIS REFERENCE POINTS: ANATOMICAL SITE	(ENTER TOTAL REFERENCE POINT DOSE CORRESPONDING TO EACH OFF-AXIS DOSE - TREATMENT AREA LISTED ABOVE)					
A.						
B.						
C.						
D.						
E.						
F.						
G.						
H.						
I.						
INTERRUPTION:						
FROM:						
TO:						
REASON:						

After completion of Radiotherapy, mail along with: 1) copy of patient's therapy sheet showing daily doses, 2) all Dose calculations.

TO: QUALITY ASSURANCE REVIEW CENTER
 ROGER WILLIAMS MEDICAL CENTER
 825 CHALKSTONE AVE.
 PROVIDENCE, RI 02908