

RADIATION THERAPY ONCOLOGY GROUP

RTOG 93-11

**A PHASE I/II DOSE ESCALATION STUDY
USING THREE DIMENSIONAL CONFORMAL RADIATION THERAPY
IN PATIENTS WITH INOPERABLE, NON-SMALL CELL LUNG CANCER**

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SCHEMA

All patients must have a completed 3D plan prior to entering this protocol

Group 1* < 25%	Dose level 1:	70.9 Gy/33 fx/7-8 wks (closed 1/8/98)
	Dose level 2:	77.4 Gy/36 fx/7-8 wks (closed 9/23/98)
	Dose level 3:	83.8 Gy/39 fx/8-9 wks (closed 12/20/99)
	Dose level 4:	90.3 Gy/42 fx 9-10 wks (opened 12/20/99)
Group 2* 25% - < 37%	Dose level 5:	70.9 Gy/33 fx/7-8 wks (closed 6/14/99)
	Dose level 6:	77.4 Gy/36 fx/7-8 wks (opened 6/14/99)
	Dose level 7:	83.8 Gy/39 fx/8-9 wks
Group 3*+ ≥ 37%	Dose level 8:	64.5 Gy/30 fx/6-7 wk (closed 7/1/99)
	Dose level 9:	70.9 Gy/33 fx/7-8 wks
	Dose level 10:	77.4 Gy/36 fx/7-8 wks

+ Group 3 closed to accrual 7/1/99 for all dose levels.

Dose escalation stratified by risk group (**% of total lung volume receiving > 20 Gy*).

Total lung volume is defined as the total volume of both lungs minus the PTV
Only one dose level per stratification Group will open at one time

Dose prescription is to the ICRU 50 reference point - See Section 6.0

Eligibility (See Section 3.0 for details)

- Squamous cell, adeno, undifferentiated large cell carcinoma
- Stage I-III B (*unresected*)
- Age ≥ 18
- Karnofsky Performance Status ≥ 70
- No malignant pleural effusion, positive supraclavicular nodes, or massive atelectasis
- Study-specific consent form

Required Sample Size: Maximum 15-36 to each dose level

6/14/99
7/1/99
12/20/99

Institution # _____

RTOG 93-11
Case # _____

ELIGIBILITY CHECK (12/20/99)
(page 1 of 2)

- _____(Y/N) 1. Has the histology been confirmed a non-small cell type (*squamous cell*), undifferentiated large cell carcinoma or adenocarcinoma?
_____(Y) If no, does cytological examination confirm malignancy?
- _____(I-IIIb) 2. What is the tumor stage group?
- _____(N) 3. Is there evidence of supraclavicular lymph node involvement?
- _____(Y) 4. Is there measurable disease on the 3D planning CT?
- _____(N) 5. Is there evidence of distant metastasis or massive atelectasis?
- _____(N) 6. Is there evidence of pericardial effusion or superior vena cava syndrome?
- _____(Y/N) 7. Is there evidence of pleural effusion? (*If no, skip to Q8*)
_____(Y) If yes, has malignant pleural effusion been ruled out according to Section 3.2.11.1 of the protocol?
- _____(N) 8. Is the patient's tumor recurrent after prior treatment?
- _____(N) 9. Has the patient undergone surgical resection or is the patient eligible for definitive surgery?
- _____(N) 10. Other than non-melanoma skin cancer, has the patient had a second malignancy within the past 5 years?
- _____(N) 11. Has the patient ever received prior radiotherapy to the thorax?
- _____(N) 12. Has the patient ever been treated with biologic response modifiers?
- _____(Y/N) 13. Has the patient ever received chemotherapy? (*If no, skip to Q19*)
- _____(Y/N) 14. Has the patient received cisplatin, velban, VP-16, Taxol, carboplatin, or Navelbine within the last 4 months?
- _____(N) 15. Has the patient received bleomycin, mitomycin, adriamycin, or cytoxan within the last six months?
- _____(N) 16. Has the patient had any other chemo?
- _____(Y) 17. Have all chemo-related toxicities been resolved?
- _____(N) 18. Did the patient have a complete response to chemotherapy?
- _____(Y) 19. Is the patient's pre-chemotherapy CT scan available for review?

Institution # _____

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ELIGIBILITY CHECK (12/20/99)

Case # _____

(page 2 of 2)

- _____(≥ 70) 20. What is the Karnofsky performance status?
- _____(≥ 18) 21. What is the patient's age?
- _____(Y) 22. Have all the required tests been performed and are these within the time frame specified in Section 4.0?
- _____(Y) 23. Has the patient signed a study-specific consent form?
- _____(Y) 24. Can all detectable tumor be encompassed by the radiation fields?

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Name
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Social Security Number
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Treatment Start Date
- _____ 17. (1-3) Stratification Group (*See Schema*)
- _____ 18. Treatment Assignment

Completed by _____

Date _____

1.0 BACKGROUND INFORMATION

1.1 Introduction (6/3/96)

The specific goal of 3D conformal radiation therapy (3D CRT) is to provide a mechanism for increasing the tumor dose as a means of enhancing local tumor control.²⁶ Laboratory and clinical reports indicate that there is a direct correlation between radiation dose and the probability of achieving local control in a variety of tumors.^{20,21,36,45,47,63} The maximum dose that can be delivered to the tumor has classically been restricted by the tolerance of normal tissues within the high-dose volume. The radiation dose-response relationships for tumor control and normal tissue injury are site-specific and are influenced by a number of factors. The more important technical factors include the precision of target volume definition and of dose delivery, the dose given to this volume, and the degree to which uninvolved normal tissues are excluded from the treatment volume.^{10,15,50,57} With 3D CRT it is possible to design the spatial dose distribution to conform to the target volume while not increasing or even reducing the dose to normal tissues.⁵⁴ This approach, therefore, has the potential to decrease the probability of normal tissue toxicity and permit dose escalation to the tumor to produce higher rates of local control.^{22,24,42,44,63}

Radiotherapy represents one of the primary treatment modalities for patients with carcinoma of the lung.^{13,16} With radiotherapy, local control is directly related to dose,^{7,14,52} as well as the technical accuracy with which the dose is delivered to the target volume.^{15,16} The proximity of critical normal structures (*i.e. the spinal cord and the lungs*) to the primary tumor sets a limit on the prescription dose to between 60 and 70 Gy. In an effort to reduce the dose to the normal structures, a variety of "boost" techniques have evolved including oblique ports,^{13,16} brachytherapy,^{27,28} high LET particle beams³⁴ and intraoperative radiotherapy.⁵

In 1994, approximately 170,000 new cases of lung cancer will be diagnosed.⁴ Of these, approximately 16% presented with localized disease. For this group of patients, when treated with surgery (\pm *postoperative radiotherapy*) five-year survival of approximately 40%-50% have been achieved.³⁹ Many patients with otherwise early or technically resectable disease cannot undergo radical surgery because of co-morbid disease status (*i.e. poor pulmonary or cardiac function*). In these persons, definitive radiotherapy has resulted in lower survival than with surgery and higher local failures.^{31,48,58,59,65} Approximately 37% of these patients presented with distant metastasis to whom systemic therapy and/or palliative localized radiotherapy can be offered. An additional 32% of patients presented with regional disease for which radiation therapy has been the principle mode of treatment. Results of conventional radiation therapy in this group of patients have been disappointing. Five-year survival in a series of RTOG studies up to a total dose of 60 Gy in 30 fractions, were approximately 5% to 10%.⁴⁹ Hyperfractionation studies have been investigated by RTOG during the 1980s and have resulted in only a modest improvement in a short term survival rate in a subset of patients with good prognostic factors who received 69.6 Gy.^{7,8} It is not clear whether this modest improvement will result in significant long term improvement in patient survival. Combined chemoradiotherapy has also been investigated for this group of patients as well. Two studies, (*Dillman et al.*⁹ and *Le Chevalier et al.*)³⁵ showed modest improvement in short term survival of these patients. In reanalysis of published data by Cox et al.,^{7,8} the modest improvement in short term results with chemoradiotherapy of the CALGB study was similar to hyperfractionation studies by RTOG. In a phase III randomized protocol, RTOG compared platin-based chemoradiotherapy versus hyperfractionated radiotherapy of 69.6 Gy versus conventional radiotherapy (RTOG 88-08). Initial analysis of this study^{66,67} revealed superiority of either hyperfractionated radiotherapy or chemoradiotherapy over conventional radiotherapy alone.

However, numerous chemotherapy trials have failed to show an advantage to the addition of chemotherapy.^{40,46,60} Thus, clinicians are left to evaluate the data and try to judge on an individual basis which patients may or may not benefit.

1.2 Dose-Response Relationships in Carcinoma of the Lung

At the present time there is no clear evidence to define the best dose of radiation to treat non-small cell bronchogenic carcinoma.³³ One of the problems in determining the optimal dose of radiation for this disease, is the high incidence of distant metastasis, which results in an unrelenting prognosis, according to some, without regard to status of intrathoracic tumor. When the advanced status of lung cancer patients seen in the radiotherapy departments is considered, it becomes evident that the modest doses of 40 Gy to 50 Gy are inadequate to control the tumor. Eisert et al.¹¹ reported local tumor control of 27% of patients receiving less than 1450 rets in contrast to 51% of patients treated with higher doses. Rissanen et al.⁵⁶

reported no carcinoma in the tumor volume of 30% of patients treated with radiation to 60 Gy. In contrast, viable tumor was found more frequently in patients treated with doses below 40 Gy. A report by Arriagada² revealed 17% local control after RT dose of 65 Gy, when the local control was assessed by biopsy.

From basic principles advocated by Fletcher²¹ it is thought that doses up to 100 Gy may be required to sterilize the size of tumors frequently treated in bronchogenic carcinoma. Due to the proximity of critical structures in the thorax such as the spinal cord, esophagus, heart, etc. and the severe limitations of conventional techniques of radiation therapy, delivering such doses to these tumors with current technology has been an impossible task.¹⁹ Three dimensional radiotherapy offers the unique opportunity to explore increasing the total dose of radiotherapy to deliver to lung cancer while also testing a higher dose per fraction and shorter overall course schedules in order to gain therapeutic advantage radiobiologically. Because three-dimensional treatment therapy potentially can better target the tumor areas and spare normal tissues, the normal tissues should be able to be excluded from the high dose per fraction regions and thus maintain acceptable acute and long term toxicity. If these theories are in fact borne out, then improved local control may result in improved survival in these patients.

1.3 Volumetric Consideration in the Era of Conformal Radiotherapy (added 6/3/96)

In a study from the University of Michigan by Hazuka et al.⁶⁸ the investigators treated one group of patients with volumes smaller than conventionally used for treating lung cancer, eliminating contralateral hilum and supraclavicular nodal areas. When they compared the results of this group with another group of patients treated with more conventional radiated volumes, the results of patients treated with smaller volumes were significantly superior to the patients treated with conventional volumes. Both groups had volumetric and BEV based treatment planning. In a retrospective analysis of RTOG database by Emami et al.⁶⁹ the impact of dose and volume of individual nodal areas on the outcome of patients with inoperable unresectable lung cancer was assessed. With the exception of ipsilateral hilum, the treatment parameters of none of the other nodal bearing regions (*volume or dose*) had any impact on the outcome of these patients. Leibel et al.⁷⁰ reported on their experience of treating 45 patients with unresectable bronchogenic carcinoma with three dimensional conformal radiotherapy. The treatment volume included only the gross tumor seen on CT scan with adequate margins were irradiated. None of the conventionally known nodal bearing areas were included in the irradiated volume. They reported median and 2-year survival rates of 16.5 months and 33%, respectively. These results compare very favorable with any other report in the literature. For example, in a CALGB trial by Dillman et al.⁹ the median and 2-year survival rate was 13.8 mos and 24%, respectively.

A possible explanation may be that in a group of patients with high local failure of about 90%² the impact of prophylactic treatment of clinically uninvolved nodal areas is negligible.

Therefore, there is a strong trend to exclude thoracic and nodal areas, not clinically or radiographically involved, from irradiation volumes. We plan to pursue this idea in the current protocol.

1.4 Influence of Local Control on Survival

Most clinical results available today have been obtained with doses ranging from 40 Gy to 65 Gy.^{6,36} A total of 376 patients with stages T1-3 N0-2 carcinoma of the lung accessioned to RTOG studies to evaluate the effect of different doses of radiation. The results indicated a better 3-year survival with 60 Gy compared to lower doses of radiation.⁵⁰ Patients treated with 60 Gy had an overall intrathoracic failure rate of 33% at three years compared to 42% of those treated with 50 Gy, 44% for patients receiving 40 Gy split-course and 52% for those treated with 40 Gy continuous course.⁵¹ Patients surviving 6 to 12 months exhibited a statistically significant increased survival when the intrathoracic tumor was controlled. Patients treated with 50 Gy to 60 Gy showing tumor control had a 3-year survival rate of 22% versus 10% if they had intrathoracic failure ($p = 0.05$). In patients treated with 40 Gy (*split or continuous*) the respective survival rate was 25% in patients with thoracic tumor control versus 5% if the tumor was not controlled. This and additional studies have concluded that higher doses of radiation yielded a greater proportion of complete response, higher intrathoracic tumor control, and better survival in non-small cell carcinoma of the lung.^{3,52}

In RTOG 73-01, tumors less than 3 cm in diameter had a tumor control of 60% in contrast to only 40% for larger lesions.⁵³ These observations support the need for higher doses of radiation to control larger tumors. However, this must be tempered by the effect of increasing dose of radiation on the surrounding normal tissues and the possibility of inducing life-threatening or fatal complications.¹² Three dimensional

radiotherapy by virtue of the fact that it offers a unique tool for significant decrease in the dose of radiation to normal tissues offers the unique possibility for increasing tumor dose and decreasing dose to normal tissues. Thus, it may be possible to selectively increase the tumor dose to volumes with larger tumor burden, without inducing undue complications. In protocol 83-12, by using CT scans, computerized treatment planning and dose optimization procedures, 75 Gy in 28 fractions is delivered to the gross tumor volume seen on chest x-ray on CT scan, while the potentially involved lymph nodes in the hila and mediastinum received 50.4 Gy in 28 fractions.¹⁸ The results of this study revealed a median survival of 10 months with a one year survival of 41% and a 3 year survival of 18%. These results were very comparable to a CALGB protocol which analyzed only good risk patients and gave chemotherapy followed by 60 Gy of conventional fractionated radiotherapy. The importance of this study was a significant proportion of the patients in the RTOG 83-12 protocol would not have been eligible for the CALGB protocol based on exclusion criteria requiring a high performance status or minimal weight loss. Unfortunately, these characteristics are very common to lung cancer patients and thus the results of RTOG 83-12 suggested that accelerated fractionation concomitant boost radiotherapy alone could have at least equal results to combined chemo-radiotherapy regimens with considerably less toxicity.

The RTOG conducted a multi-institutional prospective phase II study on the effect of hyperfractionation on tumor control and survival of patients with non-small cell lung cancer. Fractions of 1.2 Gy were administered twice a day (*at 4 to 6 hour intervals*). Patients were randomized to minimum total doses of 60.0 Gy, 64.8 Gy, 69.6 Gy, 74.4 Gy and 79.2 Gy. Among 519 patients, 248 were favorable (*performance status 70 to 100 and weight loss of less than 5%*); 271 were unfavorable. No significant difference in disease-free survival was found in unfavorable patients among the five arms. In favorable patients, there was a benefit in survival for tumor dose level of 69.6 Gy when compared with lower doses.^{7,8}

1.5 Experience with 3D Treatment Planning and Conformal Therapy

Three dimensional treatment planning can lead to a number of changes in the clinical approach to patient treatment. For example, 3D treatment planning allows; 1) an improved ability to target the tumor and conform the dose to the target volume; 2) an improved ability to delineate normal tissues and thus quantitate normal tissue tolerances;²⁴ and 3) the ability to develop new treatment approaches involving non-coplanar fields in order to escalate dose in an attempt to increase local tumor control while minimizing normal tissue complications.⁵⁴

Clinical experience has shown that there are significant differences in tumor coverage when blocking is designed using a 3D planning system as opposed to conventional simulator approach. In a study by Vijayakumar et al.⁶⁴ the authors utilized a relatively limited 3D planning technique, namely using beam's eye view for treating 14 patients with non-small cell lung cancer. They have shown that there is significant improvement in tumor coverage and sparing normal tissue using beam's eye view technique as opposed to 2D technique.²⁵ In a study by Hodapp et al.²⁹ similar observations were made.

1.6 Use of Non-Coplanar Plans

One of the driving forces spurring the development of 3D treatment planning is the need for treatment techniques which allow more conformation of the high dose region to the target volume while minimizing normal tissue doses. Ten Haken et al.⁶¹ reported a comparison of various techniques used for external beam boost treatment for stage C prostate cancer. After devising a 6-field plan consisting of opposed lateral and 45° oblique fields, and the use of computer designed conformal blocks in all fields for use clinically, a comparison of 6-field technique to other boost technique was undertaken. Plans using various standard techniques, and the 6-field conformal plan consisting of opposed lateral and 45 oblique fields using computer designed conformal blocks in all fields, were generated for 27 consecutive patients. Full 3D calculations and dose volume histograms analysis were performed on all plans. The conformal 6-field plane was shown to be better than each of the other more traditional plans used for comparison. Studies by Emami et al.¹⁷ showed similar results.

Studies on 3D radiotherapy planning on lung cancer at the Radiation Oncology Center at Washington University, St. Louis was initiated in 1986 with participation in National Cancer Institute contract "Evaluation of High Energy Photon External Beam Treatment Planning".¹³ In these planning experiments the patients with advanced lung cancer were planned either two dimensionally with standard and/or traditional techniques as well as with 3D technology available at institutions involved in that contract.^{17,55} Results of that investigation revealed that 3D treatment planning has shown significant potential for

improving radiation treatment planning of lung cancer, both for tumor coverage and for sparing of normal tissue from high doses of radiation, and thus has shown the potential of being a significant step towards uncomplicated loco-regional control of lung cancer.

The Radiation Oncology Center of Washington University in St. Louis has compared traditional beam arrangements (*as routinely practiced in their clinic*) and 3D conformal treatment plans in 10 patients with advanced bronchogenic carcinoma using full 3D technology. Evaluations were done using dose volume histograms (*DVH*), dose statistics, dose surfaces and evaluation program developed through NCI contract. Analysis confirms an earlier observation that the 3D technology has produced better delineation of target volumes, better coverage of target volumes by the prescribed dose and significantly improved protection of the critical structures from high doses of radiation therapy. It has also allowed them to plan treatment doses to up to 80 Gy while maintaining acceptable expected tissue tolerance. It was also found that commonly used beam arrangements for the treatment of non-small cell lung cancer were inadequate to safely deliver tumor doses of greater than 70 Gy. Three-dimensional conformal treatment plans with multiple beam arrangements to a large volume allowed dose to a smaller volume or (*gross tumor*) to be escalated to at least 80 Gy while maintaining acceptable or improved doses to the normal surrounding tissues. The main dose limiting structure for tumors of the lung is the surrounding lung tissue. While this tissue has a very low threshold dose for injury (*approximately 20 Gy with conventional fractionation*), the volume of normal lung tissue that can receive this dose, particularly in diseased lungs, remains unanswered. Preliminary data from Memorial Sloan Kettering published by Armstrong et al.¹ reported on 18 patients with non-small cell lung cancer treated with 3D technology. In this small series they did experience one grade 3 and one grade 5 pulmonary toxicity. The lung volume most correlated with these higher grade pulmonary toxicities were 49% of the lung volume receiving > 25 Gy. Martel et al.³⁷ from the University of Michigan have also reported on mean lung doses to 42 lung cancer patients who were divided into groups that did or did not have pulmonary complications. She reported that an average mean dose of 35 Gy to the ipsilateral lung was most correlated with the incidence of complications. Early results from early evaluations of 25 patients treated with 3D technology at the Radiation Oncology Center at Washington University have also been able to correlate the incidence and grade of pneumonitis with the radiation dose to a given percent volume of lung. When 60% of the ipsilateral lung exceeded 35 Gy, or 50% of the total lung volume exceeded 20 Gy, the incidence of grade 3-5 pneumonitis was increased.²⁶ The incidence of pneumonitis was also correlated with mean lung doses.

From the University of Michigan have evaluated normal tissue, patient probability model and dose volume histogram reduction scheme in the design and implementation of dose escalation protocols for both lung and liver tumors. The histogram reduction method of Kutcher and Burman³² allows one to generate a single step dose volume histogram from the 3D dose distributions using the effective volume (*V_{effective}*) reduction scheme. Using this, Dr. Ten Haken and his colleagues at the University of Michigan have developed and implemented a dose escalation protocol stratifying patients based on their effective volume (*V_{effective}*) as a parameter to assess the risk of the development of pneumonitis after treatment.⁶² While this protocol has escalated patients up to at least 90 Gy (*and it is expected to go even higher*) the development of pneumonitis has been low and acceptable.³⁸

As we contemplate escalating the dose delivered to patients in a cooperative group setting, there is concern that patients with large tumors or large volumes of their ipsilateral lungs being escalated may not tolerate dose escalation whereas those with smaller tumors or those in portions of the lung where volumes of the lung are not necessary to irradiate may benefit from dose escalation. Thus, in an attempt to identify what would be the best way to stratify patients for their risk of development of pneumonitis a study was done at Washington University whereby various parameters were evaluated to predict the development of pneumonitis. Graham et al. evaluated 70 patients who had been treated with three dimensional treatment planning and looked at stratifying the patients for the development of pneumonitis by the cubic volume of the gross tumor (*GTV in cc*), the mean ipsilateral lung dose (*n Gy*), the percentage of the ipsilateral lung receiving greater than 20 Gy, the percentage of the total lung volume receiving greater than 20 Gy and the effective volume (*V_{effective}*). The data for the development of > grade II and > grade III incidence of pneumonitis in the 70 patients is charted in Table 1.

TABLE 1A (6/3/96)
INCIDENT OF PNEUMONITIS
≥ GRADE 2

QUARTILE (by rank order of patients)	GTV (cc) (%)	MEAN DOSE (Gy) (%)	% OF IPSI LATERAL LUNG RECEIVING > 20 Gy (%)	% OF TOTAL LUNG RECEIVING > 20 Gy (%)	V _{eff} (%)
1st	32	20	7	8	0
2nd	12	21	10	23	23
3rd	27	25	38	29	25
4th	27	29	42	33	45

TABLE 1B (6/3/96)
INCIDENT OF PNEUMONITIS
≥ GRADE 3

QUARTILE (by rank order of patients)	GTV (cc) (%)	MEAN DOSE (Gy) (%)	% OF IPSI LATERAL LUNG RECEIVING > 20 Gy (%)	% OF TOTAL LUNG RECEIVING > 20 Gy (%)	V _{eff} (%)
1st	11	10	7	8	0
2nd	6	11	0	0	5
3rd	13	8	21	19	14
4th	20	24	25	27	36

Review of this table reveals that stratifying patients by GTV or mean dose to the ipsilateral lung fail to adequately stratify the patients for the development of pneumonitis. However, a percent volume of either the ipsilateral or total lung volumes or the effective volume appear to equally stratify the patients according to risk. The percent volume of the total lung exceeding 20 Gy in the development of ≥ grade II pneumonitis was almost as good as stratifying by the V_{effective} for either grade II or III ≥ grade II or III pneumonitis. The skill and technology of various institutions in being able to calculate a V_{effective} was thought to be variable in the institutions that are expected to participate in this protocol. It was thought that an easier parameter for the involved institutions whereby to stratify for risk would be the percentage of either ipsilateral or total lung receiving a threshold dose of 20 Gy. Thus, this protocol has been designed to stratify the patients for the dose escalation based on the percentage of the total lung receiving greater than 20 Gy. This will require that patients have completed their three dimensional plans prior to entering on this study in order to be able to put them into the proper bin or level for dose escalation.

2.0 OBJECTIVES

- 2.1 The primary endpoint of this study will be treatment related morbidity. Tumor response, local-regional control, and survival will be followed as they relate to standard patient management, but these parameters do not represent primary endpoints for this phase I/II study.
- 2.2 To establish the maximum tolerable dose of radiation that can be delivered to patients with non-small cell lung cancer using three dimensional conformal radiation therapy (3D-CRT) techniques. The data derived from this study will be used in future phase III 3D-CRT protocols.
- 2.3 To evaluate the morbidity of high dose 3D-CRT in carcinoma of the lung.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (6/3/96)

- 3.1.1 Patients with histologically-proven, by biopsy or cytology, unresected lung cancer of the following histologic types:
 - Squamous cell carcinoma

- Adenocarcinoma
 - Undifferentiated large cell carcinoma
 - Nonsmall cell; not otherwise specified (*NOS, diagnosis on cytology alone*)
- 3.1.2 Patients with AJC Stage I-III (*Appendix III*) if all detectable tumor can be encompassed by radiation therapy fields, including both the primary tumor and the involved regional lymph nodes. Patients with positive supraclavicular lymph nodes (*N3*) are not eligible.
- 3.1.3 Age \geq 18.
- 3.1.4 Karnofsky performance status \geq 70. (*See Appendix II*).
- 3.1.5 Patients must have measurable disease on the 3D planning CT.
- 3.1.6 Patients must sign a study-specific informed consent form. (*See Appendix I*).
- 3.1.7 If the patient received chemotherapy prior to this radiotherapy, the prechemotherapy CT must be available for review.
- 3.1.8 Patients should not be eligible for RTOG phase III protocols for which they may be potential candidates.
- 3.2 Ineligibility Criteria (6/3/96, 4/28/97)**
- 3.2.1 Undifferentiated small cell (*oat cell*) carcinoma, any stage.
- 3.2.2 Stage IV.
- 3.2.3 Complete tumor resection, recurrent disease, or those patients eligible for definitive surgery.
- 3.2.4 Karnofsky Performance status < 70 scale
- 3.2.5 Patients < 18.
- 3.2.6 Prior or concurrent malignancy except non-melanomatous skin cancer unless disease-free for five years or more.
- 3.2.7 Prior radiotherapy to the thorax.
- 3.2.8 Concurrent chemotherapy or previous biologic response modifiers. Patients may have received prior cisplatin, velban VP-16, Taxol, carboplatin, or Navelbine chemotherapy for the current lung cancer but chemotherapy must have been delivered within 4 months prior to the planned radiotherapy and hematologic recovery has occurred. Patients may not have received bleomycin, mitomycin, adriamycin or cytoxan within 6 months of the current course of radiotherapy.
- 3.2.9 Distant metastases or supraclavicular lymph node involvement, or massive atelectasis.
- 3.2.10 Patients who have not had the pre-treatment evaluations in Section 4.0.
- 3.2.11 Pleural effusion with positive cytology is excluded.
- 3.2.11.1 Other pleural effusions are eligible only: a) if when present before medianoscopy or exploratory thoracotomy, must be a transudate with negative cytology on two separate thoracenteses. b) if present only after preregistration, exploratory or staging thoracotomy, but not before, may either transudate or exudate with negative cytology on a single thoracentesis; and c) if a pleural effusion is present only on the CT and not the chest x-ray and it is deemed too small to tap under either CT or ultrasound guidance, then this must be clearly documented on the data forms and the patient is eligible.
- 3.2.12 Patients with either pericardial effusions or superior vena cava syndrome are ineligible.
- 3.2.13 Patients who have had complete radiographic response to chemotherapy are not eligible.

4.0 EVALUATIONS (4/28/97)

- 4.1 All lab tests and radiographic studies should be done within 6 weeks prior to registration. The only exception to this would be for patients receiving pre-radiation chemo who have been evaluated by the treating radiation oncologist prior to the initiation of chemo and who have had their 3D scan prior to the initiation of chemo. These patients should have at minimum a chest x-ray to evaluate progression of disease prior to the initiation of radiation treatment but do not require repeating all the evaluations in Section 4.0 if they already had these prior to chemo treatment.
- 4.1.1 Complete history, physical examination, and evaluation of Karnofsky Performance Status.
- 4.1.2 Pathological (*biopsy*) or cytological proven non-small cell lung cancer.
- 4.1.3 CT with contrast of chest and upper abdominal to include the liver and adrenals.
- 4.1.4 Chest X-ray.
- 4.1.5 Bone scan (*if \approx bone pain and/or elevated alkaline phosphatase*).
- 4.1.6 Pulmonary function tests - FEV₁, lung volumes, DLCO.
- 4.1.7 Completed baseline dyspea index (*see Appendix VI*)
- 4.1.8 If the patient received chemotherapy prior to this radiotherapy, the prechemotherapy CT must be available for review.

5.0 REGISTRATION PROCEDURES

- 5.1** Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in Appendix VII (*3D Conformal Radiation Therapy Quality Assurance Guidelines for RTOG 93-11*) may enter patients to this study. The 3D questionnaire (*one per institution, Appendix IX*) is to be sent to the Washington University (WU) 3D Quality Assurance (QA) Center for review prior to entering any cases. Upon review and successful completion of "Dry-Run" QA test (*See Appendix VII*), the WU 3D QA Center will notify both the registering institution and RTOG Headquarters that the institution is eligible to enter patients onto this study.
- 5.2** Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:
- Institution Name & Number
 - Patient's Name & ID Number
 - Verifying Physician's Name
 - Eligibility Criteria Information
 - Demographic Data
 - Treatment Start Date
 - Stratification Group
- 5.3** After the patient is registered to a treatment arm, RTOG will notify the WU 3D QA Center (*by FAX*) providing the following information:
- Case Number
 - Institution Name
 - Institution Number
 - Date of Registration
 - Treatment Option
 - Stratification Group
- 5.4** After the patient is registered to a treatment arm, the institution will submit the required data (*both hardcopy and digital*) to the WU 3D QA Center (*See Section 12.2*) and to the RTOG. (*See Section 12.1*).

6.0 RADIATION THERAPY

6.1 Dose Specifications

- 6.1.1** The prescription dose will be specified at the ICRU50 reference point which is defined in Section 6.4.3. Note, this point will usually be the isocenter (*intersection of the beams*). The isodose curve representing 93% of the prescription dose must encompass the entire planning target volume (PTV) which is defined in Section 6.4.2.
- 6.1.2** The daily prescription dose will be 2.15 Gy at the ICRU reference point. 2.0 Gy (*which corresponds to the 93% isodose curve*) is to be delivered to the periphery of the PTV.
- 6.1.3** The prescription dose to PTV (*Section 6.4.2*) shall be according to the following dose escalation schema:

Group 1

If the total lung volume that exceeds 20 Gy is less than 25% of the total lung volume, then the total prescription dose at the ICRU reference point will be escalated as follows:

- Dose Level 1: 70.9 Gy/33 fx/7-8 wks
- Dose Level 2: 77.4 Gy/36 fx/7-8 wks
- Dose Level 3: 83.8 Gy/39 fx/8-9 wks
- Dose Level 4: 90.3 Gy/42 fx/9-10 wks

(only one of these dose levels will be open at any one time)

Group 2 (2/1/96)

If the total lung volume that exceeds 20 Gy is > 25% but < 37% of the total lung volume, then the total prescription dose at the ICRU reference point will be escalated as follows:

- Dose Level 5: 70.9 Gy/ 33 fx/7-8 wks
- Dose Level 6: 77.4 Gy/36 fx/7-8 wks
- Dose Level 7: 83.8 Gy/39 fx/8-9 wks

(only one of these dose levels will be open at any one time)

Group 3

If the total lung volume that exceeds 20 Gy is > 37% of the total lung volume, then the total prescription dose at the ICRU reference point will be escalated as follows:

Dose Level 8: 64.5 Gy/30 fx/6-7 wks

Dose Level 9: 70.9 Gy/33 fx/7-8 wks

Dose Level 10: 77.4 Gy/36 fx/7-8 wks

(only one of these dose levels will be open at any one time)

6.1.4 The reported doses shall include the dose to the ICRU Reference Point. The maximum point dose, minimum point dose, and mean dose to PTV will also be reported.

6.1.5 The method used for tissue heterogeneity calculations shall be reported. Both uncorrected and corrected dose distributions shall be calculated and submitted to the RTOG 3D QA Center. Dose escalation is to be based on the **uncorrected** dose distribution.

6.1.6 If a patient has $\leq 25\%$ of their total lung volume exceeding 20 Gy when planned to any of the dose levels in Group 2 (*whichever is currently open*), an attempt to increase the dose and place them in Group 1 should be done. However, if this increases their total lung volume to $> 25\%$ exceeding 20 Gy, they should remain in Group 2 at the level currently open. **(2/1/96)**

6.2 External Beam Equipment

6.2.1 Megavoltage equipment is required with effective photon energies ≥ 6 MV.

6.2.2 3-D conformal radiotherapy capabilities is required as defined and confirmed by the QA Center. See Appendix VII for 3D Quality Assurance Guidelines.

6.3 Treatment Planning Imaging and Localization Requirements (6/3/96)

6.3.1 A volumetric treatment planning CT study will be required to define *gross tumor volumes (GTV)*, and *planning target volume (PTV)*. For this study, GTV will be equal to the clinical target volume (*CTV*) (*Appendix VII*). Each patient will be positioned in an individualized immobilization device in the treatment position on a flat table. Contiguous CT slices, 3-5 mm thickness of the regions harboring gross tumor and grossly enlarged nodes and 8-10 mm thickness of the remaining regions are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the liver. The GTV, and PTV and normal organs will be outlined on all appropriate CT slices and displayed using beam's eye view. Normal tissues to be contoured include both lungs, both brachial plexus, skin, heart, spinal cord, esophagus and liver. A measurement scale for the CT image shall be included.

6.3.2 IV contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessel. If not, i.v. contrast should be given during the planning CT.

6.3.3 Optimal immobilization is critical for this protocol. Alpha cradle or approved alternate immobilization system is required. Alternate immobilization systems must be approved by the protocol chairman.

6.4 Volume and ICRU Reference Point Definitions

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.³⁰

6.4.1 Gross Tumor Volume (GTV) is defined by the physician as all known gross disease as defined by the planning CT and clinical information. Gross tumor includes the primary tumor (*GTV-P*) and abnormally enlarged regional lymph nodes > 1.0 cm (*short axis measurement*) (*GTV-N*).^{23,41} These volume(s) may be disjoint. Note ICRU Report #50 also defines a clinical target volume (*CTV*) which includes the area of subclinical involvement around the GTV. For this protocol, we have chosen to define the CTV as equal to the GTV.

6.4.2 Planning Target Volumes (PTV) will provide margin around the GTV to compensate for variabilities in treatment setup, breathing, or motion during treatment. The PTV for which dose escalation will be occurring must include GTV-P and the GTV-N for all cases. A margin around the GTV will define the PTV. The PTV volume must include a minimum of 10 mm around the GTV. More margin may be necessary if the tumor movement is increased because of physiologic movement which should be checked by fluoroscopy. **(2/1/96)**

6.4.3 The ICRU Reference Point is to be located in the central part of PTV. Typically this point should be located on the beam axis or at the intersection of the beam axis (*isocenter*).

6.5 3D Planning

6.5.1 Planning Volume (PTV) - The PTV is to be treated with any combination of coplanar or noncoplanar three-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of the volumetric dose including DVH analyses of the PTV and critical normal structures. **(2/1/96)**

6.6 Normal Tissue Volume and Tolerances

6.6.1 The normal tissues in the table below are to be contoured in their entirety.

6.6.2 The following organs and doses by volume are guidelines for the 3-dimensional treatment plan. Physician/dosimetrist should make every effort not to exceed these tolerance levels. All normal tissues assume treatment at 2 Gy/fx (uncorrected).

Table 2 (6/3/96)

ORGAN	VOLUME	TOLERANCE DOSE TD 5/5	END POINT
Lung (<i>See Table 2</i>)	(<i>Table 1</i>)	(<i>Table 1</i>)	Clinical Pneumonitis
Esophagus	1/3	65 Gy	Clinical Stricture and Perforation
	2/3	58 Gy	
	3/3	55 Gy	
Brachial Plexus	point dose	60 Gy	Clinically Manifested Nerve Damage
Spinal Cord	5 cm	50 Gy	Myelitis
	10 cm	50 Gy	Myelitis
	20 cm	47 Gy	Myelitis
Heart	1/3	66 Gy	Clinical Pericarditis
	2/3	50 Gy	Clinical Pericarditis
	3/3	40 Gy	Clinical Pericarditis
Liver	1/2	35 Gy	Clinical Hepatitis
	2/2	30 Gy	Clinical Hepatitis

6.6.3 It is expected that the dose to the lungs will be the primary dose-limiting structure. Every effort to keep the total lung dose to a minimum should be performed. Since most lung tumors are localized to one lung, efforts to keep the contralateral lung at a minimum should also be performed. The patient's overall lung function is evaluated by the FEV₁ and DLCO should also be evaluated in determining an individual's lung function reserve and thus the ability to radiate.

6.6.4 When planning the beam arrangement to the PTV, the heart, esophagus and spinal cord should be out of the field to the extent possible. The dose per fraction to the lungs, heart, esophagus and spinal cord should be maintained at 2 Gy or less per fraction to the extent possible. If tolerance dose to any of the normal organs is exceeded, alternate beam arrangements should be used.

6.6.5 **Total lung volume is defined as the lung volume of both lungs minus the PTV.**

6.7 **Treatment Verification**

6.7.1 First day port films or portal images of each field must be obtained and sent to the Quality Assurance Center. Twice weekly (*at least 48 hours apart*) verification films or images of orthogonal views (*anterior to posterior and lateral projection*) must be reviewed by the treating physician. The required accuracy of patient positioning and the use of multi-leaf collimator apertures suggests the daily use of on-line imaging may be desirable.

6.8 **Quality Assurance of Target Volumes and Critical Structure Volumes**

6.8.1 The 3D QA Center will review PTV, GTV and designated critical structures on, as a minimum, the first five cases submitted by each institution. After an institution has demonstrated compliance with protocol, future cases will be spot checked only.

6.8.2 Each treatment shall be judged as documented in Quality Assurance Guidelines (*Appendix VII*).

6.9 **Quality Assurance of Field Placement**

The 3D QA Center will review the first placement films.

6.10 **Quality Assurance of Dose Distribution**

6.10.1 The 3D QA Center will display, and compare with hard copies, isodose distributions for the axial, sagittal, and coronal planes through the planning target volume.

6.10.2 The 3D QA Center will display, and compare with hard copies, dose-volume histograms for the PTV, designated critical structures, and unspecified tissues.

6.10.3 Each treatment shall be judged as documented in Quality Assurance Guidelines (*Appendix VII*).

6.10.4 **Dose Heterogeneity**

Maximum dose to PTV should not exceed the prescription dose by >7%. The maximum point dose to critical normal structures outside the PTV including the unspecified tissue should not exceed the prescription dose. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

6.11 RTOG 3D-CRT Summary of 1993 ICRU Report on Recommendations for Prescribing, Recording, and Reporting External Beam Radiation Therapy

- 6.11.1 Complete descriptions of volumes to be treated have been included in the 3D-CRT protocols in order to minimize the institutional variation of tumor and target volume delineation for protocol cases. Please consult the ICRU 1993 document for complete descriptions of the various target volumes defined. The next paragraphs summarize the ICRU definitions which are relevant for this protocol (*see Appendix VIII for diagrams*).
- 6.11.2 The gross tumor volume (*GTV*) includes the known disease as determined by physical examination, imaging studies and other diagnostic information. More than one *GTV* can be defined (*i.e. GTV-P or GTV-N*).
- 6.11.3 The clinical target volume (*CTV*) includes the area of subclinical involvement around the *GTV*. The *CTV* is the *GTV* plus the margin for micro extensions of the tumor. More than one *CTV* can be defined. For this protocol *CTV* = *GTV*.
- 6.11.4 The planning target volume (*PTV*) is the *CTV* plus a margin to ensure that the prescribed dose is actually delivered to the *GTV*. This margin accounts for variations in treatment delivery, including variations in set-up between treatments, patient motion during treatment, movement of the tissues which contain the *GTV* (*e.g. respiration*), and size variations in the tissue containing the *GTV*. The *PTV* is a geometric concept.

6.12 Criteria for Toxicity

- 6.12.1 Acute and late toxicity related to radiation therapy includes fatigue, myelosuppression, skin erythema, subcutaneous fibrosis, esophagitis, carditis, myelitis, acute radiation pneumonitis and late pulmonary fibrosis, and esophageal stricture.
- 6.12.2 Acute toxicity monitoring: Acute (≤ 90 days from *RT* start) side effects of radiation therapy will be documented using the RTOG Acute Radiation Morbidity Scoring Criteria (*Appendix IV*).
- 6.12.3 Late toxicity monitoring: Late (> 90 days since *RT* start or persisting beyond 90 days) post-treatment complications will be evaluated and graded according to the RTOG Late Radiation Morbidity Scoring Scale (*Appendix IV*).
- 6.12.4 All fatal toxicities (*grade 5*) resulting from protocol treatment must be reported by telephone to the Group Chairman, to ACR Headquarters Data Management and to the Study Chairman within 24 hours of discovery.
- 6.12.5 All life-threatening (*grade 4*) toxicities from protocol treatment must be reported by telephone to Group Chairman, ACR Headquarters Data Management Staff and to the Study Chairman within 24 hours of discovery.
- 6.12.6 Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report (*FAX # 215/928-0153*).

7.0 DRUG THERAPY

Does not apply to this study.

8.0 SURGERY

Does not apply to this study.

9.0 OTHER THERAPY

Does not apply to this study.

10.0 PATHOLOGY

Does not apply to this study.

11.0 PATIENT ASSESSMENTS

11.1 Parameters (4/28/97)

Assessments	Pre Tx	Weekly During RT	4 wks	3 mos	6 mos	9 mos	12 mos	16 mos	20 mos	24 mos & per Sec 12.0
History & Phys. and Karnofsky	X	X	X	X	X	X	X	X	X	X
PFT's	X				X		X			

Bronchoscopy	X ^c			X ^c						
CXR	X		X		X		X			X ^a
CT Scan ^b	X				X		X			X ^a
Morbidity Evaluation		X	X	X	X	X	X	X	X	X
Dyspnea Score Index	X		X	X	X	X	X			X ^a

- a. then yearly
- b. thoracic/upper abdominal
- c. not required for biopsy-proven disease; however, if patient was initially diagnosed by bronchoscopy and had visible tumor, it is strongly encouraged they have a 3 month-post treatment bronchoscopy.

11.2 Control

11.2.1 The patient will be considered to be in local control if the CT scan does not show progression of local tumor. Length of survival with or without local-regional recurrence or distant metastasis will be recorded.

11.3 Evaluation and Follow-up

11.3.1 Evaluation during treatment

11.3.1.1 Patients will be seen and evaluated at least weekly during radiation therapy with documentation of tolerance, including acute reactions and weight.

11.3.2 Evaluation following treatment

11.3.2.1 At each visit the patient will have an interval history, complete physical examination and assessment of Karnofsky performance status.

11.3.2.2 Patients will be evaluated every 3 months for the first year, every 4 months in the second year, every six months for the next 3 years, and yearly thereafter.

11.3.2.3 A chest CT at 6 and 12 months

11.3.2.4 Pulmonary function tests at 6 and 12 month follow-up visits.

11.3.2.5 Interim Dyspnea Index scoring 8 weeks and at 3, 6, 9, 12, months then at yearly follow-up visits. Grade 4 complications will continue to be considered unacceptable.

12.0 DATA COLLECTION

12.1 Summary of Data Submission RTOG

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

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 1 week of study entry
Initial Evaluation Form (I1) Diagnostic Pathology Report (P1)	Within 2 weeks of study entry
Radiotherapy Form (T1) <i>(copy, original to WU per Section 12.2)</i>	Within 1 week of end of RT
Follow-up Form (F1) start for 1 year; q 4 months x 1 then	Every 3 months from treatment year, q 6 months x 3 years, annually. Also at progression/ relapse and at death
Autopsy Report (D3)	As applicable

12.2 Summary of RT QA Requirements (Washington University)

Preliminary Dosimetry Information: Within 1 week of start of RT
 Digital Patient Submission Information Form (T2)
 CT data, critical normal structures, all GTV/CTV
 and PTV contours
 Films and/or digital film images for simulation,

first day portals, and one orthogonal set-up pair (*as required*)
Digital dose data and beam geometry data for all beam sets is required
Hard copy isodose distributions as defined in QA Guidelines
Digital DVH data

Final Dosimetry Information: Within 1 week of RT end
Radiotherapy Form (T1)
Daily Treatment Record

12.2.1 For Mail or Federal Express:

James A. Purdy, Ph.D.
RTOG 3D QA Center
Washington University School of Medicine
510 S. Kingshighway
St. Louis, MO 63110
tel. 314/362-2631 Fax# 314/362-2682

12.2.2 To send over Internet or using magnetic tape:

Digital data submission may be accomplished using magnetic tape or the Internet. For network submission, the ftp account assigned to the submitting institution shall be used and e-mail identifying the data set(s) being submitted shall be sent to:

rtog3dqa@ castor.wustl.edu

For tape submission, please contact the 3D QA Center about acceptable tape types and formats.

12.3 **Timely Data Submission for Toxicity Evaluation**

Timely data submission is critical in order to meet the study's objectives for toxicity evaluation and to safety assign treatment levels.

13.0 **STATISTICAL CONSIDERATIONS (2/1/96, 6/3/96)**

13.1 **Study Endpoint**

The frequency of patients developing unacceptable (Grade 3 or higher) acute toxicities attributable to radiotherapy. Acute radiotherapy toxicities are defined as those toxicities which occur within 90 days from the start of radiotherapy. The Phase II portion of this study will monitor the combined acute/late morbidity rate.

13.2 **Sample Size**

In order to establish the maximum tolerated dose (MTD) of radiotherapy that can be delivered using three-dimensional conformal radiation treatment (3D-CRT), acceptable morbidity criteria must be defined. A 15% Grade 3 or Grade 4 toxicity (non-hematologic) rate is determined to be dose limiting, a Grade 5 toxicity will suspend accrual until the Study Chair reviews the case.

In this study, there are three separate groups determined by the amount of lung treated. The groups are: Group 1, < 25% of total lung treated; Group 2, 25% - 37% of total lung treated; and, Group 3, > 37% of total lung treated.

Each institution must be approved by the QA Center before they can begin accrual. This approval will consist of a submission of a "dry run", i.e., the demonstration of correct data exchange and the successful planning for one patient at the lowest dose level in that patient's registered group. When the QA Center has approved the institution, the Center will notify the Study Chair, Protocol Administrator, and Study Statistician in writing. A more detailed description of these procedures are provided within the QA Guidelines Section of this protocol.

When an institution is approved by the QA Center, that institution will be able to begin accruing to the highest available dose levels within the three groups, as described below.

Within each separate group (Group 1, 2, and 3), the dose escalation will be determined as follows: Initially, 15 evaluable patients will be accrued to the current dose level. If no Grade 3 or Grade 4 non-hematologic toxicities are observed within 90 days from the start of radiotherapy, then the dose will be escalated to the next dose level. This will provide at least 90% confidence (0/15) that the true toxicity rate is less than 15%. However, if one Grade 3 or Grade 4 non-hematologic toxicity is observed, then an additional evaluable 10 patients will be accrued. If no further Grade 3 or Grade 4 non-hematologic toxicities are observed, then the dose will be escalated to the next dose level. This will provide at least 90% confidence (1/25) that the true morbidity rate is less than 15%. If 2 or more Grade 3 or Grade 4 non-hematologic toxicities are observed in the first 25 patients, then this dose will be deemed too toxic. This design has 73% power if the true toxicity rate is < 10%. If at any time a Grade 5 toxicity is observed, then accrual will be suspended and the event will be reviewed by the Study Chair.

In order to facilitate accrual of data on the last patient prior to escalation, each dose arm will be permitted to accrue, at most, an additional 11 patients; therefore, each dose level will accrue between 15 to 36 patients

13.3 Patient Accrual

The patient accrual is projected to be 8 cases per month; however, since there are three separate groups, this translates to approximately 3 patients per month per group. At this rate, it will take a minimum of 5 months and a maximum of 12 months to accrue enough patients to determine each dose level for each group. If the average monthly accrual rate is less than three patients per group, the study will be re-evaluated with respect to feasibility.

13.4 Dose Escalation (6/3/96)

After 15 evaluable patients (*based on QA review of the treatment plan and treatment delivery*) have been followed for a minimum of 90 days from the start of radiotherapy, the current dose arm will be carefully evaluated with respect to treatment morbidity. If no Grade 3 or Grade 4 non-hematologic toxicities were observed, then the radiotherapy dose will be escalated. If one Grade 3 or Grade 4 non-hematologic toxicity is observed, then an additional 10 evaluable patients will be accrued. A total of 25 evaluable cases will then be analyzed for non-hematologic toxicity, and if there is less than two Grade 3 or Grade 4 non-hematologic toxicities observed, then the dose will be escalated to the next level. If at any time a Grade 5 toxicity is observed, then accrual will be suspended and the event will be reviewed by the Study Chair.

While the Phase I portion of this study is the determination of dose-limiting acute toxicities, combined acute/late toxicities will also be monitored. If the cumulative incidence, at any time, of combined acute/late toxicity estimates the rate to be greater than 15% of any level within a group, then the Executive Committee will be notified and the committee will determine whether that arm should be closed.

When a patient is entered by an institution to be approved by the QA Center and the current dose level for that group is at the lowest dose, then that patient will be used in determining the dose escalation as described above. Otherwise, the patient will be followed, but not used to determine dose escalation.

13.5 Analysis Plans

13.5.1 Interim Analyses

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

- a) the patient accrual rate with a projected completion date for the accrual phase;
- b) compliance rate of treatment delivery with respect to protocol prescription; and,
- c) the frequency and severity of the toxicities.
- d) the cumulative incidence of acute/late toxicities.

Any problems will be reported to the RTOG committee responsible for this study and, if necessary, the Executive Committee, so that corrective action can be taken.

13.5.2 Analysis for Reporting the Initial Treatment Results

This analysis will be undertaken when the MTD has been established for each group and each patient has been potentially followed for a minimum of 3 months following radiotherapy. The usual components of the analysis are:

- a) tabulation of all cases entered and any excluded from the analysis, with reasons for the exclusion;
- b) reporting institutional accrual;
- c) distribution of important prognostic baseline variables; and,
- d) observed results with respect to the endpoint described in Section 13.1. Further subgroup analyses will not be undertaken due to the small sample sizes.

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* **Added 6/3/96**

APPENDIX I

RTOG 93-11

**A PHASE I/II DOSE ESCALATION STUDY USING
THREE DIMENSIONAL CONFORMAL RADIATION THERAPY
IN PATIENTS WITH LOCALLY ADVANCED INOPERABLE,
NON-SMALL CELL LUNG CANCER**

Sample Patient Consent Form

RESEARCH STUDY

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

PURPOSE OF THE STUDY

I have a malignant tumor (*cancer*) in my lung. I may or may not have had surgery to remove most of the tumor. The Department of Radiation Oncology is involved in a study which delivers radiation therapy using a treatment planning technique called 3-dimensional conformal radiation therapy. This technique allows the radiation beam to treat an area shaped like my tumor and also as deeply as my tumor is located. By treating this way the dose of radiation to the healthy areas near my tumor are minimized and the dose to my tumor is maximized. This study will try to increase the amount of radiation to the tumor above what has been achievable using standard treatment planning techniques. I have been asked to participate in this study.

DESCRIPTION OF PROCEDURES (6/3/96)

I will be placed in the position in which I will be treated and will have treatment planning x-rays taken. I will be positioned in a special device while I am lying in the treatment position on a flat table. This ensures that I am treated in the exact same position every day that I have my radiation treatments. Either that same day or shortly thereafter, I will have a computed tomography (*CT*) scan for the three dimensional treatment planning that will be done when I am not in the hospital. I may also have an MRI scan for tumor localization as well.

I will receive my radiation treatments every day, Monday through Friday for six to eight weeks (*each treatment takes only a few minutes a day*). The dose of radiation I receive will depend on the size of my tumor and how many patients have entered the study before me. The first few patients entered on the study will receive a dose of radiation that previous research suggests will be safe. If they have no serious problems, the next patients will receive a higher dose. My doctor can tell me what dose I will receive before I make a decision about participating in the study. I may or may not receive chemotherapy prior to entering the study. This is determined by my treating physicians and does not affect the way radiotherapy is given.

I will have follow-up examinations in the Department of Radiation Oncology after finishing treatment. Follow-up examination will include periodic laboratory tests, x-rays, and scans. This schedule is similar to that of patients not participating in a research study, except that additional scans may be required.

RISKS AND DISCOMFORTS (6/3/96)

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

Risks from radiation: Radiation to the chest may cause redness, dryness or itching of my skin and hair loss within the treated area. It may cause pain or burning sensation with swallowing, loss of taste or appetite, fatigue, and weight loss. Rarely, it may cause tissue injury ("*necrosis*") in the area treated. Late developing effects may include some irritation of my lung called pneumonitis (*a pneumonia-like condition*) which could lead to fibrosis (*scarring*) of my lung. This could occur weeks to months after treatment and result in chronic shortness of breath and a cough. This could be potentially fatal. I may also have some fibrosis of my esophagus, which could cause it to become narrower and could result in difficulty swallowing. This may require stretching by inserting a tube in my esophagus. Radiation to the chest can cause damages to my heart or spinal cord; however, this is rare since these organs will be shielded during radiation therapy to reduce this risk.

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

It is unknown what effects this treatment may have on an unborn child. For this reason, I should practice effective birth control while on this study.

CONTACT PERSONS

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

BENEFITS (6/3/96)

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

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

ALTERNATIVES

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

My physician will explain any procedures related solely to research which would not otherwise be necessary. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

VOLUNTARY PARTICIPATION

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

CONFIDENTIALITY

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

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

Patient Signature (*or Legal Representative*)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

APPENDIX III

ANATOMICAL STAGING FOR LUNG CANCER (IUCC-AJCC, 1988)

TNM CATEGORIES (Note Definitions)

T-Primary Tumor

- TX** Tumor proven by the presence of malignant cells in broncho-pulmonary secretions but no visualized roentgenographically or bronchoscopically, or any tumor that cannot be assessed as 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 effusions.

Definitions

- T1** 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.
- T4** 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.

N-NODAL INVOLVEMENT

- 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

M0 No (known) distant metastasis

M1 Distant metastasis present - Specify Site(s)

STAGE GROUPING OF CARCINOMA OF THE LUNG

Occult Carcinoma	TX	N0	M0
Stage 0	TIS	Carcinoma in situ	
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T1	N1	M0
	T2	N1	M0
Stage IIIa T3	N0		M0
	T3	N1	M0
	T1-3	N2	M0
Stage IIIb Any T	N3		M0
	T4	Any N	M0
Stage IV Any T	Any N		M1

APPENDIX V

ADVERSE REACTION REPORTING GUIDELINES

A. General Guidelines

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3214). When telephone reporting is required, the Principal Investigator should have all relevant material available. See the specific protocol for criteria to grade the severity of the reaction.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone .
3. A written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to RTOG Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol. (FAX #215/928-0153)
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

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

6. The Principal Investigator, when participating in RTOG coordinated Intergroup studies is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. Radiation Toxicity Guidelines

1. All fatal toxicities (*grade 5*) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (*grade 4*) toxicities resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

APPENDIX VII

3-D CONFORMAL RADIATION THERAPY PROSTATE GROUP QUALITY ASSURANCE GUIDELINES

I. Purpose

To establish QA guidelines for the radiation oncologist, physicist, dosimetrist, technologist, and data manager pertaining to 3-D conformal radiation therapy (3-D CRT) Prostate Phase I, II and III studies.

II. Background

The report of the Collaborative Working Group on the Evaluation of Treatment Planning for External Photon Beam Radiotherapy published in the May 15, 1991 issue of the International Journal of Radiation Oncology, Biology, Physics (Vol 21, No 1) should be referred to for background information regarding 3-D treatment planning.

III. Technology Requirements and Baseline Physics Information

A. The following information must be submitted by each institution prior to enrolling patients in the protocols.

1. Treatment equipment: Documentation of linac model, energies to be used, and description of collimation to be used to define conformal fields, e.g. multileaf, cerrobend. Documentation of isocenter accuracy for gantry, collimator, and couch rotations.
2. Immobilization/repositioning system: Documentation of immobilization - repositioning system to be used. Submit copy of patient motion study (set-up uncertainty, organ movement).
3. Treatment verification system: Documentation of verification imaging system to be used, e.g., film, on-line imager.
4. Computer planning system: Documentation of 3-D RTP system to be used. To participate in Prostate 3-D CRT studies, the institution's 3-D RTP system must have the following capabilities:
 - a. CT data - system must be able to handle at least 40 axial CT slices.
 - b. Beam's-eye-view (BEV) display showing tumor and target volumes, critical structures, and beam aperture.
 - c. Calculate volumetric 3-D dose matrix for photon and electron beams. The minimum dose matrix size shall have a maximum dose point spacing of 3 mm or 10,000 points in axial planes (whichever has least number of dose points). The spacing between axial planes must be such that, at the minimum, a transverse distribution is computed for each axial slice.
 - d. Display and hardcopy of superimposed isodose distributions on 2D CT images (axial, saggital, and coronal planes).
 - e. Calculate dose-volume histograms (DVH) using dose-volume element sampling at least as fine as the dose calculation grid in axial planes and shall, at the minimum, use spacing in the orthogonal direction identical to the CT slice spacing. Display and hardcopy of dose-volume histograms (DVHs) according to format specified by 3-D CRT Group. (See example attached).
 - *f. Non-coplanar beams - system must provide capability of simulating each of the treatment machine motion functions including collimator length, width and angle, gantry angle, couch angle, and couch lateral, longitudinal and vertical position for both beam geometry definition and dose computation.

*g. Calculate and display digital reconstructed radiographs (DRRs) with superimposed target volume, critical structure contours and treatment aperture.

*recommended not required

5. Basic beam data: submit central axis dose ratios and dose profiles for 3 field sizes (small, medium and large), and corresponding isodose curves generated by 3-D RTP system for each beam modality and energy to be used. Submit three dose distributions (via tape exchange format) for a water phantom for a small, medium and large fields, for each beam modality and energy to be used.
6. Data transfer: Demonstrate capability of digital data exchange with the 3-D CRT QA Center. NCI 3-D RTP Contracts tape exchange format (expanded to include beam modality/geometry specification, fractionation, digital film images and dose-volume histograms) will be used and all data will conform to treatment protocol requirements and these Quality Assurance Guidelines.
 - a. Patient CT data
 - b. Contours - gross tumor volume (GTV), clinical target volumes (CTV), planning target volumes (PTV) and critical normal tissues.
 - c. 3-D dose distribution data
 - †d. Beam modality/geometry specification
 - †e. Digital sim/portal images
 - †f. Fractionation information
 - †g. Dose-volume histograms
- †To be added to NCI 3-D RTP Contracts Tape Exchange Specification in early 1994.
7. Physics QA:
 - a. A computer simulated phantom and dose distribution will be distributed to each institution which is to be input into the institution's 3-D RTP system and the dose-volume histogram generated. DVH hardcopies are to be submitted to the 3-D QA Center for validation.
 - b. A TLD dosimetry - treatment plan verification phantom will be sent to each institution. The phantom is to be scanned and the dose calculated for a defined protocol. The TLD dosimeters are then to be placed in the phantom and the phantom treated according to protocol. The data are to be submitted to the 3-D QA Center for validation.

IV. Protocol Data and Quality Assessment Parameters

- A. The following information is to be submitted for each protocol patient
 1. Hardcopy isodose distribution for the axial, saggital, and coronal planes through the planning target volume.
 - a. The 20, 50, 80, 95 percent and 100% (prescription) isodose lines and the maximum dose shall be included.
 - b. The above isodoses shall be superimposed over the treatment planning CT images.
 - c. A measurement scale for the CT image shall be included on the hardcopy.
 2. Hardcopy of DVHs for each PTV, each critical structure, and the unspecified tissue.

3. Dosimetry and imaging digital data.
 - †a. Volumetric CT data
 - †b. GTV, CTV, PTV and critical structure contours. (Must be contoured on all slices in which structure exists.
 - †c. Volumetric 3-D dose distribution data
 - †d. Beam modality, beam geometry and fractionation specifications
 - e. †DRR and, if possible, simulation verification radiograph
 - f. Portal radiograph or †on-line image, if possible
 - †g. DVH's

† To be submitted via NCI 3-D RTP Contracts Tape Exchange Specification

V. QA Review

A. Quality Assurance of Target Volumes and Critical Structure Volumes

The 3-D QA Center will review PTV, CTV, GTV and designated critical structures on, as a minimum, the first 5 cases submitted by each institution. After institution has demonstrated compliance with protocol, future cases will be spot checked only.

B. Quality Assurance of Field Placement

The 3-D QA Center will review initial placement films on, as a minimum, the first 5 cases submitted by each institution. At least one port film or pretreatment alignment film per field along with the digitally reconstructed radiograph from the treatment planning program or, alternatively, a simulation verification radiograph shall be submitted for evaluation. After institution has demonstrated compliance with protocol, future cases will be spot checked only.

C. Quality Assurance of Dose Distribution

1. The 3-D QA Center will display, and compare with hardcopies, isodose distribution for the axial, saggital, and coronal planes through the planning target volume.
2. The 3-D QA Center will display, and compare with hardcopies, dose-volume histograms for the PTV, designated critical structures, and unspecified tissue.

D. The following QA score will be assigned to each case:

1. No variation (total coverage): prescription isodose surface covers at least 100% of planning target volume.
2. Minor variation (marginal coverage): prescription isodose surface covers between $\geq 95\%$ to $<100\%$ of planning target volume.
3. Major variation (miss): prescription isodose surface covers less than 95% of the planning target volume.

E. Dose heterogeneity

1. The maximum dose within the PTV shall not exceed the prescription dose by greater than 7%.

APPENDIX VIII

Excerpts from ICRU-50

Fig. 2.2 Schematic illustration of the different volumes.

Gross Tumor Volume (GTV) denotes the demonstrated tumor.

Clinical Target Volume (CTV) denotes the demonstrated tumor (*when present*) and also volumes with suspected (*subclinical*) tumor (*e.g. margin around the GTV, and e.g. regional lymph nodes, N[*]/*, *considered to need treatment*). The CTV is thus a pure anatomic-clinical concept.

Planning Target Volume (PTV) consists of the CTV(s) and a margin to account for variations in size, shape, and the position relative to the treatment beam(s). The PTV is thus a geometrical concept, used to ensure that the CTV receives the prescribed dose, and it is (*like the patient/tissues concerned*) defined in relation to a fixed coordinate system. Note that in the example, the magnitude of foreseen movements of the CTV is different in different directions.

Treated Volume is the volume that receives a dose that is considered important for local cure or palliation.

Irradiated Volume is the volume that receives a dose that is considered important for normal tissue tolerance (*other than those specifically defined for organs at risk*).

*/= according to the TNM classification (*UICC 1987*).

Examples of Gross Tumor Volume (*GTV*), Clinical Target Volumes (*CTVs*), and Planning Target Volume (*CTVs*), and Planning Target Volume (*PTV*) for a patient with a bronchial carcinoma. T3 N0 M0 (*according to the TNM - classification [UICC 1987]*) of the right lung.

Fig. 2.3.a One frontal chest radiograph and one transverse CT-section at the level of the center of the demonstrated tumor are shown, and considered here to represent the true three-dimensional situation. Structures above and below the transverse section are projected into the section.

Fig.2.3.b The demonstrated tumor in the right hilar region extending into the lung tissue, but not involving the chest wall is the GTV and is shown by the striated area.

Fig. 2.3.c A margin is added around the GTV to include presumed local subclinical involvement around the demonstrable tumor, due to individual malignant cells, small cell clusters, or microextensions, which can not be detected clinically. This constitutes the CTV I, and is shown by the broken line.

Fig. 2.3.d There were no mediastinal lymph node metastases that could be demonstrated by clinical investigations. However, the mediastinal lymph nodes as well as the medial parts of the contralateral hilar region are considered to be at high risk, and to be treated for subclinical disease as CTV II, shown by the broken line.

Fig. 2.3.e The patient's condition did not allow for radical therapy, and the prescribed dose is the same (*and relatively low*) for both CTV I and CTV II. The two CTVs will be treated with the same beams, and are here shown joined.

Fig 2.3.f The geometrical relationship between the CTV and other relevant part of the patient on one hand and the treatment beam(s) on the other hand should be stable and not change during or between fractions. This relation should be correlated to a fixed coordinate system relative to a point in/at the patient (*e.g. the sternal notch*). However, in relation to the fixed coordinate system the CTV will move e.g. with respiration, and the patient as a whole will not be perfectly immobilized during each fraction.

Furthermore, there may be minor random variations in the set up (*positioning of the beams in relation to the fixed coordinate system, small variations in beam size and blockings, etc.*). Therefore treatment has to be planned for a larger volume than the CTV, and a suitable PTV (*indicated by the thick solid line*) is defined for treatment planning purpose and for dose recording and reporting. Note that in this example the PTV extends into healthy tissues (*the chest wall*).