



Gary Ernest Smith. *Fence Above Medical Springs*. Oil on canvas, 9" × 12".
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*Improvements in radiation therapy
planning and delivery for non-small-cell
cancer of the lung are reviewed.*

Image-Guided Conformal Radiation Therapy Planning and Delivery for Non-Small-Cell Lung Cancer

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Background: *Our understanding of both the importance of local control for survival of patients with unresectable lung cancer and the inadequacy of conventional radiation therapy (RT) to provide this local control has undergone marked changes in the past 2 decades.*

Methods: *A review was conducted of recent studies and meta-analyses in the literature that have convincingly demonstrated the value of thoracic irradiation in increasing long-term survival in patients with both small-cell lung cancer and non-small-cell lung cancer (NSCLC).*

Results: *Large cooperative trials have shown long-term local control of only approximately 10% for NSCLC using conventionally planned radiation to doses of 60-64 Gy either as a single modality or when preceded by induction chemotherapy. Concurrent chemotherapy may modestly improve local control at the cost of greater acute esophageal toxicity. Simple escalation of radiation dose is limited by the tolerance of normal intrathoracic organs. Recent developments in anatomic and functional imaging, computerized RT planning, and RT delivery, as well as a reassessment of the appropriate target volumes for RT in the context of combined modality therapy, provide the capability to better conform regions of high dose to the target volume and test the hypothesis that increases in tumor dose will improve local control and survival.*

Conclusions: *Encouraging phase II data have been reported from single institutions using individually developed software and hardware. The availability of commercial tools for planning and delivering such conformal treatment will allow prospective assessment of the true value of these technologies in the management of patients with lung cancer.*

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Introduction

In the United States, lung cancer causes more deaths than the next three cancer types combined. The past several decades have seen modest improvement in treatment outcomes for patients with locally advanced disease, largely through improved survival resulting from combining systemic chemotherapy with thoracic radiation. However, overall survival for patients with unresectable disease (primarily stage IIIA and IIIB) is only approximately 10% at 5 years. In addition to the appropriate emphasis on systemic adjuvant therapy for patients with apparently localized disease, there is increasing realization that local control is a prerequisite for long-term survival and that local control has not often been attained with conventional radiation therapy (RT). Several recent trials and meta-analyses have convincingly demonstrated the value of thoracic irradiation in increasing long-term survival in patients with both small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC).^{1,2}

Studies conducted in the 1970s by the Radiation Therapy Oncology Group (RTOG) compared various dose schedules and found a modest improvement in 2-year survival by increasing the dose from 40 Gy in 4 weeks to 60 Gy in 6 weeks, although long-term survival was not improved.³ The analysis of these trials reported “failure to observe local progression” as a surrogate for local control. With early death of patients from distant metastatic disease, often before local failure could manifest itself, as well as the difficulty in distinguishing between local persistence or recurrence and fibrosis, these figures were high, in the range of 50%. This led to a period of over-optimism about the effectiveness of RT

in NSCLC and the erroneous belief that all that was needed for therapeutic improvement was better systemic therapy.

Considering that the ability of RT to control local disease is a function of the local tumor bulk, it is not surprising that a dose of 60 Gy, which is appropriate in treating true vocal cord tumors measuring several millimeters, is insufficient for controlling a lung tumor measuring several centimeters and whose volume may be a thousand-fold greater. The TNM staging system does not explicitly include tumor volume and is thus not well suited for classifying tumors treated nonsurgically. Several recent studies have reported a clear correlation between tumor volume and treatment outcome (local control and survival) in patients treated with definitive RT or chemoradiotherapy.^{4,6} (Table 1 presents an explanation of planning volume terminology.)

Reassessment with more appropriate actuarial assessment of local control (as distinct from crude absence of local failure) has indicated that long-term local control has been less than 10% in NSCLC.^{7,8} Furthermore, several recent trials for patients with unresectable (predominantly stage IIIA/B) NSCLC have shown that, despite the predominantly distant pattern of relapse, more aggressive local treatment that improves local control can also produce significant and clinically meaningful improvements in survival. The European Organization for Research and Treatment of Cancer (EORTC) compared split-course RT as a single modality or combined with either daily or weekly cisplatin.⁹ The use of this concurrent radiosensitizing chemotherapy had no effect on the rate of development of distant metastases but significantly improved both local control and overall survival. Furuse et al¹⁰ have reported a randomized trial comparing sequential vs concurrent chemoradiation for patients with stage III NSCLC. The concurrent schedule resulted in better local control and overall survival but no significant difference in systemic relapse. A phase III RTOG trial similarly showed improved local control and median survival using concurrent rather than sequential administration or radiation and chemotherapy, although a third arm of the trial using twice-daily RT with concurrent chemotherapy had the best local control but not the best survival.¹¹ Saunders et al¹² conducted a prospective trial comparing conventionally fractionated RT with a continuous hyperfractionated accelerated RT (CHART) schedule that delivered 57.6 Gy in 36 fractions over 2.5 weeks. The accelerated regimen produced significantly improved both local control and overall survival.

While these studies support the concept that improvement in local control for patients with locally advanced NSCLC can lead to statistically significant and

Table 1. — ICRU Planning Volume Terminology

Acronym	Term	Meaning
GTV	Gross tumor volume	Macroscopic tumor volume as determined by clinical examination, surgical exploration, and imaging studies
CTV	Clinical target volume	GTV plus additional volume to account for possible microscopic spread of disease to regional lymph nodes, adjacent soft tissues, along fascial planes, etc, according to the natural history of the particular neoplasm
PTV	Planning target volume	CTV plus additional volume to account for variation in day-to-day setup, physiologic patient motion of tumor, and other positional uncertainties

ICRU = International Commission on Radiation Units and Measurements

clinically worthwhile improvements in survival, not all trials have confirmed this. One of the more striking discrepancies between improvement in local control and survival came in the Lung Cancer Study Group (LCSG) trial of adjuvant postoperative mediastinal RT for patients with resected stage II and III squamous cell carcinoma of the lung. The addition of postoperative mediastinal irradiation almost eliminated local recurrence as a first event from 20% in the control group to 1% in the treated group, but it had no significant effect on disease-free or overall survival.¹³ In a disease such as lung cancer, in which both distant metastases and intercurrent disease account for a large number of deaths, the correlation between local control and survival can be expected to be less strong than in diseases such as malignant gliomas or cancer of the head and neck, where local events dominate survival. Our efforts to improve the treatment of stage III NSCLC should focus on a search for mutually effective combinations of local and systemic treatment modalities rather than a competition between the two.

Escalation of Radiation Dose: Physical and Biological Effects

The poor local control achieved with doses of 60 to 64 Gy suggests dose escalation as one potentially useful strategy in treating lung cancer. With conventional approaches to treatment planning limited by the ability to define target volume and deliver treatment, the typical treatment plan for patients with stage III NSCLC involved treatment with opposed anterior and posterior beams to doses of 40 to 45 Gy followed by treatment with opposed oblique or lateral beams for an additional 20 to 25 Gy. Thus the total dose that can be delivered to the tumor is in the range of 65 Gy.

A simple increase in the dose by giving additional fractions (and increasing overall treatment time) has several potential disadvantages. First, there are major constraints on conventional dose escalation imposed by the tolerance doses of surrounding normal tissues. The situation is particularly difficult in that the typical lung tumor with mediastinal node metastases is in proximity to both parallel and serial normal tissues. While there are relatively absolute constraints to dose to the spinal cord (a serial organ with critical function), the lung clearly tolerates ablation of portions with relative impunity but shows marked volume dependence of toxicity. The esophagus occupies a more complex position in that acute toxicity (pain, mucositis) appears volume (length and circumference) dependent, while late strictures are more closely related to dose to any given segment, acting like a parallel organ for acute and a serial organ for late toxicity.¹⁴⁻¹⁶

Particularly, if the philosophy of electively treating the full mediastinum for patients with any N2 involvement is adopted, it rapidly becomes difficult to dose escalate while protecting normal organs. Secondly, there is increasing evidence that protraction of treatment time, either by breaks or by extending a continuous treatment course, is deleterious to local control.¹⁷ Increases in the proliferative rate of surviving tumor clonogens during a course of fractionated treatment offset gains potentially achieved from increasing the total dose. In this setting, more benefit would be obtained by shortening the overall treatment time. With conventional planning, such acceleration of treatment is invariably associated with an increase in acute toxicities, particularly mucositis, although late esophageal and other toxicities are not necessarily increased.¹²

In addition to inadequate dose, conventional RT of NSCLC has frequently failed to adequately cover the target volume. In a retrospective review of patients treated on the CALGB 8433 trial, Boxwala and Rosenman¹⁸ found that tumor was either missed or at the field edge in approximately one fourth of cases. Even in the absence of dose escalation, adequate coverage of gross disease should result in better local control and survival. Some further improvement in conventionally planned treatment may also come from a better understanding of tumor volume as seen on computed tomography (CT) scan and the anatomic extent of microscopic tumor infiltration of surrounding lung tissue. Giraud et al¹⁹ prospectively compared tumor extension as seen on CT and in resection specimens of patients with lung tumors. They found that the extent of microscopic infiltration varied by histology and was not necessarily encompassed by 1-cm margins around grossly visible disease.

Three-dimensional conformal RT (3D-CRT) should be considered a tool, or better as a set of tools, that can potentially allow us to deliver higher doses of RT to properly defined target volumes while sparing critical normal tissues. It is not an end in itself. The achievement of elegant isodose curves and dose-volume histograms without demonstration of clinical benefit (improved local control, reduced acute or late normal tissue toxicity, median or landmark survival) may be stimulating academic activity but does not necessarily constitute clinical progress. It is an interesting exercise to compare the parallels between CRT and high-dose chemotherapy with cytokine and stem cell support, both of which were initially introduced with vast enthusiasm and minimal data (Table 2). Demonstration of the overall validity of the physical techniques and biologic assumptions supporting the development and current implementation of 3D-CRT awaits the performance and mature analysis of randomized clinical trials

Table 2. — Comparison of High-Dose Chemotherapy and Conformal Radiation Therapy as Clinical Research Strategies

	High-Dose Chemotherapy	Conformal Radiation Therapy
Driving Hypothesis	Increase in drug dose, or dose density, leading to increased cell kill and possibly eradicating residual disease	Increase in tumor dose leading to improved local control and/or maintaining tumor dose; reduction in dose to normal tissues producing fewer acute and late complications
Enabling Technologies	Harvest and preservation of hematopoietic stem cells; development of recombinant hematopoietic cytokines; suppression of graft-vs-host disease in allotransplantation	Three dimensional anatomic and functional imaging; image fusion; 3D dose calculation; beam's-eye view display; dose-volume histogram display; multileaf collimators; computer-controlled linear accelerator gantry and couch movement; gating of treatment planning and delivery to respiratory cycle
Intermediate Endpoints	Response rate, molecular complete response rate, time to progression	Isodose distributions; maximal tumor dose for equivalent normal tissue complication probability; functional imaging by ¹⁸ F-fluorodeoxyglucose or annexin V binding
Clinical Benefits	Clear in some leukemias and lymphomas; not for metastatic breast cancer; possible as adjuvant for some patient with multiple positive node breast cancer	Probable in prostate and head and neck (improved normal tissue sparing); dose escalation trials in progress

that can test these, either in combination or one by one, against the current standards of practice.

Thus, the potential benefit of 3D treatment planning and delivery is improved coverage of the target volume with better protection of normal tissues. In a disease such as lung cancer, in which local control has historically been poor, the first effort will be to explore higher doses and/or accelerated fractionation while maintaining an acceptable level of acute and late complications. In other diseases where local control is satisfactory with current techniques, the benefits from conformal treatment may come more from a reduction in toxicity.

The current approach to 3D-CRT in NSCLC includes at least three distinct domains, each theoretically separate but often interdependent in their clinical application. These three domains include target delineation, choice of biologically relevant target, and dose-escalation.

Treatment Planning

The process of treatment planning begins with the choice of anatomic position the patient will assume during treatment. The appropriate choice is one that minimizes placement of normal tissues in the possible radiation beams, is reasonable comfortable for the patient, and is accurately reproducible on a day-to-day basis. Particularly for treatment using multiple radiation beams and requiring precise positioning, the use of a variety of immobilization devices is common. For lung, external plastic casts or vacuum-locked bags of Styrofoam beads are widely used. There is little uniformity, however, with regard to immobilization techniques, and relatively little research has been done to document their value.²¹⁻²⁶

After the patient has been positioned and immobilized, radiographic studies — almost always CT scans — are obtained with the patient in the treatment position. For lung tumors, scans are typically obtained every 4 or 5 mm through the target volume and every 8 to 10 mm throughout the remainder of the thorax. The administration of intravenous contrast during the planning CT is helpful in distinguishing mediastinal nodes from vessels, although it will perturb electron density measurements used in tissue inhomogeneity calculations. In addition to the anatomic information from CT, there is burgeoning interest in functional data from studies such as magnetic resonance imaging (MRI), positron emission tomographic (PET) scanning, or radiolabeled antibody imaging and technologies to fuse images obtained from multiple modalities.²⁷

Following the acquisition of this anatomic dataset, the physician, dosimetrist, or physicist must outline on each CT image the boundaries of tumor and normal organ volumes. While this process has been partially automated in distinguishing boundaries between structures with greatly differing CT Hounsfield numbers, it is largely limited to normal tissue contouring. The determination of the target volume still requires detailed clinical input and is highly labor intensive.

Choice of Target Volume

The choice of target volume has been a contentious issue in lung cancer RT. The predominant philosophy in the 1970s and 1980s was to treat large volumes that encompassed both known primary and nodal disease as well as one or more additional nodal echelons. Such elective nodal irradiation (ENI) was thought to be important in controlling tumors that

grew in a stepwise Halstedian manner, spreading first to regional lymph nodes and only then to distant sites. Treatment protocols by the RTOG during that time routinely included the supraclavicular nodes and contralateral hilar nodes for patients with N2 NSCLC. In the early 1980s, a move to reduce the electively irradiated volume began, with elimination of supraclavicular nodal irradiation in a number of clinical trials in both NSCLC and SCLC. Failure in un-irradiated nodes was infrequent — only approximately 5% in these trials — and elective supraclavicular nodal has been abandoned in recent trials of the North American Cooperative Groups.

The recognition that locoregional failure predominantly in areas of known macroscopic disease has provided further impetus to the move to reduce target volumes in order to facilitate dose escalation. The current philosophy of a number of groups that have been instrumental in implementing 3D-CRT for lung cancer can be summarized as follows:

- Include all areas of known disease as visualized on imaging studies or ascertained by surgical staging procedures. While this may seem straightforward, distinguishing on planning CT scans between tumor and atelectatic lung is not an easy task, and one where there is much consistency among radiation oncologists.
- Treat all areas of known disease to the same dose. While in theory bulkier disease might require higher doses for control, we have not defined doses routinely capable of controlling more moderate but macroscopic (eg, 2 cm) NSCLC. When local nodal disease is routinely controlled, escalation of dose to only the primary tumor would be reasonable (assuming that the primary is larger than the nodal mass, which is not always the case, especially with small peripheral adenocarcinomas and extensive mediastinal adenopathy).
- Do not intentionally irradiate other nodal sites, either next echelon nodes or lymphatic pathways connecting the primary tumor with sites of known nodal involvement. In practice, many of these “elective” nodal stations will receive a substantial dose, even when not explicitly included in the target volume.²⁸ This exclusion is justified by the argument that the inclusion of systemic chemotherapy should be adequate to control microscopic nodal as well as systemic disease. If not, the patient is likely to die of systemic metastases and would not have benefited clinically from controlling microscopic nodal disease with irradiation.

While this is a reasonable and internally consistent set of arguments, the true optimal target volume for patients with known involvement of mediastinal nodes

remains unknown and has not been well studied in prospective trials. Two issues are involved. The first pertains to adjuvant irradiation of nodes in stations not demonstrably involved. Such prophylactic irradiation of the full mediastinum (and in many trials the contralateral hilum and supraclavicular fossae) has been the norm for most of the last decades, at least in North American practice and clinical trials. It is increasingly recognized, however, that the use of such large target volumes greatly limits the ability to dose escalate.

Schraube et al²⁹ reported a series of 20 patients with locally advanced NSCLC who were planned using both 2D and 3D technology. Target volumes included both known primary and nodal disease as well as electively treated mediastinal nodes. While 3D planning provided better coverage of the target volume, the dose to normal lung and the normal tissue complication probability were not reduced. The authors were doubtful that significant dose escalation would be possible, at least if large volumes were to be treated.

McGibney et al^{30,31} investigated the role of 3D planning in considering patients who were being treated with the accelerated CHART regimen. They studied 18 patients with stages Ib through IIIB NSCLC (15 of 18 had stage III) and generated plans according to three different approaches: conventional 2D with inclusion of ENI (as had been used in the original CHART regimen), and both 2D and 3D plans without ENI. They found that coverage of the planning target volume was suboptimal with either of the 2D approaches and improved only with 3D planning without ENI. The proportion of the planning target volume receiving >95% of the prescribed dose was 87.38% for conventional 2D and 88.5% for 2D without ENI compared with 100% for 3D without ENI. The use of 3D planning significantly reduced doses to the spinal cord, heart, and esophagus but did not improve lung sparing. This would suggest that acute tolerance (where esophagitis is often the limiting toxicity, both for accelerated RT schedules and for concurrent chemoradiation) might be more favorably affected than long-term ability to dose escalate if this is limited by pulmonary toxicity.

The true incidence of microscopic involvement of normal-sized nodes has been evaluated in several recent studies. In general, CT staging using a size cutoff of 1 cm for the short axis of lymph nodes is reported to have approximately a 25% false-negative rate. While involved nodes are, as a group, larger than uninvolved nodes, there is substantial overlap between the groups as well as substantial false-positive and false-negative rates using CT scanning for nodal staging.³² In a series of 348 patients with clinical N0 NSCLC undergoing surgical resection, Sawyer et al²⁰ were able to define four dis-

Table 3. — Likelihood of Regional Lymph Node or Local Recurrence Involvement in Resected Clinical N0 NSCLC

Risk Group	Characteristics	N1/N2 or Local Recurrence
Low	Bronchoscopy (–) grade 1/2	15.6%
Low/Intermediate	Bronchoscopy (–) grade 3/4	35.2%
High/Intermediate	Bronchoscopy (+) CT size <3 cm	41.7%
High	Bronchoscopy (+) CT size >3 cm	68.2%

From Sawyer et al.²⁰ Reprinted with permission from Elsevier.

crete risk groups for occult nodal involvement based on histologic grade, tumor location, and tumor size. For the lowest risk group (well-differentiated peripheral tumors), the risk was 15.6%, and it rose to as high as 68.2% for patients with central tumors more than 3 cm in size (Table 3). Several groups have reported that even for small peripheral tumors, only those below 1 cm in size may be reliably considered to be without nodal metastases (Table 4).^{33,34}

The practical question, however, is not so much how often nodes are involved but rather how often are they the sole cause of clinical failure. Several retrospective series have reported a low (<5%) incidence of isolated nodal failure in patients with clinical stage I and II NSCLC who were treated with radiation to the primary tumor volume only.^{35,36} Local failure and distant metastatic disease dominate patterns of failure. Until such time as these are no longer problems, any incremental gains in survival achieved by elective irradiation of microscopically involved regional nodes, either in medically inoperable early-stage or stage III disease, are likely to be minimal. Furthermore, to the extent that chemotherapy is able to eradicate small volumes of systemic disease, as evidenced by the improved long-term as well as median survivals in several trials of RT alone or preceded by induction chemotherapy, it may also be able to sterilize occult nodal disease. These trials that indicated a reduction of distant failure gave chemotherapy in full dose and

Table 4. — Histologic Involvement of Regional Nodes in Peripheral Clinical T1-N0 NSCLC

Author	Tumor Diameter (cm)	N0	N1	N2	Total
Konaka ³³ (1999)	≤1.0	19 (100%)	0	0	19
	>1.0 to ≤1.5	43 (86%)	4	3	50
	>1.5 to ≤2.0	80 (78%)	6	16	102
Miller ³⁴ (2002)	≤1.0	93 (93%)	5	2	100

an intermittent schedule.^{37,38} Trials using daily or weekly low-dose chemotherapy, while also showing survival gain, appear to have achieved this more from enhanced local control than effective suppression of extrathoracic disease.⁹ The details of combining radiation and chemotherapy may become increasingly important as we attempt to reduce radiation target volumes and increase dose and schedules that combine the local radiosensitizing effects as well as the systemic adjuvant effects of chemotherapy may prove to be most effective.

Treatment Delivery: Multiple Sessions and Moving Targets

The initial concerns in developing reproducible treatment setups in 3D-CRT planning and delivery have concentrated on assuring reproducibility of patient positioning and anatomic setup in relatively static organs such as the prostate. Issues of intrinsic positional uncertainty, variation in positioning for imaging, treatment planning, and treatment delivery are common to all 3D-CRT approaches for all disease sites. The treatment of lung cancer adds the issues of physiologic motion of the target volume with the cardiac and respiratory cycles. These issues are not resolved, and a number of strategies are being proposed to deal with them. One set of approaches entails treating the patient at a fixed phase of the respiratory cycle, either by voluntary breath holding at deep inspiration^{39,40} or by the use of mechanical ventilation to limit the degree of inspiration when the treatment beam is turned on.⁴¹ A second approach allows the patient to breathe freely but gates the treatment beam on and off to allow treatment only in a limited portion of the respiratory cycle. This is generally determined by external markers of respiration such as airflow or position of markers located on the external chest surface. Such free-breathing approaches may be more acceptable than breath-holding methods to patients who are already dyspneic or anxious.

Both of these approaches attempt to limit the effect of organ motion by limiting the amount of motion during the time of treatment. Alternatively, one may allow free motion of the tumor but track it accurately in real time with imaging devices mounted on the treatment accelerator and dynamically adjust the position of the treatment beam relative to the patient to follow the tumor motion. In some systems, this requires placement of radio-opaque fiducial markers within the tumor to allow accurate tracking. Several prototype devices for such treatment have been developed and their use described in treatment of medically inoperable patients with small peripheral lung tumors.^{42,43}

Tissue inhomogeneities have often been ignored in lung cancer treatment planning. None of the North American Cooperative Groups require or allow the routine use of corrections for inhomogeneity in lung cancer treatment planning. Yet “normal” lung tissue has a density of approximately 0.33, and the often emphysematous lungs of lung cancer patients are often significantly less dense. Neglecting this fact in routing calculations results in central axis depth-doses that are measurably higher than those calculated when homogeneity is not taken into account. An additional factor that will be of increasing significance with the use of smaller fields or small beamlets as used in multileaf-collimator-based intensity-modulated RT (IMRT) is the effect of reduced electron density on side scatter and dose equilibrium at the interface between low-density lung and tumor. Several studies using Monte Carlo calculations have documented that there is a potential for significant underdosing and that this is exacerbated by the use of high-energy photon beams (eg, 10 MV and higher), which have been the standard for lung cancer treatment in many institutions.⁴⁴⁻⁴⁷ Attention to such details of dosimetry will be essential to the proper evaluation of new treatment techniques.

Clinical Experience

Several centers have published results of early therapeutic trials of 3D-CRT for patients with NSCLC

(Table 5).⁴⁸⁻⁵³ As these generally represent results from a period during which therapeutic techniques were in evolution, radiation doses often spanned a wide range as clinicians became more comfortable with dose escalation strategies. They also contain variable mixtures of patients with early-stage but medically inoperable disease (stage I or II) and those with bulky stage IIIA or IIIB disease. Thus all of these series should be viewed as works in progress rather than as definitive assessments of the clinical value of 3D-CRT.

Investigators at the University of Michigan⁵⁴⁻⁵⁶ reported a dose escalation trial in which the dose for a particular patient was determined in part by the calculated normal tissue complication probability, based on lung volume without accounting for regional variations in lung function. Target volumes included only gross disease plus margin without ENI. For patients in the low-risk group, doses have been escalated to 84 Gy without excessive pulmonary or other toxicity. Failure in un-irradiated adjacent nodes has not been observed.

Armstrong and colleagues⁵⁷ at the Memorial Sloan-Kettering Cancer Center are conducting a dose escalation trial, also using conventional fractionation. Preliminary reports are encouraging for survival despite adverse patient clinical characteristics. In order to continue dose escalation, they have found it necessary to eliminate ENI and target only known primary and nodal disease.

Table 5. — Selected Large Trials of Conformal Radiation Therapy for NSCLC

Author	No. of Patients	Stage (No.)	Dose (Median)	Median Survival (mos)	2-Yr Survival (%)	Local Control at 2 Yrs (%)	Comments
Rosenman ⁴⁸ (2002)	62	IIIA (28) IIIB (34)	60-74 Gy (74 Gy)	24.0	50	NR	Phase I-II trial with 32 patients treated to 74 Gy; treated elective nodal sites
Armstrong ⁴⁹ (1997)	28	I/II (4) IIIA (12) IIIB (12)	52.2-72 Gy (70.2 Gy)	15.7	32	NR	Phase I dose escalation trial
Robertson ⁵⁰ (1997)	48	I/II (20) IIA (17) IIIB (11)	63-84 Gy	6.0			Phase I dose escalation trial
Sibley ⁵¹ (1995)	37	IIIA (18) IIIB (19)	60-70 Gy (66 Gy)	19.5	37	23	Phase I dose escalation trial
Graham ⁵² (1995)	70	I (15) II (7) IIIA (36) IIIB (12)	60-74 Gy (69 Gy)	16.5	33	NR	Phase I dose escalation trial; treated elective nodal sites
Hazuka ⁵³ (1993)	88	I/II (19) IIIA (44) IIIB (25)	60-74 Gy	24.0	37	49	Phase I trial; no elective nodal radiation

NR = not reported
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At Washington University, Graham and colleagues²⁸ performed several trials of 3D-CRT with dose escalation to 74 Gy. Their initial approach was to begin with fairly traditional treatment planning approaches using the tools of 3D-RTP for evaluation of tumor coverage and normal tissue dose-volume histograms. Unlike some other groups, they have tended to avoid noncoplanar beam arrangements, believing that these add little and result in limited lung sparing.

Investigators at the University of Pittsburgh have advocated a technique that relies heavily on beams that are unopposed and may be noncoplanar in order to limit lung dose.⁵⁸ Their approach relies heavily on the use of coplanar but non-opposing beams that treat large amounts of lung to low dose (from one beam only) but limit the volume of beam overlap to the immediate vicinity of the tumor. Preliminary data on 31 patients indicates acceptable acute toxicity, although target doses were not escalated above 65 Gy.⁵⁹ Derycke et al^{60,61} developed a somewhat similar approach using multiple parasagittal beams with intensity modulation that gives good sparing of both lung and spinal cord and that may be amenable to development of class solutions, somewhat simplifying the treatment planning process.

Sibley et al³¹ reported their experience with treatment of patients with stage III NSCLC using 3D-CRT to total doses of 66 Gy. With a median survival of 19.5 months and a 2-year survival rate of 37%, their results with RT as a single modality compare favorably or surpass those reported with combined-modality approaches. Caution should be taken in comparing single institution experience with cooperative group experiences. They also found that despite this favorable survival benefit, local control was poor, with only 23% of patients free of local progression at 2 years.

Issues for Consideration and Future Development

Most current data on lung tolerance are based on patients with either Hodgkin's disease or cancer of the lung. These two groups differ substantially in median age, smoking history, and probable survival, and data from the two groups may not be entirely comparable. The techniques of RT used on the patients from whom these data have been derived were typically classic opposed fields, either anterior/posterior or obliques. The typical beam arrangement in conformal planning for stage III NSCLC or limited SCLC produces dose distributions that are much more conformal for the high-dose volume but may treat larger volumes of lung tissue to lower doses that are usually satisfactorily tolerated

(eg, >20 Gy). How well such large-volume, modest-dose irradiation will be tolerated in the context of sequential or concurrent chemotherapy is not well characterized and will be a challenge for current and future clinical trials. Particularly with drugs that are radiation sensitizers (eg, gemcitabine), caution is needed before assuming that full-dose chemotherapy and full-dose radiation can be safely combined.⁶²

The esophagus may well emerge as a dose-limiting organ in chest RT. Because of its proximity to mediastinal lymph nodes, it is frequently difficult if not impossible to establish a significant dose differential between nodal metastases and adjacent esophagus. Elimination of ENI will reduce the length of esophagus irradiated but not necessarily the maximum dose. Both of these factors have been correlated with toxicity.^{14,15} The use of concurrent chemotherapy (and possibly anterior chemotherapy as well) worsens acute esophagitis with as yet not well characterized effects on late tolerance.

An alternative approach to CRT with photon beams involves the use of other radiation beams with intrinsic physical advantages in dose distribution. This approach has been most studied for proton beams. The relative lack of side scatter and controllable depth of penetration in tissue with most energy being deposited in the region of the Bragg peak theoretically allow substantial reductions in dose delivered to normal tissues. At present, proton beams optimized for clinical RT are available only in a small number of institutions worldwide. Little has been published to date on their use in patients with lung cancer, but preliminary data are encouraging. Several recently commissioned clinical proton beam facilities will provide additional information on this approach.⁶³

It has long been recognized that there is an interdependent relation between staging of cancer and its treatment. Staging is of greatest importance in a setting of partially effective therapies. With no effective therapy, staging is irrelevant, and a therapy that is effective regardless of disease extent does not require a complex staging system. The ongoing modifications of the TNM staging system for lung cancer, both in its official rubric and in multiple suggested ad hoc modifications, are reflective of the current changes in lung cancer therapy. The present staging system was derived primarily from data on surgically treated patients and reflects this heritage. Particularly for the T component, proximity to unresectable normal structures is given more importance than size. While this makes sense surgically, it does not accord with well-established radiobiologic principles relating tumor volume and probability of achieving local control. The only explicit consideration of tumor size is in the distinction

between T1 and T2 lesions using a 3-cm cutoff. However, a 1-cm peripheral tumor involving visceral pleura would be staged as T2, while a 2.9-cm tumor without pleural involvement is staged as T1. Martel et al⁶⁴ examined tumor volume in patients with NSCLC receiving 3D-TRT and have shown that total tumor volume is not correlated with stage, but for patients without nodal involvement, it is strongly correlated with survival. Several other groups have reported similar findings.⁴⁶ One caution here is that the reproducibility of tumor volume measurements made from planning CT scans by several physicians is rather poor.^{65,66}

Functional Imaging

Initial approaches to 3D-CRT have focused on the optimization of anatomic dose distribution. It has been realized that this was not an optimum approach and that conventional CT imaging did not give important information on tissue type and function. In the past several years, the growing ability to combine images obtained by various technologies such as CT with MRI or PET has become increasingly available. Such tools can be valuable not only in evaluating both adequacy of coverage of the tumor, but also in selecting treatment plans based on the effect of normal tissue function in addition to normal tissue volume.⁶⁷

While the incorporation of data from PET imaging may have a direct beneficial effect on lung cancer treatment planning by providing better delineation of both primary tumor volume, differentiating between tumor and distal atelectasis and metastatic disease in normalized lymph nodes, it will also have an indirect effect in improving survival of patients with stage III NSCLC by detecting occult extrathoracic metastases in a portion of these patients and moving them to stage IV. Such stage migration has been reported in approximately 20% of patients with apparent stage III NSCLC being considered for radical chemoradiation and may significantly improve the apparent survival of patients with both stage III and stage IV disease.⁶⁸

PET scanning with ¹⁸F-fluorodeoxyglucose has become widely used in the management of patients with a variety of malignancies in the past several years. For NSCLC, PET has shown considerable promise in several domains. First, PET scanning has greater sensitivity and specificity in detecting mediastinal nodal metastases than does CT scanning, and a combination of the two modalities is currently the state of the art for noninvasive mediastinal staging.⁶⁹ Second, whole-body PET scanning can reveal otherwise undetected extrathoracic metastatic disease in a substantial proportion of patients with locally advanced (typically stage III) disease otherwise thought

to be candidates for potentially curative chemoradiation. Such detection is of high prognostic value and will guide therapy for individual patients.⁷⁰⁻⁷² It will also appear to improve the survival outcomes of patients for both those remaining in stage III and those migrating to stage IV, when compared to historical controls. The influence of such stage migration on survival of patient subsets, the so-called "Will Rogers effect," must be taken into account when introducing any new mode of tumor staging and/or classification. Third, the functional information obtained with PET scanning can be combined with the anatomic data from CT to aid in target volume delineation and treatment planning for RT. There is a rapid proliferation of reports on the effect of such combined information on treatment planning. Considerable variation exists between series in exactly how the CT and PET information were obtained and combined in the planning process. In the simplest models, the physician had access to the PET images while drawing the target volume on the planning CT, and any fusion done was performed in his or her head. In a second generation of trials, formal attempts of image fusion using internal anatomic references and/or external fiducial markers have been described. Most recently, the availability of dual-purpose imaging machines that perform both CT and PET imaging in the same study session are being investigated. Great care must be taken in fusing images obtained with the patient in somewhat different imaging positions, none of which may correspond precisely with the treatment position unless rigorous care is made to ensure consistent patient immobilization. Tumor motion with the respiratory and cardiac cycles, a factor we are just beginning to grapple with in four-dimensional RT, becomes an even greater complexity when the time required for CT and PET image set acquisition differs by several orders of magnitude.

The application of respiratory gating to PET image acquisition for RT planning is in its infancy.⁷³ Despite these significant complexities and potential problems, however, the early investigations of including PET data in RT planning for NSCLC have shown two general themes: (1) the mediastinal component of the gross tumor volume increases as nodes normal by CT size criteria are shown to be highly glucose avid on PET, (2) the primary tumor component of the gross tumor volume often decreases as densities peripheral to central obstruction tumors are, if cold on PET, interpreted as atelectasis rather than tumor.⁷⁴ Such interpretations remain somewhat subjective and may be influenced by choice of standardized uptake value threshold for interpretation.⁷⁵

The final domain in which PET may be useful in managing patients with NSCLC is in assessing response to treatment. It has been recognized for some time that the measurement of tumor response to RT or chemoradiation by CT does not correlate well with long-term

treatment outcome.⁷⁶ Several recent studies have suggested that posttreatment PET scan response is much more predictive of ultimate tumor control and patient outcome.⁷⁷ It is not known, however, what the optimal time following chemotherapy of chemoradiation for such imaging may be. Particularly after RT, inflammatory changes in normal lung can complicate PET interpretation and yield false-positive results.

In addition to CT, MRI, and PET, a burgeoning number of newer functional imaging techniques are on the horizon and can provide potentially important information for RT planning.^{78,79} These techniques may allow in situ noninvasive measurement of tumor hypoxia,⁸⁰ proliferation rate,⁸¹ apoptosis,⁸² expression of a variety of surface receptors, and other parameters of interest. If we can reliably acquire such maps of biologic function and correlate them with anatomic structure, the ability to differentially direct radiation dose to areas of greater tumor burden or functional radioresistance will usher in a new era of treatment optimization based on radiobiology in addition to physics.⁸³ While this promises to be a daunting task, it offers the possibility of truly individualized therapy.

Cost Effectiveness of 3D-CRT

The development of CRT is occurring at a time when the cost of all medical procedures is coming under heavy scrutiny; new, often costly, technologies are being required to justify themselves by producing demonstrably better outcomes. For CRT, these outcomes could be either a reduction of the incidence of acute or late complications (and the costs of managing these) or improved survival outcomes if the dose escalation allowed by conformal therapy results in improved local control and survival. Clinical trials designed to assess these issues are currently being performed in several common disease sites, including NSCLC.

Several authors have investigated the economic aspects of CRT.⁸⁴⁻⁸⁷ While the initial cost of purchasing new hardware and software for treatment planning and delivery can be high, the greater ongoing expense is likely to be associated with the greater time and effort associated with conformal planning. Hohenberg et al⁸⁵ found in a survey of German radiotherapy facilities that had begun conformal planning that the number of hours spent per case doubled during the initial period of adoption of the new technologies. Increases were seen for physician, dosimetrist, and physicist time. After approximately 1 year, the time requirements plateaued at about 150% of that required for conventional planning. While improved technologies such as automated contouring of target and normal tissue volumes may

improve the picture somewhat, it is clear that 3D planning is and will remain labor intensive. The implementation of IMRT, an outgrowth of 3D-CRT, will further increase time and resource requirements.⁸⁸

Conclusions

Compared with 20 years ago, present technology for treatment delivery can deliver conventional doses much more accurately. The first developmental generation of technologies and clinical trials has shown the feasibility of applying 3D-CRT technology to the treatment of patients with lung cancer. What now remains is the evaluation of the clinical utility of these technologies in large clinical trials. Two approaches may be reasonably taken. In the first, a more conservative approach, 3D-CRT will be used to assure better tumor coverage and normal tissue protection while maintaining conventional dose and fractionation regimens. It is currently a topic of considerable controversy whether this approach ought to be compared with current conventional therapy or to large volume treatment. A more challenging set of trials will investigate whether the escalation of radiation dose from the current 65 Gy "standard" to doses in the range of 80 to 100 Gy produces clinically useful improvements in local control and survival. In this setting, the desire to avoid major protraction of overall treatment time as well as to reduce the normal tissue receiving the full fraction size will likely lead to the adoption of some form of accelerated fractionation. Fraction sizes to the planning target volume may increase from the present standard of 1.8-2.0 Gy to 2.5-3.0 Gy or more, or treatment may accelerate by the use of multiple fractions per day as in the CHART, HART, or CHARTWEL (CHART weekend-less) regimens.

While some elements of 3D-CRT, such as better visualization that we are actually covering the planned target volume, are so intuitively beneficial that they do not require large-scale validation in clinical trials. Other aspects, particularly that higher radiation doses are necessarily better, are best considered as promising hypotheses. To avoid a backlash by reimbursement agencies as well as the public, careful evaluation of the true costs and benefits of 3D-CRT in lung cancer and other tumor sites should be a priority in this decade.

References

1. Arriagada R, Pignon JP, Ihde DC, et al. Effect of thoracic radiotherapy on mortality in limited small cell lung cancer: a meta-analysis of 13 randomized trials among 2,140 patients. *Anticancer Res.* 1994;14(1B):333-335.
2. Kubota K, Furuse K, Kawahara M, et al. Role of radiotherapy in combined modality treatment of locally advanced non-small-cell lung cancer. *J Clin Oncol.* 1994;12:1547-1552.
3. Perez CA, Pajak TF, Rubin P, et al. Long-term observations of

- the patterns of failure in patients with unresectable non-small-cell carcinoma of the lung treated with definitive radiotherapy. *Cancer*. 1987;59:1874-1881.
4. Willner J, Baier K, Caragiani E, et al. Dose, volume, and tumor control predictions in primary radiotherapy of non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2002;52:382-389.
 5. Bradley JD, Ieumwananonthachai N, Purdy JA, et al. Gross tumor volume, critical prognostic factor in patients treated with three-dimensional conformal radiation therapy for non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys*. 2002;52:49-57.
 6. Etiz D, Marks LB, Zhou SM, et al. Influence of tumor volume on survival in patients irradiated for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2002;53:835-846.
 7. Arriagada R, Le Chevalier T, Quoix E, et al. ASTRO (American Society for Therapeutic Radiology and Oncology) plenary. Effect of chemotherapy on locally advanced non-small cell lung carcinoma: a randomized study of 353 patients. GETCB (Groupe d'Etude et Traitement des Cancers Bronchiques), FNCLCC (Federation Nationale des Centres de Lutte Contre le Cancer) and the CEBI trialists. *Int J Radiat Oncol Biol Phys*. 1991;20:1183-1190.
 8. Arriagada R, Kramar A, Le Chevalier T, et al. Competing events determining relapse-free survival in limited small-cell lung carcinoma. *J Clin Oncol*. 1992;10:447-451.
 9. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy in inoperable non-small-cell lung cancer. *N Engl J Med*. 1992;326:524-530.
 10. Furuse K, Hosoe S, Masuda N, et al. Impact of tumor control on survival in unresectable stage III non-small cell lung cancer (NSCLC) treated with concurrent thoracic radiotherapy (TRT) and chemotherapy (CT). *Proc Annu Meet Am Soc Clin Oncol*. 2000;19:1893. Abstract.
 11. Curran W Jr, Scott C, Langer C, et al. Phase III comparison of sequential vs concurrent chemoradiation for PTS with unresected stage III non-small cell lung cancer (NSCLC): initial report on Radiation Therapy Oncology Group (RTOG) 9410. *Proc Annu Meet Am Soc Clin Oncol*. 2000;19. Abstract 1891.
 12. Saunders M, Dische S, Barrett A, et al. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomized multicenter trial. CHART Steering Committee. *Lancet*. 1997;350:161-165.
 13. The Lung Cancer Study Group. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. *N Engl J Med*. 1986;27:1377-1381.
 14. Choy H, LaPorte K, Knill-Selby E, et al. Esophagitis in combined modality therapy for locally advanced non-small cell lung cancer. *Semin Radiat Oncol*. 1999;9(2 suppl 1):90-96.
 15. Maguire PD, Sibley GS, Zhou SM, et al. Clinical and dosimetric predictors of radiation-induced esophageal toxicity. *Int J Radiat Oncol Biol Phys*. 1999;45:97-103.
 16. Singh AK, Lockett MA, Bradley JD. Predictors of radiation-induced esophageal toxicity in patients with non-small-cell lung cancer treated with three-dimensional conformal therapy. *Int J Radiat Oncol Biol Phys*. 2003;55:337-341.
 17. Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol*. 1988;27:131-146.
 18. Boxwala AA, Rosenman JG. Retrospective reconstruction of three-dimensional treatment plans from two-dimensional planing data. *Int J Radiat Oncol Biol Phys*. 1994;28:1009-1015.
 19. Giraud P, Antoine M, Larrouy A, et al. Evaluation of microscopic tumor extension in non-small-cell lung cancer for three-dimensional conformal radiotherapy planning. *Int J Radiat Oncol Biol Phys*. 2000;48:1015-1024.
 20. Sawyer TE, Bonner JA, Gould PM, et al. Predictors of subclinical nodal involvement in clinical stages I and II non-small cell lung cancer: implications in the inoperable and three-dimensional dose-escalation settings. *Int J Radiat Oncol Biol Phys*. 1999;43:965-970.
 21. Bentel GC, Marks LB, Krishnamurthy R. Impact of cradle immobilization on setup reproducibility during external beam radiation therapy for lung cancer. *Int J Radiat Oncol Biol Phys*. 1997;38:527-531.
 22. Booth JT, Zavgorodni SE. Set-up error and organ motion uncertainty: a review. *Australas Phys Eng Sci Med*. 1999;22:29-47.
 23. Halperin R, Roa W, Field M, et al. Setup reproducibility in radiation therapy for lung cancer: a comparison between T-bar and expanded form immobilization devices. *Int J Radiat Oncol Biol Phys*. 1999;43:211-216.
 24. Mirimanoff R-O. Immobilization devices in conformal radiotherapy for non-small cell lung cancer. In: Mornex F, van Houtte P, eds. *Treatment Optimization for Lung Cancer: From Classical to Innovative Procedures*. Paris, France: Elsevier; 1998:103-108.
 25. Samson MJ, van Sornsen de Koste JR, de Boer HC, et al. An analysis of anatomic landmark mobility and setup deviations in radiotherapy for lung cancer. *Int J Radiat Oncol Biol Phys*. 1999;43:827-832.
 26. Thilmann C, Adamietz IA, Mose S, et al. Which factors modify the reproducibility of patient positioning in the daily irradiation routine? [in German]. *Strahlenther Onkol*. 1997;173:422-427.
 27. Chen T, Pellizari C, Vijaykumar S. Imaging: the basis for effective therapy. In: Meyer JL, Purdy JA, eds. *Frontiers in Radiation Therapy and Oncology*. Vol 29. Basel, Switzerland: Karger; 1996:31-42.
 28. Graham M. 3-D conformal radiotherapy for lung cancer: the Washington University experience. In: Meyer JL, Purdy J, eds. *Frontiers of Radiation Therapy and Oncology*. Vol 29. Basel, Switzerland: Karger Press Inc; 1996:188-198.
 29. Schraube P, Spahn U, Oetzel D, et al. Effect of 3D compared with 2D radiotherapy planning within a conventional treatment schedule of advanced lung cancer [in German]. *Strahlenther Onkol*. 2000;176:32-39.
 30. McGibney C. The potential impact of 3-D conformal radiotherapy (3DCRT) on continuous hyperfractionated accelerated radiotherapy (CHART) for NSCLC. *Lung Cancer*. 1997;18(suppl 1): 486. Abstract.
 31. McGibney C, Holmberg O, McClean B, et al. Dose escalation of chart in non-small cell lung cancer: is three-dimensional conformal radiation therapy really necessary? *Int J Radiat Oncol Biol Phys*. 1999;45:339-350.
 32. Prenzel KL, Monig SP, Sinning JM, et al. Lymph node size and metastatic infiltration in non-small cell lung cancer. *Chest*. 2003;123:463-467.
 33. Konaka C, Ikeda N, Hiyoshi T, et al. Peripheral non-small cell lung cancers 2.0 cm or less in diameter: proposed criteria for limited pulmonary resection based upon clinicopathological presentation. *Lung Cancer*. 1998;21:185-191.
 34. Miller DL, Rowland CM, Deschamps C, et al. Surgical treatment of non-small cell lung cancer 1 cm or less in diameter. *Ann Thorac Surg*. 2002;73:1545-1550.
 35. Hayakawa K, Mitsuhashi N, Saito Y, et al. Limited field irradiation for medically inoperable patients with peripheral stage I non-small cell lung cancer. *Lung Cancer*. 1999;26:137-142.
 36. Sibley G. Radiotherapy for patients with medically inoperable stage I nonsmall cell lung carcinoma: smaller volumes and higher doses. A review. *Cancer*. 1998;82:433-438.
 37. Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial of 353 patients. *J Natl Cancer Inst*. 1991;83:417-423.
 38. Sause W, Kolesar P, Taylor S IV, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest*. 2000;117:358-364.
 39. Hanley J, Debois MM, Raben A, et al. Deep inspiration breath-hold technique for lung tumors: the potential value of immobilization and reduced lung density in dose escalation. *Int J Radiat Oncol Biol Phys*. 1996;36(suppl 1):188.
 40. Rosenzweig KE, Hanley J, Mah D, et al. The deep inspiration breath-hold technique in the treatment of inoperable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2001;48:81-87.
 41. Wong JW, Sharpe MB, Jaffray DA, et al. The use of active breathing control (ABC) to reduce margin for breathing motion. *Int J Radiat Oncol Biol Phys*. 1999;44:911-919.
 42. Shimizu S, Shirato H, Ogura S, et al. Detection of lung tumor movement in real-time tumor-tracking radiotherapy. *Int J Radiat Oncol Biol Phys*. 2001;51:304-310.
 43. Uematsu M, Shiota A, Suda A, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. *Int J Radiat Oncol Biol Phys*. 2001;51:666-670.

44. Yorke ED, Wang L, Rosenzweig KE, et al. Evaluation of deep inspiration breath-hold lung treatment plans with Monte Carlo dose calculation. *Int J Radiat Oncol Biol Phys.* 2002;53:1058-1070.
45. Brugmans MJ, van der Horst A, Lebesque JV, et al. Beam intensity modulation to reduce the field sizes for conformal irradiation of lung tumors: a dosimetric study. *Int J Radiat Oncol Biol Phys.* 1999;43:893-904.
46. Saitoh H, Fujisaki T, Sakai R, et al. Dose distribution of narrow beam irradiation for small lung tumor. *Int J Radiat Oncol Biol Phys.* 2002;53:1380-1387.
47. Johnson H, Schreiber E, Cullip T, et al. Significant underdosing of small tumors or portions of tumor in lung cancer treatment. *Proc Annu Meet Am Soc Ther Radiol Oncol.* 2002;1072. Abstract.
48. Rosenman JG, Halle JS, Socinski MA, et al. High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: technical issues and results of a phase I/II trial. *Int J Radiat Oncol Biol Phys.* 2002;54:348-356.
49. Armstrong J, Raben A, Zelefsky M, et al. Promising survival with three-dimensional conformal radiation therapy for non-small cell lung cancer. *Radiother Oncol.* 1997;44:17-22.
50. Robertson JM, Ten Haken RK, Hazuka MB, et al. Dose escalation for non-small cell lung cancer using conformal radiation therapy. *Int Radiat Oncol Biol Phys.* 1997;37:1079-1085.
51. Sibley GS, Mundt AJ, Shapiro C, et al. The treatment of stage III nonsmall cell lung cancer using high dose conformal radiotherapy. *Int J Radiat Oncol Biol Phys.* 1995;33:1001-1007.
52. Graham MV, Purdy JA, Emami B, et al. Preliminary results of a prospective trial using three dimensional radiotherapy for lung cancer. *Int J Radiat Oncol Biol Phys.* 1995;33:993-1000.
53. Hazuka MB, Turrisi AT 3rd, Lutz ST, et al. Results of high-dose thoracic irradiation incorporating beam's eye view display in non-small cell lung cancer: a retrospective multivariate analysis. *Int J Radiat Oncol Biol Phys.* 1993;27:273-284.
54. Hayman JA, Martel MK, Ten Haken RK, et al. Dose escalation in non-small-cell lung cancer using three-dimensional conformal radiation therapy: update of a phase I trial. *J Clin Oncol.* 2001;19:127-136.
55. Hayman J, Hayman J, Martel M, Ten Haken RK, et al. Dose escalation in non-small cell lung cancer (NSCLC) using conformal 3-dimensional radiation therapy (C3DRT): update of a phase I trial. *Proc Annu Meet Am Soc Clin Oncol.* 1999;18:1772. Abstract.
56. Hazuka MB, Turrisi AT III, Martel MK, et al. Dose-escalation in non-small cell lung cancer (NSCLC) using conformal 3-dimensional radiation treatment planning (3DRT): preliminary results of phase I study. *Proc Annu Meet Am Soc Clin Oncol.* 1994;13. Abstract.
57. Armstrong J, McGibney C. The impact of three-dimensional radiation on the treatment of non-small cell lung cancer. *Radiother Oncol.* 2000;56:157-167.
58. Greenberger J, et al. Development of a technique for three-dimensional conformal radiotherapy of lung cancer using a total lung dose-volume histogram computational algorithm. *Radiat Oncol Invest Clin Basic Res.* 1996;3:243-255.
59. Greenberger JS, Bahri S, Jett J, et al. Considerations in optimizing radiation therapy for non-small cell lung cancer. *Chest.* 1998;113(1 suppl):46S-52S.
60. Derycke S, De Gersem WR, Van Duyse BB, et al. Conformal radiotherapy of stage III non-small cell lung cancer: a class solution involving non-coplanar intensity-modulated beams. *Int J Radiat Oncol Biol Phys.* 1998;41:771-777.
61. Derycke S, Van Duyse B, De Gersem W, et al. Non-coplanar beam intensity modulation allows large dose escalation in stage III lung cancer. *Radiother Oncol.* 1997;45:253-261.
62. Scalliet P, Goor C, Galdermans D, et al. Gemzar (gemcitabine) with thoracic radiotherapy: a phase II pilot study in chemo-naive patients with advanced non-small cell lung cancer (NSCLC). *Proc Annu Meet Am Soc Clin Oncol.* 1998;17:1923. Abstract.
63. Bush DA, Slater JD, Bonnet R, et al. Proton-beam radiotherapy for early-stage lung cancer. *Chest.* 1999;116:1313-1319.
64. Martel MK, Strawderman M, Hazuka MB, et al. Volume and dose parameters for survival of non-small cell lung cancer patients. *Radiother Oncol.* 1997;44:23-29.
65. Bowden P, Fisher R, Mac Manus M, et al. Measurement of lung tumor volumes using three-dimensional computer planning software. *Int J Radiat Oncol Biol Phys.* 2002;53:566-573.
66. Caldwell CB, Mah K, Ung YC, et al. Observer variation in contouring gross tumor volume in patients with poorly defined non-small-cell lung tumors on CT: the impact of 18FDG-hybrid PET fusion. *Int J Radiat Oncol Biol Phys.* 2001;51:923-931.
67. Munley MT, Marks LB, Scarfone C, et al. Multimodality nuclear medicine imaging in three-dimensional radiation treatment planning for lung cancer: challenges and prospects. *Lung Cancer.* 1999;23:105-114.
68. MacManus MP, Hicks RJ, Matthews JP, et al. High rate of detection of unsuspected distant metastases by PET in apparent stage III non-small cell lung cancer: implications for radical radiation therapy. *Int J Radiat Oncol Biol Phys.* 2001;50:287-293.
69. Silvestri GA, Tanoue LT, Margolis ML, et al. The noninvasive staging of non-small cell lung cancer: the guidelines. *Chest.* 2003;123(1 suppl):147S-156S.
70. Hicks RJ, Kalff V, MacManus MP, et al. (18)F-FDG PET provides high-impact and powerful prognostic stratification in staging newly diagnosed non-small cell lung cancer. *J Nucl Med.* 2001;42:1596-1604.
71. Hicks RJ, MacManus MP. 18F-FDG PET in candidates for radiation therapy: is it important and how do we validate its impact? *J Nucl Med.* 2003;44:30-32.
72. Seltzer MA, Yap CS, Silverman DH, et al. The impact of PET on the management of lung cancer: the referring physician's perspective. *J Nucl Med.* 2002;43:752-756.
73. Nehmeh SA, Erdi YE, Ling CC, et al. Effect of respiratory gating on quantifying PET images of lung cancer. *J Nucl Med.* 2002;43:876-881.
74. Nestle U, Walter K, Schmidt S, et al. 18F-deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: high impact in patients with atelectasis. *Int J Radiat Oncol Biol Phys.* 1999;44:593-597.
75. Black Q, Yan D, Kestin LL, et al. Defining a radiography target with positron emission tomography. *Int J Radiat Oncol Biol Phys.* 2002;54(suppl 1):34.
76. Werner-Wasik M, Xiao Y, Pequignot E, et al. Assessment of lung cancer response after nonoperative therapy: tumor diameter, bidimensional product, and volume. A serial CT scan-based study. *Int J Radiat Oncol Biol Phys.* 2001;51:56-61.
77. Kostakoglu L, Goldsmith SJ. 18F-FDG PET evaluation of the response to therapy for lymphoma and for breast, lung, and colorectal carcinoma. *J Nucl Med.* 2003;44:224-239.
78. Ling CC, Humm J, Larson S, et al. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. *Int J Radiat Oncol Biol Phys.* 2000;47:551-560.
79. Rosenman J. Incorporating functional imaging information into radiation treatment. *Semin Radiat Oncol.* 2001;11:83-92.
80. Popple RA, Ove R, Shen S. Tumor control probability for selective boosting of hypoxic subvolumes, including the effect of reoxygenation. *Int J Radiat Oncol Biol Phys.* 2002;54:921-927.
81. Pugsley JM, Schmidt RA, Vesselle H. The Ki-67 index and survival in non-small cell lung cancer: a review and relevance to positron emission tomography. *Cancer J.* 2002;8:222-233.
82. Belhocine T, Steinmetz N, Hustinx R, et al. Increased uptake of the apoptosis-imaging agent (99m)Tc recombinant human Annexin V in human tumors after one course of chemotherapy as a predictor of tumor response and patient prognosis. *Clin Cancer Res.* 2002;8:2766-2774.
83. Brahme A. Optimized radiation therapy based on radiobiological objectives. *Semin Radiat Oncol.* 1999;9:35-47.
84. Grant W 3rd, Woo SY. Clinical and financial issues for intensity-modulated radiation therapy delivery. *Semin Radiat Oncol.* 1999;9:99-107.
85. Hohenberg G, Sedlmayer F. Costs of standard and conformal photon radiotherapy in Austria. *Strahlenther Onkol.* 1999;175(suppl 2):99-101.
86. Martin P, Dubray B. Economic aspects of conformal radiotherapy [in French]. *Cancer Radiother.* 1999;3:437-440.
87. Panten T, Hoss A, Bohsung J, et al. Time requirements in conformal radiotherapy treatment planning. *Radiother Oncol.* 1999;51:211-214.
88. Wong T. Intensity-modulated radiation therapy. Oncology Roundtable Annual Meeting. Washington, DC. The Advisory Board; 2000:1-14.