Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2007 April 1; 67(5): 1360–1369.

THE IMPACT OF INDUCTION CHEMOTHERAPY AND THE ASSOCIATED TUMOR RESPONSE ON SUBSEQUENT RADIATION-RELATED CHANGES IN LUNG FUNCTION AND TUMOR RESPONSE

Jingfang Mao, MD^{1,2}, Zafer Kocak, MD^{1,3}, Sumin Zhou, PhD¹, Jennifer Garst, MD⁴, Elizabeth S. Evans, BS¹, Junan Zhang, PhD¹, Nicole A. Larrier, MD¹, Donna R. Hollis, MS⁵, Rodney J. Folz, MDPH⁶, and Lawrence B. Marks, MD¹

*1*Department of Radiation Oncology, Duke University Medical Center, Durham, NC, USA

*2*Department of Radiation Oncology, Cancer Hospital, Fudan University, Shanghai, China

*3*Department of Radiation Oncology, Trakya University Hospital, Edirne, Turkey

*4*Department of Medicine, Duke University Medical Center, Durham, NC, USA

*5*Biostatistics, Duke University Medical Center, Durham, NC, USA

*6*Pulmonary, Allergy, and Critical Care, Duke University Medical Center, Durham, NC, USA

Abstract

Purpose—To assess the impact of induction chemotherapy, and associated tumor shrinkage, on the subsequent radiation-related changes in pulmonary function and tumor response.

Methods and Materials—As part of a prospective IRB-approved study, 91 evaluable patients treated definitively with thoracic RT for unresectable lung cancer were analyzed. The rates of RT-associated pulmonary toxicity and tumor response were compared in the patients with and without pre-RT chemotherapy. In the patients receiving induction chemotherapy, the rates of RT-associated pulmonary toxicity and tumor response were compared in the patients with and without a response (modified RECIST criteria) to the pre-RT chemotherapy. Comparisons of the rates of improvements in PFTs post-RT, dyspnea requiring steroids, and percent declines in PFTs post-RT were compared in patient subgroups using Fisher's exact test, analysis of variance, and linear or logistic regression.

Results and conclusion—The use of pre-RT chemotherapy appears to increase the rate of radiation-induced pneumonitis ($p=0.07-0.01$), but has no consistent impact on changes in PFTs. The degree of induction-chemotherapy-associated tumor shrinkage is *not* associated with the rate of subsequent-RT-associated pulmonary toxicity. The degree of tumor response to chemotherapy is not related to the degree of tumor response to RT. Additional study is needed to better clarify this issue.

Corresponding author: Lawrence B. Marks, MD, Mailing address: Department of Radiation Oncology, Duke University Medical Center, Box 3085 DUMC, Durham, NC 27710Tel: (919) 668-5640; Fax: (919) 684-3953; Email: lawrence.marks@duke.edu

Presented at the 47th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), Oct 16-20, 2005, Denver, CO (Abstract #2307).

The department of radiation oncology at Duke receives grant support from Varian Medical systems, and the Lance Armstrong Foundation.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

radiation-induced pneumonitis; pulmonary function tests; tumor response; induction chemotherapy; lung cancer

INTRODUCTION

Predicting the pulmonary consequences of thoracic radiation therapy (RT) is challenging. One of the possible confounding factors that make this enterprise difficult is the impact of induction chemotherapy.

There have been several studies demonstrating that the addition of chemotherapy, either before (i.e. induction) RT (1-3), and/or concurrent chemoradiation (4,5), improves the outcome vs. treatment with RT alone. Thus, induction and/or concurrent chemotherapy is often used for patients with lung cancer. However, few of these studies have systematically assessed the impact of induction chemotherapy, and its associated tumor response, on the development of pulmonary toxicity post-RT.

We have been conducting prospective studies of the pulmonary-toxic effects of RT for many years (6-9). We herein extract data from these studies to better assess the impact of induction chemotherapy, and the associated tumor response, on subsequent RT-related changes in lung function and tumor shrinkage. Three specific aims were addressed:

Aim #1: To assess the impact of *pre-RT chemotherapy* on the development of post-RT dyspnea and reductions in pulmonary function tests (PFTs);

Aim #2: To assess the impact of *chemotherapy-induced tumor shrinkage* on the development of post-RT dyspnea and reductions in pulmonary function tests (PFTs).

Prior studies from our group (10) and others (11-13) suggest that changes in RT-induced pulmonary function are related to the competing effects of RT-induced toxicity (tending to reduce function), and RT-induced tumor shrinkage (tending to improve function). Hence, we hypothesized that chemotherapy, and its associated pre-RT shrinkage of a tumor, will lead the patient to be more likely to experience subsequent decline in PFTs following RT since they have already, *prior* to RT, experienced some chemotherapy-induced tumor shrinkage and associated improvements in PFTs. Based on this hypothesis, greater rates and magnitudes of declines in PFTs and a higher rate of RT-induced dyspnea were expected in patients with induction chemotherapy and in patients with a greater response to chemotherapy, vs. those without chemotherapy (aim #1) or without a response to chemotherapy (aim #2).

Aim #3: To assess if the degree of tumor response to chemotherapy is related to the degree of tumor response to subsequent RT.

METHODS AND MATERIALS

1. Patient population

Between 9/1991 and 9/2004, 303 patients with lung cancer were enrolled in a prospective IRB-approved clinical study to better understand RT-induced lung injury. Of these, 91 patients with intact tumors *prior* to RT and with evaluable PFTs data *pre-* and *post-*RT were studied. Patients, who had surgery prior to or after RT, and/or clear evidence of intrathoracic tumor growth in 4 months following RT that would impact on the PFTs, were excluded. For all patients, changes in PFTs and the development of symptoms were scored *prospectively*. For the present analysis,

we *retrospectively* measured tumor sizes on the available diagnostic/planning computed tomography (CT) images. Patient sub-groups were defined as follows:

1. No induction chemotherapy prior to RT
2. Yes induction chemotherapy prior to RT
 - a. Tumor response to induction chemotherapy
 - b. No Tumor response to induction chemotherapy

2. Treatment

Induction chemotherapy—The induction chemotherapy used was somewhat variable. Participation in the current study did not dictate the therapy to be received. However, many of the patients were also enrolled onto other protocols where the induction chemotherapy was specified (14,15). Further, a multidisciplinary team of physicians that specialize in lung cancer planned most of the patients' therapies and hence the varied chemotherapy use reflects, in part, the evolution of "standard" chemotherapy for patients with lung cancer. The 42 patients of the induction-chemotherapy group had received totally 140 cycles of chemotherapy (median: 2; range: 1-8) with a median interval of 28.5 days between the finishing of induction chemotherapy and the beginning of RT (mean: 35 ± 22 days). More than half of the patients (52%, 22/42) received 2 cycles. The majority of patients received carboplatin/cisplatin-based regimen of chemotherapy (95%, 40/42; to an AUC of 6); typically combined with taxol (n=15; 200 mg/m²), vinorelbine (n=12; 20mg/m²), VP-16 (n=12; 100 mg/m²), gemcitabine (n=2; 1000mg/m²), and velban (n=1; 25mg/m²). One patient received navelbine alone, and another received VP-16/adriamycin/cytosan.

Radiation—All patients received the 3-dimensionally-planned external beam radiation treatment. The treated volumes were somewhat variable, again since the exact treatment volumes are not specified by the current study. Nevertheless, many of the patients were treated on prospective studies where the target volume and doses were specified (14-17). The target volumes generally included all radiologically abnormal areas of the lung or regional nodes. Elective regional nodal irradiation was frequently used. For those patients receiving induction chemotherapy, the prechemotherapy volumes were used to define the parenchymal target, and all previously-involved nodal *regions* were considered target.

Most patients were treated with conventional beam arrangements [i.e., initial opposed anterior-posterior (AP/PA) fields to include the gross tumor volume (GTV) and the elective nodal volumes, or clinical target volume, followed by off-cord parallel oblique reductions to GTV]. Some patients were treated with multiple beam arrangements using non-axial and noncoplanar beams.

In 77% of patients, the delivered dose was > 60 Gy (range 36-86.4, mean 65.5, median 66), generally given at 2 Gy daily fractions, 5 fractions/week. Thirty-three patients (37%) were treated using a concurrent boost technique, with the clinical target volume and GTV receiving 1.25 Gy and 1.6 Gy twice daily, respectively, with a minimum 6-hour inter-fraction interval (14-16,18).

3. Measurements of tumor size and definitions of tumor response to chemotherapy and RT

The majority of the tumor measurements were taken from axial images from the diagnostic or RT treatment-planning CT (in the treatment position). A scan thickness of 3-10 mm was typically used. The longest tumor diameter was retrospectively measured as the tumor size. As the tumors are generally visible at multiple axial levels, care was taken to select a level where the *maximal* tumor was easily visible and measure tumors at different therapy phases, on the

same axial level and at comparable window/level of the CT images. The primary lesion was generally the measured tumor. In some cases, the mediastinal nodal disease was more readily visible and assessable than was the primary lesion, and thus was measured. In others, the mediastinal nodes and primary lesion were immediately adjacent to each other, and thus were assessed in concert. In all cases, we used our clinical judgment to obtain measurements to accurately assess response.

Tumor sizes were measured at different treatment phase for patients receiving induction chemotherapy:

Pre-chemotherapy: within 1~2 weeks before chemotherapy

Pre-RT: within 1~2 weeks before RT (this was also the post-induction chemotherapy measurement)

Post-RT: ~3 months of finishing RT.

The percent tumor shrinkage (attributed to chemotherapy or to RT) was computed as $100 * (pre-post)/pre$ based on the longest tumor diameters. The modified Response Evaluation Criteria in Solid Tumor (RECIST) (19) were used to define CR (complete response), PR (partial response: at least 30% reduction in tumor size), SD (stable disease), and PD (progressive disease). The subgroups were defined as following:

Responders (PR+CR): tumor shrinkage (attributed to chemotherapy) of $\geq 30\%$

Non-responders (SD + PD): tumor shrinkage (attributed to chemotherapy) of $< 30\%$ or progressed.

4. Pulmonary function tests (PFTs)

Pulmonary function tests were performed as described previously (20). The current analysis considered only the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and diffusion capacity for carbon monoxide (DLCO) tests, since these are the metrics most commonly considered clinically. The latter was corrected for Hemoglobin (HB) as: $Corrected = Measured * (10.22 + HB) / (1.7 * HB)$.

As part of the protocol, patients were to have PFTs performed pre-RT and $\approx 3, 6$ and 12 months post-RT. The pre-RT PFTs were typically obtained within one week (and all within 2 weeks) prior to the initiation of RT. The “percentage of predicted” of normal PFTs’ values (i.e. adjusted for age, gender, height) were used when analyzing. The minimum post-RT PFTs’ values were chosen to valuate the decline in PFTs:

$$\% \text{ Decline in PFTs} = 100 * (pre \text{ RT PFTs} - \text{minimum post PFTs}) / pre \text{ RT PFTs}$$

A negative percentage decline represents an improvement in PFTs post-RT.

5. Evaluation of radiation-induced symptomatic pneumonitis

The modified common toxicity criteria version 2.0 of National Cancer Institute (21) were used to grade symptomatic radiation-induced shortness of breath/pneumonitis:

Grade 1 - no intervention taken;

Grade 2 - treated with medication, typically steroids;

Grade 3 - requiring oxygen or hospitalization;

Grade 4 - death.

Grade ≥ 2 radiation-induced pneumonitis was considered as an event. Patients with radiologic/physiologic changes *without* symptoms were not scored as having toxicity.

Pneumonitis was scored prospectively by the treating physicians. In addition, three physicians reviewed the medical records to confirm the diagnosis and grade of pneumonitis. Cases where the physicians were uncertain of the diagnosis (such as due to equivocal tumor progression or pre-existing pulmonary disease exacerbation), were marked as “hard to score” pneumonitis. They were included in the statistical analysis assumed as “real” pneumonitis. The statistical analysis described below was repeated after excluding the patients with “hard to score” pneumonitis. This was done to exclude the possible confounding effects of including these patients.

6. Statistical analysis

The incidences of pneumonitis, and rates of declines in PFTs post-RT (relative to pre-RT values), were compared in the chemotherapy-defined patient subgroups (yes-chemotherapy vs. no-chemotherapy) and chemotherapy-associated tumor-shrinkage-extent-defined subgroups (responders vs. non-responders) using Fisher’s exact test. Mean lung dose (MLD), percent declines in PFTs and tumor sizes, and other numeric variances were compared using analysis of variance (ANOVA). Pearson correlation was used to calculate correlation coefficients. Comparison of PFTs’ values between pre- and post-chemotherapy was analyzed using Wilcoxon signed ranks test. Correlation coefficient was calculated to evaluate the relationships using Pearson analysis. Analysis was repeated after excluding patients with small cell lung cancer (SCLC). In addition, a multivariate analysis (MVA) was performed to address the impact of chemotherapy, in the context of other variables that may also impact on RT-induced lung injury. Variables included within the MVA included induction chemotherapy (or not), age, sex, race, SCLC (or not), central tumor (or not), ongoing smoker at the time of diagnosis (or not), MLD, and pre-RT PFTs. Logistic regression was used for the endpoint of PFTs improvement vs. not (dichotomy: yes vs. no); Linear regression was used for the endpoint of the *percentage* reduction in PFTs (as a continuous variable).

RESULTS

I. Aim #1

(1) General information—Forty-two of 91 patients (46%) were treated with induction chemotherapy and forty-nine patients (54%) were not. In general, there are no dramatic differences between the groups with and without induction chemotherapy, with the exception of the age, rates of patients with small cell lung cancer (SCLC), and rates of patients with early stage (stage I-II) non-small cell lung cancer (NSCLC) (left-hand side of table 1).

(2) Changes in PFTs post-RT—The fraction of patients with improvements in FVC and FEV1 appeared slightly higher in the no-induction-chemotherapy group than in the yes-induction-chemotherapy group (left-hand side of table 2); consistent with our hypothesis. The p values were 0.01 for FVC and 0.2 for FEV1. This was not seen for DLCO (p=0.8). However, the *magnitudes* of the declines were relatively modest (left-hand side of table 3). The average percent decline in PFTs was similar in the chemotherapy vs. no-chemotherapy groups (all p values >0.05).

(3) Pneumonitis—Twenty-eight of ninety-one patients (31%) developed symptomatic (grade $\geq$ 2) RT-induced pneumonitis (22 Grade 2 and 6 Grade 3). Nine of the 28 pneumonitis patients were “hard to score”, and six of these received induction chemotherapy. The incidence of pneumonitis in the yes-induction-chemotherapy group is slightly higher than without-induction-chemotherapy (left-hand side of table 4).

(4) Multivariate analysis—On MVA, the use of chemotherapy prior to RT was associated with a higher rate of improvements in DLCO (p=0.04) with similar trends seen for FEV1

($p=0.1$) and FVC ($p=0.08$) (the 3rd-5th columns of table 5). Similarly, pre-RT chemotherapy was associated with a higher rate of RP in the multivariate models ($p=0.009-0.03$, the 2nd column of table 5). The use of pre-RT chemotherapy was not associated with the *magnitude* of changes in PFTs (the 6-8th columns of table 5).

II. Aim #2

(1) General information and tumor response to induction chemotherapy—

Nineteen of 42 patients (45%) with induction chemotherapy had $\geq 30\%$ tumor shrinkage post chemotherapy (responders) and twenty-three did not (non-responders). In general, there are no apparent differences between responders and non-responders, with the exception of the smoking history (pack years and quit-smoking years), rates of patients with early stage NSCLC and MLD (right-hand side of table 1).

The average tumor sizes of the responders and non-responders, at each phase of therapy, are summarized in table 7. The pre-treatment sizes were similar.

(2) Changes in PFTs post-RT and pneumonitis—The fractions of patients with improvement in PFTs post-RT are *higher* in responders to induction chemotherapy than in non-responders (right-hand side of table 2); counter to our hypothesis. Similarly, the average declines in PFTs were similar (for FVC and FEV1) in the two subgroups, or higher (for DLCO) in the non-responders (right-hand side of table 3), again counter to our hypothesis. The rates of pneumonitis were similar in the responders and non-responders (right-hand side of table 4).

There was no apparent relationship between the degree of chemotherapy-induced reductions in tumor size and the degree of subsequent RT-associated decline in PFTs, nor the incidence of RT-induced pneumonitis (figure 1).

The analysis was repeated (for both aim #1 and aim #2) with the “hard to score” patients excluded, and the results did not qualitatively change.

(3) Multivariate analysis—The percent shrinkage of tumor volume (as a continuous variable), had no clear association with changes in PFTs, nor the incidence of symptomatic radiation-induced pneumonitis (table 6).

III. Aim #3

Thirty-six patients with pre-chemotherapy, pre-RT (post-chemotherapy) and post-RT tumor measurements were evaluable. There is no clear association between the percent reductions in tumor size achieved after the chemotherapy vs. the degrees of subsequent reduction in tumor size seen after RT, nor the incidence of pneumonitis (figure 2 and table 7).

IV. Re-analysis excluding patients with SCLC

Analysis was repeated for only the patients with NSCLC. For aim #1, the results are similar. The *incidence of radiation-induced pneumonitis* in the yes- vs. no-chemotherapy groups were 50% vs. 23%, $p=0.03$. For aim #2, the results were also similar in the NSCLC group. On MVA, response to chemotherapy was borderline associated with a lesser risk of radiation-induced pneumonitis ($p=0.03-0.1$).

DISCUSSION

Radiation-induced lung injury is fairly common and is one of the primary dose-limiting factors in thoracic therapy. The reported incidence of symptomatic pulmonary injury is typically $\approx 10\sim 30\%$ (22-25). This variation is likely due to differences in the grading system, patient

population, and other clinical variables. The use of induction chemotherapy might also be a confounding clinical variable in these studies.

Agents' toxicities to normal tissue

The chemotherapy agents may cause injury to the lung, rendering the patient more likely to experience RT-associated lung injury.

Bleomycin is a well-recognized pulmonary toxin (26-33). Less data is available for other pulmonary agents. Dimopoulou et al. conducted a prospective study of pulmonary function in 33 patients treated with paclitaxel and carboplatin (34). They demonstrated no significant changes in most of the PFTs (FVC, FEV1, FEV1/FVC ratio, alveolar volume, or total lung capacity). However, there was a reduction in DLCO. Brooks et al. reported marked *improvements* in FEV1 and vital capacity following cyclophosphamide, methotrexate, lomustine, cincristine, doxorubicin, and procarbazine (35). Hence, it is reasonable to consider that the induction chemotherapy used in the present study had little negative impact on our patient's PFTs. In fact, pre-and post-chemotherapy PFTs were available in 12 of the patients included in the present study. There were no significant differences between the pre and post-chemotherapy percent values of FVC (75% vs. 77%, $p=0.6$), FEV1 (61% and 62%, $p=0.5$) and DLCO (69% vs. 66%, $p=0.1$); respectively (2-tailed Wilcoxon signed ranks test).

Impact of chemotherapy on tumor mass

Aim #1—In this study, we hypothesized that patients who received induction chemotherapy may be *more likely* to suffer RT-induced reductions in PFTs since they would present for RT after some chemotherapy-induced tumor shrinkage. That is, there would be *less* opportunity for RT-induced tumor shrinkage to offset the toxic effects of the RT on the lung. Stated another way, patients who do *not* receive induction chemotherapy experience changes in lung function that reflect both improvements in function due to tumor shrinkage, and reductions in function due to the RT effects on the lung itself. Patients receiving induction chemotherapy may be less likely to experience the tumor shrinkage component of these competing effects.

If this hypothesis were true, fewer improvements in PFTs and more toxicity should be observed in the patients receiving induction chemotherapy. Overall, there was no consistent difference in the *rate or magnitude* of changes in PFTs post-RT, between the patients receiving and not receiving induction chemotherapy. However, induction chemotherapy was associated with a higher rate of pneumonitis ($p=0.07$ on univariate analysis, $p=0.01$ on multiple analysis).

Aim #2—In the subgroup of patients with induction chemotherapy, the responders to chemotherapy had a *similar* rate of toxicity (both declines in PFTs and grade ≥ 2 RT-induced pneumonitis) than did the non-responders. Similarly, on the MVA, the degree of tumor shrinkage pre-RT was not related to either the rate of declines in PFTs nor symptomatic pneumonitis. This is counter to our hypothesis. In fact, the non-responders appeared to have a slightly higher rate of pneumonitis, and a higher mean percent decline in DLCO, compared to the responders. This likely is due to the slightly higher mean of MLDs in the non-responders, vs. the responders (right-hand side of table 1). This, in turn, likely reflects the slightly higher rates of NSCLC (vs. SCLC), stage III-IV (vs. stage I-II), and larger average pre-RT tumor size (right-hand of table 1, and table 7) in the non-responders compared to the responders. In other words, the non-responders appeared to have more advanced tumors at diagnosis (more stage III-IV), and larger targets at the time of RT. A higher MLD has been associated with an increased rate of pneumonitis in many trials [9,21-26].

Aim #3—The comparison of the extent of chemotherapy- vs. RT-associated tumor shrinkage is interesting (figure 2). First, most patients respond to both RT and chemotherapy. Second,

most of the patients who experienced tumor growth during chemotherapy have a subsequent response to RT. Similarly, most, but not all, of the responders to chemotherapy will have a further response to RT. There appears to be no association between the degree of response to chemotherapy and RT, nor the incidence of radiation-induced pneumonitis. This observation is consistent with the finding that the degree of chemotherapy-induced tumor response is generally *not* predictive for the later development of either changes in PFTs (right-hand side of table 2, 3) or pneumonitis (right-hand side of table 4).

Study limitations

The current study has several limitations. First, the number of patients analyzed is relatively small. Nevertheless, this issue has not been previously systematically studied, and thus the data from this limited number of patients is useful. Additional study with a larger number of patients would certainly be helpful to better understand these issues.

Second, the patients were not assigned randomly to receive or not receive chemotherapy, thus resulting in some of the imbalances noted in table 1. Several of these clinical factors, such as gender (8,16,23,36-43), age (36-39,41-46) and tobacco use (18,22,36-38,45,47), may have an impact on RT-induced lung injury, and are not considered in our analysis. For the analysis of responders vs. non-responders, it is not possible to control for all of the clinical variables (such as rates of patients with SCLC, or early stage lesions) since the phenotype of responders and non-responders may be fundamentally different.

Third, the definition of tumor size might not be optimal. When this study was initiated, it was not clear if the measurements should be taken of the primary lesion, any node/nodes, or the sum of tumor and nodes, and whether the results would change if different portions of the tumor were assessed. Therefore, in the initial 14 patients, the primary lesion and the enlarged mediastinal node were each measured separately. In these pilot patients, the maximum tumor “area” (the longest tumor diameter multiplied by the greatest perpendicular diameter, as defined in the 1979 WHO criteria for reporting results of cancer treatment (48)) of each patient’s lesions [i.e. the primary lesion and the enlarged mediastinal lymph node(s)], on both pre- and post-chemotherapy (pre-RT) CT images, were measured. The degrees of shrinkage to multiple lesions *within the same patient* were compared. Twenty pairs of lesions (primary lesion and lymph node) were evaluable (in several of the 14 patients with more than one node, multiple comparisons of primary lesion vs. node were possible). The mean percent reduction in size of the primary lesion and the nodal mass was 32% and 27%, respectively. These degrees of shrinkage were correlated with each other ($r=0.7$, $p=0.001$; Pearson correlation analysis), and the difference between the 2 groups was not statistically significant ($p=0.6$, 2-tailed compared t-test). Thus, when there are multiple evaluable lesions, their degrees of response to chemotherapy are comparable. Therefore, based on the result noted above, it seemed reasonable to consider measurements of the primary lesion, nodes or both as we did in the present study.

Fourth, the measurements used in the study were based on unidimensional (the longest tumor diameter) assessments from CT based on RECIST. Volumetric assessments may have provided a better estimate of overall tumor response. It was not possible for such in-depth measurements, as this component of the study was performed retrospectively. To address this, 37 patients receiving induction chemotherapy with bi-dimensional measurements were studied. The percent reductions in the longest tumor diameter (one dimension) and the maximum tumor “area” (two dimensions) were compared and found to be highly correlated with each other (figure 3). Thus, response based on unidimensional measurement appears to be a reasonable surrogate for bi-dimensional product. However, bi-dimensional measurement remains suboptimal since it is not the real area (i.e. the defined “area” is only an approximation) and the third dimension information is lacking. Further, the cutpoint of 30% reduction to denote a

partial response is an arbitrary convention (19). We reanalyzed the differences between responders and non-responders using 50% as cut point and the results were similar.

Fifth, we herein assumed that all post-RT changes were due to the RT only. In the patients receiving induction chemotherapy, some of tumor and normal lung changes seen post-RT may have been, in part, also related to “delayed” effects from the previous chemotherapy.

Sixth, the analysis was conducted in patients with either small- or non-small cell lung cancer since patients in both types of histology were enrolled onto our studies and hence were evaluable. The degrees of tumor response maybe different in the small vs. non-small cell subgroups. The analysis was repeated in patients with NSCLC, and the results were not qualitatively changed.

CONCLUSION

In summary, the use of pre-RT chemotherapy appears to increase the risk of radiation-induced pneumonitis, but has no consistent impact on changes in PFTs. The degree of induction-chemotherapy-associated tumor shrinkage is *not* associated with the rate of subsequent-RT-associated pulmonary toxicity. The extent of tumor shrinkage to chemotherapy pre-RT is not correlated to the extent of tumor response to subsequent-RT. Since induction chemotherapy is often used to treat patients with lung cancer (1,3,5,14) and the limitations of the current study noted above, additional study is needed to better clarify this issue.

Acknowledgements

Supported, in part, by NIH grant R01-CA69579. Thanks to UNC for PLUNC planning software.

References

1. Dillman RO, Herndon J, Seagren SL, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996;88:1210–1215. [PubMed: 8780630]
2. 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 in 353 patients. *J Natl Cancer Inst* 1991;83:417–423. [PubMed: 1847977]
3. Sause WT, Scott C, Taylor S, et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst* 1995;87:198–205. [PubMed: 7707407]
4. Reboul F, Brewer Y, Vincent P, et al. Concurrent cisplatin, etoposide, and radiotherapy for unresectable stage III nonsmall cell lung cancer: a phase II study. *Int J Radiat Oncol Biol Phys* 1996;35:343–350. [PubMed: 8635942]
5. Argiris A, Liptay M, LaCombe M, et al. A phase I/II trial of induction chemotherapy with carboplatin and gemcitabine followed by concurrent vinorelbine and paclitaxel with chest radiation in patients with stage III non-small cell lung cancer. *Lung Cancer* 2004;45:243–253. [PubMed: 15246197]
6. Marks LB, Yu X, Vujaskovic Z, et al. Radiation-induced lung injury. *Semin Radiat Oncol* 2003;13:333–345. [PubMed: 12903021]
7. Fan M, Marks LB, Lind P, et al. Relating radiation-induced regional lung injury to changes in pulmonary function tests. *Int J Radiat Oncol Biol Phys* 2001;51:311–317. [PubMed: 11567804]
8. Hernando ML, Marks LB, Bentel GC, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. *Int J Radiat Oncol Biol Phys* 2001;51:650–659. [PubMed: 11597805]
9. Kocak Z, Evans ES, Zhou SM, et al. Challenges in defining radiation pneumonitis in patients with lung cancer. *Int J Radiat Oncol Biol Phys* 2005;62:635–638. [PubMed: 15936538]

10. Marks LB, Hollis D, Munley M, et al. The role of lung perfusion imaging in predicting the direction of radiation-induced changes in pulmonary function tests. *Cancer* 2000;88:2135–2141. [PubMed: 10813726]
11. Choi NC, Kanarek DJ. Toxicity of thoracic radiotherapy on pulmonary function in lung cancer. *Lung Cancer* 1994;10(Suppl 1):S219–230. [PubMed: 8087514]
12. De Jaeger K, Seppenwoolde Y, Boersma LJ, et al. Pulmonary function following high-dose radiotherapy of non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003;55:1331–1340. [PubMed: 12654445]
13. Abratt RP, Willcox PA, Smith JA. Lung cancer in patients with borderline lung functions--zonal lung perfusion scans at presentation and lung function after high dose irradiation. *Radiother Oncol* 1990;19:317–322. [PubMed: 2284442]
14. Marks LB, Garst J, Socinski MA, et al. Carboplatin/paclitaxel or carboplatin/vinorelbine followed by accelerated hyperfractionated conformal radiation therapy: report of a prospective phase I dose escalation trial from the Carolina Conformal Therapy Consortium. *J Clin Oncol* 2004;22:4329–4340. [PubMed: 15514374]
15. Socinski MA, Marks LB, Garst J, et al. Carboplatin/paclitaxel or carboplatin/vinorelbine followed by accelerated hyperfractionated conformal radiation therapy: a preliminary report of a phase I dose escalation trial from the Carolina Conformal Therapy Consortium. *Oncologist* 2001;6(Suppl 1):20–24. [PubMed: 11182001]
16. Anscher MS, Marks LB, Shafman TD, et al. Using plasma transforming growth factor beta-1 during radiotherapy to select patients for dose escalation. *J Clin Oncol* 2001;19:3758–3765. [PubMed: 11533099]
17. Garst J, Shafman T, D'Amico T, et al. A phase II trial of neo-adjuvant concurrent carboplatin and vinorelbine chemotherapy with radiation followed by surgical resection in patients with stage IIB/IIIA non-small cell lung cancer. *Proc Am Soc Clin Oncol JCO* 2002;21:318a.(abstract 1268)
18. Maguire PD, Marks LB, Sibley GS, et al. 73.6 Gy and beyond: hyperfractionated, accelerated radiotherapy for non-small-cell lung cancer. *J Clin Oncol* 2001;19:705–711. [PubMed: 11157021]
19. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216. [PubMed: 10655437]
20. Marks LB, Munley MT, Bentel GC, et al. Physical and biological predictors of changes in whole-lung function following thoracic irradiation. *Int J Radiat Oncol Biol Phys* 1997;39:563–570. [PubMed: 9336133]
21. Arbuck, SG.; Ivy, SP.; A, S., et al. Common Toxicity Criteria v 2.0. 1997. <http://ctep.info.nih.gov>
22. Fay M, Tan A, Fisher R, et al. Dose-volume histogram analysis as predictor of radiation pneumonitis in primary lung cancer patients treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;61:1355–1363. [PubMed: 15817337]
23. Kocak Z, Yu X, Zhou SM, et al. The impact of pre-radiotherapy surgery on radiation-induced lung injury. *Clin Oncol (R Coll Radiol)* 2005;17:210–216. [PubMed: 15999420]
24. Kwa SL, Lebesque JV, Theuws JC, et al. Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients. *Int J Radiat Oncol Biol Phys* 1998;42:1–9. [PubMed: 9747813]
25. Schraube P, Schell R, Wannenmacher M, et al. Pneumonitis after radiotherapy of bronchial carcinoma: incidence and influencing factors. *Strahlenther Onkol* 1997;173:369–378. [PubMed: 9265259]
26. Hirsch A, Vander Els N, Straus DJ, et al. Effect of ABVD chemotherapy with and without mantle or mediastinal irradiation on pulmonary function and symptoms in early-stage Hodgkin's disease. *J Clin Oncol* 1996;14:1297–1305. [PubMed: 8648387]
27. Kharasch VS, Lipsitz S, Santis W, et al. Long-term pulmonary toxicity of multiagent chemotherapy including bleomycin and cyclophosphamide in osteosarcoma survivors. *Med Pediatr Oncol* 1996;27:85–91. [PubMed: 8649325]

28. Lucraft HH, Wilkinson PM, Stretton TB, et al. Role of pulmonary function tests in the prevention of bleomycin pulmonary toxicity during chemotherapy for metastatic testicular teratoma. *Eur J Cancer Clin Oncol* 1982;18:133–139. [PubMed: 6178590]
29. Wolkowicz J, Sturgeon J, Rawji M, et al. Bleomycin-induced pulmonary function abnormalities. *Chest* 1992;101:97–101. [PubMed: 1370265]
30. Theuws JC, Muller SH, Seppenwoolde Y, et al. Effect of radiotherapy and chemotherapy on pulmonary function after treatment for breast cancer and lymphoma: A follow-up study. *J Clin Oncol* 1999;17:3091–3100. [PubMed: 10506604]
31. Jensen JL, Goel R, Venner PM. The effect of corticosteroid administration on bleomycin lung toxicity. *Cancer* 1990;65:1291–1297. [PubMed: 1689606]
32. Niitani H. Bleomycin. *Gan To Kagaku Ryoho* 1987;14:3173–3179. [PubMed: 2445296]
33. Theuws JC, Kwa SL, Wagenaar AC, et al. Prediction of overall pulmonary function loss in relation to the 3-D dose distribution for patients with breast cancer and malignant lymphoma. *Radiother Oncol* 1998;49:233–243. [PubMed: 10075256]
34. Dimopoulou I, Galani H, Dafni U, et al. A prospective study of pulmonary function in patients treated with paclitaxel and carboplatin. *Cancer* 2002;94:452–458. [PubMed: 11900231]
35. Brooks BJ Jr, Seifter EJ, Walsh TE, et al. Pulmonary toxicity with combined modality therapy for limited stage small-cell lung cancer. *J Clin Oncol* 1986;4:200–209. [PubMed: 3003259]
36. Tsujino K, Hirota S, Endo M, et al. Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. *Int J Radiat Oncol Biol Phys* 2003;55:110–115. [PubMed: 12504042]
37. Claude L, Perol D, Ginestet C, et al. A prospective study on radiation pneumonitis following conformal radiation therapy in non-small-cell lung cancer: clinical and dosimetric factors analysis. *Radiother Oncol* 2004;71:175–181. [PubMed: 15110451]
38. Inoue A, Kunitoh H, Sekine I, et al. Radiation pneumonitis in lung cancer patients: a retrospective study of risk factors and the long-term prognosis. *Int J Radiat Oncol Biol Phys* 2001;49:649–655. [PubMed: 11172945]
39. Kim TH, Cho KH, Pyo HR, et al. Dose-volumetric parameters for predicting severe radiation pneumonitis after three-dimensional conformal radiation therapy for lung cancer. *Radiology* 2005;235:208–215. [PubMed: 15703313]
40. Novakova-Jiresova A, Van Gameren MM, Coppes RP, et al. Transforming growth factor-beta plasma dynamics and post-irradiation lung injury in lung cancer patients. *Radiother Oncol* 2004;71:183–189. [PubMed: 15110452]
41. Rancati T, Ceresoli GL, Gagliardi G, et al. Factors predicting radiation pneumonitis in lung cancer patients: a retrospective study. *Radiother Oncol* 2003;67:275–283. [PubMed: 12865175]
42. Robnett TJ, Machtay M, Vines EF, et al. Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. *Int J Radiat Oncol Biol Phys* 2000;48:89–94. [PubMed: 10924976]
43. Yamada M, Kudoh S, Hirata K, et al. Risk factors of pneumonitis following chemoradiotherapy for lung cancer. *Eur J Cancer* 1998;34:71–75. [PubMed: 9624240]
44. Gagliardi G, Bjohle J, Lax I, et al. Radiation pneumonitis after breast cancer irradiation: analysis of the complication probability using the relative seriality model. *Int J Radiat Oncol Biol Phys* 2000;46:373–381. [PubMed: 10661344]
45. Monson JM, Stark P, Reilly JJ, et al. Clinical radiation pneumonitis and radiographic changes after thoracic radiation therapy for lung carcinoma. *Cancer* 1998;82:842–850. [PubMed: 9486572]
46. Quon H, Shepherd FA, Payne DG, et al. The influence of age on the delivery, tolerance, and efficacy of thoracic irradiation in the combined modality treatment of limited stage small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1999;43:39–45. [PubMed: 9989512]
47. Johansson S, Bjerner L, Franzen L, et al. Effects of ongoing smoking on the development of radiation-induced pneumonitis in breast cancer and oesophagus cancer patients. *Radiother Oncol* 1998;49:41–47. [PubMed: 9886696]
48. Organization WH. WHO handbook for reporting results of cancer treatment. 1979.

Figure 1.

The relationship between subsequent RT-associated percent declines in FEV1 and percent reductions in tumor size to induction chemotherapy are shown ($r=0.2$, $p=0.2$; Pearson correlation analysis). Patients with radiation-induced grade 2-3 pneumonitis appeared to be randomly distributed. Results were similar for percent declines in FVC (forced vital capacity) and DLCO (diffusion capacity for carbon monoxide). (RT: radiotherapy, FEV1: forced expiratory volume in 1 second)

Figure 2.

Comparison of the degree of tumor shrinkage ascribed to induction chemotherapy vs. subsequent RT. No correlation was found ($r=0.2$, $p=0.3$; Pearson correlation analysis). Patients with radiation-induced pneumonitis appeared to be randomly distributed. (RT: radiotherapy)

Figure 3.

Pre-RT unidimensional measurements (the longest tumor diameter: cm) and bi-dimensional measurements are highly correlated (Values of r and p were calculated using Pearson correlation.). Similar results were obtained in pre-chemotherapy and post-RT tumor measurement data sets.

Table 1

Patient characteristics

Characters	All patients	Without pre-RT chemo	With pre-RT chemo	* (No-chemo vs. Yes-chemo)	Non-responders (<50% Shrinkage to chemo)	Responders (≥50% Shrinkage to chemo)	* (Responders vs. Non-responders)
Gender, % (n)							
Male	52%(47/91)	61%(30/49)	40%(17/42)	0.06	48%(11/23)	32%(6/19)	0.4
Female	48%(41/91)	39%(19/49)	60%(25/42)		52%(12/23)	68%(13/19)	
Race, % (n)							
White	88%(80/91)	86%(42/49)	91%(38/42)	0.5	87%(20/23)	95%(18/19)	0.6
Others [‡]	12%(11/91)	14%(7/49)	9%(4/42)	0.005	13%(3/23)	5%(1/19)	0.8
Age, years (range)	64(40-87)	67(40-87)	62(46-74)		61(46-73)	62(46-74)	
Smoking history							
Pack years (range)	52(0-125)	54(0-120)	50(0-125)	0.5	39(0-100)	63(20-125)	0.02
Quit years (range)	7(0-45)	8(0-45)	5(0-30)	0.3	9(0-30)	2(0-8)	0.009
Tumor status, % (n)							
SCLC	15%(14/91)	4%(2/49)	29%(12/42)	0.002	22%(5/23)	37%(7/19)	0.3
NSCLC	85%(77/91)	96%(47/49)	71%(30/42)		78%(18/23)	63%(12/19)	
I-II	25%(19/77)	34%(16/47)	10%(3/30)	0.03	0%(0/18)	25%(3/12)	0.05
III-IV/Recurrence	75%(58/77)	66%(31/47)	90%(27/30)		100%(18/18)	75%(9/12)	
Central tumor, % (n)	67%(61/91)	61%(30/49)	74%(31/42)	0.2 [‡]	74%(17/23)	74%(14/19)	1 [‡]
RT dose, Gy (range)	66(36-86)	66(36-86)	65(40-86)	0.9	66(54-86)	64(40-86)	0.7
MLD, Gy (range)	19(3-35)	18(3-35)	20(6-29)	0.3	22(15-29)	17(6-25)	0.001

Abbreviations: RT=radiotherapy, chemo=chemotherapy, SCLC=small cell lung cancer, NSCLC=non-small cell lung cancer, RT=radiotherapy, MLD=mean lung dose

* p values were calculated using Fisher's exact test for nominal parameters and analysis of variance for others.

[‡] Others: Black and Asian

[‡] Central tumors (involvement of primary tumor or lymph node to hilum or mediastinum) vs. peripheral tumors

Table 2

Rates of patients with improvement in PFTs post-RT as a function of use of chemotherapy, and the tumor response to chemotherapy

Rates of patients with improvement in:
All patients
Without pre-RT chemo
With pre-RT chemo
 p^* (No-chemo vs. Yes-chemo)
Non-responders (<50% Shrinkage to chemo)
Responders ($\geq$ 50% Shrinkage to chemo)
 p^* (Responders vs. Non-responders)

FVC, % (n)	18% (16/87)	28% (13/46)	7% (3/41)	0.01	4% (1/24)	11% (2/18)	0.6
FEV1, % (n)	14% (11/81)	19% (8/43)	8% (3/38)	0.2	5% (1/21)	12% (2/17)	0.6
DLCO, % (n)	21% (17/82)	19% (8/43)	23% (9/39)	0.8	14% (3/21)	32% (6/19)	0.3

Abbreviations: PFTs=pulmonary function tests, RT=radiotherapy, chemo=chemotherapy, FVC=forced vital capacity, FEV1=forced expiratory volume in 1 second, DLCO= diffusion capacity for carbon monoxide

* p values were calculated using Fisher's exact test.

Table 3

Means of percent declines in PFTs post-RT as a function of use of chemotherapy, and the tumor response to chemotherapy

All patients	Without pre-RT chemo	With pre-RT chemo	<i>p</i> * (No-chemo vs. Yes-chemo)	Non-responders (<50% Shrinkage to chemo)	Responders (≥50% Shrinkage to chemo)	<i>p</i> * (Responders vs. Non-responders)
FVC	13%	11%	0.3	18%	13%	0.5
FEV1	14%	13%	0.7	17%	13%	0.7
DLCO	17%	18%	0.9	27%	5%	0.02

Abbreviations: PFTs=pulmonary function tests, RT=radiotherapy, chemo=chemotherapy, FVC=forced vital capacity, FEV1=forced expiratory volume in 1 second, DLCO= diffusion capacity for carbon monoxide

* *p* values were calculated using analysis of variance.

Table 4

Incidences of radiation-induced pneumonitis (RP)						
% (n)	All patients	Without pre-RT chemo	With pre-RT chemo	<i>p</i> [*] (No-chemo vs. Yes-chemo)	Non-responders (<50% Shrinkage to chemo)	Responders (≥50% Shrinkage to chemo)
Grade 2-3 RP	31% (28/91)	22% (11/49)	40% (17/42)	0.07 [†]	43% (10/23)	37% (7/19)
"Hard to score" excluded	23% (19/82)	17% (8/46)	31% (11/36)	0.2 [‡]	32% (6/19)	29% (5/17)
						0.8 [‡]
						1 [‡]

Abbreviations: RT=radiotherapy, chemo=chemotherapy

^{*} *p* values were calculated using Fisher's exact test.

[†] Grade 2-3 vs. Grade 0-1 radiation-induced pneumonitis.

[‡] "Hard to score" vs. classic radiation-induced pneumonitis.

Table 5
Multivariate analysis for predicting changes in PFTs and radiation-induced pneumonitis

Patient number	RP	Logistic regression			Linear regression		
		Rate of improvement in FVC	Rate of improvement in FEV1	Rate of improvement in DLCO	%reduction in FVC	%reduction in FEV1	%reduction in DLCO
	n=81	n=86	n=81	n=81	n=91	n=91	n=91
Pre-RT chemotherapy	0.009	0.08	0.1	0.04	0.4	0.5	0.3
Age	0.6	0.5	0.9	0.2	0.6	0.7	0.04
Sex	0.1	0.2	0.6	0.08	0.2	0.2	1
Race	0.3	0.1	0.8	0.5	0.8	0.6	0.2
SCLC	0.09	0.06	0.06	0.9	0.001	0.002	0.7
Central tumor	0.8	0.3	0.7	0.4	0.2	0.2	1
Ongoing Smoker	0.7	0.3	0.4	0.6	0.4	0.7	0.5
MLD	0.08	0.9	0.4	0.5	0.2	0.4	0.9
Pre-RT PFTs (FEV1)	0.009	0.004	0.7	0.001	0.003	0.1	<0.001

Abbreviations: PFTs=pulmonary function tests, RP=radiation-induced pneumonitis, FVC=forced vital capacity, FEV1=forced expiratory volume in 1second, DLCO= diffusion capacity for carbon monoxide, RT=radiotherapy, SCLC=small cell lung cancer, MLD=mean lung dose

Table 6
Multivariate analysis for predicting changes in PFTs and radiation-induced pneumonitis in patients with chemotherapy

Patient number	RP	Logistic regression			Linear regression		
		Improvement in FVC	Improvement in FEV1	Improvement in DLCO	% reduction in FVC	% reduction in FEV1	% reduction in DLCO
	n=38	n=40	n=38	n=38	n=91	n=91	n=91
Age	0.5	1	1	0.6	0.7	0.8	0.04
Sex	0.3	1	1	0.2	0.7	0.9	0.8
Race	0.6	1	1	1	0.8	0.7	0.6
SCLC	0.06	1	1	0.7	0.02	0.07	0.7
Central tumor	0.9	1	1	0.4	0.4	0.7	1
Ongoing Smoker	0.7	1	1	0.1	0.2	0.2	0.2
MLD	0.8	1	1	0.5	0.5	0.5	0.7
% tumor shrinkage to chemotherapy	0.1 (rr=1.02)	1	1	0.07	0.3	0.2	0.7
Pre-RT FEV1	0.02	1	1	0.08	0.06	0.4	<0.001

Abbreviations: PFTs=pulmonary function tests, RP=radiation-induced pneumonitis, FVC=forced vital capacity, FEV1=forced expiratory volume in 1second, DLCO= diffusion capacity for carbon monoxide, RT=radiotherapy, SCLC=small cell lung cancer, MLD=mean lung dose, rr=risk ratio

Table 7

Means of tumor sizes at different phases of therapy

	Patients with chemotherapy	Non-responders	Responders	p *
Tumor size pre-chemotherapy	5.5 cm; n=40	5.0 cm	6.3 cm	0.1
Tumor size pre-RT (post-chemotherapy)	3.9 cm; n=42	5.0 cm	2.7 cm	0.001
Tumor size post-RT	2.6 cm; n=36	3.4 cm	1.7 cm	0.03
Percent reduction in tumor size to chemotherapy	22%; n=42	-5%	55%	0.001
Percent reduction in tumor size to RT	33%; n=36	27%	41%	0.4

Abbreviations: RT=radiotherapy

* p values were calculated using analysis of variance.