Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2018 November 15; 102(4): 709–715. doi:10.1016/j.ijrobp.2017.10.032.

Positron Emission Tomography—Adjusted Intensity Modulated Radiation Therapy for Locally Advanced Non—Small Cell Lung Cancer

Nitin Ohri, MD*, William R. Bodner, MD*, Rafi Kabarriti, MD*, Viswanathan Shankar, DrPH[†], Haiying Cheng, MD, PhD[‡], Tony Abraham, DO[§], Balazs Halmos, MD[‡], Rasim Gucalp, MD[‡], Roman Perez-Soler, MD[‡], Shalom Kalnicki, MD*, and Madhur Garg, MD*

*Department of Radiation Oncology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York

[‡]Department of Oncology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York

[§]Department of Radiology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York

[†]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York

Abstract

Purpose—To perform a prospective trial examining positron emission tomography (PET)-based, dose-painted intensity modulated radiation therapy (IMRT) in the setting of locally advanced non—small cell lung cancer (NSCLC).

Methods and Materials—Patients with stage IIB-III NSCLC were treated with 25 fractions of dose-painted IMRT. Tumors or lymph nodes with metabolic tumor volume exceeding 25 cm³ were deemed “high risk” and received 65 Gy. Smaller lesions were treated with 57 Gy or 52.5 Gy (after November 2014). Patients received concurrent weekly carboplatin (area under the curve = 2) and paclitaxel (45 mg/m²). The primary study endpoint was the absence of high residual metabolic activity (maximum standardized uptake value > 6) in treated lesions on PET 12 to 16 weeks after completion of IMRT.

Results—Thirty-five subjects with 116 hypermetabolic lesions were eligible for analysis. The primary endpoint was met for 24 of 30 patients (80%) who underwent posttreatment PET, satisfying our efficacy objective. With a median follow-up duration of 23.8 months for living patients, progression in a lesion targeted with radiation therapy has been observed in 5 patients (14%). Treating progression in other sites and death without progression as competing risks, 2-year cumulative incidence rates of local disease progression in high-risk lesions (n=24) and low-

Reprint requests to: Nitin Ohri, MD, Department of Radiation Oncology, Albert Einstein College of Medicine, Montefiore Medical Center, 111 East 210th St, Bronx, NY 10467. Tel: (718) 920-7750; ohri.nitin@gmail.com.

Conflict of interest: none.

risk lesions (n=92) are 9% and 3%, respectively. The actuarial rate of overall survival at 2 years is 52%.

Conclusions—Dose-painted IMRT based on pretreatment PET metrics with concurrent chemotherapy yields high rates of metabolic response and local disease control for locally advanced NSCLC. Future trials should test this approach to maximize the therapeutic ratio of thoracic radiation therapy.

Introduction

Standard treatment for fit patients with locally advanced non—small cell lung cancer (NSCLC) is a combination of thoracic radiation therapy with concurrent chemotherapy. Radiation therapy is typically directed at pulmonary tumors and regional lymph nodes thought to bear disease according to radiographic and pathologic evaluations (1), and all target volumes are typically treated with a dose of approximately 60 Gy (2).

¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a key component of the staging workup for NSCLC (3). Recent reports indicate that disease burden on PET is a powerful prognostic factor for NSCLC patients treated with definitive chemoradiotherapy (4), and local disease progression most often occurs in tumors or lymph nodes with high metabolic tumor volume (MTV) on pretreatment PET (5). Exposure of nearby organs at risk to high doses of radiation therapy has been associated with reduced survival times in this patient population (6). We therefore conducted a prospective trial to examine the strategy of using dose-painted intensity modulated radiation therapy (IMRT) based on pretreatment PET metrics.

Methods and Materials

Study design and participants

This was a single-institution, single-arm, phase 2 study. Adult patients with stage IIB-III NSCLC, Eastern Cooperative Oncology Group performance status 0 to 2, and no prior treatment with chemotherapy or radiation therapy for lung cancer were eligible. Patients with radically treated brain metastases and no other evidence of metastatic disease were also eligible, but no such patients were enrolled. Staging PET/computed tomography (CT) and brain magnetic resonance imaging were required within 42 days before study entry. If PET/CT was performed more than 42 days before study entry and could not be repeated, CT demonstrating stable disease was required.

This study protocol was approved by the Albert Einstein College of Medicine institutional review board. All subjects provided written informed consent before any study-related treatment or procedures commenced.

Procedures

For FDG-PET, patients were instructed to fast for at least 4 hours before intravenous administration of a weight-adjusted ¹⁸F-FDG dose of 5.18 MBq/kg. Approximately 60 minutes after radiopharmaceutical administration, images from the base of skull to mid-

thighs were acquired on a Philips Gemini TF time-of-flight PET/CT scanner (Philips Medical Systems, Cleveland, OH) with a spatial resolution of 5 mm in the center of the field of view, with emission scan acquired from 1 minute at 40 seconds per frame in 3-dimensional acquisition mode. Computed tomography scanning without contrast was performed in spiral CT mode from mid-thighs to the base of skull at 100 mAs and 120 keV and utilized for non-uniform attenuation correction. All PET/CT scans were performed on the same scanner. The PET/CT scans were not performed in the radiation therapy treatment position. Images were transferred to a commercially available software package (MIMvista, Cleveland, OH). Using a semiautomatic gradient-based contouring algorithm ("PET Edge"), all visible thoracic hypermetabolic tumors and lymph nodes were contoured. On the basis of previous analyses of patterns of failure in this setting (5), lesions with MTV below 25 cm³ were deemed "low-risk," and lesions with MTV exceeding 25 cm³ were deemed "high risk."

All patients were treated with a 25-fraction course of dose-painted IMRT over 5 weeks. High-risk lesions were treated with a dose of 65 Gy (2.6 Gy per fraction) unless they were adjacent to the brachial plexus or spinal cord, in which case a dose of 60 Gy (2.4 Gy per fraction) could be used. Low-risk lesions were treated with 57 Gy (2.28 Gy per fraction) until November 2014, when the study was amended according to newly released data (2, 5) to reduce the prescription dose for such lesions to 52.5 Gy (2.1 Gy per fraction). The initial doses of 65 Gy for high-risk lesions and 57 Gy for low-risk lesions were selected because they yield similar time-adjusted biologically equivalent doses to the 2 dose levels tested in Radiation Therapy Oncology Group (RTOG) protocol 0617 (7, 8). The modified dose of 52.5 Gy for low-risk lesions represents a conservative 10% reduction in time-adjusted biologically equivalent dose.

Target lesions were delineated on simulation CT imaging, using lung or mediastinal window levels as appropriate. Elective nodal irradiation was not used. Standard dosimetric constraints for normal tissues were used. Treatments were delivered using daily image guidance. Adaptive planning was not used.

All patients received concurrent weekly carboplatin (area under the curve = 2) and paclitaxel (45 mg/m²) during radiation therapy, and adjuvant chemotherapy was optional. Patients underwent posttreatment PET 12 to 16 weeks after completion of IMRT and then were followed with CT or PET every 3 months for 2 years and then every 6 months. Adverse events were scored using Common Terminology Criteria for Adverse Events version 4.0 at each study visit. Adverse events occurring within 90 days of radiation therapy completion were categorized as acute toxicities, and subsequent adverse events were categorized as late toxicities.

Statistical analyses

The primary study endpoint was the absence of high residual metabolic activity (maximum standardized uptake value [SUV] > 6.0) in the primary tumor and regional (hilar, mediastinal, and supraclavicular) lymph nodes on posttreatment PET. This endpoint was selected because it is comparable to a peak SUV of 5.0, which was found to be a prognostic factor in American College of Radiology Imaging Network (ACRIN) 6668/RTOG 0235 (9). We hypothesized that the primary endpoint would be achieved in 85% of subjects treated on

this protocol, compared with the observed rate of approximately 65% in ACRIN 6668/ RTOG 0235. A total sample size of 39 subjects was projected to yield 31 posttreatment PET studies. Achievement of the primary endpoint in at least 24 subjects would lead us to accept the study hypothesis.

Secondary endpoints included time to local disease progression, time to progression at any site, and time to death, calculated from the date of study registration. Overall survival (OS) and progression-free survival (PFS) rates were estimated using the Kaplan-Meier method. Local failure rates for individual tumors and lymph nodes, as well as in-field failure rates for study subjects, were calculated using the cumulative incidence method, treating progression at other sites and death from any cause as competing risks.

All analyses were performed using MATLAB (Math-Works, Natick, MA).

Results

Patient and treatment characteristics

Between August 2013 and July 2016, 35 eligible study subjects were enrolled. Four additional subjects signed study consent but were not treated on the protocol because of consent withdrawal (n=2) or being deemed ineligible for chemotherapy (n=2). Patient characteristics are summarized in Table 1. Median follow-up time is 5.5 months for the entire cohort and 23.8 months for surviving patients. One subject has been found to harbor an actionable *EGFR* mutation, and no actionable *ALK* rearrangements have been identified.

The 35 evaluable subjects had a total of 116 hypermetabolic lesions (34 primary tumors and 82 regional lymph nodes, median 3 lesions per subject, range 1–8) that were targeted with radiation therapy. Of 116 lesions, 24 (21%) were classified as high risk according to MTV and were treated with a dose of 65 Gy (n=20) or 60 Gy (n=4), on the basis of proximity to the spinal cord or brachial plexus. Of 34 primary tumors, 21 (62%) were classified as high risk. Of 116 lesions, 92 (79%) were classified as low risk and treated with doses of 57 Gy (n=20) or 52.5 Gy (n=72), according to the date of enrollment. Of 82 lymph nodes, 79 (96%) were classified as low risk. All subjects received weekly carboplatin and paclitaxel concurrent with radiation therapy. Seven subjects (20%) received at least 1 cycle of adjuvant chemotherapy.

Response on PET

Thirty out of 35 patients underwent posttreatment PET/CT 12 to 16 weeks after completion of radiation therapy. Two patients missed several PET/CT appointments and underwent PET/CT several months later than planned, and 3 patients did not undergo posttreatment PET/CT owing to clinical decompensation (n=2) or death (n=1). The primary endpoint of achieving a maximum SUVof <6.0 in the primary tumor and regional lymph nodes on posttreatment PET/CT was achieved in 24 of 30 patients (80%), satisfying our prespecified primary efficacy endpoint.

Clinical outcomes

At the time of this analysis, 22 of 35 patients have developed disease progression. Eleven patients have died, 7 of whom developed disease progression before death. Median PFS duration is 7.0 months, and the median OS duration has not been reached. The 24-month rates of PFS and OS are 23% and 52%, respectively. Kaplan-Meier curves for PFS and OS are shown in Figure 1. Median PFS duration for the 6 patients who did not meet the primary imaging endpoint was 4.6 months, and median PFS duration for the 24 patients who met that endpoint was 7.5 months. Median OS duration for patients who did not meet the primary imaging endpoint was 12.9 months, and the median OS duration for patients who met that endpoint has not been reached.

Adverse events are summarized in Table 2. No grade 5 adverse events were observed, and all grade 4 events were hematologic. Grade 3 nonhematologic acute adverse events included dehydration in 4 subjects (11%), dermatitis in 2 subjects (6%), dysphagia in 2 subjects (6%), nausea in 2 subjects (6%), and pneumonitis in 2 subjects (6%). In total, grade 3 adverse events were observed at any time in 30 of 35 subjects (86%). Grade 3 nonhematologic adverse events were observed at any time in 15 of 35 subjects (43%).

Patterns of local disease progression

In 5 of the 23 patients with progressive disease, the first site(s) of progression included a tumor or lymph node treated with radiation therapy. Time to progression for those patients ranged from 6.3 to 10.8 months, and all 5 of those patients are still alive, with follow-up of 2.5 to 22.6 months after local progression. Treating progression in other sites and death without progression as competing risks, 1- and 2-year cumulative incidence rates of local disease progression for study subjects were both 15%.

Four of the 5 lesions targeted with radiation therapy that became the first site of progressive disease were primary lung tumors. The fifth was a supraclavicular lymph node. Two of those 5 lesions were deemed high risk according to MTV (36-cm^3 and 62-cm^3 primary tumors), and 3 were classified as low risk (2-cm^3 lymph node, 2-cm^3 tumor, and 21-cm^3 tumor). Treating progression in other sites and death without progression as competing risks, 1- and 2-year cumulative incidence rates of local disease progression for low-risk lesions were both 3%. The 1- and 2-year cumulative incidence rates of local disease progression for high-risk lesions were both 9% (Fig. 2). A scatterplot of radiation therapy dose received (minimum dose received by 90% of the planning target volume) versus MTV for individual tumors and lymph nodes is shown in Figure 3.

Discussion

To our knowledge this is the first completed prospective trial using dose-painted radiation therapy for locally advanced NSCLC based on pretreatment imaging metrics. We have demonstrated that this approach is feasible and well tolerated, and responses on posttreatment PET/CT and early clinical outcomes seem to be favorable compared with historical series.

Our rationale for exploring dose-painted radiation therapy was 2-fold. We hypothesized that increasing both the total radiation therapy dose and the daily radiation therapy dose delivered to high-risk lesions (compared with a standard schedule of 60 Gy in 30 fractions) might enhance our ability to achieve local control of large tumors and lymph nodes. This concept has been challenged, to some extent, by the results of RTOG 0617 (2) and recent meta-analyses (10, 11) demonstrating that dose escalation may not improve local control in this setting. Additional strategies to improve local control of large lesions, such as a boost with stereotactic radiosurgery (12) or the incorporation of surgical resection for appropriate patients (13), should be explored. Although most locally advanced NSCLC patients treated with chemoradiotherapy in current practice develop metastatic disease, improvements in systemic therapy may be expected to increase the importance of local disease control in the future (14).

Our second hypothesis was that the use of a relatively low radiation therapy dose for low-risk lesions will reduce treatment-related morbidity without compromising efficacy. We previously demonstrated that in-field disease progression most often occurs in tumors or lymph nodes with high MTV, and we did not observe an association between radiation therapy dose and local control in small lesions (5, 15). The low rates of local progression in low-risk lesions treated with 52.5 or 57 Gy in the present study support the notion that dose de-escalation for selected lesions will not compromise disease control rates. Reducing the radiation therapy dose delivered to small tumors and lymph nodes, which accounted for approximately 80% of lesions in this trial, can be expected to reduce acute toxicities, such as esophagitis (16), and may lead to meaningful reductions in cardiac toxicity (17, 18), which has recently been recognized to be an important consequence of thoracic irradiation in this setting. Reduced irradiation of thoracic structures may be particularly advantageous when immunotherapy is incorporated into the management of locally advanced NSCLC (19), owing to reduced immunosuppression (20) and reduced risk of pulmonary toxicity (21).

Comparison of our clinical outcomes with other published data is somewhat difficult, owing to this trial's modest sample size and broad inclusion criteria. Overall survival rates in our trial are similar to those reported for the control (60-Gy) arm of RTOG 0617 (2). However, our study included subjects with Eastern Cooperative Oncology Group performance status scores of 2 and allowed enrollment of subjects with supraclavicular or contralateral hilar nodal involvement. These subjects would not have been eligible for RTOG 0617 and would be expected to have relatively poor outcomes with respect to both disease control and treatment-related toxicity. Randomized data will be needed to more meaningfully compare our treatment approach with standard techniques. We are now performing a randomized trial evaluating patient-reported outcomes after dose-painted accelerated chemoradiotherapy or conventionally fractionated chemoradiotherapy.

Modest radiation therapy hypofractionation with concurrent carboplatin and paclitaxel has been explored in several studies. In Cancer and Leukemia Group B 31102, the maximum tolerated daily radiation therapy fraction size when delivering a total dose of 60 Gy to the entire target volume was found to be 2.5 Gy (22). In a previous study, a concomitant boost was used to deliver 60 in 20 fractions to primary lung tumors while delivering 44 Gy to regional lymph nodes, and 2 out of 5 subjects developed serious nonhematologic late

toxicity (23). These experiences highlight the fact that the use of large fraction sizes for treating locally advanced NSCLC should be tested carefully and may not be safe when treating large target volumes.

Several other groups are exploring dose painting for locally advanced NSCLC. In the PET-boost trial, involved lymph nodes are treated with a dose of 66 Gy in 24 fractions, whereas primary tumors receive a simultaneous integrated boost up to 72 Gy that is applied to the whole tumor or only to the most PET-avid portion of the tumor, according to a randomization (24). In RTOG 1106/ACRIN 6697, patients are randomized between standard chemoradiotherapy (60 Gy in 30 fractions) versus an adaptive approach in which a simultaneous integrated boost is applied to regions with residual activity on a mid-treatment PET scan. This treatment technique was previously found to yield promising results in a single-arm study (25). To our knowledge, we are the only group using dose painting to selectively reduce radiation therapy doses in the treatment of locally advanced NSCLC. Although we used a commercial gradient-based contouring algorithm to measure volumes on PET, others may replicate this approach with different software using a percent threshold approach, which would yield similar results (26).

Conclusion

Dose-painted IMRT based on pretreatment PET metrics with concurrent chemotherapy yields high rates of metabolic response and local disease control for locally advanced NSCLC. Future trials should test this approach to maximize the therapeutic ratio of thoracic radiation therapy.

Acknowledgments

This work was supported by a Paul Calabresi K12 Career Development Award for Clinical Oncology.

References

1. Yuan S, Sun X, Li M, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. *Am J Clin Oncol*. 2007; 30:239–244. [PubMed: 17551299]
2. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus highdose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): A randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015; 16:187–199. [PubMed: 25601342]
3. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med*. 2009; 361:32–39. [PubMed: 19571281]
4. Ohri N, Duan F, Machtay M, et al. Pretreatment FDG-PET metrics in stage III non-small cell lung cancer: ACRIN 6668/RTOG 0235. *J Natl Cancer Inst*. 2015;107.
5. Ohri N, Piperdi B, Garg MK, et al. Pre-treatment FDG-PET predicts the site of in-field progression following concurrent chemoradiotherapy for stage III non-small cell lung cancer. *Lung Cancer*. 2015; 87:23–27. [PubMed: 25468149]
6. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non—small-cell lung cancer: A secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. *J Clin Oncol*. 2017; 35:56–62. [PubMed: 28034064]
7. Machtay M, Bae K, Movsas B, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with

chemoradiation: An analysis of the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys.* 2012; 82:425–434. [PubMed: 20980108]

8. Fowler JF, Chappell R. Non-small cell lung tumors repopulate rapidly during radiation therapy. *Int J Radiat Oncol Biol Phys.* 2000; 46:516–517. [PubMed: 10661362]
9. Machtay M, Duan F, Siegel BA, et al. Prediction of survival by [18F] fluorodeoxyglucose positron emission tomography in patients with locally advanced non-small-cell lung cancer undergoing definitive chemoradiation therapy: Results of the ACRIN 6668/ROG 0235 trial. *J Clin Oncol.* 2013; 31:3823–3830. [PubMed: 24043740]
10. Ramroth J, Cutter DJ, Darby SC, et al. Dose and fractionation in radiation therapy of curative intent for non-small cell lung cancer: Meta-analysis of randomized trials. *Int J Radiat Oncol Biol Phys.* 2016; 96:736–747. [PubMed: 27639294]
11. Yamoah K, Showalter TN, Ohri N. Radiation therapy intensification for solid tumors: A systematic review of randomized trials. *Int J Radiat Oncol Biol Phys.* 2015; 93:737–745. [PubMed: 26530740]
12. Feddock J, Arnold SM, Shelton BJ, et al. Stereotactic body radiation therapy can be used safely to boost residual disease in locally advanced non-small cell lung cancer: A prospective study. *Int J Radiat Oncol Biol Phys.* 2013; 85:1325–1331. [PubMed: 23265574]
13. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomised controlled trial. *Lancet.* 2009; 374:379–386. [PubMed: 19632716]
14. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med.* 2016; 375:1823–1833. [PubMed: 27718847]
15. Ohri N, Bodner WR, Halmos B, et al. 18 F-fluorodeoxyglucose/positron emission tomography predicts patterns of failure after definitive chemoradiation therapy for locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2017; 97:372–380.
16. Palma DA, Senan S, Oberije C, et al. Predicting esophagitis after chemoradiation therapy for non-small cell lung cancer: An individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys.* 2013; 87:690–696. [PubMed: 24035329]
17. Wang K, Eblan MJ, Deal AM, et al. Cardiac toxicity after radiotherapy for stage III non-small-cell lung cancer: Pooled analysis of dose-escalation trials delivering 70 to 90 Gy. *J Clin Oncol.* 2017; 35:1387–1394. [PubMed: 28113017]
18. Dess RT, Sun Y, Matuszak MM, et al. Cardiac events after radiation therapy: Combined analysis of prospective multicenter trials for locally advanced non-small-cell lung cancer. *J Clin Oncol.* 2017; 35:1395–1402. [PubMed: 28301264]
19. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med.* 2017; 377:1919–1929. [PubMed: 28885881]
20. Tang C, Liao Z, Gomez D, et al. Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes. *Int J Radiat Oncol Biol Phys.* 2014; 89:1084–1091. [PubMed: 25035212]
21. Nishino M, Sholl LM, Hatabu H, et al. Anti-PD-1-related pneumonitis during cancer immunotherapy. *N Engl J Med.* 2015; 373:288–290. [PubMed: 26176400]
22. Urbanic J, Wang X, Bogart J, et al. Phase 1 study of accelerated hypofractionated radiation therapy with concurrent chemotherapy for stage III non-small cell lung cancer: CALGB 31102 (Alliance). *Int J Radiat Oncol Biol Phys.* 2015; 93:S86.
23. Machtay M, Washam C, Devine P. Pilot study of accelerated radiotherapy with concurrent chemotherapy for stage III non-small cell lung cancer. *Semin Oncol.* 2005; 32(2 Suppl 3):S9–S12.
24. van Elmpt W, De Ruysscher D, van der Salm A, et al. The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. *Radiother Oncol.* 2012; 104:67–71. [PubMed: 22483675]
25. Kong FM, Ten Haken RK, Schipper M, et al. Effect of midtreatment PET/CT-adapted radiation therapy with concurrent chemotherapy in patients with locally advanced non-small-cell lung cancer: A phase 2 clinical trial. *JAMA Oncol.* 2017; 3:1358–1365. [PubMed: 28570742]

26. Werner-Wasik M, Nelson AD, Choi W, et al. What is the best way to contour lung tumors on PET scans? Multiobserver validation of a gradient-based method using a NSCLC digital PET phantom. *Int J Radiat Oncol Biol Phys.* 2012; 82:1164–1171. [PubMed: 21531085]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Summary

The authors performed a prospective trial using dose-painted intensity modulated radiation therapy (IMRT) based on pretreatment PET metrics with concurrent chemotherapy for locally advanced non—small cell lung cancer (NSCLC). This approach yields high rates of metabolic response on posttreatment positron emission tomography (PET). Use of a relatively low dose for low-risk tumors and lymph nodes does not seem to compromise local control of those lesions. This approach should be pursued to maximize the therapeutic ratio of radiation therapy in this setting.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 1. Kaplan-Meier curves for overall survival and progression-free survival. Tick marks indicate censoring. Dotted lines represent 95% confidence intervals. Numbers at risk are depicted above the x axis.

Fig. 2.
Cumulative incidence curves for disease progression in individual tumors or lymph nodes.
Abbreviation: MTV = metabolic tumor volume.

Fig. 3.

Scatterplot of radiation therapy dose (PTV D90, minimum dose received by 90% of the planning target volume) versus metabolic tumor volume. Metabolic tumor volume is plotted on a logarithmic scale. Squares represent primary tumors, whereas circles denote lymph nodes. Lesions that were the first site of disease progression are shaded in black.

Table 1

Patient characteristics, pretreatment PET metrics, and radiation therapy dosing

Characteristic	Value
Sex	
Male	19 (54)
Female	16 (46)
Age (y), mean (range)	68 (46–83)
Clinical stage	
IIB	2 (6)
IIIA	24 (69)
IIIB	9 (26)
ECOG performance status	
0	5 (14)
1	27 (77)
2	3 (9)
Histology	
Squamous cell carcinoma	15 (43)
Adenocarcinoma	14 (40)
Not specified	6 (17)
Days from PET to treatment start, median (range)	33 (6–79)
No. of hypermetabolic lesions, median (range)	3 (1–8)
Maximum SUV, median (range)	13.0 (4.0–24.4)
Metabolic tumor volume (cm ³), median (range)	50 (5–328)
Highest RT dose (Gy)	
52.5	10 (29)
57.0	2 (6)
60.0	4 (11)
65.0	19 (54)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PET = positron emission tomography; RT = radiation therapy; SUV = standardized uptake value.

Values are number (percentage) unless otherwise noted.

Table 2

Adverse events

Toxicity	Acute					Late				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anorexia	8 (23)	6 (17)	0 (0)	0 (0)	0 (0)	4 (12)	1 (3)	2 (6)	0 (0)	0 (0)
Constipation	7 (20)	1 (3)	0 (0)	0 (0)	0 (0)	5 (15)	4 (12)	0 (0)	0 (0)	0 (0)
Cough	22 (63)	3 (9)	1 (3)	0 (0)	0 (0)	12 (36)	6 (18)	1 (3)	0 (0)	0 (0)
Dehydration	1 (3)	5 (14)	4 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dermatitis radiation	17 (49)	2 (6)	2 (6)	0 (0)	0 (0)	0 (0)	1 (3)	1 (3)	0 (0)	0 (0)
Dysphagia	9 (26)	15 (43)	2 (6)	0 (0)	0 (0)	4 (12)	2 (6)	1 (3)	0 (0)	0 (0)
Fatigue	20 (57)	2 (6)	2 (6)	0 (0)	0 (0)	14 (42)	2 (6)	0 (0)	0 (0)	0 (0)
Fever	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)	2 (6)	1 (3)	0 (0)	0 (0)	0 (0)
Hemoglobin decreased	16 (46)	8 (23)	4 (11)	0 (0)	0 (0)	12 (35)	10 (29)	4 (12)	0 (0)	0 (0)
Hypokalemia	3 (9)	1 (3)	0 (0)	0 (0)	0 (0)	6 (18)	0 (0)	0 (0)	0 (0)	0 (0)
Leukopenia	15 (43)	11 (31)	3 (9)	1 (3)	0 (0)	9 (26)	5 (15)	1 (3)	0 (0)	0 (0)
Lymphopenia	2 (6)	8 (23)	19 (54)	4 (11)	0 (0)	5 (15)	9 (26)	8 (24)	3 (9)	0 (0)
Nausea	10 (29)	2 (6)	2 (6)	0 (0)	0 (0)	6 (18)	1 (3)	0 (0)	0 (0)	0 (0)
Neutropenia	5 (14)	4 (11)	2 (6)	1 (3)	0 (0)	2 (6)	3 (9)	1 (3)	0 (0)	0 (0)
Oral mucositis	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pneumonitis	1 (3)	3 (9)	2 (6)	0 (0)	0 (0)	1 (3)	6 (18)	1 (3)	0 (0)	0 (0)
Thrombocytopenia	11 (31)	2 (6)	1 (3)	0 (0)	0 (0)	5 (15)	3 (9)	2 (6)	0 (0)	0 (0)
Vomiting	5 (14)	1 (3)	0 (0)	0 (0)	0 (0)	2 (6)	1 (3)	0 (0)	0 (0)	0 (0)
Weight loss	10 (29)	3 (9)	0 (0)	0 (0)	0 (0)	3 (9)	8 (24)	2 (6)	0 (0)	0 (0)

Values are number (percentage).