Published in final edited form as:

JAMA Oncol. 2017 October 01; 3(10): 1358–1365. doi:10.1001/jamaoncol.2017.0982.

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

Feng-Ming Kong, MD, PhD, **Randall K. Ten Haken, PhD**, **Matthew Schipper, PhD**, **Kirk A. Frey, MD, PhD**, **James Hayman, MD**, **Milton Gross, MD**, **Nithya Ramnath, MD**, **Khaled A. Hassan, MD**, **Martha Matuszak, PhD**, **Timothy Ritter, PhD**, **Nan Bi, MD, PhD**, **Weili Wang, MD, PhD**, **Mark Orringer, MD**, **Kemp B. Cease, MD**, **Theodore S. Lawrence, MD, PhD**, and **Gregory P. Kalemkerian, MD**

Department of Radiation Oncology, University of Michigan, Ann Arbor (Kong, Ten Haken, Schipper, Hayman, Matuszak, Ritter, Bi, Wang, Lawrence); IU Simon Cancer Center, Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, Indiana (Kong, Wang); Department of Biostatistics, University of Michigan, Ann Arbor (Schipper); Division of Nuclear Medicine and Molecular Imaging, University of Michigan, Ann Arbor (Frey, Gross); VA Ann Arbor Healthcare System, Ann Arbor, Michigan (Gross, Ramnath, Ritter, Cease); Department of Internal Medicine, University of Michigan, Ann Arbor (Ramnath, Hassan, Cease, Kalemkerian); Section of Thoracic Surgery, Department of Surgery, University of Michigan, Ann Arbor (Orringer)

Abstract

Corresponding Author: Feng-Ming (Spring) Kong, MD, PhD, Department of Radiation Oncology, IU Simon Cancer Center, Indiana University School of Medicine, 535 Barnhill Dr, Indianapolis, IN 46202 (fskong@iupui.edu).

Author Contributions: Dr Kong and coinvestigator Dr Schipper had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Kong, Ten Haken, Frey, Matuszak, Lawrence, Kalemkerian.

Acquisition, analysis, or interpretation of data: Kong, Ten Haken, Schipper, Hayman, Gross, Ramnath, Hassan, Matuszak, Ritter, Bi, Wang, Orringer, Cease, Kalemkerian.

Drafting of the manuscript: Kong, Schipper, Orringer, Lawrence, Kalemkerian.

Critical revision of the manuscript for important intellectual content: Kong, Ten Haken, Schipper, Frey, Hayman, Gross, Ramnath, Hassan, Matuszak, Ritter, Bi, Wang, Orringer, Cease, Kalemkerian.

Statistical analysis: Kong, Schipper.

Obtained funding: Kong, Ten Haken, Lawrence.

Administrative, technical, or material support: Kong, Ten Haken, Frey, Hassan, Matuszak, Bi, Wang, Cease, Kalemkerian.

Study supervision: Kong, Ten Haken, Frey, Gross, Lawrence, Kalemkerian.

Conflict of Interest Disclosures: Dr Kong and Dr Ten Haken report grants from National Institutes of Health (NIH) during the conduct of the study; grant and travel support from Varian Medical System, outside the submitted work. Dr Frey reports Grant support from NIH/NCI and NIH/NINDS, common stock ownership in General Electric, Bristol-Myers Squibb, Novo Nordisk, and Merck, and consultation positions at Siemenns Medical, Avid Radiopharmaceuticals, and MIM Software, Inc. Dr Matuszak reports grants from NIH, National Cancer Institute, during the conduct of the study and grants from Varian Medical Systems outside the submitted work. Dr Kalemkerian reports grants from Millennium, Pfizer, GlaxoSmithKline, Astex, OncoMed, and Merck outside the submitted work.

Additional Contributions: We thank Daniel Normolle, PhD, for the trial design; Dan Tatro, CMD; David Jarema, CMD, for the radiation and adaptive radiation planning; Issam El Naqa, PhD, for double checking the target volume data; Mrs. Jody Sharp and her team for clinical trial management; Matthew Stenmark, MD; Dawn Owens, MD; and Shruti Jolly, MD, for their help in updating the long-term outcome data; Doug Arenberg, MD; and Jeffrey L. Curtis, MD, for pulmonary function assessment and patient care; Morand Piert, MD, for PET-CT imaging quality assessment and guidance in target delineation. All are affiliated with the University of Michigan. We also thank the many other individuals who helped and supported this trial and/or were directly involved in patient care, and all the patients and families who participated this trial. None of the contributors were compensated.

IMPORTANCE—Our previous studies demonstrated that tumors significantly decrease in size and metabolic activity after delivery of 45 Gy of fractionated radiatiotherapy (RT), and that metabolic shrinkage is greater than anatomic shrinkage. This study aimed to determine whether ^{18}F-fludeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT) acquired during the course of treatment provides an opportunity to deliver higher-dose radiation to the more aggressive areas of the tumor to improve local tumor control without increasing RT-induced lung toxicity (RILT), and possibly improve survival.

OBJECTIVE—To determine whether adaptive RT can target high-dose radiation to the FDG-avid tumor on midtreatment FDG-PET to improve local tumor control of locally advanced non–small-cell lung cancer (NSCLC).

DESIGN, SETTING, AND PARTICIPANTS—A phase 2 clinical trial conducted at 2 academic medical centers with 42 patients who had inoperable or unresectable stage II to stage III NSCLC enrolled from November 2008, to May 2012. Patients with poor performance, more than 10% weight loss, poor lung function, and/or oxygen dependence were included, providing that the patients could tolerate the procedures of PET scanning and RT.

INTERVENTION—Conformal RT was individualized to a fixed risk of RILT (grade >2) and adaptively escalated to the residual tumor defined on midtreatment FDG-PET up to a total dose of 86 Gy in 30 daily fractions. Medically fit patients received concurrent weekly carboplatin plus paclitaxel followed by 3 cycles of consolidation.

MAIN OUTCOMES AND MEASURES—The primary end point was local tumor control. The trial was designed to achieve a 20% improvement in 2-year control from 34% of our prior clinical trial experience with 63 to 69 Gy in a similar patient population.

RESULTS—The trial reached its accrual goal of 42 patients: median age, 63 years (range, 45–83 years); male, 28 (67%); smoker or former smoker, 39 (93%); stage III, 38 (90%). Median tumor dose delivered was 83 Gy (range, 63–86 Gy) in 30 daily fractions. Median follow-up for surviving patients was 47 months. The 2-year rates of infield and overall local regional tumor controls (ie, including isolated nodal failure) were 82% (95% CI, 62%–92%) and 62% (95% CI, 43%–77%), respectively. Median overall survival was 25 months (95% CI, 12–32 months). The 2-year and 5-year overall survival rates were 52% (95% CI, 36%–66%) and 30% (95% CI, 16%–45%), respectively.

CONCLUSIONS AND RELEVANCE—Adapting RT-escalated radiation dose to the FDG-avid tumor detected by midtreatment PET provided a favorable local-regional tumor control. The RTOG 1106 trial is an ongoing clinical trial to validate this finding in a randomized fashion.

TRIAL REGISTRATION—clinicaltrials.gov Identifier: NCT01190527

Lung cancer remains the leading cause of cancer-related death in the United States,[1] and non–small-cell lung cancer (NSCLC) accounts for 80% to 85% of cases. Radio-therapy (RT) is the mainstay local treatment for patients with inoperable or unresectable stages I to III disease.[2] Despite remarkable advancements in RT technology, tumor control remains suboptimal in locally advanced disease that is not suitable for stereotactic body RT.[3,4] Overall, most patients ultimately develop local-regional failure during their course of disease.[4,5]

Evidence from institutional and old Radiation Therapy Oncology Group (RTOG) trials demonstrated: (1) high-dose radiation was associated with improved local-regional tumor control (LRTC) either alone or when combined with chemotherapy[6–8]; (2) limiting treatment duration to 6 weeks may improve tumor control[9]; (3) RT-induced lung toxicity (RILT) are a major factor limiting dose[10,11]; and (4) RILT may be predicted by lung normal tissue complication probability (NTCP) models, allowing restraints within tolerable limits.[12] However, it is often challenging to deliver an adequate RT dose without exceeding the normal tissue tolerances in locally advanced NSCLC. With concurrent chemoradiation, the maximum tolerated dose was reported to be less than 74 Gy in 2 Gy daily fractions,[10–12] which was tested in the experimental arm in RTOG 0617. In our prior (unpublished data) dose escalation study using a conventional approach in which lung NTCP was limited to 15%, only about 40% of patients with stage III NSCLC could receive more than 66 Gy and the study was closed prematurely. Safe RT is limited by damage to centrally located critically structures[11] and by large tumor volumes.

We previously demonstrated that tumors significantly decrease in size and metabolic activity after delivery of 45 Gy of fractionated RT, and that metabolic shrinkage is greater than anatomic shrinkage.[13,14] Using ^{18}F-fludeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT) acquired during the course of treatment, we were able to escalate the tumor dose while keeping the lung NTCP unchanged.[15] In this trial, we hypothesized that adapting the planning target volume to the responding tumor defined on midtreatment PET, while also limiting lung NTCP, would allow us to deliver higher-dose radiation to the more aggressive areas of the tumor to improve local tumor control without increasing RILT. We repeated CT simulation and FDG-PET/CT at 40 to 50 Gy and redefined the treatment target according to this midtreatment scan. The total dose was escalated to as high as 86 Gy in 30 daily fractions, while lung NTCP was kept lower than 17.2% (approximately equivalent to 20 Gy mean lung dose),[16] and doses to other normal structures were confined to the limits of standard practice.

Methods

Study Population

Patients with inoperable or unresectable, stages I to III NSCLC requiring daily fractionated RT were eligible. The study was approved by the institutional review boards of the University of Michigan Hospitals and Ann Arbor Veterans Affairs Health System. Written informed consent was obtained from each patient, and they were not compensated for participating. The trial protocol is included in Supplement 1. Karnofsky performance status was required to be 70 or greater. There were no eligibility restrictions for weight loss, comorbidities, pulmonary function, or cardiac function. Pretreatment tests were per standard of care. All FDG-PET/CT scans were performed with the patient in the treatment position on a flat palette imaging couch within 2 weeks from radiation start and after 40 to 50 Gy had been delivered.

Trial Design and Study Treatment

All patients received an RT dose individualized to an uninvolved lung NTCP up to 17.2% for grade 2 or greater pneumonitis (Figure 1) (corresponding to a mean lung dose of less than 20 Gy, computed from lung dose distributions corrected to equieffective doses at 2 Gy per fraction [EQD2] using the linear-quadratic model and an α/β of 2.5 Gy and the Lyman-Kutcher-Burman NTCP model)[12] and practice limits of other organs, in compliance to NCCN recommendations. The RT was delivered in 30 daily fractions of 2.1 to 5.0 Gy: 2.1 to 2.85 Gy fractions for the initial dose of approximately 50 Gy EQD2, 2.85 to 5.0 Gy for the adaptive phase of treatments up to a total RT dose of 86 Gy physical dose; equivalent to EQD2s of 102 Gy for RILT (α/β = 2.5 Gy); and EQD2s of 92 Gy and biological effective doses (BEDs) of 120 Gy for tumor (α/β = 10 Gy). The detailed fractionation schema is shown in eTable 1 in Supplement 2.

Patients with stage II or III disease, when medically fit, were given concurrent, weekly carboplatin AUC 2 plus paclitaxel, 40 mg/m^2, for 6 weeks followed by consolidation carboplatin with an area under the curve (AUC) of 6 plus paclitaxel, 200 mg/m^2, every 21 days for 3 cycles starting 4 to 6 weeks after completion of RT, when acute toxic effects were not clinically significant.

All patients underwent CT and PET-based treatment planning at baseline and had CT resimulation and PET-CT in the original position after an EQD2 of 40 to 50 Gy to tumor was delivered. The first round of approximately 50 Gy EQD2 of radiation to the tumor was given based on targets defined by PET and CT acquired prior to treatment, and the remaining dose was delivered to the target defined by PET-CT acquired during the course of RT. In addition to keeping lung NTCP to 17.2% or less, the RT dose was prescribed such that (when normal tissue constraints permit) pre-RT PTV, pre-RT CTV, and during- RT CTPTV would receive tumor EQD2s of at least 50, 60, and 70 Gy (Figure 2), respectively.

Gross tumor volumes (GTV) were defined on simulating CT scans. Gross tumor volume was a composite volume of the primary tumor (GTVT) and nodal diseases (GTVN). The following guidelines were used to contour GTVs:

1. For free-breathing treatment with a 4D CT simulation, the GTVs were composite volumes from CT scans throughout the breathing phases, with inclusion of target motion.
2. For free-breathing treatment without 4D CT simulation, GTVs were composite volumes from inhale and exhale CT scans, with inclusion of target motion.
3. For motion-controlled treatments, the GTVs were generated from a contrast-enhanced CT scan at the motion-controlled state. Active breathing control was used for such cases.
4. Whenever possible, a locally registered contrast-enhanced CT scan was recommended to aid in accurate GTV delineation.

Elective nodal irradiation was not intended. Delineation of GTVN followed the principles below:

1. Lymph nodes 1 cm or larger in short axis on composite volumes of 4D CT or both exhale and inhale CT.
2. Lymph nodes that were growing or with abnormal structure.
3. Lymph nodes with abnormal FDG-avidity on PET scan or containing biopsy-proven NSCLC.
4. Two or more lymph nodes that were visible and clustered in the high-risk nodal stations within the first echelon from the gross tumor.
5. Lymph nodes at the first echelon or within 1 cm of the primary tumor.

Metabolic tumor volumes (MTVs) were delineated from PET scans as previously prescribed.[14] This same method was used for target delineation of midtreatment scans for adaptive planning.

The treatment technique and number of fields of initial and midtreatment FDG-PET/CT–guided adaptive radiation (PART) plans were individually tailored for each patient. Dose-volume histograms (DVHs) were evaluated to limit doses for normal organs and to provide objective criteria for the selection of an appropriate treatment plan. Suitable treatment plans were those that maximized target doses relative to constraining NTCP of 17.2% or more, and limiting doses to other critical organs at risk to the standard limits. Organs at risk, such as lung, heart, esophagus, spinal cord, and brachial plexus were contoured in the treatment planning system when they were included in the field of irradiation. If any of these tolerance doses could not be met, the prescription doses were decreased heterogeneously according to these limits.

Follow-up and Definition of Failure

Patients were followed with chest CT per standard of care. Both PET-CT and chest CT with intravenous contrast scans were required to document disease relapse or progression, with PET progression criteria described previously.[13] Biopsy of the relapse or progression site was encouraged, and performed whenever possible. Progression was defined per RECIST 1.0 criteria. Infield failure was defined as recurrent tumors mapped within dose escalated PTV, as previously described.[17]

Statistical Considerations

The primary study end point was LRTC. The study was designed to detect a 20% improvement in 2-year LRTC to 54%, from the 34% observed in our prior study (UMCC9204) in patients treated with 63 to 69 Gy,[5] ie, the dose range of the standard of care. Forty-two patients yielded 80% power to detect such an improvement based on a 1-sided .05 level test. Considering that the definition of local tumor control was not clearly defined in the literature including our previous trial, LRTC endpoint in this study was further characterized using infield LRTC and overall LRTC with inclusion of outfield nodal failure. The local-regional progression-free survival (LR-PFS) was also captured. Secondary endpoints included progression-free survival (PFS), overall survival, and severe lung or esophageal toxic effects. Kaplan-Meier curves were used to summarize survival endpoints

and to estimate their values at fixed time points, including 2 years. The statistical analyses were carried out using SAS statistical software (version 9.3, SAS Institute Inc).

Results

Patient Characteristics

The trial reached its accrual goal of 42 patients, with characteristics summarized in eTable 2 in Supplement 2. The minimum and median follow-ups were 24 months and 47 months for surviving patients, respectively. Thirty-eight patients (90%) had stage III disease. The median (range) planning target volumes at pre-RT and during RT were 455 (53–1177) cm^3 and 231 (30–867) cm^3, respectively. Median prescription dose was 83 Gy (63–86 Gy) in 2.1 to 4.5 Gy daily fractions. Median (range) EQD2 and BED10 were 90 Gy (64–92 Gy) and 107 Gy (76–110 Gy), respectively. Of 42 patients, 38 (94%) received more than 74 Gy EQD2. Of 42 patients, 39 (93%) received concurrent carboplatin and paclitaxel followed by consolidation chemotherapy. All patients received adaptive RT; 41 of 42 (98%) patients received dose-escalated RT (≥66 Gy). Figure 3 shows an example of an adaptive dose prescription.

Local-Regional Tumor Control and Overall Survival

Figure 4 shows infield LRTC, overall LRTC, LR-PFS, and overall survival. The accumulated rates of infield and overall LRTC at 2 years were 82% (95% CI, 62%–92%) and 62% (95% CI,43%–77%), respectively. Median LR-PFS was 14 months and the 2-year LR-PFS rate was 38% (95% CI, 24%–52%). Median PFS was 13 months and the 2-year PFS rate was 31%. Overall, 18 patients (43%) developed disease progression and 20 patients (48%) had died at 2-year follow-up. Among the 18 participants who progressed, 8 (40%) received other regimens of chemotherapy, 5 (30%) local radiation to either chest or brain, and 5 (30%) received no treatment owing to poor performance and/or comorbidity. Median overall survival was 25 months (95% CI, 12%–32%), and the 2- and 5-year overall survival rates were 52% (95% CI, 36%–66%) and 30% (95% CI, 16%–45%), respectively. Tumor shrinkage may continue after 1 year posttreatment (eFigure 1 in Supplement 2).

Patterns of First Failure

The pattern of first failure is shown in Figure 5. Eighteen patients (43%) had progression of disease: 4 (22%) initially at local (primary tumor) progression alone,4(22%) regional (nodal) progression alone, 1 (6%) both local and regional progression, and 9 (50%) had distant disease as part of first evidence of progression. Ultimately, there were a total of 6 (14%) infield progressions and 11 (26%) distant failures.

Toxic Effects

Radiation-related adverse events are listed in eTable 3 in Supplement 2. The rates of grade 3 radiation-induced esophagitis and pneumonitis were 5 (12%) and 3 (7%), respectively. One (2%) patient had grade 3 radiation-induced lung fibrosis. In addition, 2 (5%) had grade 3 or higher dyspnea without evidence of pneumonitis or fibrosis. Twelve (28%) had cardiac events, including 11 pericardial effusions (2 also with arrhythmia) and 1 grade 3 chronic heart failure. Four died from massive bleeding: 2 clearly from the lung, 1 during an upper

gastrointestinal tract endoscopic procedure for esophagitis, 1 unknown etiology (patient was found dead at home with blood around the house). All these 4 patients had T4 diseases with some degree of great vessel invasion.[18]

Discussion

This study demonstrated that midtreatment PART allows dose-escalated RT to persistent active tumor in most patients with locally advanced NSCLC. The trial achieved its primary goal to improve 2-year LRTC rates, with an infield tumor control rate of 82% and overall LRTC rate of 62%. To our knowledge, this is the first study that has adapted treatment to the individual patient's PET response, a strategy that represents a novel and potentially useful approach in RT.

The infield LRTC of 82% is promising. An LRTC of 62% is remarkably better than our historical control of 34%, and considerably better than that of patients treated with standard RT under similar staging workup by the same physicians (unpublished data). This also seems to be better than those noted in several recently reported studies.[3,4,8,11,19,20] For example, in a study of patients with stage III NSCLC treated with 64 Gy or less, the LRTC rate was 24%.[7] The infield LRTC rates of RTOG 0617 were 69% and 61% at 2 years for the 60 Gy and 74 Gy arms, respectively.[21] The infield LRTC rates from a recently published PROCLAIM was 63% and 54% at 2 years for arms 1 and 2, respectively.[22] The LRTC of patients treated with the adaptive treatment was also higher than that seen in the same stage patients treated with conventional RT (60–70 Gy) at our institutions during the same time period.[23,24] Although not based on randomized data, this apparent improvement in local tumor control may be attributable to: (1) a higher dose of radiation being targeted to the more aggressive tumor area; (2) the treatment duration being constrained to within 30 treatment days; and/or (3) larger tumors receiving an accelerated dose of adaptive RT, whereas smaller tumors did not. This study suggests that isotoxicity-based adaptive RT dose escalation may improve local tumor control in locally advanced NSCLC, as it does for those with early-stage disease.[6–8]

The results of this study differ from the recent report of RTOG 0617[21] in which high-dose RT resulted in poorer LRTC. The reason high-dose RT failed to improve tumor control in RTOG 0617 remains unclear and is under active investigation. However, a key difference between our study and RTOG 0617 is that the latter prescribed uniform tumor dose escalation whereas our approach directs the higher doses of RT only to the FDG–PET-avid regions of the tumor identified at midtreatment. In addition, our trial applied modern technology, such as 4-dimensional motion control and PET planning, which RTOG 0617 did not mandate. It is thus reasonable to hypothesize that high-dose RT can increase local tumor control if it is delivered precisely and adapted to the individual patient's response using FDG-PET to identify residual active tumor. This hypothesis is now being tested in a randomized phase 2 multicenter trial (RTOG 1106).

The overall rate of distant failure (26%) in this study is similar to that reported from other studies,[3,4,8,19] but the proportion of patients with distant failure (61%) relative to all progressions was higher than in prior studies owing to a reduction of local failure. For

example, RTOG9410 reported roughly equal proportions (45%–50%) of patients with local-regional and distant failure.[4] This change of failure pattern may be a reflection of improved local regional tumor control in the current study. It is also important to note that 3 patients (7%) had isolated nodal failure. All 3 of these patients had visible, but radiographically normal appearing lymph nodes on pretreatment imaging and 1 of them also had a negative lymph node biopsy result. Although this overall rate of isolated nodal failure is relatively low and consistent with previous studies,[25] target delineation with more sensitive imaging or more aggressive mediastinal staging may help identify such high-risk cases. As infield LRTC improves with more conformal techniques, isolated regional failure may become a more important problem. Future studies to identify and avoid such failures may improve treatment outcomes.

The survival outcome of 5-year overall survival of 30% and median survival of 25 months is encouraging for this poor-prognosis population. This is remarkably better than that (5-year survival of 4% and median survival of 12 months) of our previous trial of similar patients who received 63 to 69 Gy.[6] This favorable survival may be owing to improved local tumor control. However, although this median survival is better than that noted in the 74 Gy arm of RTOG 0617 (20 months), it is inferior to the median survival reported in the 60 Gy arm of RTOG 0617 (29 months). This is likely owing to a number of factors regarding patient and tumor selection. First, our study had more liberal eligibility criteria (eg, performance status, weight loss, cardiopulmonary function, comorbidities), which were meant to encourage enrollment of a population that would be more reflective of real-world practice. Twelve percent of patients had more than 20% weight loss, and an additional 12% had an ECOG performance status (PS) of 2. These more lenient criteria may explain the 20% of patients on the current trial who died of other diseases or unknown causes during the first year without evidence of tumor progression. The RTOG 0617 trial required patients to have an excellent PS of 0–1, weight loss of 10% or less, and a forced expiratory volume at the first second above 1.3 L, while the current study also enrolled patients using home oxygen therapy. Second, the current study has more patients with more stage IIIB disease (52%) than RTOG0617 (35%). In addition, our study also included patients with supraclavicular and lower cervical or contralateral hilar lymph node involvement (N3) or a separate nodule in a different ipsilateral lobe (T4) who were excluded from RTOG0617. However, comparison between studies can be difficult. The RTOG 1106 trial is ongoing to compare this PET-adaptive RT approach with conventional uniform-dose of 60 Gy in a randomized fashion.

Limitations

This study is limited by the non randomized design and the relatively heterogeneous group of patients. Stricter eligibility criteria resulting in selection of a healthier patient population might have yielded more favorable survival outcomes, but would also have limited the generalizability of the results because most patients with locally advanced NSCLC have marginal performance status, impaired pulmonary function, and considerable comorbidities. It is unclear if the number of patients who died from noncancer- or treatment-related causes is higher than that seen with conventional radiation because such data are not commonly reported in the literature. While such mortality is likely owing to comorbid baseline conditions, studies are ongoing in our group to investigate whether some of these deaths

might be owing to unidentified treatment related toxic effects that may be avoidable with more advanced, personalized treatment planning.

Conclusions

This single arm phase 2 trial demonstrated that adaptive treatment with escalated radiation dose to the FDG-avid region according to mid-treatment PET scans achieved 82% local tumor control at 2 years and favorable survival in patients with high risk locally advanced non–small-cell lung cancer. This innovative adaptive regimen provides a promising approach for the new era of personalized dose-escalated RT to improve treatment outcomes in locally advanced locally advanced non–small-cell lung cancer. Results from RTOG1106, a randomized phase 2 study, are eagerly awaited. A phase 3 study is needed before this adaptive approach can be used routinely in the clinic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: This work was supported in part by institutionally approved use of resources and facilities at the Veterans Administration Ann Arbor Healthcare System, NIH grants R01CA142840 (Kong) and P01CA059827 (Ten Haken and Lawrence).

Role of the Funder/Sponsor: The Veterans Administration Ann Arbor Healthcare System and the National Institutes of Health played no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013; 63(1):11–30. [PubMed: 23335087]
2. Tyldesley S, Boyd C, Schulze K, Walker H, Mackillop WJ. Estimating the need for radiotherapy for lung cancer: an evidence-based, epidemiologic approach. Int J Radiat Oncol Biol Phys. 2001; 49(4): 973–985. [PubMed: 11240238]
3. Schytte T, Nielsen TB, Brink C, Hansen O. Pattern of loco-regional failure after definitive radiotherapy for non-small cell lung cancer. Acta Oncol. 2014; 53(3):336–341. [PubMed: 24369735]
4. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011; 103(19):1452–1460. [PubMed: 21903745]
5. Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR. 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(17):1210–1215. [PubMed: 8780630]
6. Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. Int J Radiat Oncol Biol Phys. 2005; 63(2):324–333. [PubMed: 16168827]
7. Rengan R, Rosenzweig KE, Venkatraman E, et al. Improved local control with higher doses of radiation in large-volume stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2004; 60(3):741–747. [PubMed: 15465190]

8. 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(1):425–434. [PubMed: 20980108]
9. Martel MK, Strawderman M, Hazuka MB, Turrisi AT, Fraass BA, Lichter AS. Volume and dose parameters for survival of non-small cell lung cancer patients. Radiother Oncol. 1997; 44(1):23–29. [PubMed: 9288853]
10. Lin Q, Liu YE, Ren XC, et al. Dose escalation of accelerated hypofractionated three-dimensional conformal radiotherapy (at 3 Gy/fraction) with concurrent vinorelbine and carboplatin chemotherapy in unresectable stage III non-small-cell lung cancer: a phase I trial. Radiat Oncol. 2013; 8(1):201. [PubMed: 23957889]
11. Cannon DM, Mehta MP, Adkison JB, et al. Dose-limiting toxicity after hypofractionated dose-escalated radiotherapy in non-small-cell lung cancer. J Clin Oncol. 2013; 31(34):4343–4348. [PubMed: 24145340]
12. Seppenwoolde Y, Lebesque JV, de Jaeger K, et al. Comparing different NTCP models that predict the incidence of radiation pneumonitis. Normal tissue complication probability. Int J Radiat Oncol Biol Phys. 2003; 55(3):724–735. [PubMed: 12573760]
13. Kong FM, Frey KA, Quint LE, et al. A pilot study of [18F]fluorodeoxyglucose positron emission tomography scans during and after radiation-based therapy in patients with non small-cell lung cancer. J Clin Oncol. 2007; 25(21):3116–3123. [PubMed: 17634490]
14. Mahasittiwat P, Yuan S, Xie C, et al. Metabolic Tumor Volume on PET Reduced More than Gross Tumor Volume on CT during Radiotherapy in Patients with Non-Small Cell Lung Cancer Treated with 3DCRT or SBRT. J Radiat Oncol. 2013; 2(2):191–202. [PubMed: 23795245]
15. Feng M, Kong FM, Gross M, Fernando S, Hayman JA, Ten Haken RK. Using fluorodeoxyglucose positron emission tomography to assess tumor volume during radiotherapy for non-small-cell lung cancer and its potential impact on adaptive dose escalation and normal tissue sparing. Int J Radiat Oncol Biol Phys. 2009; 73(4):1228–1234. [PubMed: 19251094]
16. Kong FM, Hayman JA, Griffith KA, et al. Final toxicity results of a radiation-dose escalation study in patients with non-small-cell lung cancer (NSCLC): predictors for radiation pneumonitis and fibrosis. Int J Radiat Oncol Biol Phys. 2006; 65(4):1075–1086. [PubMed: 16647222]
17. Hunter KU, Kong FM, Chetty IJ, et al. Pattern of failure after high-dose thoracic radiation for non-small cell lung cancer: the University of Michigan experience. J Radiat Oncol. 2012; 1(3):267–272. [PubMed: 24575170]
18. Han CB, Wang WL, Quint L, et al. Pulmonary artery invasion, high-dose radiation, and overall survival in patients with non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2014; 89(2): 313–321. [PubMed: 24685448]
19. Nguyen NP, Bishop M, Borok TJ, et al. Pattern of failure following chemoradiation for locally advanced non-small cell lung cancer: potential role for stereotactic body radiotherapy. Anticancer Res. 2010; 30(3):953–961. [PubMed: 20393019]
20. Chien CR, Chen SW, Hsieh CY, et al. Intra-thoracic failure pattern and survival status following 3D conformal radiotherapy for non-small cell lung cancer: a preliminary report. Jpn J Clin Oncol. 2001; 31(2):55–60. [PubMed: 11302342]
21. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose 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(2):187–199. [PubMed: 25601342]
22. Senan S, Brade A, Wang LH, et al. PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2016; 34(9):953–962. [PubMed: 26811519]
23. Kong FM, Ten Haken RK, Schipper M, et al. A phase II trial of mid-treatment FDG-PET adaptive, individualized radiation therapy plus concurrent chemotherapy in patients with non-small cell lung cancer (NSCLC). J Clin Oncol. 2013; 31(suppl 15) abstr 7522.

24. Kong FM, Ten Haken RK, Schipper M, et al. A phase 2 trial of midtreatment fdg-pet adaptive, individualized radiation therapy plus concurrent chemotherapy in patients with non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys. 2013; 87(suppl 76) abstr 197.

25. Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys. 2005; 61(2):318–328. [PubMed: 15667949]

Key Points

Question

Can adaptive treatment target high-dose radiation to the residual tumor to improve local tumor control in locally advanced non–small-cell lung cancer (NSCLC)?

Findings

This phase 2 clinical trial, involving patients with stage II/III NSCLC from 2008 to 2012, demonstrated that adaptive radiotherapy-escalated radiation dose to the ^{18}F-fludeoxyglucose (FDG)-avid region detected by midtreatment positron emission tomography (PET) achieved 82% local tumor control at 2 years, with a reasonable rate of radiotherapy-induced toxicity.

Meaning

This innovative adaptive radiotherapy can deliver personalized dose-escalated treatment to the resistant active tumor detected by midtreatment FDG-PET to improve local tumor control in patients with locally advanced NSCLC.

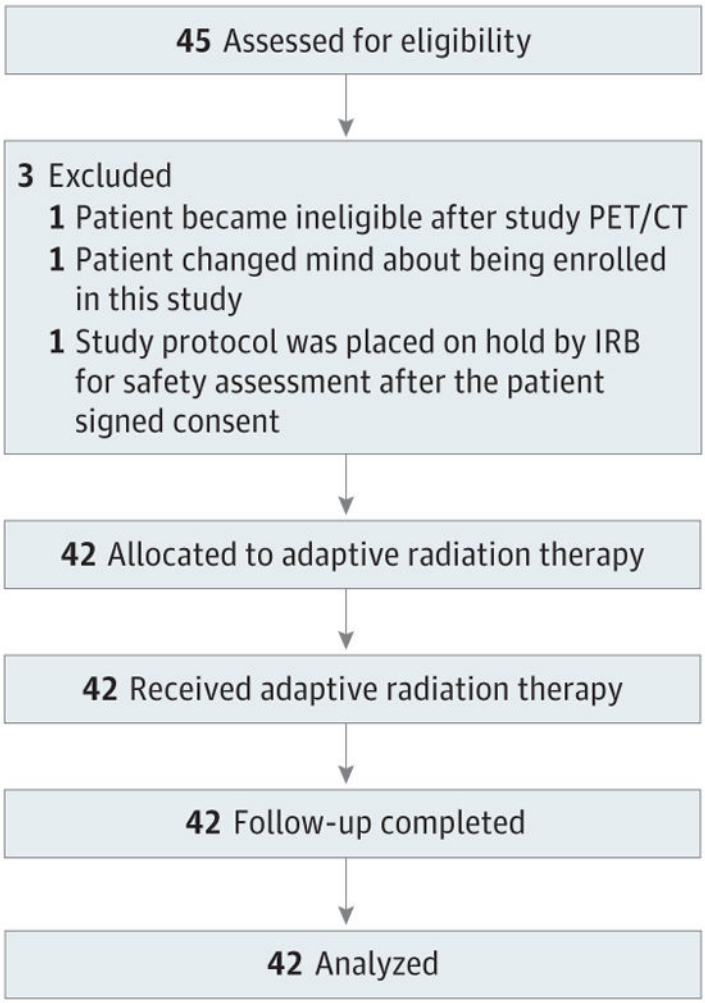

Figure 1. CONSORT Flow Diagram of Study Enrollment

IRB indicates institutional review board; PET/CT, positron emission tomography in conjunction with computed tomography.

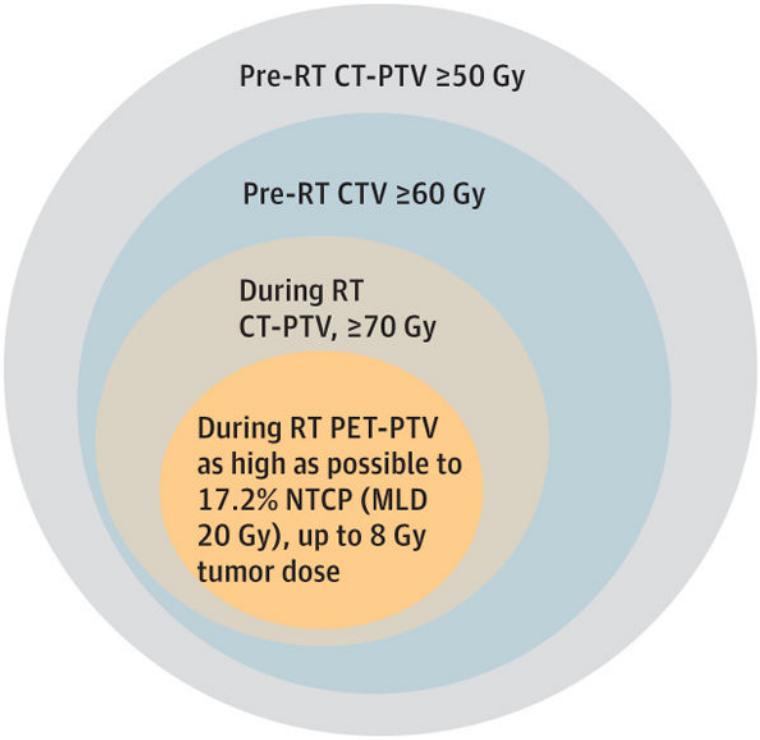

Figure 2. Radiation Dose Prescriptions

The dose was prescribed so that every patient had an opportunity of receiving a maximum dose of 86 Gy to during RT PET-PTV in 30 daily fractions of 2.1 to 3.8 Gy. Dose was also limited by tolerances of other organs at risk, such as heart, esophagus, and cord per standard practice. CT indicates computed tomography; CTV, clinical target volume; MLD, mean lung dose; NCTP, normal tissue complication probability; PET, positron emission tomography; PTV, planning target volume; RT, radiation therapy.

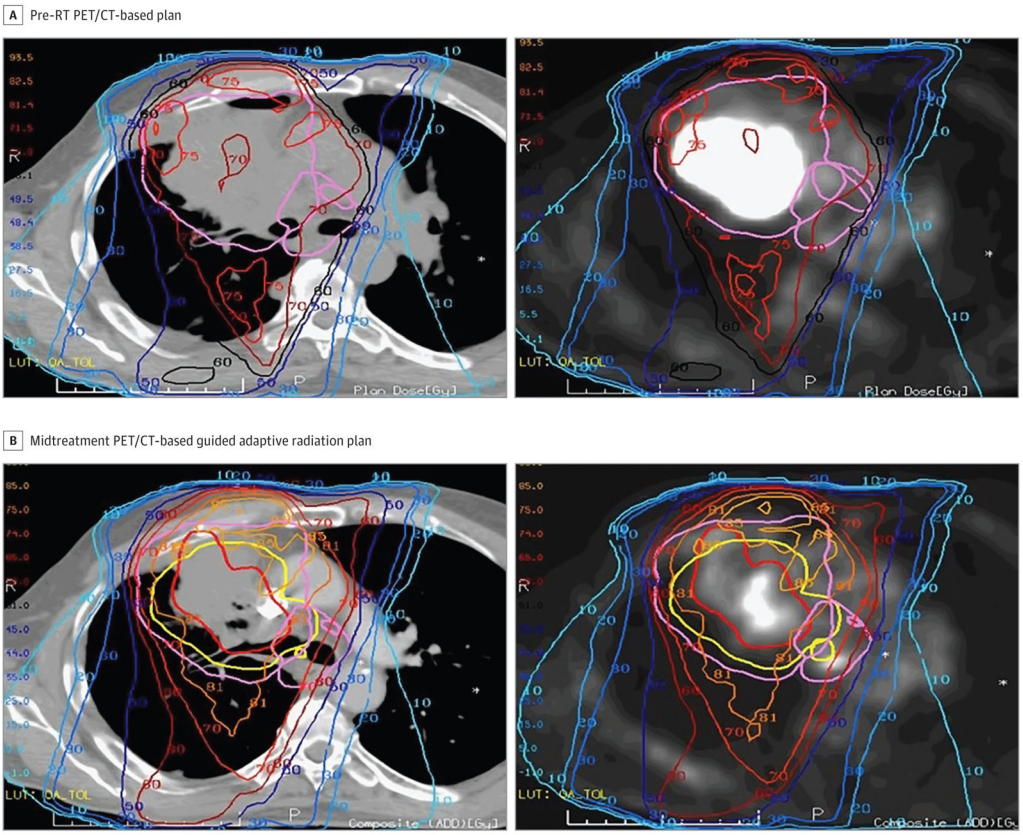

Figure 3. Escalating Dose to Tumor Without Increasing Dose to Normal Tissues

Pretreatment and midtreatment PET/CT-guided RT planning in a patient who was oxygen dependent after a futile thoracotomy. Based on the midtreatment PET-CT, the patient received an added 11 Gy to the residual ^{18}F-fludeoxyglucose–avid tumor while maintaining normal tissue toxicity probability (NTCP) of the lung at 17.2%. This patient remains alive and off oxygen therapy more than 4 years after treatment. In addition to dose-marked color lines, the purple line represents planning target volume or pretreatment, and the yellow line is the target volume during treatment planning. CT Indicates computed tomography; PET, positron emission tomography; RT, radiotherapy.

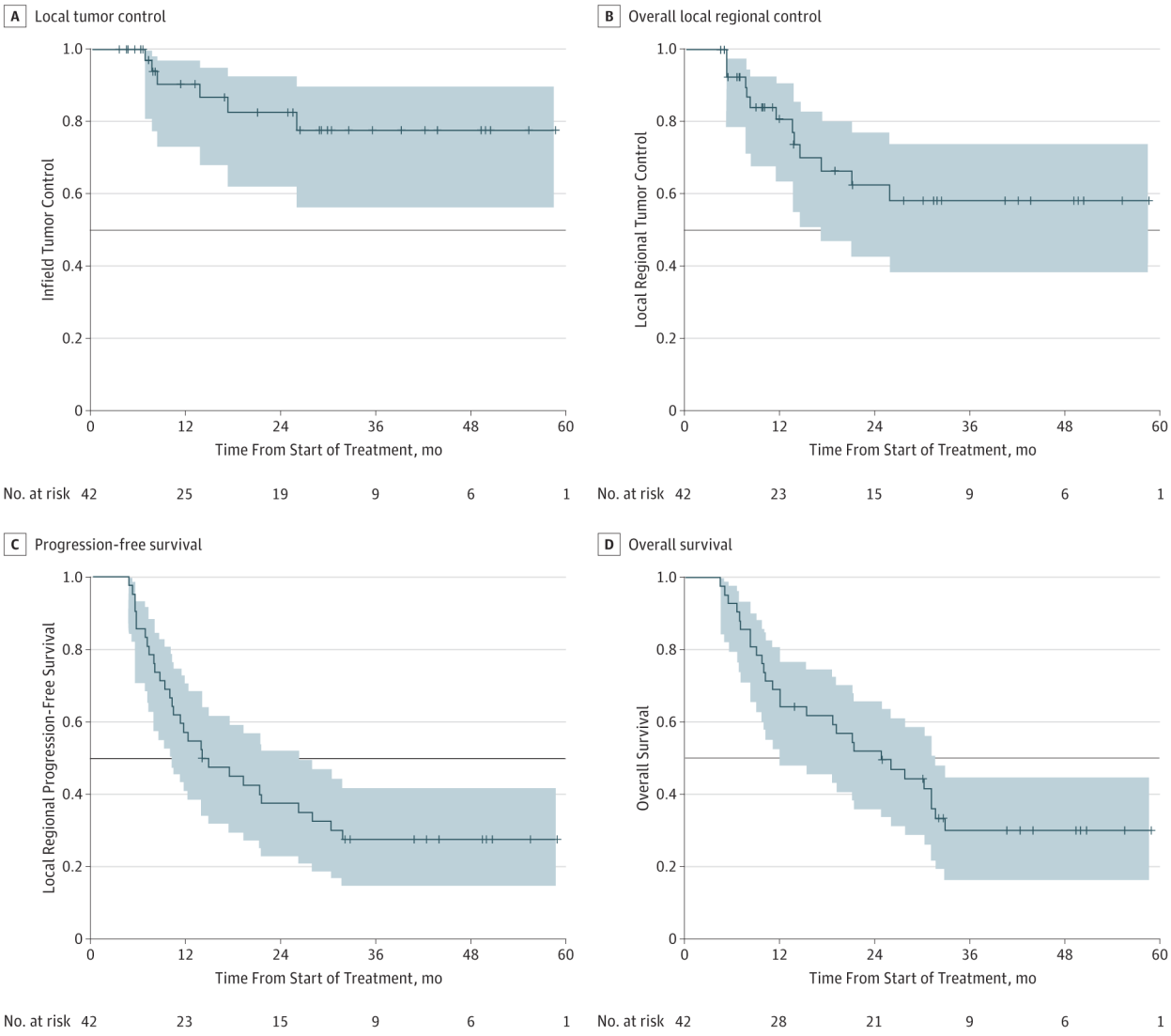

Figure 4. Tumor Control and Survival After Adaptive Treatment

A, Local tumor control (corresponding to infield local-regional control). B, Overall local regional control. C, Local regional progression-free survival. D, Overall survival.

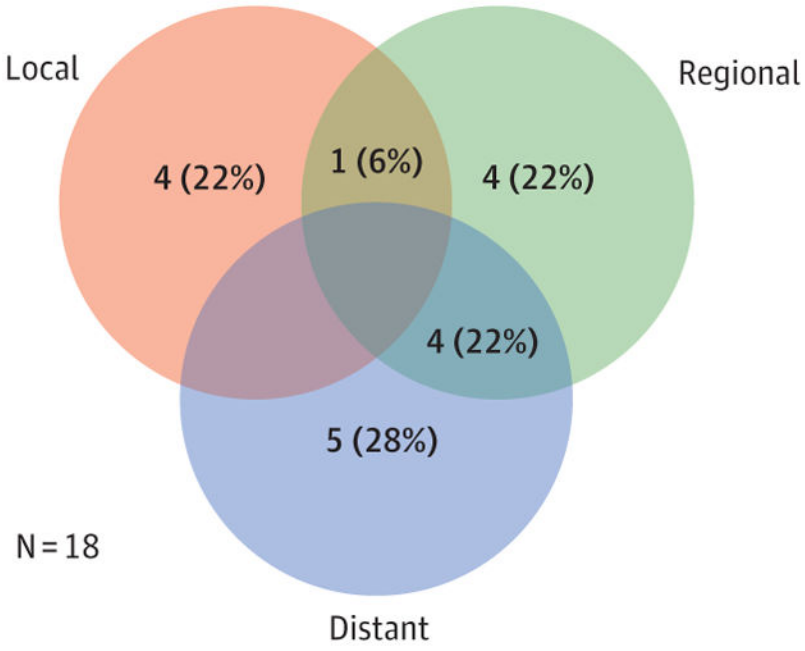

Figure 5. Patterns of First Failure

Venn diagram with number and percentage of patients in each category.