# Local Radiotherapy Intensification for Locally Advanced Non–small-cell Lung Cancer – A Call to Arms

Noah S. Kalman,[1] Elisabeth Weiss,[1] Paul R. Walker,[2] Julian G. Rosenman[3]

## Abstract

Chemoradiotherapy, the standard of care for locally advanced non–small-cell lung cancer (NSCLC), often fails to eradicate all known disease. Despite advances in chemotherapeutic regimens, locally advanced NSCLC remains a difficult disease to treat, and locoregional failure remains common. Improved radiographic detection can identify patients at significant risk of locoregional failure after definitive treatment, and newer methods of escalating locoregional treatment may allow for improvements in locoregional control with acceptable toxicity. This review addresses critical issues in escalating local therapy, focusing on using serial positron emission tomography-computed tomography to select high-risk patients and employing stereotactic radiotherapy to intensify treatment. We further propose a clinical trial concept that incorporates the review's findings.

*Clinical Lung Cancer,* Vol. 19, No. 1, 17-26 © 2017 Elsevier Inc. All rights reserved.
**Keywords:** PET-CT, Serial imaging, Stage III lung cancer, Stereotactic body radiotherapy, Therapy escalation

## Introduction

### *Magnitude of the Problem*

Lung cancer is the second most common cancer in men and women, but it is the most common cause of cancer death in the United States. An estimated 225,000 new cases of lung cancer were diagnosed in 2016.[1] Approximately 30% of these patients presented with locally advanced, but still potentially curable, stage III disease.[2] At most, 25% of these patients will be cured.[3] Therefore, up to 40,000 potentially curable patients with stage III non–small-cell lung cancer (NSCLC) will die each year.

### *What Is Known About the Best Treatment for Stage III NSCLC*

Clinical trials of patients with stage III NSCLC have demonstrated the benefit of chemotherapy and radiation therapy together versus radiation therapy alone[4] or chemotherapy alone.[5] In addition, there is reasonable evidence that giving both modalities at the same time (concurrently) as opposed to one following the other (sequentially) leads to better outcomes.[6] However, beyond these general principles, little more is known about how to optimize treatment for these patients. Chemotherapeutic regimens and targeted agents that have slowly increased survival in patients with NSCLC with metastatic disease have not increased survival in patients with stage III disease.[7-12] Immunotherapy has opened a new treatment avenue in patients who have metastatic disease, with long term responses seen in a small subset of patients[13]; nonetheless, most patients fail treatment. Ongoing studies are evaluating its efficacy in patients with stage III disease, but no results are currently available to support its use. In summary, clinicians have seen little improvement in patient outcomes with stage III NSCLC in the last 10 to 15 years.

## Why Do We Fail to Cure Stage III NSCLC?

### *The Problem of Locoregional Control*

Chemoradiotherapy is the standard of care for locoregional control of locally advanced NSCLC, an absolutely necessary step for curing the patient. However, there is evidence that this modality, by itself, is not adequate for this task. For example, in the seminal study RTOG (Radiation Therapy Oncology Group) 06-17, which compared 2 radiation doses (60 Gy and 74 Gy), 30% to 40% of patients experienced radiographic evidence of locoregional failure at 2 years, suggesting the persistence of locoregional disease despite definitive therapy[14] (Figure 1). A meta-analysis regarding patterns of

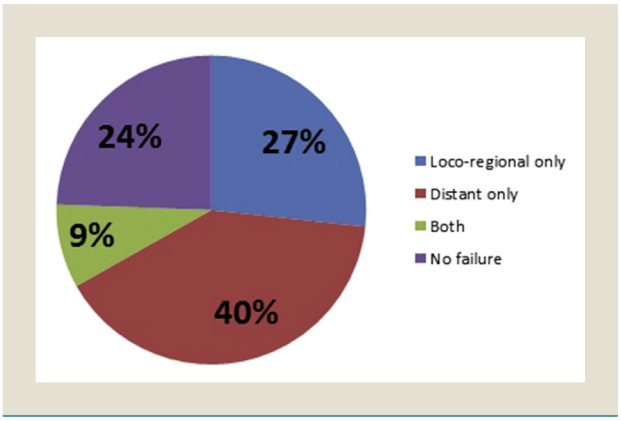
[1]Department of Radiation Oncology, Virginia Commonwealth University, Richmond, VA
[2]Division of Hematology/Oncology, Department of Internal Medicine, East Carolina University, Greenville, NC
[3]Department of Radiation Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC

Submitted: Mar 8, 2017; Revised: May 24, 2017; Accepted: May 30, 2017; Epub: Jun 16, 2017

Address for correspondence: Noah S. Kalman, MD, MBA, 401 College St, Box 980058, Richmond, VA 23298-0058
E-mail contact: noah.kalman@vcuhealth.org

1525-7304/$ - see frontmatter © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.cllc.2017.05.024

**Figure 1** Pattern of Failure in RTOG (Radiation Therapy Oncology Group) 06-17, 60-Gy Arm




failure reported locoregional failure rates between 31% and 100% and mediastinal recurrence rates between 4% and 56%.[15] However, all of these studies relied on radiographic findings to determine the rates of locoregional failure.

Pathologic findings offer more definitive assessments than radiographic ones, and there is accumulating experience in treating patients with stage III operable disease with neoadjuvant chemoradiotherapy followed by surgery. In these patients, a pathologic assessment of response to therapy can be made. Table 1 demonstrates that fewer than half of patients with operable stage III NSCLC achieved pathologic locoregional tumor control following chemoradiotherapy. Higher doses appear to increase control rates,[16-21] with 60 Gy leading to a 35% pathologic complete response rate.[20]

### *Historical Attempts to Improve Locoregional Tumor Control*

Increasing the radiotherapy dose with conventional fractionation would seem to be a logical way to improve locoregional tumor control. Single-arm studies suggested improvements in survival in locally advanced NSCLC with higher doses, but the large phase III study (RTOG 06-17) failed to show improvement using 74 Gy as compared with 60 Gy.[14] Indeed, the higher radiotherapy dose was associated with poorer survival, with possible explanations including increased normal tissue dose (eg, to the heart), worse compliance with radiotherapy planning specifications, and/or poorer treatment tolerability. Locoregional control was also numerically worse in the 74 Gy arm, but this difference was not statistically significant. A recent meta-analysis concluded that dose escalation above 60 Gy with conventional fractionation did not benefit patients receiving concurrent chemotherapy.[22]

Alternative fractionation regimens have been examined, but direct comparisons to 60 Gy chemoradiotherapy are lacking.[23] The randomized trials continuous hyperfractionated accelerated radiotherapy (CHART) and CHART weekend-less (CHARTWEL), which used hyperfractionated/accelerated fractionation regimens, showed some improvement in overall survival relative to radiotherapy alone, but with increased toxicity.[24,25] Interestingly, a multi-institutional study (RTOG 94-10) demonstrated improved local control with twice daily chemoradiotherapy to 69.6 Gy compared with daily chemoradiotherapy to 60 Gy, but survival was higher in the 60 Gy arm.[26] Such accelerated regimens offer a potential benefit over conventionally fractionated dose-escalation regimens by avoiding longer treatment periods and the potential for tumor repopulation.

Surgical resection has also been evaluated in operable patients but has not shown a survival benefit after neoadjuvant chemoradiotherapy in randomized trials.[17,19] However, neither study reported patterns of failure, so the impact of surgery on locoregional control is unknown.

### *The Effect of Locoregional Control on Overall Disease Control*

Treatment failures can be divided into those that stem from failure to remove or sterilize locoregional disease and those owing to preexisting occult disease not identified by current staging methods. In the first case, lack of locoregional disease control leads to death from local progression and/or subsequent distant site seeding. In the second case, disease has already disseminated from the primary and/or regional tumor. In RTOG 06-17, only 20% to 30% of patients remained disease-free at 2 years,[14] with mixed patterns of failure (Figure 1).

**Table 1** Complete Pathologic Downstaging as a Function of Radiation Dose

| Study | No. Patients | Years | Chemoradiation Therapy | Interval to Surgery | Pathologic CR, % |
|---|---|---|---|---|---|
| Pisters[16] | 169 | 1999-2004 | 3 cycles of carboplatin and paclitaxel. No radiation. | 3-8 wk | 9 |
| Albain[17] | 164 | 1994-2001 | 45 Gy with induction and concurrent chemotherapy | 3-5 wk | 18 |
| Kim[18] | 233 | 1989-2008 | 45 Gy split course with concurrent chemotherapy | Not reported | 22 |
| Eberhardt[19] | 81 | 2004-2013 | 45 Gy BID with induction and concurrent chemotherapy | 3-9 wk (median 5) | 33 |
| Cerfolio[20] | 185 | 1998-2008 | 60 Gy with concurrent chemotherapy | Not reported | 35 |
| Edelman[21] | 40 | 1994-2000 | 69.6 Gy BID with concurrent chemotherapy | 3-4 wk[a] | 45 |

Abbreviation: BID = twice a day.
[a]Reassessment performed at 3-4 weeks with surgery after reassessment.

These results and the pathologic outcomes showed in Table 1 suggest that lack of locoregional disease control is a large factor in the poor cure rates currently seen. There are 2 cautions in interpreting these results: first, pathologic complete response rates may underestimate locoregional disease control just as radiographic findings may over- or underestimate true recurrence rates owing to pseudoprogression or occult residual disease; second, better staging could identify occult distant disease as the dominant mode of failure, limiting the number of patients with stage III disease that are curable with improved locoregional disease control. Despite these caveats, locoregional disease control is a prerequisite for cure in these patients.

### *A Way Forward*

Lack of locoregional control will lead to failure and subsequent death in nearly 100% of cases. Although attempts to escalate dose using conventional radiation fractionation have been largely unsuccessful, newer methods of escalating locoregional treatment may allow for improvements in locoregional control with acceptable toxicity, especially if patients at significant risk of locoregional failure can be identified.

## Critical Issues in Escalating Therapy

In developing a path forward to improve locoregional treatment for stage III NSCLC, 2 critical issues must be considered: first, patients at significant risk of locoregional failure must be identified; second, effective and safe therapy escalation must be administered. Herein, pertinent data to guide these decisions is reviewed.

### *Identifying Those at Significant Risk of Locoregional Failure*

*Modality of Radiographic Assessment.* Positron emission tomography–computed tomography (PET-CT) has emerged as the most effective imaging modality to evaluate pretreatment disease, with a reported sensitivity of 77% to 81% and specificity of 79% to 90% for detecting mediastinal involvement depending on the criterion used.[27] It has been both claimed and disputed that pretreatment PET-CT findings are prognostic in patients with lung cancer,[28-34] with larger and more recent studies failing to demonstrate prognostic value (Table 2). CT-based assessments of pretreatment tumor volume have also demonstrated prognostic value, and pretreatment magnetic resonance imaging can predict response to therapy.[35] However, prognostic information provided by pretreatment scans does not alter initial therapy, as attempts to escalate initial therapy have lacked benefit and increased toxicity. More important is whether serial peritreatment scans can identify those at significant risk of locoregional failure despite receiving definitive therapy, so that treatment can subsequently be adapted.

Serial PET-CT imaging has demonstrated prognostic value in assessing treatment response that is more robust than the data supporting other radiographic modalities (CT, magnetic resonance imaging).[35-37] Cerfolio et al and others showed that PET-CT performed after neoadjuvant chemotherapy or chemoradiotherapy predicted pathologic complete response rates.[38-40] Similarly, PET-CT response predicted survival in studies of chemoradiotherapy with or without subsequent surgery[32,41-44] (Table 3). In these reports, patients with greater declines in tumor PET avidity on posttreatment scans relative to pretreatment scans had improved disease control outcomes. For the minority of patients that meet these PET response thresholds after treatment, further therapy may not be required. However, the majority of patients remain at high risk of locoregional failure, and serial PET-CT assessment can be used to identify these patients that are most appropriate for escalation of locoregional therapy.

*Timing of Serial Imaging.* Studies involving serial PET-CT imaging vary widely in their timing, but can be grouped into posttreatment and intratreatment categories.[45] Serial PET-CT roughly 2 weeks following completion of radiation therapy has demonstrated the ability to predict pathologic response and survival in patients receiving chemoradiotherapy for stage III NSCLC[38-43] (Table 3). With the exception of Ryu et al,[40] these studies assessed the change in maximum standardized uptake value ($SUV_{max}$) on serial scans, with decreases between 50% and 80% indicating improved prognosis. Repeat PET-CT imaging at longer intervals (2-3 months) following radiotherapy showed similar results.[32,44] Although discrete cut-offs were examined in these studies, many authors concluded that decrease in $SUV_{max}$ can be considered a continuous variable with larger changes in $SUV_{max}$ conferring greater benefit in patient response to treatment.

**Table 2** Prognostic Value of Pretreatment PET-CT

| Study | Publication Year | No. Patients | Stage | Definition of Threshold | Prognostic Value |
|---|---|---|---|---|---|
| Cerfolio[28] | 2005 | 315 | I-IV | $SUV_{max} \geq 10$ | DFS: yes<br>OS: yes |
| Borst[29] | 2005 | 51 | I-III | $SUV_{max} \geq 15$ | OS: yes |
| Eschmann[30] | 2006 | 159 | III | $SUV_{avg} \geq 12$ | OS: yes |
| Hoang[31] | 2008 | 214 | III-IV | $SUV_{max} \geq 11.1$ | OS: no |
| Machtay[32] | 2013 | 226 | III | $SUV_{max}$ and $SUV_{peak}$ | OS: no |
| Calais[33] | 2015 | 39 | II-III | $SUV_{max}$ | Local relapse: yes |
| Ohri[34] | 2015 | 28 | III | MTV total >60 cc<br>MTV lesion >25 cc | DFS: yes<br>Lesion recurrence: yes |

Abbreviations: DFS = disease-free survival; max = maximum; MTV = metabolic tumor volume; OS = overall survival; PET-CT = positron emission tomography-computed tomography; SUV = standard uptake value.

**Table 3 Prognostic Value of Posttreatment PET-CT**

| Study | Publication Year | No. Patients | Stage | Interval | Prior Therapy | Subsequent (Planned) Therapy | Definition of Threshold | Prognostic Value |
|---|---|---|---|---|---|---|---|---|
| Cerfolio[38] | 2004 | 56 | I-III | Within 1 mo | Chemotherapy or chemoradiotherapy | Surgery | $SUV_{max}$ decrease >80% | pCR: yes |
| Cerfolio[39] | 2006 | 93 | III | NR[c] | Chemoradiotherapy | Surgery | $SUV_{max}$ decrease >75% (primary) or >50% (LN) | pCR: yes |
| Ryu[40] | 2002 | 26 | III | 2 wk | 42 Gy in 1.5 Gy fx BID (10-day break after 21 Gy) with concurrent 5-FU, cisplatin, and vinblastine | Surgery followed by 12-18 Gy with concurrent chemotherapy | $SUV_{mean}$ >3 | pCR: yes |
| Eschmann[41] | 2007 | 70 | III | 2 wk | Weekly carboplatin-paclitaxel × 4c → 45 Gy in 1.5 Gy fx BID with concurrent weekly carboplatin-paclitaxel | Surgery | $SUV_{max}$ decrease >80% | OS: yes |
| Pöttgen[42] | 2006 | 43 | III | NR[a] | Cisplatin doublet q3wk × 3c → 44-45 Gy in 1.5 Gy fx BID or 2 Gy qd with concurrent cisplatin doublet | Surgery | SUVmax decrease >50% | OS: no<br>ECP: yes |
| Pöttgen[43] | 2016 | 124 | III | NR[b] | Cisplatin-paclitaxel q3wk × 3c | Chemoradiotherapy 45 Gy in 1.5 Gy fx BID followed by surgery or radiotherapy boost | $SUV_{max}$ decrease >50% | OS: yes<br>PFS: yes<br>ECP: yes |
| Machtay[32] | 2013 | 173 | III | 14 wk | ≥60 Gy in 2 Gy fx qd with concurrent platinum doublet ± adjuvant chemotherapy | None | $SUV_{peak}$ >3.5 or 5 | OS (3.5): no<br>OS (5): yes |
| Mac Manus[44] | 2005 | 88 | I-III | 70 d | 60 Gy in 2 Gy fx qd ± concurrent chemotherapy | None | CMR | OS: yes<br>DM: yes<br>LRF: yes |

Abbreviations: BID = twice a day; CMR = complete metabolic response; DM = distant metastases; ECP = extracerebral progression; fx = fractions; 5-FU = fluorouracil; LRF = locoregional failure; max = maximum; OS = overall survival; pCR = pathologic complete response; PET-CT = positron emission tomography-computed tomography; PFS = progression-free survival; qd = once a day; q3w = once every 3 weeks.

[a]Average interval of 83 days from start of neoadjuvant therapy to follow up PET-CT, suggesting no interval after completion of therapy.

[b]Average interval of 57 days from the start of neoadjuvant therapy to follow up PET-CT, suggesting a ~2-week interval after the start of the final chemotherapy cycle.

[c]Timing of post-neoadjuvant therapy PET-CT not known, but presumed to be within 1 month per prior studies from the same group.

*Adapted from van Loon et al.*[45]

**Table 4** Prognostic Value of Mid-treatment PET-CT

| Study | Publication Year | No. Patients | Stage | Timing of PET-CT | Therapy | Subsequent (Planned) Therapy | Definition of Threshold | Prognostic Value |
|---|---|---|---|---|---|---|---|---|
| Toma-Dasu[46] | 2015 | 27 | III | Week 2 of radiotherapy | Cisplatin-gemcitabine × 3c → 79.2 Gy in 1.8 Gy fx qd OR cisplatin-vinorelbine × 1c → 45 Gy in 1.5 Gy fx BID then 2 Gy fx qd up to 69 Gy with concurrent cisplatin-vinorelbine | None | Average change in SUV per dose delivered (continuous variable) | OS: yes |
| Usmanij[47] | 2013 | 28 | III | Beginning week 3 of radiotherapy | 66 Gy in 2 Gy fx qd with concurrent cisplatin-etoposide ± lobectomy | None | TLG decrease >38% | PFS: yes |
| Yossi[48] | 2015 | 31 | II-III | After 30 Gy | 66-70 Gy in 2 Gy fx qd with concurrent platinum doublet | None | TLG decrease >15% | OS: yes<br>PFS: yes |
| Huang[49] | 2011 | 37 | III-IV | After 40 Gy | 40 Gy in 2 Gy fx qd with concurrent cisplatin doublet then 1.4 Gy fx BID up to 62.4-68 Gy | Adjuvant cisplatin doublet X 2-4c | SUVmax decrease MTV | CT response 4 weeks post-tx: yes |
| Zhang[50] | 2011 | 46 | III | After 40-50 Gy | 60-65 Gy in 1.8-2 Gy fx qd with concurrent cisplatin doublet ± adjuvant chemotherapy | None | SUVmax decrease >50% | OS: yes |
| Kong[51] | 2007 | 15 | I-III | After 45 Gy | 60+ Gy in 2+ Gy fx qd ± concurrent and adjuvant carboplatin-paclitaxel | None | CMR | CT response: yes |
| Huang[52] | 2015 | 53 | III | After 40 Gy | 40 Gy in 2 Gy fx qd with concurrent cisplatin doublet then 1.4 Gy fx BID up to 62.4-76.4 Gy | 2-4c adjuvant cisplatin doublet | MTV decrease >29.7% | LRFS: yes |

Abbreviations: BID = twice a day; fx = fraction; LRFS = local relapse-free survival; MTV = metabolic tumor volume; OS = overall survival; PFS = progression-free survival; qd = once a day; TLG = total lesion glycolysis.
*Adapted from van Loon et al.*[45]

Intratreatment serial PET-CT offers the ability to adapt therapy mid-treatment, but data supporting this timing is limited to small series. In patients undergoing thoracic radiotherapy or chemoradiotherapy, decreases in overall tumor activity (not $SUV_{max}$) 2 to 3 weeks into treatment correlated with overall survival and/or progression free survival.[46-48] Series examining PET-CT changes 4 to 5 weeks into chemoradiotherapy treatment also appeared to stratify responders and nonresponders,[49-52] but only one study showed an association of PET-CT changes with survival,[50] and these studies differed significantly in their benchmarks to evaluate PET-CT response. Table 4 summarizes these results. The current multi-institutional study RTOG 11-06 uses PET-CT at 5 weeks to identify tumor lesions amenable to dose escalation, with the treatment dose based on retrospective data.[53] However, this approach has not been definitively proven.

There have been concerns that areas of radiotherapy-induced inflammation, which are fluorodeoxyglucose (FDG)-avid, can limit the diagnostic accuracy of serial PET-CT imaging in the peritreatment period. However, these concerns are not substantiated in published reports. Quantitative assessments of lung parenchyma PET avidity 3 months after radiotherapy show minor changes from baseline in normal lung tissue relative to large changes from baseline in lung tumors.[54] In one study, radiotherapy-induced inflammatory lung changes were actually lower on intratreatment PET-CT scans compared with 3-month PET-CT scans.[51]

In light of the data supporting early response assessment after completion of initial therapy, serial scans at roughly 2 weeks post-treatment appear to allow identification of patients appropriate for immediate therapy escalation. This small break limits the degree of tumor repopulation, consistent with timing of surgery in most protocols with neoadjuvant chemoradiotherapy.[17,19] Tumors often shrink during and immediately following radiotherapy,[55] so a small break provides the additional benefit of treating a smaller target. Furthermore, the data supporting this approach is more robust than that supporting intratreatment assessment.

*Criteria for Determining Likelihood of Residual Disease.* Of the studies that evaluated response to therapy with PET-CT early following completion of chemoradiotherapy, a decrease in $SUV_{max}$ of

**Table 5** Series of SBRT Following Chemoradiotherapy

| Study | Publication Year | No. Patients | Initial Therapy | Subsequent Boost Therapy | Target | Timing of Boost | Boost Criteria | Median Follow-up, mo | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Feddock[61] | 2013 | 35 | 60 Gy chemoradiotherapy with platinum doublet | 10 Gy × 2 fx (peripheral) or 6.5 Gy × 3 fx (medial) | Residual disease + 1-cm cranio-caudal, 0.5-cm radial expansion | Median time to completion of SBRT 2 mos after initial treatment | Residual disease ≤5 cm on PET-CT ∼1 mo after chemoradiotherapy without nodal or distant disease | 13 | LC 1 y: 83%<br>Gr 3 RP: acute 11%, late 3%<br>Gr 2 + RP: acute 17%, late 9%<br>2 Gr 5 pulmonary hemorrhage[a] |
| Karam[62] | 2013 | 16 | 50.4 Gy chemoradiotherapy | 5 Gy × 5 fx | Residual disease on CT + 0.5-cm expansion | Median 20 d after initial treatment | All patients received boost to primary ± LNs | 14 | OS 1 y: 78%<br>PFS 1 y: 42%<br>LC 1 y: 76%<br>RC 1 y: 79%<br>DC 1 y: 71%<br>Gr 2 acute RP: 25% |
| Hepel[63] | 2016 | 12 | 50.4 Gy chemoradiotherapy with platinum doublet | 8-14 Gy × 2 fx (42% also received adjuvant chemotherapy) | Residual disease + 0.5-cm expansion | 1-4 wk after initial treatment | Primary tumor <120 cc, nodal volume <60 cc | 15.5 | LC 1 y: 78% (60% if <24 Gy; 100% if ≥24 Gy)<br>OS 1 y: 67%<br>No Gr 3 RP<br>1 Gr 5 toxicity[b] |
| Trovo[64] | 2014 | 17 | 50-60 Gy chemoradiotherapy | 30 Gy in 5-6 fx | Residual disease + 0.5-cm expansion | Median 18 mo after initial treatment | In field recurrent or persistent central tumor on PET-CT | 18 | LC 1 y: 86%<br>DM 1 y: 47%<br>OS 1/2 y: 59%/29%<br>Gr 3 + RP: 35%<br>2 Gr 5 toxicity[c] |

Abbreviations: DM = distant metastasis; fx = fraction; LC = local control; LM = lymph node; OS = overall survival; PET-CT = positron emission tomography-computed tomography; PTV = planning target volume; RP = radiation pneumonitis; SBRT = stereotactic body radiation therapy.

[a]Occurred at 9 and 10 months after SBRT boost. Both had developed cavitary recurrences involving the hilum; in 1 case, the hilum was included within the high-dose PTV.

[b]Bronchopulmonary hemorrhage 13 months after SBRT boost; patient had received 12 Gy × 2 fx. On review, dose to the proximal bronchovascular tree was higher than all other patients.

[c]One with pneumonitis 4 months after SBRT, one with hemoptysis 2 months after SBRT.

> 50% to 80% was used to predict both residual disease and overall survival.[38,39,41-43] Recent updated PET-CT guidelines use PET response criteria in solid tumors (PERCIST) criteria to evaluate tumor response to therapy.[56] Complete metabolic response is defined as "complete resolution of FDG uptake within measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood-pool levels." In effect, any residual FDG uptake is suspicious for persistent disease. This definition conforms fairly well to thresholds used in surgical series[38-40] and can be used to identify high-risk patients.

### *Escalating Locoregional Therapy*

*Mode of Escalation.* Having identified patients at high risk for locoregional failure following chemoradiotherapy, possible interventions can be considered. Surgery has been a mainstay of therapy for stage III NSCLC for many years.[17,19,20,41] However, most patients are inoperable, even after initial therapy, owing to comorbidities or tumor location. In a recent nonrandomized study, RTOG 02-29, only two-thirds of operable patients underwent surgery after chemoradiotherapy, with 15% developing significant postoperative complications.[57] Therefore, other options are needed.

Stereotactic body radiotherapy (SBRT) has gained prominence in lung cancer owing to its effectiveness in treating early stage lesions.[58] With SBRT, a higher biologically effective dose (BED) is delivered relative to conventionally fractionated radiotherapy, with an accepted threshold dose of 100 Gy in lung cancer.[59] Such high doses delivered in short time periods have the potential to provide better tumor control above the limited effects seen in conventionally fractionated dose escalation regimens for stage III NSCLC.[22] Several institutions have taken the tools of lung SBRT and applied them to locally advanced disease.[60] Four prospective studies have examined SBRT to boost residual disease or treat isolated recurrences[61-64] (Table 5). In these studies, the total delivered BED ranged between 100 and 150 Gy.

In the largest study, Feddock et al delivered a SBRT boost to 35 patients immediately following the completion of chemoradiotherapy to 60 Gy. The boost target was defined by the residual disease seen on PET-CT performed roughly 1 month after completing initial therapy. Patients with residual primary tumors > 5 cm or residual nodal disease were excluded. The initial boost dose was 20 Gy in 2 fractions, but after 2 grade 5 toxicities, the dose for central lesions was modified to 19.5 Gy in 3 fractions.[61] Karam et al delivered a SBRT boost of 20 to 30 Gy in 5 fractions after an initial 50.4 Gy of chemoradiotherapy. Boost treatment started within a month after completion of initial therapy, and the target volume included involved mediastinal lymph nodes. No grade 3 to 5 toxicity was observed in this cohort.[62] In a recently published dose-escalation study, Hepel et al provided a SBRT boost after 50.4 Gy chemoradiotherapy. The SBRT boost, which targeted the residual primary tumor and lymph nodes, was escalated in 4 Gy increments from 16 Gy to 28 Gy in 2 fractions (3 patients per dose level). Interestingly, patients who received 24 or 28 Gy had 100% local control at 1 year compared with 60% in the patients treated to 16 and 20 Gy. One grade 5 toxicity occurred in a patient treated to 24 Gy with high dose delivered to the proximal bronchovascular tree. However, toxicity in the remaining patients was limited.[63]

Other methods of dose escalation that use modestly hypofractionated radiotherapy are under examination (RTOG 11-06), although results are not yet available. Different radiotherapy modalities such as proton therapy and carbon ion therapy have also been explored in treating lung cancer, and may offer improved dosimetry relative to photons,[65] although their availability is limited. Interventions such as radiofrequency ablation have been tested in early stage lung cancer, but studies comparing radiofrequency ablation with SBRT found SBRT to be superior.[66]

Immunotherapy, now commonly used in the metastatic setting, has been proposed for adjuvant treatment in patients with stage III disease after chemoradiotherapy.[67] Interestingly, the combination of SBRT and immunotherapy may have a synergistic effect. Multiple reports have shown that SBRT can potentiate the effect of immunotherapy across multiple tumor types, including NSCLC.[68] Data is limited to patients with metastatic disease, but further investigation may show that combination therapy offers better locoregional and distant disease control than either alone.

Multiple series across different institutions have documented the feasibility of lung SBRT after chemoradiotherapy. SBRT, whether using photons or heavy particles, has been shown to be feasible across patients with varying degrees of comorbidities and appears to be the optimal method to escalate therapy. Further study is required to consider combining radiotherapy and immunotherapy.

*Target Definition for SBRT.* Primary Versus Lymph Nodes

There is some debate whether the primary tumor is the only site that requires dose escalation or whether involved lymph nodes are also at significant risk. The lower volume of disease in lymph nodes is more likely to be cleared with lower doses of radiation relative to the larger primary sites.[69] However, the pattern of recurrence in stage III NSCLC is both local and regional.[15] Limited series have demonstrated that PET-CT detects residual nodal disease after chemoradiotherapy.[39] In addition, the study RTOG 02-35 demonstrated that residual PET avidity in lymph nodes independently predicted for locoregional failure.[70] These results support the treatment of all residual disease, whether it involves the primary tumor or mediastinal lymph nodes.

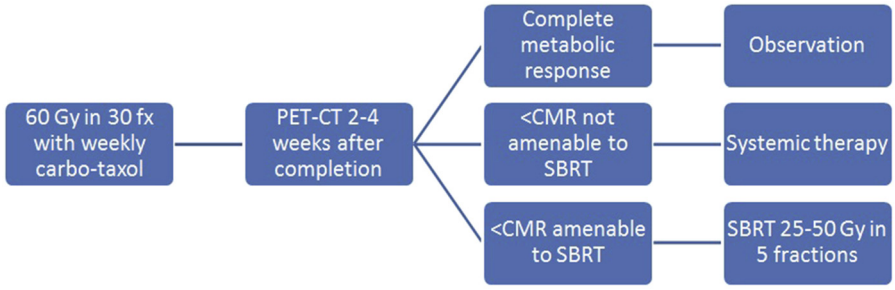
Correlation of PET Avidity and Residual Tumor

PET-avid areas represent sites with the highest likelihood of harboring residual tumor. However, PET avidity is an imperfect representation of tumor presence, as hypoxic or necrotic tumor volumes may demonstrate little FDG uptake despite the presence of viable cells, and non−tumor-bearing areas can appear PET-avid.[71] As residual PET avidity is associated with poorer outcomes, 2 current studies utilize FDG uptake to direct boost therapy (RTOG 11-06 and a Dutch study)[72] for increased dose deposition.

Concern for Microscopic Disease at Residual Disease Sites

In delineating targets in stage III NSCLC, radiation oncologists expand the target beyond the gross target volume (GTV) to ensure coverage of microscopic disease extension, with the expansions related to histology and location of disease. However, typically no target expansion is performed in lung SBRT, with the rationale that disease extension is more limited at early stages and that the intermediate radiation dose received by the tissue surrounding the target volume is sufficiently high to eradicate microscopic disease. In patients that have already received full-dose chemoradiotherapy with target expansions to address microscopic disease, expanding the SBRT boost target would be unlikely to increase tumor control.

**Figure 2** Protocol Schema




Abbreviations: CMR = complete metabolic response; fx = fractions; PET-CT = positron emission tomography-computed tomography; SBRT = stereotactic body radiation therapy.

Therefore, limiting the boost target to the volume of residual PET avidity will likely reduce toxicity without sacrificing disease control.

*Normal Tissue Tolerance.* Organs at Risk

Established dose constraints for thoracic radiotherapy exist for both conventionally fractionated radiation and SBRT. Organs at risk include the lung, spinal cord, chest wall, esophagus, heart, great vessels, brachial plexus, and large and small airways. Treating tumors adjacent to large airways with SBRT has generated particular concern, with multiple publications reporting increased toxicity when treating lesions surrounding the proximal bronchovascular tree.[59,73-75] Indeed, grade 5 toxicities in patients receiving a SBRT boost after chemoradiotherapy were associated with central lesions.[61,62] RTOG 08-13, a dose-finding study that examined SBRT specifically for early stage lesions abutting the proximal bronchovascular tree and/or mediastinum, reported that treatment was safe and effective,[76] although grade 5 toxicities occurred. Overall, the study's dose constraints appear to be a reasonable starting point, with BED conversions used to estimate the combined effect of conventionally fractionated radiotherapy and SBRT.

After dose constraints are established, various methods can be employed to help meet these constraints. Active breath hold or respiratory gating can limit the area of irradiated lung tissue if patients can tolerate these measures. Image guidance with cone-beam CT would be mandatory to reduce required treatment margins.[77] Mediastinal or central targets would likely require that setup priority be given to critical structures to reduce the risk of treatment toxicity.

Boost Dose

The necessary dose to treat early stage lesions is well established at > 100 Gy BED,[59] but the effect of combining conventional and hypofractionated radiation is less known, as is the effect of a 4- to 6-week treatment break. Most protocols set a target dose, and if treatment plans cannot sufficiently spare normal tissue, those patients are excluded from the study. Another method that has increased in frequency is to set normal tissue constraints and escalate dose to the target until these constraints are reached. Indeed, differential doses could be given to mediastinal and primary tumor sites in a given patient to limit dose to the proximal bronchovascular tree. Because the effect of combining conventionally fractionated radiotherapy with SBRT is not known, a dose-escalation study design has the added benefit of establishing dose thresholds for disease eradication and normal tissue toxicity. Although toxicity will likely be higher in these patients, escalating dose is necessary given the near certainty of death without further treatment.

## Clinical Trial Concept

We propose a clinical trial concept that builds on the ideas discussed in this article (Figure 2). In patients with stage IIIA to B NSCLC, initial treatment would consist of the standard arm of RTOG 06-17, which was radiation with 60 Gy in 30 daily fractions with concurrent weekly chemotherapy carboplatin and paclitaxel. Intensity-modulated radiation therapy planning would be preferred to increase treatment conformality. A baseline PET-CT would be obtained prior to starting chemoradiotherapy, as is commonly done for routine staging. Pathologic confirmation would be required through sampling of an involved lymph node station or primary tumor.

Roughly 2 weeks following the completion of chemoradiotherapy, a repeat PET-CT would be performed. At this point, patients would be separated into 3 groups: (1) patients with complete metabolic response to all sites of disease by PERCIST criteria; (2) patients without complete metabolic response with residual disease not amenable to SBRT; and (3) patients without complete metabolic response but with residual disease amenable to SBRT.

Patients with complete metabolic response would not receive additional therapy. Patients without complete metabolic response and not amenable to SBRT would receive systemic therapy at the treating oncologists' discretion and would be restaged at a later date for consideration of SBRT if disease regressed sufficiently.

Patients with residual disease amenable to SBRT would undergo resimulation and receive SBRT (heavy particle therapy would be allowed if available). Treatment would consist of 5 fractions delivered over 2 weeks with a minimum dose per fraction of 5 Gy marginal dose (cumulative dose ~110 Gy BED). If normal tissue constraints are met, the dose can be escalated up to 10 Gy per fraction, which would represent 100 Gy BED not including the initial course of chemoradiotherapy.

The primary treatment outcome would be progression-free survival at 24 months. Progression would be defined by PERCIST criteria for progressive disease (> 25% increase in SUV from

posttreatment imaging or presence of new FDG-avid lesions). Secondary outcomes would include time to locoregional and distant failure, overall survival, and acute and late treatment toxicity. Criteria for early stopping would be significantly increased development of grade 4/5 toxicity relative to historical series. Because the patients that receive SBRT would represent a higher risk population than an unselected stage III cohort, the benchmark for trial success would be to match the 20% to 30% progression-free survival at 24 months seen in RTOG 06-17 in this group.

## A Call to Arms

We challenge the thoracic oncology community to contact the authors to assist with designing a comprehensive protocol and to submit for institutional funding. Stage III lung cancer has stubbornly resisted efforts to improve control rates in the past 10 to 15 years. With new diagnostic and treatment tools, progress can be made in this aggressive but curable disease.

## Disclosure

The authors have stated that they have no conflicts of interest.

## References


1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; 66: 7-30.
2. Morgensztern D, Ng SH, Gao F, Govindan R. Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database Survey. *J Thorac Oncol* 2010; 5:29-33.
3. Reck M, Heigener DF, Mok T, Soria J-C, Rabe KF. Management of non-small-cell lung cancer: recent developments. *Lancet* 2013; 382:709-19.
4. 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; 88:1210-5.
5. Kubota K, Furuse K, Kawahara M, et al. Role of radiotherapy in combined modality treatment of locally advanced non-small-cell lung cancer. *J Clin Oncol* 1994; 12:1547-52.
6. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non−small-cell lung cancer. *J Clin Oncol* 2010; 28:2181-90.
7. Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. *J Clin Oncol* 2010; 28: 3739-45.
8. 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; 34:953-62.
9. Wang L, Wu S, Ou G, et al. Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer. *Lung Cancer* 2012; 77:89-96.
10. Tsujino K, Kurata T, Yamamoto S, et al. Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung cancer? A pooled analysis of the literature. *J Thorac Oncol* 2013; 8:1181-9.
11. Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol* 2008; 26:2450-6.
12. Komaki R, Allen PK, Wei X, et al. Adding erlotinib to chemoradiation improves overall survival but not progression-free survival in stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2015; 92:317-24.
13. Simone CB 2nd, Burri SH, Heinzerling JH. Novel radiotherapy approaches for lung cancer: combining radiation therapy with targeted and immunotherapies. *Transl Lung Cancer Res* 2015; 4:545-52.
14. 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; 16:187-99.
15. 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; 30:953-61.
16. Pisters KM, Vallieres E, Crowley JJ, et al. Surgery with or without preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. *J Clin Oncol* 2010; 28:1843-9.
17. 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; 374:379-86.
18. Kim AW, Liptay MJ, Bonomi P, et al. Neoadjuvant chemoradiation for clinically advanced non-small cell lung cancer: an analysis of 233 patients. *Ann Thorac Surg* 2011; 92:233-41 [discussion: 241-3].
19. Eberhardt WE, Pottgen C, Gauler TC, et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). *J Clin Oncol* 2015; 33: 4194-201.
20. Cerfolio RJ, Bryant AS, Jones VL, Cerfolio RM. Pulmonary resection after concurrent chemotherapy and high dose (60Gy) radiation for non-small cell lung cancer is safe and may provide increased survival. *Eur J Cardiothorac Surg* 2009; 35: 718-23 [discussion: 723].
21. Edelman MJ, Suntharalingam M, Burrows W, et al. Phase I/II trial of hyperfractionated radiation and chemotherapy followed by surgery in stage III lung cancer. *Ann Thorac Surg* 2008; 86:903-10.
22. 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; 96:736-47.
23. Kelsey CR, Das S, Gu L, Dunphy FR 3rd, Ready NE, Marks LB. Phase 1 dose escalation study of accelerated radiation therapy with concurrent chemotherapy for locally advanced lung cancer. *Int J Radiat Oncol Biol Phys* 2015; 93:997-1004.
24. Baumann M, Herrmann T, Koch R, et al. Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC). *Radiother Oncol* 2011; 100:76-85.
25. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. *Radiother Oncol* 1999; 52:137-48.
26. 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; 103:1452-60.
27. Schmidt-Hansen M, Baldwin DR, Hasler E, Zamora J, Abraira V, Roque IFM. PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer. *Cochrane Database Syst Rev* 2014: CD009519.
28. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA. The maximum standardized uptake values on positron emission tomography of a non-small cell lung cancer predict stage, recurrence, and survival. *J Thorac Cardiovasc Surg* 2005; 130:151-9.
29. Borst GR, Belderbos JSA, Boellaard R, et al. Standardised FDG uptake: a prognostic factor for inoperable non-small cell lung cancer. *Eur J Cancer* 2005; 41: 1533-41.
30. Eschmann SM, Friedel G, Paulsen F, et al. Is standardised (18)F-FDG uptake value an outcome predictor in patients with stage III non-small cell lung cancer? *Eur J Nucl Med Mol Imaging* 2006; 33:263-9.
31. Hoang JK, Hoagland LF, Coleman RE, Coan AD, Herndon JE 2nd, Patz EF Jr. Prognostic value of fluorine-18 fluorodeoxyglucose positron emission tomography imaging in patients with advanced-stage non-small-cell lung carcinoma. *J Clin Oncol* 2008; 26:1459-64.
32. 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/RTOG 0235 trial. *J Clin Oncol* 2013; 31:3823-30.
33. Calais J, Thureau S, Dubray B, et al. Areas of high 18F-FDG uptake on preradiotherapy PET/CT identify preferential sites of local relapse after chemoradiotherapy for non-small cell lung cancer. *J Nucl Med* 2015; 56:196-203.
34. 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; 87:23-7.
35. Nishino M, Hatabu H, Johnson BE, McLoud TC. State of the art: response assessment in lung cancer in the era of genomic medicine. *Radiology* 2014; 271:6-27.
36. Coroller TP, Grossmann P, Hou Y, et al. CT-based radiomic signature predicts distant metastasis in lung adenocarcinoma. *Radiother Oncol* 2015; 114:345-50.
37. Weiss E, Ford JC, Olsen KM, et al. Apparent diffusion coefficient (ADC) change on repeated diffusion-weighted magnetic resonance imaging during radiochemotherapy for non-small cell lung cancer: a pilot study. *Lung Cancer* 2016; 96: 113-9.
38. Cerfolio RJ, Bryant AS, Winokur TS, Ohja B, Bartolucci AA. Repeat FDG-PET after neoadjuvant therapy is a predictor of pathologic response in patients with non-small cell lung cancer. *Ann Thorac Surg* 2004; 78:1903-9 [discussion: 1909].
39. Cerfolio RJ, Bryant AS, Ojha B. Restaging patients with N2 (stage IIIa) non−small cell lung cancer after neoadjuvant chemoradiotherapy: a prospective study. *J Thorac Cardiovasc Surg* 2006; 131:1229-35.
40. Ryu JS, Choi NC, Fischman AJ, Lynch TJ, Mathisen DJ. FDG-PET in staging and restaging non-small cell lung cancer after neoadjuvant chemoradiotherapy: correlation with histopathology. *Lung Cancer* 2002; 35:179-87.
41. Eschmann SM, Friedel G, Paulsen F, et al. 18F-FDG PET for assessment of therapy response and preoperative re-evaluation after neoadjuvant radiochemotherapy in stage III non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2007; 34:463-71.

42. Pottgen C, Levegrun S, Theegarten D, et al. Value of 18F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography in non-small-cell lung cancer for prediction of pathologic response and times to relapse after neoadjuvant chemoradiotherapy. *Clin Cancer Res* 2006; 12:97-106.
43. Pottgen C, Gauler T, Bellendorf A, et al. Standardized uptake decrease on [18F]-fluorodeoxyglucose positron emission tomography after neoadjuvant chemotherapy is a prognostic classifier for long-term outcome after multimodality treatment: secondary analysis of a randomized trial for resectable stage IIIA/B non-small-cell lung cancer. *J Clin Oncol* 2016; 34:2526-33.
44. Mac Manus MP, Hicks RJ, Matthews JP, Wirth A, Rischin D, Ball DL. Metabolic (FDG-PET) response after radical radiotherapy/chemoradiotherapy for non-small cell lung cancer correlates with patterns of failure. *Lung Cancer* 2005; 49:95-108.
45. van Loon J, van Baardwijk A, Boersma L, Ollers M, Lambin P, De Ruysscher D. Therapeutic implications of molecular imaging with PET in the combined modality treatment of lung cancer. *Cancer Treat Rev* 2011; 37:331-43.
46. Toma-Dasu I, Uhrdin J, Lazzeroni M, et al. Evaluating tumor response of non-small cell lung cancer patients with (1)(8)F-fludeoxyglucose positron emission tomography: potential for treatment individualization. *Int J Radiat Oncol Biol Phys* 2015; 91:376-84.
47. Usmanij EA, de Geus-Oei LF, Troost EG, et al. 18F-FDG PET early response evaluation of locally advanced non-small cell lung cancer treated with concomitant chemoradiotherapy. *J Nucl Med* 2013; 54:1528-34.
48. Yossi S, Krhili S, Muratet JP, Septans AL, Campion L, Denis F. Early assessment of metabolic response by 18F-FDG PET during concomitant radiochemotherapy of non-small cell lung carcinoma is associated with survival: a retrospective single-center study. *Clin Nucl Med* 2015; 40:e215-21.
49. Huang W, Zhou T, Ma L, et al. Standard uptake value and metabolic tumor volume of (1)(8)F-FDG PET/CT predict short-term outcome early in the course of chemoradiotherapy in advanced non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2011; 38:1628-35.
50. Zhang HQ, Yu JM, Meng X, Yue JB, Feng R, Ma L. Prognostic value of serial [18F]fluorodeoxyglucose PET-CT uptake in stage III patients with non-small cell lung cancer treated by concurrent chemoradiotherapy. *Eur J Radiol* 2011; 77:92-6.
51. 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; 25:3116-23.
52. Huang W, Liu B, Fan M, et al. The early predictive value of a decrease of metabolic tumor volume in repeated (18)F-FDG PET/CT for recurrence of locally advanced non-small cell lung cancer with concurrent radiochemotherapy. *Eur J Radiol* 2015; 84:482-8.
53. 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; 63:324-33.
54. McCurdy MR, Castillo R, Martinez J, et al. [18F]-FDG uptake dose—response correlates with radiation pneumonitis in lung cancer patients. *Radiother Oncol* 2012; 104:52-7.
55. Hugo GD, Weiss E, Badawi A, Orton M. Localization accuracy of the clinical target volume during image-guided radiotherapy of lung cancer. *Int J Radiat Oncol Biol Phys* 2011; 81:560-7.
56. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving Considerations for PET response criteria in solid tumors. *J Nucl Med* 2009; 50(Suppl 1):122S-50S.
57. Suntharalingam M, Paulus R, Edelman MJ, et al. Radiation Therapy Oncology Group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* 2012; 84:456-63.
58. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; 303:1070-6.
59. Senthi S, Haasbeek CJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. *Radiother Oncol* 2013; 106:276-82.
60. De Ruysscher D, Faivre-Finn C, Le Pechoux C, Peeters S, Belderbos J. High-dose re-irradiation following radical radiotherapy for non-small-cell lung cancer. *Lancet Oncol* 2014; 15:e620-4.
61. 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; 85:1325-31.
62. Karam SD, Horne ZD, Hong RL, McRae D, Duhamel D, Nasr NM. Dose escalation with stereotactic body radiation therapy boost for locally advanced non small cell lung cancer. *Radiat Oncol* 2013; 8:179.
63. Hepel JT, Leonard KL, Safran H, et al. Stereotactic body radiation therapy boost after concurrent chemoradiation for locally advanced non-small cell lung cancer: a phase 1 dose escalation study. *Int J Radiat Oncol Biol Phys* 2016; 96:1021-7.
64. Trovo M, Minatel E, Durofil E, et al. Stereotactic body radiation therapy for re-irradiation of persistent or recurrent non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2014; 88:1114-9.
65. Wink KC, Roelofs E, Solberg T, et al. Particle therapy for non-small cell lung tumors: where do we stand? A systematic review of the literature. *Front Oncol* 2014; 4:292.
66. Bi N, Shedden K, Zheng X, Kong F-M. Comparison of the effectiveness of radiofrequency ablation with stereotactic body radiation therapy in inoperable stage I non-small cell lung cancer: a systemic review and pooled analysis. *Int J Radiat Oncol Biol Phys* 2016; 95:1378-90.
67. Durm GA, Kio EA, Fisher WB, et al. Phase II trial of consolidation pembrolizumab following concurrent chemoradiation in patients (pts) with unresectable or inoperable stage III non-small cell lung cancer (NSCLC): initial safety data from HCRN LUN 14-179. *J Clin Oncol* 2016; 34(suppl) (abstract e20025).
68. Schoenhals JE, Seyedin SN, Tang C, et al. Preclinical rationale and clinical considerations for radiotherapy plus immunotherapy: going beyond local control. *Cancer J* 2016; 22:130-7.
69. Kong FM, Zhao J, Wang J, Faivre-Finn C. Radiation dose effect in locally advanced non-small cell lung cancer. *J Thorac Dis* 2014; 6:336-47.
70. Markovina S, Duan F, Snyder BS, Siegel BA, Machtay M, Bradley JD. Regional lymph node uptake of [(18)F]fluorodeoxyglucose after definitive chemoradiation therapy predicts local-regional failure of locally advanced non-small cell lung cancer: results of ACRIN 6668/RTOG 0235. *Int J Radiat Oncol Biol Phys* 2015; 93:597-605.
71. Christensen JD, Colby TV, Patz EF Jr. Correlation of [18F]-2-fluoro-deoxy-D-glucose positron emission tomography standard uptake values with the cellular composition of stage I nonsmall cell lung cancer. *Cancer* 2010; 116:4095-102.
72. 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.
73. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006; 24:4833-9.
74. Mangona VS, Aneese AM, Marina O, et al. Toxicity after central versus peripheral lung stereotactic body radiation therapy: a propensity score matched-pair analysis. *Int J Radiat Oncol Biol Phys* 2015; 91:124-32.
75. Lindberg K, Bergström P, Brustugun OT, et al. The Nordic HILUS trial - first report of a phase II trial of SBRT of centrally located lung tumors. *World Conference on Lung Cancer* 2016; 12:S340, (abstract OA24.05).
76. Bezjak A, Paulus R, Gaspar LE, et al. Efficacy and toxicity analysis of NRG Oncology/RTOG 0813 trial of stereotactic body radiation therapy (SBRT) for centrally located non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2016; 96:S8.
77. Grills IS, Hugo G, Kestin LL, et al. Image-guided radiotherapy via daily online cone-beam CT substantially reduces margin requirements for stereotactic lung radiotherapy. *Int J Radiat Oncol Biol Phys* 2008; 70:1045-56.