Winter 2011 | NO 43

National Jewish Health®
Science Transforming Life®

Lung Cancer FRONTIERS

The Forum for Early Diagnosis and Treatment of Lung Cancer

Brian D. Kavanagh, MD, MPH

Sterotactic Body Radiation Therapy for Early Stage Lung Cancer

By Brian D. Kavanagh, MD, MPH

In recent issues of *Lung Cancer Frontiers*, the bedeviling issue that is lung cancer screening has been tackled with wit and wisdom. Dr. Silvestri[1] kicked things off by voicing the common frustrations of everyone who just wants the data to answer a simple question: should we or shouldn't we screen for lung cancer? Dr. Mulshine[2] followed up a few issues later with an analysis emphasizing the challenges of establishing a non-invasive imaging methodology with appropriately high sensitivity that avoids excess false positivity. Among the numerous technical and clinical entanglements is the pesky possibility that in certain circumstances, *screening might be too good*. It would not serve anyone's best interest if early stage lung cancer were over diagnosed in a population of patients for whom competing morbidity risks eclipsed the therapeutic benefit of available treatment modalities.

Then, a sudden newsflash on November 4, 2010: early results of the National Lung Screening Trial (NLST), a randomized trial that enrolled more than 53,000 current and former heavy smokers aged 55 to 74, demonstrated that screening with low-dose helical computed tomography (CT) led to 20% fewer lung cancer deaths among trial participants relative to what was achieved with standard diagnostic chest x-rays.[3] The seismic implications of the NLST trial results will undoubtedly take years to appreciate and implement, but a clear victory for screening advocates and some high-risk patients has been secured.

Nevertheless, there are lingering questions about how broadly the results can be interpreted. For example, one of the exclusion criteria of the NLST trial was the use of supplemental oxygen.[4] It is, therefore, still reasonable to ask whether patients with very poor pulmonary function, who are medically unfit for attempted surgical resection, might inevitably be doomed to succumb to non-cancer-related cardiopulmonary illness, rendering the diagnosis of an early stage lung cancer clinically irrelevant.

The purpose of ***Lung Cancer Frontiers*** is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated.

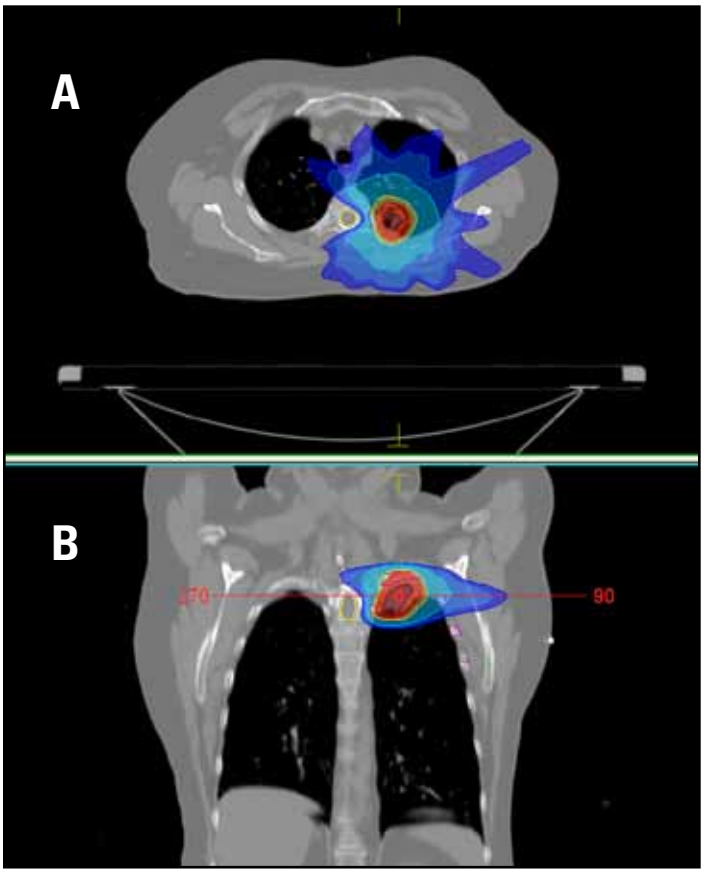
Access current and past issues of ***Lung Cancer Frontiers*** via the Internet at LungCancerFrontiers.org

In this issue

Sterotactic Body Radiation Therapy for Early Stage Lung Cancer

continued from page 1

Published evidence suggests otherwise, however, in both single-institution and large database reports. For example, the Indiana University group reviewed the fate of patients diagnosed with clinical stage I or II non-small cell lung carcinoma (NSCLC) who received no cancer treatment, either because they declined or because of medical conditions that suggested they might not fare well, regardless. Ultimately, cancer was the cause of death in more than half of the untreated patients.[5] Similarly, observations derived from a structured review of the Surveillance, Epidemiology and End Results (SEER) registry were consistent with reduced survival for early stage patients whose lung cancer was not treated.[6] With the caveat that various selection biases can never be fully known in a SEER database review, an analysis of over 4,000 patients diagnosed between 1988 and 2001 with clinical stages I and II NSCLC — presumably most of whom were judged medically inoperable — revealed a statistically significant survival benefit for patients who received radiation therapy (RT) compared with patients who did not receive either surgery or RT.



Still, with the older techniques and schedules of RT commonly applied through the 1990s, the added survival benefit from RT for medically inoperable early stage lung cancer was, at best, unspectacular, yielding a modest three-year survival in the range of 30% or so, with a very high rate of in-field recurrence of cancer. It was not until the last decade that conceptual breakthroughs in the approach to RT in this setting, facilitated by improvements in treatment delivery technology, finally achieved what is now widely agreed to be an undeniable improvement in clinical outcomes.

The generic term for the new approach is sterotactic body radiation therapy (SBRT), defined as the use of image-guided, intensive RT for a discrete extra-cranial tumor, in which the entire course of treatment is given in five or fewer sessions and the goal is permanent eradication of the treated lesion. Dozens of single-institution studies from North America, Europe and Asia document excellent clinical results with SBRT for early stage NSCLC. Multi-institutional, cooperative group studies have further strengthened the evidence. The highest-profile study among them is the Radiation Therapy and Oncology Group (RTOG) study reported in *JAMA* earlier this year.[7] Timmerman and colleagues gave a dose of 54 Gy in three treatments (18 Gy per treatment) to 59 patients with biopsy-proven peripheral T1-T2N0M0 NSCLC of maximum diameter < 5 cm. In this study, local

Figure 1. Axial and coronal images of the SBRT dose distribution for a patient with medically inoperable early stage NSCLC treated in an RTOG study comparing a single dose of 34 Gy in one fraction to a dose of 48 Gy in four fractions. The better regimen will later be compared to the prior standard of 54 Gy in three fractions to determine if equivalent local control is achieved with the same or reduced toxicity. This patient was randomized to the single dose regimen. On the axial image (A), beam modulation was used to sculpt the dose away from the spinal cord, which received less than 10 Gy to any point (outermost blue line). The coronal image (B) reveals the apical location of the tumor, a region less mobile during breathing. Four-dimensional CT image sets (not shown) confirmed a superior-inferior excursion of < 5 mm from inspiration to expiration.

Sterotactic Body Radiation Therapy for Early Stage Lung Cancer

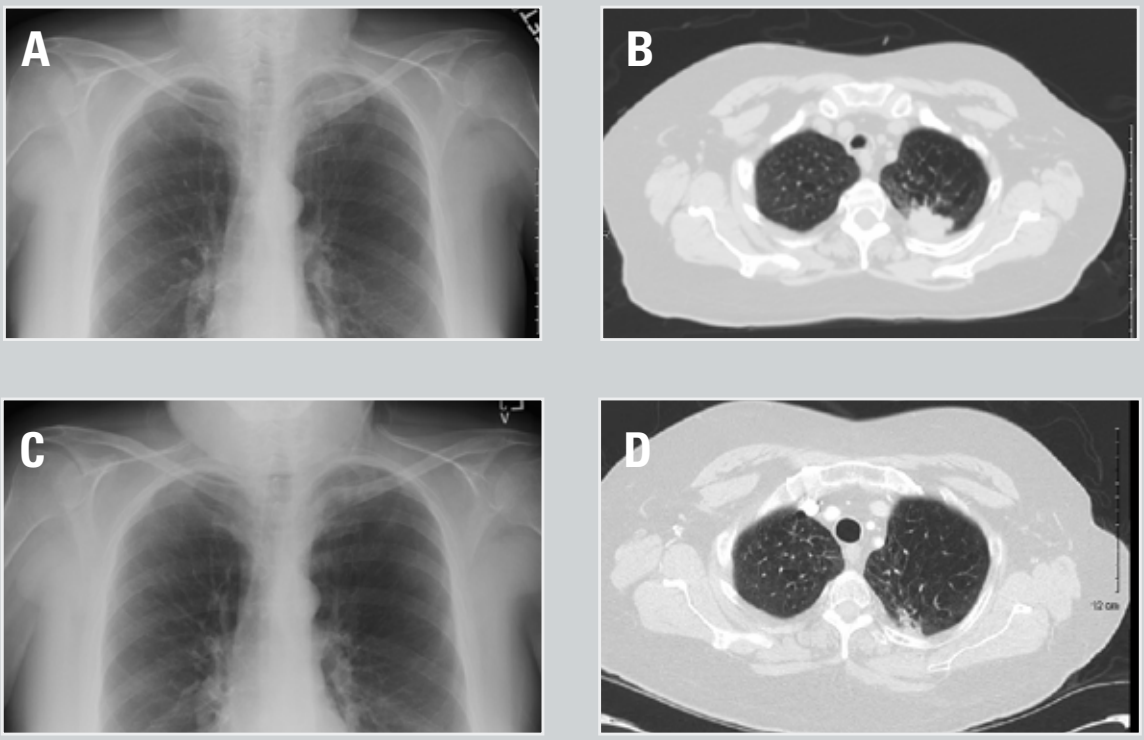
continued from page 2

tumor failure at the primary site was defined as both local enlargement of ≥ 20% increase in the longest diameter of the gross tumor volume per CT scan and evidence of tumor viability, either by PET imaging with uptake of a similar intensity to the pretreatment staging PET, or by repeat biopsy confirming carcinoma. After a median follow up of three years, only one patient had tumor recurrence in the treated site within the lung, for a three-year primary tumor control rate of 98%. Three patients had recurrence elsewhere within the involved lobe, and two patients experienced regional failure, while 11 had distant recurrence. Non-cancer related deaths occurred as expected, but the overall survival at three years was 56%, approximately double what has typically been achieved with conventional RT schedules and techniques. Very importantly, there were only two instances of treatment-related grade 4 toxicity and no grade 5 toxicities.

The purist might now argue that the next proper scientific step would be a randomized, Phase III trial to compare SBRT and the older method of giving RT in a protracted schedule over many weeks. However, such a study will never happen: the results from SBRT are so far superior and the technique is so much safer in this setting that patient advocates have nixed the idea altogether, and the National Cancer Institute will not be supporting this type of trial.

It is difficult to find an appropriate analogy in the field of pulmonology that captures the essence of how contrarian this type of treatment schedule would have been for a radiation oncologist to propose even 20 years ago. At that time, the idea of condensing a six or seven week, five day per week, course of radiation treatment into a mere three sessions would have been viewed as a combination of radiobiological heresy, guaranteed malpractice and borderline insanity. There were

Figure 2. Pre-SBRT images of the same patient described in Fig. 1 showing a left upper lobe NSCLC on chest x-ray (A) and CT (B). Follow-up chest x-ray (C) six weeks and CT (D) three months after treatment show early regression of the mass and no other parenchymal changes in normal lung.



Sterotactic Body Radiation Therapy for Early Stage Lung Cancer

continued from page 3

concerns that the large doses of radiation given in each session would set fire to a patient's insides (figuratively, not literally), in effect leaving massive non-healing scars and ulceration in all sorts of places.

The reasons why SBRT can be given safely for lung cancer is mostly a matter of attention to detail. The radiation must be aimed at the tumor from multiple directions, the amount of normal lung tissue (or other nearby sensitive normal tissue) receiving a high dose of radiation must be kept to an absolute minimum, breathing-related motion must be managed, and the target must be seen clearly and therefore relocalized prior to each treatment. Although the pioneers in the field accomplished these tasks with basic machinery augmented with homegrown add-ons, nowadays there are numerous companies which have integrated image-guidance and precision delivery technology in a composite unit that makes SBRT much easier to administer.

The vendors in this market have come up with catchy names for their products, and many treatment facilities have employed direct-to-patient advertising that highlights their own brand of technology (e.g., Accuray CyberKnife, TomoTherapy Hi-Art, Siemens ARTISTE, Varian Trilogy and TrueBeam, Elekta Synergy, and BrainLAB Novalis, to name a few). It can be confusing to patients and referring physicians, but the key point is that while each of the systems has appealing features, they are all capable of allowing a patient to be treated well with SBRT — as long as they are operated by a team of radiation oncologists and qualified support personnel with appropriate expertise. There is no proven advantage of one system over another.

For the non-surgical candidate with early stage lung cancer, there is no published guideline establishing the minimum amount of lung function necessary to be able to safely undergo SBRT. The RTOG study mentioned above did not require a minimum FEV_1 or other functional index, but good judgment must be exercised for patients with extremely limited pulmonary reserve. In my own practice, I generally estimate that a patient with a 2-3 cm tumor who is treated aggressively might lose about 5-10% of their total lung function. For a patient with a very high baseline dependency on supplemental oxygen and/or very limited spirometry, conferring with the patient's pulmonologist is important to gauge whether the additional decrement in function would be life threatening. There are minimal data available for the use of SBRT in patients with tumors > 5 cm in diameter, so caution must be exercised in that setting. Additionally, early studies raised the question of whether treating tumors located near large airways requires a dose reduction to ensure safety. The RTOG is currently conducting a dose-escalation study to establish the proper safe dose to use for tumors located within or touching the zone of the proximal bronchial tree, defined as the volume 2 cm in all directions around the carina, right and left main bronchi, right upper lobe bronchus, bronchus intermedius, right middle lobe bronchus, lingular bronchus, and right and left lower lobe bronchi.

Fortunately, since the total lung volume receiving a high dose of radiation is limited with SBRT, the rate of radiation pneumonitis (RP) requiring steroid treatment is much less than what is observed after conventionally fractionated RT, since in that setting a much larger volume of lung is often exposed to radiation. Borst and colleagues from the Netherlands Cancer Institute observed a crude rate of grade 2 or higher RP of 11% with SBRT and 18% with conventionally fractionated RT.[8] The risk in each group was a function of the mean dose of radiation to the normal lung. There are no data to suggest that patient age or tumor histology influences local control or risk of toxicity after SBRT. It is not known how SBRT compares to radiofrequency ablation (RFA) for the control of lung tumors. In September 2008, the FDA issued a clarification that RFA devices were not cleared for use in ablating lung tumors after reports of deaths following RFA for lung tumors.[9]

The success of SBRT for early stage lung cancer has prompted evaluation of this strategy for a number of other clinical indications, chief among them lung, liver or other sites of metastatic disease in patients with limited, so-called "oligometastatic" disease.[10-11] Ongoing clinical investigations are aimed at refining the use of SBRT in this setting and in the treatment of primary pancreas, prostate, and liver cancers, to name a few. There is still room for improvement, of course, in the use of SBRT for primary lung cancer. In addition to the dose-escalation trial for proximal tumors noted above, the RTOG is also conducting a randomized Phase II trial of SBRT for medically inoperable peripheral lung cancer to optimize the proper dose selection (***Figures 1 and 2***). There

Sterotactic Body Radiation Therapy for Early Stage Lung Cancer

continued from page 4

are also ongoing studies to determine whether SBRT is a viable alternative to surgery for selected early stage operable lung cancers (www.RTOG.org), including a planned study to compare SBRT to wedge resection for certain patients with small tumors and borderline lung capacity.

Stay tuned, because there will be more news about SBRT in the years to come. But in the present, at least we now have a good, solid therapeutic option for the familiar patient with serious underlying chronic lung disease who is diagnosed with early stage lung cancer.

***Brian Kavanagh, MD, MPH**, graduated from Tulane University School of Medicine and completed his residency at Duke University, where he was an American Cancer Society Clinical Oncology Fellow. He is Professor of Radiation Oncology at the University of Colorado Denver School of Medicine. With Robert Timmerman, MD, he co-edited **Sterotactic Body Radiation Therapy** (Lippincott Williams & Wilkins, 2004), the first text on this topic. Dr. Kavanagh also serves as one of four Associate Editors of the new **Journal of Radiosurgery and SBRT**.*

Disclosures

Dr. Kavanagh reports to *Lung Cancer Frontiers* that he has served as an investigator in laboratory and clinical studies of SBRT for prostate cancer funded by the U.S. Department of Defense and a clinical study of SBRT and erlotinib funded by OSI Pharmaceuticals, Inc. He has received royalties from Lippincott Williams & Wilkins for his textbook on SBRT.

References

1. Silvestri GA. *Lung Cancer Frontiers* 2009; 38:1-4
2. Mulshine JL. *Lung Cancer Frontiers* 2010; 40:6-8
3. National Cancer Institute. Lung cancer trial results show mortality benefit with low-dose CT: Twenty percent fewer lung cancer deaths seen among those who were screened with low-dose spiral CT than with chest X-ray. http://www.cancer.gov/newscenter/pressreleases/NLSTresultsRelease. Accessed November 20, 2010.
4. National Lung Screening Trial Research Team. Radiology 2011; 258:243-53
5. McGarry RC, Song G, des Rosiers P, et al. *Chest* 2002; 121:1155-8
6. Wisnivesky JP, Bonomi M, Henschke C, et al. *Chest* 2005; 128:1461-7
7. Timmerman R, Paulus R, Galvin J, et al. *JAMA* 2010; 303:1070-6
8. Borst GR, Ishikawa M, Nijkamp J, et al. *Radiother Oncol* 2009; 91:307–313
9. US Food and Drug Administration. FDA Public Health Notification: Radiofrequency Ablation of Lung Tumors - Clarification of Regulatory Status. http://www.fda.gov/MedicalDevices/ Safety/ AlertsandNotices/ PublicHealthNotifications/UCM061985. Accessed November 20, 2010.
10. Rusthoven KE, Kavanagh BD, Cardenes H, et al. *J Clin Oncol* 2009; 27:1572-8
11. Rusthoven K, Kavanagh BD, Burri SH, et al. *J Clin Oncol* 2009; 27:1579-84

Selections from the Peer-Reviewed Literature

By Steinn Jonsson, MD

***Steinn Jonsson, MD** is Associate Professor of Medicine at Landspitali-University Hospital in Reykjavik, Iceland. He has led the Icelandic research project on genetic susceptibility to lung cancer in collaboration with deCODE Genetics, Inc. and has worked with researchers at the University of Colorado Denver School of Medicine Cancer Center to study biomarkers of neoplastic change in bronchial epithelium. He is a member of the **Lung Cancer Frontiers** Editorial Board.*

Combined endoscopic-endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes through a single bronchoscope in 150 patients with suspected lung cancer

Herth FJ, Krasnik M, Kahn N, Eberhardt R, Ernst A; Department of Pulmonary and Critical Care Medicine, Thoraxklinik, Heidelberg, Germany. *Chest* 2010; 138:790-4.

BACKGROUND: For mediastinal lymph nodes, biopsies must often be performed to accurately stage lung cancer. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) allows real-time guidance in sampling paratracheal, subcarinal and hilar lymph nodes, and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) can sample mediastinal lymph nodes located adjacent to the esophagus. Nodes can be sampled and staged more completely by combining these procedures, but to date use of two different endoscopes has been required. We examined whether both procedures could be performed with a single endobronchial ultrasound bronchoscope.

METHODS: Consecutive patients with a presumptive diagnosis of non-small cell lung cancer (NSCLC) underwent endoscopic staging by EBUS-TBNA and EUS-FNA through a single linear ultrasound bronchoscope. Surgical confirmation and clinical follow-up was used as the reference standard.

RESULTS: Among 150 evaluated patients, 139 (91%; 83 men, 56 women; mean age 57.6 years) were diagnosed with NSCLC. In these 139 patients, 619 nodes were endoscopically biopsied: 229 by EUS-FNA and 390 by EBUS-TBNA. Sensitivity was 89% for EUS-FNA and 92% for EBUS-TBNA. The combined approach had a sensitivity of 96% and a negative predictive value of 95%, values higher than either approach alone. No complications occurred.

CONCLUSIONS: The two procedures can easily be performed with a dedicated linear endobronchial ultrasound bronchoscope in one setting and by one operator. They are complementary and provide better diagnostic accuracy than either one alone. The combination may be able to replace more invasive methods as a primary staging method for patients with lung cancer.

EDITORIAL COMMENT: This is an elegant study from three centers in Europe and the U.S. that illustrates the possibility of performing comprehensive mediastinal staging of patients with suspected NSCLC using a single ultrasound guided bronchoscope with biopsy of multiple lymph nodes through the bronchi and esophagus during one endoscopy session. To date, this has required two procedures and frequently two endoscopists: EBUS-TBNA to biopsy lymph nodes adjacent to the trachea and main bronchi, and EUS-FNA to access the posteroinferior mediastinum and aortopulmonary window. The study patients had enlarged (≥ 1 cm) lymph nodes and would be considered for mediastinoscopy for staging prior to surgery. On average, 4.5 nodes per patient were sampled by EUS-FNA and EBUS-TBNA, but which nodes were selected for FNA was not discussed. All procedures were performed using an available ultrasound guided bronchoscope. The sessions averaged one-half hour and were performed under moderate sedation or general anesthesia. Lymph node aspirations yielded cytology samples that were examined subsequently. Diagnoses were confirmed by thoracotomy, thoracoscopy or clinical follow up. Bronchial lymph node

Selections from the Peer-Reviewed Literature

continued from page 6

sampling showed a sensitivity of 91% and esophageal node sampling a sensitivity 89%, but when combined they had a sensitivity of 96% and a negative predictive value of 96%. The negative predictive value was high among a population referred for evaluation of lung cancer, with a high prevalence of lung cancer. This implies that the screening test did not generate many false negative results, despite a high number of lung cancer cases. There were no complications and patients were discharged the same day.

These are very impressive results. The procedure appears to be more accurate than mediastinoscopy for preoperative staging and has the added value of reaching more lymph node sites. Furthermore, this technique seems to have the added advantage of cost savings and reduced risk compared to mediastinoscopy. It would be interesting to understand the characteristics of mediastinal staging which did not diagnose cancer, but this was not discussed. Several studies are underway prospectively comparing mediastinoscopy and EBUS-TBNA/EUS-FNA for mediastinal staging. The procedure described in this study is a potentially important advance in the approach to minimally invasive staging of lung cancer patients. It is, however, fair to note that the study group is comprised of leading experts in interventional bronchoscopy and achieving the same results elsewhere will likely require dedication and training on the part of other endoscopists, but this does not reduce the potential impact of this novel technique.

Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial

Annema JT, van Meerbeeck JP, Rintoul RC, Dooms C, Deschepper E, Dekkers OM, De Leyn P, Braun J, Carroll NR, Praet M, de Ryck F, Vansteenkiste J, Vermassen F, Versteegh MI, Veseliç M, Nicholson AG, Rabe KF, Tournoy KG; Department of Pulmonology, Leiden University Medical Center, Leiden, The Netherlands. *JAMA* 2010; 304:2245-52.

CONTEXT: Mediastinal nodal staging is recommended for patients with resectable non-small cell lung cancer (NSCLC). Surgical staging has limitations, which results in the performance of unnecessary thoracotomies. Current guidelines acknowledge minimally invasive endosonography followed by surgical staging (if no nodal metastases are found by endosonography) as an alternative to immediate surgical staging.

OBJECTIVE: To compare the two recommended lung cancer staging strategies.

DESIGN, SETTING AND PATIENTS: Randomized controlled multicenter trial (Ghent, Leiden, Leuven, Papworth) conducted between February 2007 and April 2009 in 241 patients with resectable (suspected) NSCLC in whom mediastinal staging was indicated based on computed or positron emission tomography.

INTERVENTION: Either surgical staging or endosonography (combined transesophageal and endobronchial ultrasound [EUS-FNA and EBUS-TBNA]) followed by surgical staging in case no nodal metastases were found at endosonography. Thoracotomy with lymph node dissection was performed when there was no evidence of mediastinal tumor spread.

MAIN OUTCOME MEASURES: The primary outcome was sensitivity for mediastinal nodal (N2/N3) metastases. The reference standard was surgical pathological staging. Secondary outcomes were rates of unnecessary thoracotomy and complications.

RESULTS: Two hundred forty-one patients were randomized, 118 to surgical staging and 123 to endosonography, of whom 65 also underwent surgical staging. Nodal metastases were found in 41 patients (35%; 95% confidence interval [CI], 27%-44%) by surgical staging vs 56 patients (46%; 95% CI, 37%-54%) by endosonography (P = .11) and in 62 patients (50%; 95% CI, 42%-59%) by endosonography followed by surgical staging (P = .02). This corresponded to sensitivities of 79% (41/52; 95% CI, 66%-88%) vs 85% (56/66; 95% CI, 74%-92%) (P = .47) and 94% (62/66; 95% CI, 85%-98%) (P = .02). Thoracotomy was unnecessary in 21 patients (18%; 95% CI, 12%-26%) in the mediastinoscopy group vs 9 (7%; 95% CI, 4%-13%) in the endosonography group (P = .02). The complication rate was similar in both groups.

CONCLUSIONS: Among patients with (suspected) NSCLC, a staging strategy combining endosonography and surgical staging compared with surgical staging alone resulted in greater sensitivity for mediastinal nodal metastases and fewer unnecessary thoracotomies.

EDITORIAL COMMENT: This is another important study of staging that compared two approaches to staging patients with potentially operable NSCLC. Patients for whom staging was

Selections from the Peer-Reviewed Literature

continued from page 7

indicated based on CT or PET results were randomized. One group underwent conventional surgical staging with cervical mediastinoscopy (116) followed by mediastinal thoracotomy (3) or thoracoscopy (2), when needed, and the other group underwent initial evaluation with EUS-FNA and EBUS-TBNA (123) followed by surgical staging if endoscopic sampling was negative (65). The primary end point was the sensitivity in finding nodal metastases or mediastinal invasion and a secondary end point was the need for thoracotomy and the performance of unnecessary thoracotomies in the two groups. Patients found to have N2/N3 disease or mediastinal invasion on staging investigation were classified as having locally advanced disease and referred for combined modality therapy.

Mediastinoscopy alone showed a sensitivity of 79% in detecting mediastinal disease vs 85% for EUS-FNA/EBUS-TBNA alone ($p = 0.47$) and 94% for EUS-FNA/EBUS-TBNA followed by surgical staging ($p = 0.02$). Fewer patients randomized to the endoscopy group required thoracotomy (58) than the surgical staging group (70) and the number of unnecessary thoracotomies was reported as 21 in the surgical staging group (18%) vs 9 in the endoscopy group (7%), a significant difference ($p = 0.02$).

These data suggest that in expert hands endoscopic staging is indeed more sensitive than conventional surgical staging likely because more lymph nodes are accessible with this technique. This is supported by other studies that have also shown endoscopic staging carries less risk for the patient and is less expensive. The only disadvantage seems to be that the procedure requires substantial training and experience in order to be generally reproducible and accepted. The data showing fewer unnecessary thoracotomies is also important from patient care and cost reduction points of view. Although endoscopic techniques may soon become the initial staging procedure in NSCLC, surgical staging techniques will continue to play a major role in the coming years. In this study, the best results were obtained by combining the two techniques, which points out the importance of collaboration between pulmonologists and surgeons to obtain the best staging results.

Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer

Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, Ou SH, Dezube BJ, Jänne PA, Costa DB, Varella-Garcia M, Kim WH, Lynch TJ, Fidias P, Stubbs H, Engelman JA, Sequist LV, Tan W, Gandhi L, Mino-Kenudson M, Wei GC, Shreeve SM, Ratain MJ, Settleman J, Christensen JG, Haber DA, Wilner K, Salgia R, Shapiro GI, Clark JW, Iafrate AJ; Massachusetts General Hospital Cancer Center, Boston, MA. *N Engl J Med* 2010; 363:1693-703.

BACKGROUND: Oncogenic fusion genes consisting of *EML4* and anaplastic lymphoma kinase (*ALK*) are present in a subgroup of non-small-cell lung cancers, representing 2 to 7% of such tumors. We explored the therapeutic efficacy of inhibiting ALK in such tumors in an early-phase clinical trial of crizotinib (PF-02341066), an orally available small-molecule inhibitor of the ALK tyrosine kinase.

METHODS: After screening tumor samples from approximately 1500 patients with non-small-cell lung cancer for the presence of *ALK* rearrangements, we identified 82 patients with advanced *ALK*-positive disease who were eligible for the clinical trial. Most of the patients had received previous treatment. These patients were enrolled in an expanded cohort study instituted after phase 1 dose escalation had established a recommended crizotinib dose of 250 mg twice daily in 28-day cycles. Patients were assessed for adverse events and response to therapy.

RESULTS: Patients with *ALK* rearrangements tended to be younger than those without the rearrangements, and most of the patients had little or no exposure to tobacco and had adenocarcinomas. At a mean treatment duration of 6.4 months, the overall response rate was 57% (47 of 82 patients, with 46 confirmed partial responses and 1 confirmed complete response); 27 patients (33%) had stable disease. A total of 63 of 82 patients (77%) were continuing to receive crizotinib at the time of data cutoff, and the estimated probability of 6-month progression-free survival was 72%, with no median for the study reached. The drug resulted in grade 1 or 2 (mild) gastrointestinal side effects.

Selections from the Peer-Reviewed Literature

continued from page 8

CONCLUSIONS: The inhibition of ALK in lung tumors with the *ALK* rearrangement resulted in tumor shrinkage or stable disease in most patients. (Funded by Pfizer and others; ClinicalTrials.gov number, NCT00585195).

EDITORIAL COMMENT: The notion that drugs with minor side effects administered in oral form could be more effective than combination chemotherapy in the treatment of NSCLC would have been hard to imagine only a decade ago. Thus, the development of molecularly targeted drugs with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors was a conceptual breakthrough in our understanding of cancer biology and the approach to patients with advanced, inoperable NSCLC. Although treatment efficacy has been restricted to a subgroup of patients, laboratory methods have been developed to detect the involved mutations and thus target the treatment to those patients who are likely to respond. This study reports on a new and potentially important addition to our treatment options in this regard.

A Phase 1 clinical trial was conducted to investigate the efficacy of crizotinib, a newly discovered inhibitor of the anaplastic lymphoma kinase (ALK) tyrosine kinase. This mutated ALK gene is frequently fused with the echinoderm microtubule-associated protein-like 4 (ELM4) gene, forming an aberrant fusion gene that encodes for a cytoplasmic protein with kinase activity. The mutation was found in 5.5% of 1,500 NSCLC tissue samples screened by FISH analysis and RT-PCR. The vast majority were adenocarcinomas, and the patients tended to be young and have less tobacco exposure than average NSCLC patients. The optimal dose of drug was also studied and found to be 250 mg twice a day, given orally. Side effects were restricted to mild to moderate gastrointestinal symptoms, liver function abnormalities and visual disturbances. Few patients had to discontinue treatment because of side effects.

Over a six month period of treatment, 57% had an overall response and 33% had stable disease. This compares very favorably with the response to second-line chemotherapy. Although the follow-up period is short and resistance to tyrosine kinase inhibitors is known to develop, the drug could well become an important addition to our treatment options for adenocarcinoma of the lung, the most frequently diagnosed histological type of lung cancer. It is estimated that this treatment could be suitable for about 10,000 patients annually in the U.S. alone. Considering the frequency of *EGFR* and *ALK* mutations, molecularly targeted therapy could possibly be used in 15% of the lung cancer population. These data also continue to point out the fascinating differences in lung cancer in smokers vs non-smokers.

Frequent and focal *FGFR1* amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer

Weiss J, Sos ML, Seidel D, Peifer M, Zander T, Heuckmann JM, Ullrich RT, Menon R, Maier S, Soltermann A, Moch H, Wagener P, Fischer F, Heynck S, Koker M, Schöttle J, Leenders F, Gabler F, Dabow I, Querings S, Heukamp LC, Balke-Want H, Ansén S, Rauh D, Baessmann I, Altmüller J, Wainer Z, Conron M, Wright G, Russell P, Solomon B, Brambilla E, Brambilla C, Lorimier P, Sollberg S, Brustugun OT, Engel-Riedel W, Ludwig C, Petersen I, Sänger J, Clement J, Groen H, Timens W, Sietsma H, Thunnissen E, Smit E, Heideman D, Cappuzzo F, Ligorio C, Damiani S, Hallek M, Beroukhim R, Pao W, Klebl B, Baumann M, Buettner R, Ernestus K, Stoelben E, Wolf J, Nürnberg P, Perner S, Thomas RK; Max Planck Institute for Neurological Research, Klaus-Joachim-Zülch Laboratories of the Max Planck Society and the Medical Faculty of the University of Cologne, Cologne, Germany.
Sci Transl Med 2010 Dec 15;2(62):62ra93.

ABSTRACT: Lung cancer remains one of the leading causes of cancer-related death in developed countries. Although lung adenocarcinomas with *EGFR* mutations or *EML4-ALK* fusions respond to treatment by epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibition, respectively, squamous cell lung cancer currently lacks therapeutically exploitable genetic alterations. We conducted a systematic search in a set of 232 lung cancer specimens for genetic alterations that were therapeutically amenable and then performed high-resolution gene copy number analyses. We identified frequent and focal fibroblast growth factor receptor 1 (*FGFR1*) amplification in squamous cell lung cancer (n = 155), but not in other lung cancer subtypes, and, by fluorescence in situ hybridization, confirmed the presence of *FGFR1* amplifications in an independent cohort of squamous cell lung cancer samples (22% of cases). Using cell-based screening with the FGFR inhibitor PD173074 in a large (n = 83) panel of lung cancer cell lines, we demonstrated that this compound inhibited growth and induced apoptosis specifically in those lung cancer cells carrying amplified *FGFR1*. We validated the

Selections from the Peer-Reviewed Literature

continued from page 9

FGFR1 dependence of *FGFR1*-amplified cell lines by FGFR1 knockdown and by ectopic expression of an *FGFR1*-resistant allele ($FGFR1^{V561M}$), which rescued *FGFR1*-amplified cells from PD173074-mediated cytotoxicity. Finally, we showed that inhibition of FGFR1 with a small molecule led to significant tumor shrinkage in vivo. Thus, focal *FGFR1* amplification is common in squamous cell lung cancer and associated with tumor growth and survival, suggesting that FGFR inhibitors may be a viable therapeutic option in this cohort of patients.

EDITORIAL COMMENT: The discovery that protein kinases in tumor cells drive their growth and can be inhibited by small molecules that block kinase activity is one of the most important discoveries in the approach to treatment of advanced NSCLC in recent years. A number of EGFR tyrosine kinase inhibitors are now available for treatment of certain adenocarcinomas, and newly discovered ALK inhibitors may soon become important therapeutic alternatives. These drugs are, however, only active in a subgroup of adenocarcinomas in non-smokers.

This article reports the finding of frequent amplification of *FGFR1* in squamous cell lung cancer of smokers. These genetic alterations on chromosome 8p12 were found using high resolution SNP tissue arrays and FISH analysis in 22% of a cohort of 155 squamous cell lung cancer samples. The cut-off for inclusion was a copy number of nine or more, which is very high and suggests that a larger proportion of tumors may have significant *FGFR1* activity. These tests are now available in specialized reference laboratories. A small molecule inhibitor previously described and specific for FGFR1 was tested and found to induce apoptosis of squamous cell lung cancer cells *in vitro*. Furthermore the inhibitor was found to induce tumor shrinkage in a mouse model *in vivo*.

This is a very important discovery that may lead to the development of yet another inhibitor of tumor cell kinase in a larger proportion of patients with NSCLC. Although the study focussed on a high degree of amplification, it suggests the signal pathway is important in squamous cell lung cancer, and that other targets in the pathway may be "druggable." The future of this line of research seems exciting, especially because molecularly targeted kinase inhibitors are frequently more active than conventional chemotherapy and have fewer side effects. There may be light at the end of the tunnel for the large majority of lung cancer patients who have advanced disease at the time of diagnosis. The major issue may become the availability of these novel tests at specialized institutions.

Disclosures

Dr. Jonsson reported to *Lung Cancer Frontiers* that no significant conflicts of interest exist with any companies or organizations whose products or services are discussed in this article.

Lung Cancer Meetings and Symposia

Thomas L. Petty Aspen Lung Conference
54th Annual Meeting
"COPD and Lung Cancer: Common Pathogenesis, Shared Clinical Challenges"

June 8-11, 2011
Aspen, Colorado
With an emphasis on integration between basic, translational and clinical sciences, the meeting will focus on the underlying shared and unique mechanisms and clinical impact of the two diseases.
Abstract deadline is February 14, 2011.
Contact: Jeanne.Cleary@ucdenver.edu, or visit www.aspenlungconference.org

11th Annual Targeted Therapies for the Treatment of Lung Cancer Meeting

February 23-26, 2011
Santa Monica, CA
Contact: pia.hirsch@ucdenver.edu

Lung Cancer Frontiers Editorial Board

Comments may be submitted to ***Lung Cancer Frontiers***
1400 Jackson Street J210
Denver, Colorado 80206
or by e-mail to
langmacke@njhealth.org