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Defining the Genetic Predisposition to Lung Cancer and COPD

By James C. Willey, MD and Thomas M. Blomquist, MD, PhD

The overall death rate from lung cancer in the US is beginning to level off or decline, primarily due to a 44% reduction in smoking prevalence since 1965.[1, 2] Because smoking cessation programs are so effective, it is important to continue and strengthen these efforts. However, an individual's risk for lung cancer remains elevated after they stop smoking and only slowly declines over many years. Consequently, the majority of lung cancers in the US now occur in ex-smokers.[1, 2] Taking this fact and the growing worldwide prevalence of smoking into account, the high incidence of lung cancer will be a long-term problem.

In addition to smoking cessation, the most important step in reducing lung cancer mortality is to diagnose it at an early stage. Today, the overall 5-year survival rate for lung cancer is only 16%.[1] The primary reason for this low survival rate is that 85% of patients are diagnosed with advanced-stage disease that is not amenable to curative surgery. For the 15% of patients who are diagnosed when the cancer is localized, 5-year survival rates are greater than 50%. Consistent with this, multiple screening studies have shown that screening for lung cancer with low-dose computed tomography (LDCT) resulted in detection at earlier stages and improved survival.[3-5] These studies were sufficiently compelling to motivate a large, randomized controlled trial of screening for lung cancer, the NIH-funded National Lung Screening Trial (NLST).[6] This study began in 2002 and ended in 2009, when it reached its goal of demonstrating a 20% reduction in mortality. It is reasonable to expect that if annual LDCT screening is broadly implemented, it will significantly reduce lung cancer mortality in the US.[1] At the University of Toledo, we established an International Early Lung Cancer Action Program lung cancer screening program based on the NLST entrance criteria, consistent with recommendations from numerous professional consensus groups.[7] Many other institutions have established similar programs.[8]

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A timely subject

The importance of genetic susceptibility to both lung cancer and COPD is often overlooked because cigarette smoking is such an overwhelming and preventable risk factor, as was noted in recent reviews.[9,10] However, this subject has recently received more attention, including higher-profile funding from the NIH.[11] Increased research activity in this area is timely for two reasons. First, the increasing number of lung cancer screening programs is likely to incur high costs and potentially adverse patient side effects. Second, COPD is a risk factor for lung cancer, and it is likely that there is significant overlap in the genetic predisposition to these two diseases.[9, 11] For example, in the NLST study, subjects were selected for screening based on age (55-74 years) and smoking history (≥30 pack years), the two demographic characteristics most strongly associated with lung cancer risk. Currently, 7 million individuals in the US meet the NLST screening criteria.[6] However, even among individuals in this selected group, it was estimated that only 2% would develop lung cancer over 10 years and only 10-15% would develop lung cancer in their lifetimes.[7] In the NLST report, it was estimated that 320 individuals would need to participate in screening to prevent one lung cancer death. Further, even though LDCT screening reduced mortality in the NLST study, some adverse consequences were observed.[6] These included the patient risks associated with a large number of false-positive LDCT findings, such as unnecessary invasive procedures that impose significant costs on an already challenged health care system.[12] Therefore, there is broad agreement that finding a way to identify the heavy smokers at greatest risk for lung cancer, and determining how COPD interacts with this risk, will reduce costs, the rate of false-positive findings, and patient morbidity. This is a priority area for investigation. [9, 11]

Investigative strategies

Investigation in this area began nearly 50 years ago with epidemiologic studies,[9] and in the last 30 years it has progressed to molecular epidemiologic studies.[13-16] Progress was accelerated by the Human Genome Project and the databases it generated, as well as technological innovations, including dense arrays of genetic markers and rapid, low-cost sequencing.[17] These powerful tools were used in genome-wide association studies (GWAS) to test the hypothesis that particular, common DNA variants are more prevalent in a group of individuals who have lung cancer or COPD. For example, 3 such studies identified a certain heritable DNA variant (a single nucleotide polymorphism, or SNP), in chromosome region 15q24-25 that was more prevalent in lung cancer cases.[18-20] A GWAS by the Genetic Epidemiology of Lung Cancer Consortium mapped a lung cancer susceptibility locus to chromosome region 6q23-25.[21] In another study, COPD risk was associated with a SNP in the 6q27 region.[22] Although these findings reflect definite progress, together these variants account for less than 5% of the perceived heritability for lung cancer and COPD risk.[18, 19, 23-26]

One model consistent with these results is that the majority of lung cancer and COPD risk results from complex, additive and/or synergistic interactions among DNA variants, each with a small (ie, low-penetrant) effect, and that a GWAS is statistically powered to detect only the non-interacting effect of each individual variant. [10, 27-30] Using this model, the recent focus of our work has been to develop novel approaches that capture these interactive effects and identify biomarkers for disease risk determined by complex genetics.[18,19] Because mRNA-expression profiles represent the summative interactive effects of multiple low-penetrant DNA variants, they can be expected to have a closer association with lung cancer and COPD risk than GWAS-based research designs that aim to identify causative DNA variants without interactive information. In order to capture mRNA profile information with greater accuracy and resolution, we developed a method for standardized, quality-controlled measurement of mRNA expression.[31]

Susceptibility biomarkers

Molecular epidemiologic studies over the last 30 years indicate that variation in lung cancer and COPD risk is, in part, due to genetic variation in key metabolic pathways, in particular those involving key antioxidant, DNA repair, xenobiotic metabolism, and immune response genes.[13-16, 18, 24, 32-35] These genes act to protect lung epithelium from damage that may lead to loss of lung function and/or malignant transformation.[14, 15] Using optimized mRNA expression measurement methods, we identified a promising lung cancer risk test biomarker based on the mRNA expression pattern of 14 genes, including nine antioxidant (*CAT, GPX1, GPX3, GSTM3, GSTP1, GSTT1, GSTZ1, MGST1, SOD1*), three DNA repair (*ERCC4, ERCC5, XRCC1*), and two transcription-factor (*CEBPG, E2F1*) genes

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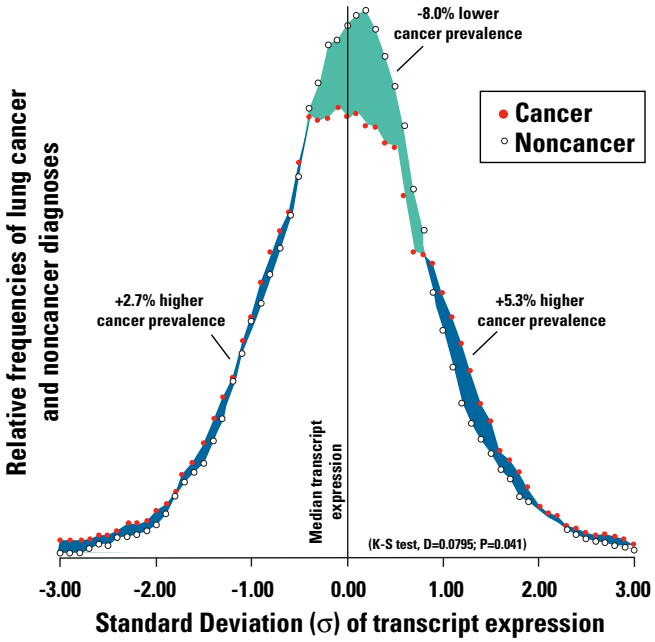

Figure 1. Characteristics of bronchial neuroendocrine tumors. *Differences in composite distribution of mRNA (ie, transcript) expression for 14 key antioxidant, DNA repair, and transcription factor genes in bronchial epithelial brushings of cytologically normal lung in individuals with and without lung cancer.[28] Adapted from reference 28, with permission.*

in normal bronchial epithelial cell (NBEC) brushings (***Figure 1***).[28] Notably, for each of these genes, the distinguishing pattern of expression in patients diagnosed with lung cancer was increased variation, or dispersion, of mRNA transcript expression around the population expression median, not change in the median expression level (***Figures 1 and 2***). In other words, a t-test to evaluate average (ie, central tendency) expression levels between those with and without lung cancer did not detect a significant difference, but an F-test to assess for difference in variation and dispersion did reveal a significant difference.

Conceptually, a lung cancer and COPD risk phenotype associated with change in dispersion and variation in mRNA expression might be best explained by the interacting effects of a large number of low-penetrant DNA variants in both amino acid coding and non-coding regions of genes.[28, 36] Thus, it is reasonable to hypothesize that uncharacterized DNA variants subtly affecting mRNA expression of key genes important for protection of airway epithelium may play a significant role in susceptibility to COPD and/or lung cancer. Supporting this hypothesis, we (and others) identified low-penetrant DNA variants associated with susceptibility for complex diseases involving the airway epithelium, including asthma and cystic fibrosis. These variants were also associated with variation in mRNA regulation of genes included in our lung cancer risk biomarker, including *ERCC5, XRCC1, GSTM3* and *CEBPG*.[37-41]

Clinical trials

We are currently conducting a National Cancer Institute (NCI)-funded, multi-site clinical trial (RC2 CA147652) to further assess the accuracy of the lung cancer risk test biomarker. The samples collected from this study will also be used in an NHLBI-funded exploratory study of genetic factors responsible for lung cancer and COPD risk (HL108016). Specifically we aim to: a) discover the role of inherited variation in regulation of antioxidant, DNA repair and transcription factor mRNA expression in NBEC in determining risk for COPD and lung cancer, and b) identify a multi-gene, mRNA-based risk biomarker for COPD risk that complements biomarkers for lung cancer risk. In the course of these studies, we will measure mRNA expression of key antioxidant, DNA repair and transcription factor genes in

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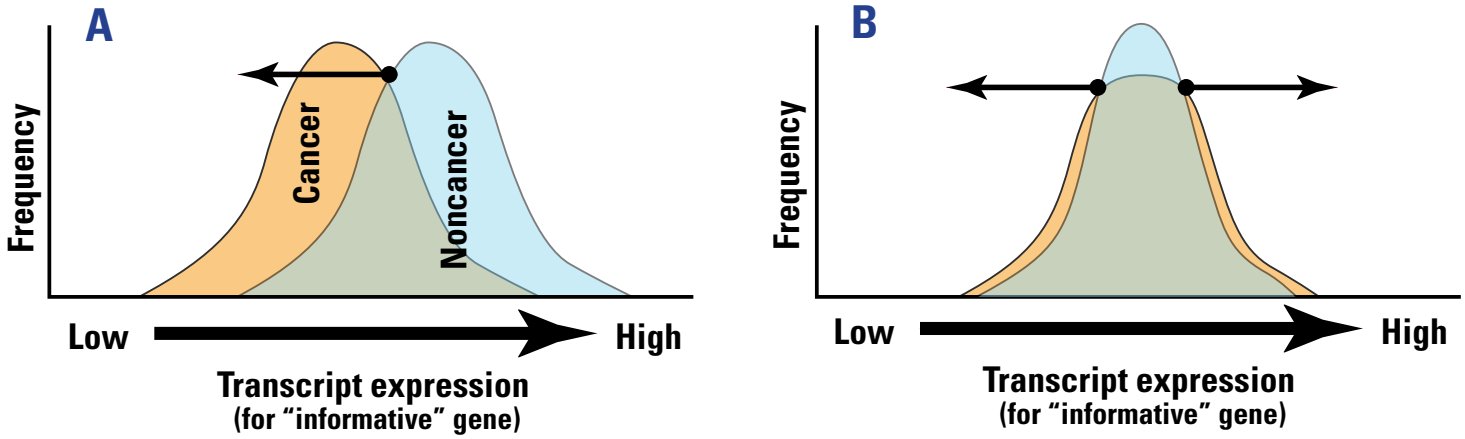

Figure 2. Transcript expression distribution. *Shown in A and B are two hypothetical depictions of mRNA (ie, transcript) expression frequency distribution plots for a trait of interest (eg, Cancer [orange] and Noncancer [blue]). Arrows stemming from the points on the frequency distribution plots indicate the range of values associated with higher prevalence of cancer diagnosis.* ***Panel A*** *represents the most common approach to identify informative genes by identification of difference in mean transcript expression between cases and controls.* ***In panel B****, however, for a set of genes with high prior likelihood of involvement in lung cancer risk,[28] a statistically significant difference in central tendency of transcript expression was not observed in normal airway tissue between lung cancer cases and controls (****Figure 1****). Instead, a lower prevalence of cancer cases was observed in the central region of the transcript expression distribution, with increased dispersion of cancer cases to extreme transcript expression levels. Adapted from reference 28, with permission.*

NBEC and then assess for differences in expression dispersion of these genes as the key phenotypic difference between diseased (COPD or lung cancer) and control subjects. In addition, we will investigate the underlying genetic cause of increased dispersion in subjects with increased COPD or lung cancer risk by focused analysis for DNA variants in the coding and regulatory regions of these genes. As part of this analysis, we will measure the association of particular DNA variants with allele-specific expression of key genes within the primary tissue of interest (eg, lung epithelium). This will provide highly controlled interrogation of the role that local inherited DNA variants (ie, cis-acting) play in regulation of these key genes in the lung cancer precursor cells.[42] We recently used this approach to determine that certain SNPs are associated with population-level dispersion of transcript abundance.[37] Although the mechanisms responsible for this association require further study, these observations support the hypothesis that many low-penetrant DNA variants in multiple genes summate to manifest as risk for lung cancer and/or COPD in a continuous rather than discrete fashion.

Summary

The studies of genetic susceptibility to lung cancer and COPD are part of a continuum of research that is expected to enable accurate identification of high-risk individuals so that they might then be selected for closer monitoring and screening. More focused selection of subjects for screening can be expected to reduce costs and false-positive findings incurred by implementation of routine LDCT screening for lung cancer. In addition, if the role of key antioxidant and DNA repair genes in risk for lung cancer and COPD is confirmed, these genes will be potential targets for chemoprevention therapies.

Disclosures

Dr. Willey reported to ***Lung Cancer Frontiers*** that he received grant funding from the NIH and Accugenomics, Inc. He also received consultancy fees from and holds stock/stock options in Accugenomics, Inc. Dr. Blomquist reported that he has received grant funding from the NCI and the NHLBI.

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Selections from the Peer-Reviewed Literature

By Laurie E. Gaspar, MD, FASTRO, FACR, MBA

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Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non-small cell lung cancer

Chang JY, Liu H, Balter P, Komaki R, Liao Z, Welsh JW, Mehran RJ, Roth JA, Swisher SG. *Radiation Oncology* 2012, 7:152. In press.

BACKGROUND: Stereotactic ablative radiotherapy (SABR) can achieve excellent local control rates in early-stage non-small cell lung cancer (NSCLC) and has emerged as a standard treatment option for patients who cannot undergo surgery or those with isolated recurrences. However, factors that may predict toxicity or survival are largely unknown. We sought here to identify predictors of survival and pneumonitis after SABR for NSCLC in a relatively large single-institution series.

METHODS: Subjects were 130 patients with stage I NSCLC treated with four-dimensional computed tomography (4D CT) —planned, on-board volumetric image—guided SABR to 50 Gy in 4 fractions. Disease was staged by positron emission tomography/computed tomography (PET/CT) and scans were obtained again at the second follow-up after SABR.

RESULTS: At a median follow-up time of 26 months, the 2-year local control rate was 98.5%. The median overall survival (OS) time was 60 months, and OS rates were 93.0% at 1 year, 78.2% at 2 years, and 65.3% at 3 years. No patient experienced grade 4-5 toxicity; 15 had radiation pneumonitis (12 [9.3%] grade 2 and 3 [2.3%] grade 3). Performance status, standardized uptake value $(SUV)_{max}$ on staging PET/CT, tumor histology, and disease operability were associated with OS on univariate analysis, but only staging SUV_{max} was independently predictive on multivariate analysis (P = 0.034). Dosimetric factors were associated with radiation pneumonitis on univariate analysis, but only mean ipsilateral lung dose ≥9.14 Gy was significant on multivariate analysis (P = 0.005).

CONCLUSIONS: OS and radiation pneumonitis after SABR for stage I NSCLC can be predicted by staging PET SUV_{max} and ipsilateral mean lung dose, respectively.

EDITORIAL COMMENT: Stereotactic ablative radiotherapy, often referred to as stereotactic body radiation therapy (SBRT), is a rapidly emerging technique in which tumors are precisely targeted with high doses of radiation delivered in 1 to 5 fractions. In this article, Chang et al. report SBRT outcomes in a relatively large number of patients treated in a single institution. This was a retrospective study in which all patients had biopsy-proven stage I NSCLC tumors. The majority of patients received 50 Gy delivered in 4 consecutive daily fractions. This differs from the SBRT regimen used at many centers of 54-60 Gy in 3 fractions delivered on alternate days over a week to a week and a half (Xiao Y et al., *Int J Radiat Oncol Biol Phys* 2009; 73:1235-42). However, the 9% incidence of symptomatic radiation pneumonitis (RP) is in the range observed with various SBRT regimens. The median time of onset of RP was 4 months, occurring up to 11 months following SBRT. The only clinical or dosimetric factor that independently predicted a higher risk of RP was an ipsilateral mean lung dose (MLD) of ≥9 Gy. Grade 2-3 RP was seen in 14 patients (11%) with a MLD of >9 Gy, as opposed to only 1 patient with a lower MLD. The authors

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presumably felt that this rate of RP in the higher MLD patients was acceptable since they do not propose any changes to their future practice.

Another important observation of this study was that neither poor FEV_1 nor severe chronic obstructive pulmonary disease (COPD) was correlated with an increased risk of grade 2-3 RP or decreased survival. Because a positive biopsy was required, patients in whom even the risk of biopsy would result in an unacceptable survival risk were excluded from this series. However, bearing that caveat in mind, the median FEV_1 in this series was 42% of predicted, with the FEV_1 as low as 15% of predicted.

With a median follow-up time of 26 months (range, 6–78 months), the median overall survival was 60 months. The only independent predictor of poor overall survival was a pretreatment PET SUV_{max} of ≥6.2. Distant recurrence was more prevalent than locoregional relapse. The authors point out that other studies have not always confirmed the predictive value of pretreatment PET SUV_{max}, suggesting that further studies are needed. It would be clinically relevant to be able to identify a group of stage I SBRT patients at high risk of distant failure in whom systemic treatment should be studied.

In summary, this study found that SBRT was associated with high local control, reasonable toxicity and survival, even in patients with poor baseline pulmonary function. Distant metastases were more common than locoregional relapse, indicating the need to identify patients for future studies of adjuvant systemic treatment.

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

Suntharalingam M, Paulus R, Edelman MJ, Krasna M, Burrows W, Gore E, Wilson LD, Choy H. Int *J Radiat Oncol Biol Phys* 2012; 842:456-63.

PURPOSE: To evaluate mediastinal nodal clearance (MNC) rates after induction chemotherapy and concurrent, full-dose radiation therapy (RT) in a phase II trimodality trial (Radiation Therapy Oncology Group protocol 0229).

PATIENTS AND METHODS: Patients (n=57) with stage III non-small cell lung cancer (pathologically proven N2 or N3) were eligible. Induction chemotherapy consisted of weekly carboplatin (AUC = 2.0) and paclitaxel 50 mg/m^2. Concurrent RT was prescribed, with 50.4 Gy to the mediastinum and primary tumor and a boost of 10.8 Gy to all gross disease. The mediastinum was pathologically reassessed after completion of chemoradiation. The primary endpoint of the study was MNC, with secondary endpoints of 2-year overall survival and postoperative morbidity/mortality.

RESULTS: The grade 3/4 toxicities included hematologic 35%, gastrointestinal 14%, and pulmonary 23%. Forty-three patients (75%) were evaluable for the primary endpoint. Twenty-seven patients achieved the primary endpoint of MNC (63%). Thirty-seven patients underwent resection. There was a 14% incidence of grade 3 postoperative pulmonary complications and 1 30-day, postoperative grade 5 toxicity (3%). With a median follow-up of 24 months for all patients, the 2-year overall survival rate was 54%, and the 2-year progression-free survival rate was 33%. The 2-year overall survival rate was 75% for those who achieved nodal clearance, 52% for those with residual nodal disease, and 23% for those who were not evaluable for the primary endpoint (P=.0002).

CONCLUSIONS: This multi-institutional trial confirms the ability of neoadjuvant concurrent chemoradiation with full-dose RT to sterilize known mediastinal nodal disease.

EDITORIAL COMMENT: The role of trimodality therapy for stage IIIA non-small cell lung cancer (NSCLC) with ipsilateral mediastinal nodes (N2) has been controversial. However, many centers utilize this approach, given the large intergroup study demonstrating that progression-free survival for stage IIIA (N2) was improved with the addition of surgery after concurrent chemoradiation to 45 Gy in 1.8 Gy daily treatments as opposed to chemoradiation alone to a dose of 61 Gy (Albain KE et al., *Lancet* 2009; 374:379-86). In the intergroup study, the MNC was 38% in the 202 evaluable patients. This Radiation Therapy Oncology Group (RTOG) study utilized a higher neoadjuvant radiation dose of 61.2 Gy in 1.8 Gy daily fractions with the ambitious MNC goal of 70%. Interestingly, this RTOG study was open to stage IIIA and IIIB (N3, excluding supraclavicular involvement) patients; however, only 1 of the 57 enrolled patients had stage

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IIIB disease. Another important difference between the two studies is that the intergroup study used a cisplatin/etoposide regimen as opposed to the low-dose, weekly carboplatin/paclitaxel regimen in the RTOG study.

This RTOG study mandated 45-50.4 Gy elective nodal irradiation to the bilateral mediastinum. The total dose of 61.2 Gy was to be given to the primary tumor and the involved lymph nodes. During chemoradiation, there was a 23% rate of grade 3 pulmonary toxicity and 1 pulmonary death. This is in addition to the 14% incidence of postoperative pulmonary complications and the 1 postoperative death. If MNC is calculated for the 57 evaluable patients, rather than just the 47 who went on to resection, the MNC falls to 47%. However, the investigators concluded that this chemoradiation regimen was both tolerable and efficacious. On the basis of this study, the RTOG's ongoing study for potentially operable stage IIIA patients is a randomized phase II trial (RTOG-0839), in which half the patients receive panitumumab, an epidermal growth factor receptor inhibitor, in addition to a trimodality regimen using 60 Gy. Elective nodal radiation has been eliminated, but patients are to have sampling of the subcarinal region and contralateral paratracheal lymph nodes to rule out microscopic involvement.

Does this mean that the "standard" radiation dose in the trimodality setting for stage IIIA patients should be 60 Gy? If 60 Gy is contemplated, the thoracic surgeon needs to be involved with the decision, because specific surgical techniques are essential. Given the moderately high pulmonary toxicity and a 2-year survival in the same range as the older intergroup study utilizing just 45 Gy, prescribing 60 Gy in the trimodality setting should probably only be done in the setting of a clinical trial.

Radical treatment of non-small cell lung cancer patients with synchronous oligometastases: long-term results of a prospective Phase II Trial (Nct01282450)

De Ruysscher D, Wanders R, van Baardwijk A, Dingemans AM, Reymen B, Houben R, Bootsma G, Pitz C, van Eijsden L, Geraedts W, Baumert BG, Lambin P. *J Thorac Oncol* 2012; 7:1547-55.

BACKGROUND: Stage IV non-small cell lung cancer (NSCLC) patients with oligometastases (<5 metastatic lesions) may experience long-term survival when all macroscopic tumor sites are treated radically, but no prospective data on NSCLCs with synchronous oligometastases are available.

METHODS: A prospective single-arm phase II trial was conducted. The main inclusion criteria were pathologically proven NSCLC stage IV with less than five metastases at primary diagnosis, amendable for radical local treatment (surgery or radiotherapy). The study is listed in clinicaltrials.gov, number NCT01282450.

RESULTS: Forty patients were enrolled, 39 of whom were evaluable (18 men, 21 women); mean age was 62.1±9.2 years (range, 44-81). Twenty-nine (74%) had local stage III; 17 (44%) brain, seven (18%) bone, and four (10%) adrenal gland metastases. Thirty-five (87%) had a single metastatic lesion. Thirty-seven (95%) of the patients received chemotherapy as part of their primary treatment. Median overall survival (OS) was 13.5 months (95% confidence interval 7.6-19.4); 1-, 2-, and 3-year OS was 56.4%, 23.3%, and 17.5%, respectively. Median progression-free survival (PFS) was 12.1 months (95% confidence interval 9.6-14.3); 1-year PFS was 51.3%, and both 2- and 3-year PFS was 13.6%. Only two patients (5%) had a local recurrence. No patient or tumor parameter, including volume and ^{18}F-deoxyglucose uptake was significantly correlated with OS or PFS. The treatment was well tolerated.

CONCLUSION: In this phase II study, long-term PFS was found in a subgroup of NSCLC patients with synchronous oligometastases when treated radically. Identification of this favorable subgroup before therapy is needed.

EDITORIAL COMMENT: The treatment of oligometastatic disease in NSCLC is currently a "hot topic" among oncologists. At the University of Colorado, we frequently treat patients with oligometastatic NSCLC with aggressive local treatment, usually stereotactic body radiation therapy (SBRT)—itself another "hot topic." De Ruysscher et al. believe this might be the first prospective trial of definitive-intent treatment in NSCLC patients presenting with oligometastatic disease, defined here as 5 or fewer metastases. However, this was essentially a study of patients with a single metastasis in which the most common site of metastasis was

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the brain. Patients were not eligible if they had a malignant pleural or pericardial effusion. Seventy-four percent of patients had intrathoracic stage III disease.

Although surgery was allowed for treatment of the intrathoracic tumor, it was not undertaken in any patient. Treatment of the primary tumor and associated lymph nodes was usually conventionally fractionated radiation with concurrent or sequential platin-based chemotherapy. Surgery was commonly utilized to resect extracranial metastases from locations such as the liver or adrenal glands. Interestingly, brain metastases could be treated with stereotactic radiosurgery (SRS) alone or with surgical resection followed by whole brain radiation therapy. The reason for requiring whole brain radiation therapy after surgery but not after SRS was not discussed. As expected, more than half of the patients undergoing SRS had an intracranial recurrence at a site distant from the original SRS site.

Aggressive local treatment was associated with the expected toxicity, and patients reported reasonable quality of life on follow-up. The authors hypothesized that this definitive approach would give a 2-year survival of at least 20%, which they thought would represent a doubling of the survival expected after chemotherapy alone. However, the 2-year survival following chemotherapy alone in such a select group of patients with oligometastatic disease is not known. Despite the optimistic tone of the abstract, the observed 2-year survival rate of 13% did not quite meet the primary study endpoint. The investigators believe that future studies should identify specific genetic characteristics that underlie oligometastatic disease and then combine targeted therapy with aggressive local treatment. It is unfortunate that the investigators have no plans for a randomized phase III study to compare this definitive approach with standard therapy, which usually consists of chemotherapy and palliative radiation therapy. Until such a study is done, we will likely continue to present the option of aggressive local therapy for oligometastatic disease, humbly acknowledging that there is no evidence to clearly support this approach.

Disclosures

Dr. Gaspar submitted an ICMJE Disclosure Form to ***Lung Cancer Frontiers***. 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

13th Annual Targeted Therapies of the Treatment of Lung Cancer Meeting

February 20-23, 2013
Santa Monica, California
Information: pia.hirsch@iaslc.org

European Multidisciplinary Conference in Thoracic Oncology

May 9-11, 2013
Lugano, Switzerland
Information: esmo.org

15th World Conference on Lung Cancer

October 27-30, 2013
Sydney, Australia
Information: 2013worldlungcancer.org

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