Management Options for Malignant Pleural Effusions

By Ali I. Musani, MD and Esther L. Langmack, MD

Malignant pleural effusion (MPE) is a common complication of advanced malignancy. It is estimated that between 150,000 and 175,000 patients in the US develop MPE each year. In most cases, MPE signifies incurable disease with a poor prognosis, typically a mean length of survival of six months from the time of diagnosis, with the exception of breast and ovarian cancer, in which survival may be longer. Dyspnea, cough, and chest pain associated with MPE can be devastating to patients already in the final stages of illness.

Conventional tube thoracostomy with chemical pleurodesis is still the most common treatment for MPE, but it is associated with significant discomfort and usually about a week of hospitalization. Current clinical experience and published studies support the selection of a palliative, rather than curative, management strategy for many patients with MPE. Medical thoracoscopy with pleurodesis and tunneled pleural catheters (TPCs) are newer, minimally invasive techniques that can be highly effective in reducing symptoms, hospital days, and treatment costs. Video-assisted thoracic surgery (VATS) with pleurodesis and pleuroperitoneal shunts remain options for selected patients.

Etiology and pathogenesis

Tumors that metastasize frequently to the mediastinal lymph nodes and lymphatics (e.g. lung, breast, ovary, and lymphoma) are associated with most MPEs. Lung cancer causes approximately 37% of all MPEs. Other malignancies associated with MPE include gastric cancer and cancer of unknown primary.

Most MPEs result from lymphatic obstruction by tumor, which renders the parietal pleura incapable of reabsorbing pleural fluid at a normal rate. Other mechanisms of MPE formation include direct tumor invasion of the pleura, hematogenous tumor spread to the parietal pleura, and release of cytokines that increase vascular and pleural membrane permeability. The presence of malignant cells in the pleural fluid establishes the diagnosis of MPE.

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Selecting a management strategy

The first step in the management of MPE is to determine if the patient achieves symptomatic benefit from therapeutic thoracentesis (Figure 1). Up to 50% of patients with MPE do not experience a significant improvement in dyspnea or exercise tolerance with thoracentesis because of comorbid conditions (e.g., COPD), or general debility from the malignancy. In these situations, there is limited utility to repeated thoracentesis, pleurodesis, or placement of a chronic drainage apparatus.

Patients who do experience symptomatic relief after pleural fluid removal fall into three categories: those without trapped lung, those with trapped lung, and those with pleural fluid loculations (Figure 1). Patient symptoms, functional status, caregiver support, life expectancy and tumor type must also be considered when selecting a management strategy (Table 1). For MPE associated with some tumor types (e.g., small cell lung cancer or breast cancer), chemotherapy may be all that is required to reduce the effusion, precluding any further intervention.

For patients who have only a few weeks or months to live, or who are unable or unwilling to undergo invasive procedures or hospitalization, repeated therapeutic thoracentesis might be an option. However, therapeutic thoracentesis is not optimal for the long-term control of MPE, as symptomatic MPE recurs on average 4-5 days after thoracentesis. Symptomatic, recurrent, and recalcitrant (to chemotherapy or radiation therapy) MPEs should be addressed with a definitive, palliative care plan.

![Figure 1. Treatment algorithm for malignant pleural effusion.](image-url)
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<thead>
<tr>
<th>Options</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Observation</td>
<td>• Noninvasive</td>
<td>• Most will progress and require therapy</td>
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<tr>
<td>Repeated therapeutic thoracentesis</td>
<td>• Good option for patients with limited life expectancy</td>
<td>• Rapid re-accumulation</td>
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<td></td>
<td>• Prompt relief of dyspnea</td>
<td>• Repeated procedures</td>
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<td>• Multiple hospital visits</td>
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<td>• Procedure-related complications</td>
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<td></td>
<td></td>
<td>• Re-expansion pulmonary edema</td>
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<td>• Reduced quality of life</td>
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<td>Tube thoracostomy with chemical pleurodesis</td>
<td>• Highly effective (pleurodesis in 81-93%)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>• Hospitalization 5 to 7 days</td>
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<td></td>
<td></td>
<td>• Expensive</td>
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<td></td>
<td></td>
<td>• Invasive</td>
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<td></td>
<td></td>
<td>• Associated morbidity</td>
</tr>
<tr>
<td>Medical thoracoscopy or VATS</td>
<td>• Highly effective (pleurodesis in &gt; 80-90%)&lt;sup&gt;15-18&lt;/sup&gt;</td>
<td>• Inpatient</td>
</tr>
<tr>
<td></td>
<td>• Diagnosis and pleurodesis can be achieved at the same time</td>
<td>• Invasive</td>
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<td></td>
<td></td>
<td>• Associated morbidity</td>
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<td></td>
<td>• Contraindicated if patient cannot tolerate single lung ventilation (VATS)</td>
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<tr>
<td>Pleuroperitoneal shunt</td>
<td>• Possible option for patients with failed chemical pleurodesis</td>
<td>• Shunt malfunction</td>
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<td></td>
<td></td>
<td>• Infection</td>
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<td>• Requires frequent pumping by the patient</td>
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<td>Tunneled pleural catheter</td>
<td>• Good option for motivated patients</td>
<td>• Family member or a visiting nurse required for home drainage</td>
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<td>• Inpatient or outpatient placement</td>
<td>• Catheter site infection</td>
</tr>
<tr>
<td></td>
<td>• Mostly outpatient management</td>
<td>• Lower pleurodesis rate than chemical pleurodesis via chest tube or VATS/medical thoracoscopy</td>
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<td></td>
<td>• Minimally invasive</td>
<td>• Controls dyspnea</td>
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<tr>
<td></td>
<td>• Cost effective</td>
<td>• Outpatient pleurodesis in 42-58%&lt;sup&gt;23-24&lt;/sup&gt; without chemicals</td>
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<td></td>
<td>• Outpatient pleurodesis</td>
<td>• Suitable for palliation in patients with trapped lung</td>
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Tube thoracostomy and pleurodesis

Tube thoracostomy and pleurodesis with a sclerosing agent is indicated for patients who do not have trapped lung or pleural fluid loculations. Standard chest tubes (18-24F) and small-bore catheters (10-12F) have been used successfully. The ideal sclerosing agent has yet to be identified, because no large, head-to-head, randomized clinical trials comparing different agents have been performed. Successful pleurodesis is achieved in 81-93% of patients with MPE, depending on the sclerosing agent used and the clinical study. In a Cochrane review and another systematic review of the literature, talc was the most effective sclerosant for preventing MPE recurrence.

Tube thoracostomy with pleurodesis typically requires an average hospital stay of 5-7 days, although “accelerated” pleurodesis protocols have been reported to be equally effective. Chest pain and fever are the most common complications of tube thoracostomy and pleurodesis. Rare complications include site infection, empyema, arrhythmias, cardiac arrest, and hypotension. Acute respiratory distress syndrome (ARDS) has been reported in 4-8% of patients after administration of small, non-calibrated talc preparations, which are believed to be absorbed into the systemic vasculature, thus causing systemic inflammation. Larger particle (mean particle size 20 microns, with no particles < 10 microns), calibrated talc preparations are now recommended for talc slurry and talc poudrage.

When initial pleurodesis for MPE fails, there are several options. Repeated therapeutic thoracentesis would be indicated for a patient with short expected survival. Other options include another attempt at pleurodesis (via tube thoracostomy, medical thoracoscopy, or VATS), pleurectomy, pleuroperitoneal shunting, or placement of a TPC.

Medical thoracoscopy

Medical thoracoscopy, also known as pleuroscopy, can be used to both diagnose and treat malignant and nonmalignant pleural effusions. It has a high diagnostic and therapeutic yield and can be performed with the patient under conscious sedation, without mechanical ventilation, making it appropriate for a relatively sick patient population. The pleuroscope, which resembles a flexible bronchoscope, is introduced through an 11-mm trocar inserted into the pleural space. Pleural fluid is evacuated through the pleuroscope, the pleural surfaces are visually inspected for tumor, and biopsies of the parietal pleura can be taken with instruments inserted through the pleuroscope’s working channel. Pleurodesis can then be performed, typically by talc poudrage, through the pleuroscope.

Talc poudrage performed during medical thoracoscopy has a mean pleurodesis success rate of greater than 80-90% in published studies. When compared to bedside tube thoracostomy with talc slurry, thoracoscopic talc poudrage was associated with fewer recurrences of MPE in a systematic review (RR, 0.21; 95% CI 0.05-0.93). In one study, the most common complications were pneumothorax (8.3%), followed by subcutaneous emphysema (5.3%), fever (3.6%), and pain (1.2%). Death, severe sepsis, pulmonary embolism, or hypopcapnic coma occurred in 0.6% of patients.

Video-assisted thoracic surgery

In contrast to medical thoracoscopy, VATS requires a higher level of surgical expertise, general anesthesia, and single-lung mechanical ventilation. It is contraindicated for patients who cannot tolerate single-lung ventilation and who have complex pleural adhesions or airway abnormalities that preclude intubation with a double-lumen endotracheal tube. Its main advantage over medical thoracoscopy is superior access to the pleural space, which provides the opportunity for adhesiolysis, mechanical pleurodesis (by abrasion of the pleura), and biopsy of the lung, visceral and/or parietal pleura. At the end of the procedure, a sclerosing agent can be insufflated into the pleural cavity. VATS with talc poudrage has a high rate of success (> 90%) on the first attempt and achieves long-term control of MPE.

Pleuroperitoneal shunts

Pleuroperitoneal shunts transfer pleural fluid from the pleural space into the peritoneal cavity when manually pumped. Pleuroperitoneal shunts may be considered for patients with trapped lung who are not candidates for decortication. This technique may be particularly suited to patients with refractory chylothorax, because it allows recirculation of chyle. Shunts are also an option for treating MPEs that have failed chemical pleurodesis. Palliation with pleuroperitoneal shunting was achieved in 80-90% of properly selected patients in two small case series.
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The use of pleuroperitoneal shunts for managing MPE has gradually fallen out of favor, largely because of difficulties with shunt failure. Shunt failure is most commonly related to clotting of the catheter. The mean duration of shunt patency ranges from 2.5 to 26 months in published studies.21-22 Shunt infections and the need for manual operation also limit use in patients with MPE.

Tunneled pleural catheters

Over the last decade, TPCs (Figure 2) have become a popular, minimally invasive approach for management of MPE. Tunneled pleural catheters can be placed using conscious sedation, in an outpatient setting, using a modified Seldinger technique.23 A valve at the proximal end of the catheter prevents fluid and air from traveling through the catheter until the drainage line and vacuum bottle are attached. A polyester cuff on the catheter induces granulation in the subcutaneous tunnel, which helps to secure it in place and prevent infection. Drainage is typically performed every other day. It takes about 15 minutes and can be done by the patient, a family member, or visiting nurse. When pleural fluid output drops to less than 50 ml on three consecutive occasions, and the absence of pleural fluid is confirmed radiographically, pleurodesis is assumed and the catheter is removed.

In a randomized study comparing a TPC with conventional tube thoracostomy and pleurodesis with doxycycline, spontaneous pleurodesis developed in 46% of TPC patients after a median of 29 days (range 8-223 days), versus 54% of chemical pleurodesis patients.24 Similar improvements were observed in procedure-related pain, dyspnea relief, and quality of life between groups. Patients treated with TPCs required significantly (p < 0.001) fewer hospital days for the procedure (median 1 day vs. 6.5 days for chemical pleurodesis).24 Median survival was similar for both groups (87 days for TPC, 90 days for chemical pleurodesis). In a retrospective study,25 hospital charges for TPC outpatients were significantly lower than for inpatients treated with tube thoracostomy and pleurodesis (mean $3,339 ± 1,753 vs. $7,830 ± 4,497, p = 0.001).

The rate of complications associated with TPCs compares favorably with that observed with other management options. In a retrospective analysis of 250 TPC insertions for MPE,23 the most common complications were symptomatic pleural

Figure 2

Pleural catheter with a one-way valve at the end (a), disposable vacuum drainage bottle with drainage tubing (b).

Photos courtesy of CareFusion Corporation or one of its subsidiaries, 2010. All rights reserved.
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fluid loculation (8.4%), unsuccessful insertion (4.0%), and asymptomatic pleural fluid loculation (4.0%). The most severe complication was empyema (3.0%), which was observed at a rate comparable to that seen with thorascopic talc poudrage in other series.\(^\text{17,26}\) Pneumothorax occurred in 2.4% of TPC patients. Rare (< 2%) complications included cellulitis, recurrent fluid, catheter dislodgement, bleeding, pain necessitating catheter removal, and tumor seeding the insertion site.

**Future directions**

Management options for MPE have expanded significantly over the last decade, especially with the growing use of minimally invasive techniques. It is now possible to provide individualized, effective palliation for MPE while minimizing patient discomfort and hospitalization time. Studies are underway to evaluate the safety and efficacy of new sclerosing agents,\(^\text{13}\) as well as intrapleural chemotherapy\(^\text{27}\) and gene therapy\(^\text{28}\) delivered via TPC. These advances may yield additional treatment options for MPE in the future.

**References**


**Disclosures**

Dr. Musani is a consultant and member of the speakers bureaus for Cardinal Health, Inc. and CareFusion Corporation, manufacturer of the Pleurx\textsuperscript{\textregistered} pleural catheter. Dr. Langmack has no financial relationship with any biomedical device or pharmaceutical company.

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**Improving survival for stage IV non-small cell lung cancer: a surveillance, epidemiology and end results survey from 1990 to 2005**

Morgensztern D, Waqar S, Subramanian J, Gao F, Govindan R; Division of Hematology-Oncology, St. Louis Veterans Hospital, St. Louis, MO. *J Thorac Oncol* 2009; 4:1524-1529

**BACKGROUND:** Although there has been a significant survival improvement for patients with metastatic NSCLC enrolled in randomized trials, it is not clear whether a similar benefit is seen in an unselected group of patients. Therefore, we conducted a study to evaluate for survival changes in a large national cancer registry database.

**PATIENTS AND METHODS:** The Surveillance, Epidemiology, and End Results (SEER) registry was queried for patients with NSCLC stage IV, aged 21 years or older, and diagnosed between 1990 and 2005. We analyzed four equally divided time periods between 1990 and 2005 (1990 to 1993 or period 1, 1994 to 1997 or period 2, 1998 to 2001 or period 3, and 2002 to 2005 or period 4) to determine changes in overall survival for all patients and according to histology.

**RESULTS:** We identified 129,337 patients meeting eligibility criteria. There was a significant improvement in overall survival since period 1. One-year and two-year overall survival increased from 13.2 and 4.5%, respectively, in period 1 to 19.4% and 7.8%, respectively, in period 4. On multivariate analysis, survival for adenocarcinoma was increased compared with squamous cell carcinoma only in period 4 (p = 0.02).

**CONCLUSIONS:** There has been a modest but statistically significant improvement in overall survival for stage IV NSCLC over the past 16 years. The recent differences in outcomes based on histology observed in period 4 may reflect the increased activity of epidermal growth factor receptor tyrosine kinase inhibitors in adenocarcinoma compared with squamous cell carcinoma.

**EDITORIAL COMMENT:** This manuscript takes the finding reported in multiple clinical trials of stage IV non-small cell lung cancer (NSCLC) subjects and evaluates whether the same results can be found in an unselected population followed in the SEER database. One year survival data from randomized clinical trials have shown improvement with therapy from 20% (early 1990’s) to 38% in contemporary platinum based doublet trials. The authors found that survival improvements are present, but to a lesser extent (6% improvement in one-year survival), which may reflect the true impact of changes in therapy. The authors do not report how often the newer regimens were offered (and this would be very important data, although difficult to ascertain). The improved survival of patients with adenocarcinoma during the 2002-2005 study period perhaps suggests that a push to more personalized care (for example, K-ras and EGFR mutational analysis on adenocarcinomas) may further improve survival rates. Another interesting finding from this study is the large number of subjects with unknown stage (11.2% for the 2002-2005 reporting period), suggesting that discrepancies in initial evaluation and care likely exist in a large number of patients. Lastly, clinicians should take note of the increasing percentage of patients who present with stage IV disease (44.6%). Stage IV disease increased over the last two periods of the study, likely reflecting the more widespread use of PET scans in staging. Increased use of PET may result
in stage migration and improved survival in all stages. This study supports the more standardized use of newer treatment regimens, though outcome improvements are modest in comparison to clinical trials.

**Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis**

Parsons A, Daley A, Begh R, Aveyard P; UK Centre for Tobacco Control Studies, Primary Care Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, UK. BMJ 2010; 340:b5569

**OBJECTIVE:** To systematically review the evidence that smoking cessation after diagnosis of a primary lung tumour affects prognosis.

**DESIGN:** Systematic review with meta-analysis.

**DATA SOURCES:** CINAHL (from 1981), Embase (from 1980), Medline (from 1966), Web of Science (from 1966), CENTRAL (from 1977) to December 2008, and reference lists of included studies.

**STUDY SELECTION:** Randomised controlled trials or observational longitudinal studies that measured the effect of quitting smoking after diagnosis of lung cancer on prognostic outcomes, regardless of stage at presentation or tumour histology, were included.

**DATA EXTRACTION:** Two researchers independently identified studies for inclusion and extracted data. Estimates were combined by using a random effects model, and the $I^2$ statistic was used to examine heterogeneity. Life tables were used to model five year survival for early stage non-small cell lung cancer and limited stage small cell lung cancer, using death rates for continuing smokers and quitters obtained from this review.

**RESULTS:** In 9/10 included studies, most patients studied were diagnosed as having an early stage lung tumour. Continued smoking was associated with a significantly increased risk of all cause mortality (hazard ratio 2.94, 95% confidence interval 1.15 to 7.54) and recurrence (1.86, 1.01 to 3.41) in early stage non-small cell lung cancer and of all cause mortality (1.86, 1.33 to 2.59), development of a second primary tumour (4.31, 1.09 to 16.98), and recurrence (1.26, 1.06 to 1.50) in limited stage small cell lung cancer. No study contained data on the effect of quitting smoking on cancer specific mortality or on development of a second primary tumour in non-small cell lung cancer. Life table modelling on the basis of these data estimated 33% five year survival in 65 year old patients with early stage non-small cell lung cancer who continued to smoke compared with 70% in those who quit smoking. In limited stage small cell lung cancer, an estimated 29% of continuing smokers would survive for five years compared with 63% of quitters on the basis of the data from this review.

**CONCLUSIONS:** This review provides preliminary evidence that smoking cessation after diagnosis of early stage lung cancer improves prognostic outcomes. From life table modelling, the estimated number of deaths prevented is larger than would be expected from reduction of cardiorespiratory deaths after smoking cessation, so most of the mortality gain is likely to be due to reduced cancer progression. These findings indicate that offering smoking cessation treatment to patients presenting with early stage lung cancer may be beneficial.

**EDITORIAL COMMENT:** This UK report by Parsons and colleagues is an important systematic review of the effects of smoking cessation on lung cancer prognosis. Their study confirms the common clinical finding that continued smoking increases the risk of all-cause mortality and recurrence in both limited stage small cell lung cancer and early stage NSCLC. Development of a second primary tumor was also associated with continued smoking in limited stage small cell lung cancer. Life table modeling shows a dramatic improvement in 5-year survival (70% vs. 33%) in patients with early stage NSCLC who quit smoking and these improvements are likely from a reduction in cancer progression not cardiopulmonary deaths. Limitations of this study include the relatively small number of studies that met criteria for inclusion (n=10), the observational nature of the studies included, and the use of life table models where multiple estimations of death rates had to be employed. Death rates typically are developed from retrospective studies and this may underestimate survival and exaggerate the effects of the intervention. The authors do not comment on how aggressively other treatments...
(for example cardiovascular interventions) are pursued in patients with a lung cancer diagnosis, but the majority of the studies reviewed included subjects with early stage disease. However, the improved survival rates are so impressive that smoking cessation should be aggressively pursued in all lung cancer patients and warrants evaluation in randomized, controlled trials. One initial step would be for current lung cancer clinical trials to closely monitor and report smoking status (with biologic confirmation, such as exhaled carbon monoxide or urine cotinine) and analyze how this affects survival.

**Genetic variants and risk of lung cancer in never smokers: a genome-wide association study**


**BACKGROUND:** Lung cancer in individuals who have never smoked tobacco products is an increasing medical and public-health issue. We aimed to unravel the genetic basis of lung cancer in never smokers.

**METHODS:** We did a four-stage investigation. First, a genome-wide association study of single nucleotide polymorphisms (SNPs) was done with 754 never smokers (377 matched case-control pairs at Mayo Clinic, Rochester, MN, USA). Second, the top candidate SNPs from the first study were validated in two independent studies among 735 (MD Anderson Cancer Center, Houston, TX, USA) and 253 (Harvard University, Boston, MA, USA) never smokers. Third, further replication of the top SNP was done in 530 never smokers (UCLA, Los Angeles, CA, USA). Fourth, expression quantitative trait loci (eQTL) and gene-expression differences were analysed to further elucidate the causal relation between the validated SNPs and the risk of lung cancer in never smokers.

**FINDINGS:** 44 top candidate SNPs were identified that might alter the risk of lung cancer in never smokers. rs2352028 at chromosome 13q31.3 was subsequently replicated with an additive genetic model in the four independent studies, with a combined odds ratio of 1.46 (95% CI 1.26-1.70, $p =$ 5.94$x10^{-6}$). A *cis* eQTL analysis showed there was a strong correlation between genotypes of the replicated SNPs and the transcription level of the gene *GPC5* in normal lung tissues ($p =$ 1.96$x10^{-4}$), with the high-risk allele linked with lower expression. Additionally, the transcription level of *GPC5* in normal lung tissue was twice that detected in matched lung adenocarcinoma tissue ($p =$ 6.75$x10^{-11}$).

**INTERPRETATION:** Genetic variants at 13q31.3 alter the expression of *GPC5*, and are associated with susceptibility to lung cancer in never smokers. Downregulation of *GPC5* might contribute to the development of lung cancer in never smokers.

**EDITORIAL COMMENT:** Li and colleagues present their work on potential genetic determinants of lung cancer in never smokers. This likely represents a distinct disease (in terms of risk factors, genetic alterations in the tumors, and potential treatment strategies) and the authors conducted a genome-wide association study (GWAS) in never smokers with lung cancer. The experimental setup and tumor types included are important for this study. The majority of the tumors studied were adenocarcinoma and carcinoid. The initial (stage 1) study included samples from the Mayo clinic (377 case-control pairs) matched for age, sex, and ethnic origin. Forty-four single nucleotide polymorphisms (SNPs) were identified and these were then tested in two external datasets (MD Anderson and Harvard) during stage 2. These studies identified two SNPs on chromosome 13 (13q31.3), and these are strongly associated with expression of the proteoglycan *GPC5*. In stage 3, the findings were tested in a fourth cohort (UCLA) and found to be associated with lung cancer risk. Lastly, in stage 4, an expression quantitative trait loci analysis investigated the association between genotypes of the original 44 SNPs and normal lung tissue from the original Mayo cohort. This confirmed the association between the two SNPs (identified during stage 2) with expression levels of *GPC5*. *GPC5* is a plasma membrane-associated proteoglycan that influences cell growth, differentiation and the cellular injury response. Normal lung tissue had twice the expression of *GPC5* at the transcriptional level compared to tumor tissue.
Limitations of the study do exist and these were largely acknowledged by the authors. First, different control groups were used for each of the studies, and this is inevitable when utilizing publicly available datasets. For example, the Harvard study used non-blood related family/friends or patients having cardiovascular surgery, while the other three used general community members. Ethnic diversity is also limited in the tumor sets (save for the UCLA group). The large majority of the 44 SNPs identified were not validated in the replication studies and this occurred because many of the confounders (COPD diagnosis, family history of lung cancer, and environmental smoke exposure) were not adjusted in the MD Anderson and Harvard cohorts. This highlights the need for investigators, particularly in genetic studies posted to publically available databases, to improve the collection of common data elements in trials so that more sophisticated comparisons can be completed.

Airway PI3K pathway activation is an early and reversible event in lung cancer development


ABSTRACT: Although only a subset of smokers develop lung cancer, we cannot determine which smokers are at highest risk for cancer development, nor do we know the signaling pathways altered early in the process of tumorigenesis in these individuals. On the basis of the concept that cigarette smoke creates a molecular field of injury throughout the respiratory tract, this study explores oncogenic pathway deregulation in cytologically normal proximal airway epithelial cells of smokers at risk for lung cancer. We observed a significant increase in a genomic signature of phosphatidylinositol 3-kinase (PI3K) pathway activation in cytologically normal bronchial airway epithelium of smokers with lung cancer and smokers with dysplastic lesions, suggesting that PI3K is activated in the proximal airway before tumorigenesis. Further, PI3K activity is decreased in the airway of high-risk smokers who had significant regression of dysplasia after treatment with the chemopreventive agent myo-inositol, and myo-inositol inhibits the PI3K pathway in vitro. These results suggest that deregulation of the PI3K pathway in the bronchial airway epithelium of smokers is an early, measurable, and reversible event in the development of lung cancer and that genomic profiling of these relatively accessible airway cells may enable personalized approaches to chemoprevention and therapy. Our work further suggests that additional lung cancer chemoprevention trials either targeting the PI3K pathway or measuring airway PI3K activation as an intermediate endpoint are warranted.

EDITORIAL COMMENT: Gustafson and colleagues report on activation of the phosphatidylinositol 3-kinase (PI3K) pathway as an early event in the development of lung cancer and how treatment with oral myo-inositol may abrogate this activation. Increased PI3K activity has been reported in a variety of cancers, including lung, and the authors chose to focus on subjects with airway dysplasia. Research on dysplastic central airway lesions has identified genetic alterations, and these alterations may be targeted with chemopreventive agents to stop the development of lung cancer. For this study, the authors examined PI3K activation in cytologically normal airway epithelial cells collected with a cytobrush from central airways (typically the mainstem bronchi). The primary and validation data sets compared subjects with lung cancer and no lung cancer, and gene expression signatures indicative of PI3K activation were compiled from published reports and overexpression of PI3K in human epithelial cells. PI3K was found to be upregulated in lung cancer subjects compared to subjects with other lung diseases. These findings were not associated with cumulative tobacco exposure. After confirming these findings in published gene expression data sets, the authors extended their studies to a relatively small number of samples from a myo-inositol chemoprevention study where PI3K activity was compared in cytobrush specimens (taken much more distally in the airways) from smokers with normal airway epithelium compared to smokers with airway dysplasia. Subjects received oral myo-inositol (9 g orally, twice a day) for three months and then had repeat specimens collected. Genes induced by PI3K activation were found to be induced in subjects with airway dysplasia, and those with a response to myo-inositol had an increased expression of genes that are repressed with PI3K overexpression.
This is a large study that combines samples collected in a variety of clinical and research settings. The fact that the investigators chose to study subjects with lung disease (but not lung cancer) as controls improves the robustness of the findings. However, they do analyze a relatively small number of subjects from the myo-inositol trial, and it was not clear if these were all the subjects in the trial (or a subset). Second, all subjects they analyzed were on treatment, so there was not a placebo arm for comparison. There were also acknowledged differences in smoking history of subjects with and without dysplasia. This study advances the field of chemoprevention by looking for gene expression findings in a distinct pathway and then using samples from a trial with an agent that acts directly on this pathway. Lung cancer chemoprevention may ultimately prove to parallel lung cancer chemotherapy in that the most effective agents will be targeted to very specific populations. Chemopreventive studies should collect clinical data and biologic specimens to allow for the next generation of studies.

Disclosures
Dr. Keith is a member of the Boehringer Ingelheim and Pfizer, Inc. speakers bureaus. He reports no financial relationship with a commercial entity that has an interest in the subject of this manuscript.
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  The longest running TB course in the US, now in our 47th year! Course highlights include MDR-TB, XDR-TB, screening for and treatment of latent TB, planning TB control programs, TB and HIV, transmission and pathogenesis of adult and pediatric TB.
  Featuring: Michael Iseman, MD and Charles Daley, MD
  **October 13-16, 2010, National Jewish Health, Denver, CO**

- **33rd Annual National Jewish Health Pulmonary & Allergy Update***
  Continuing Medical Education on pulmonary, asthma, allergy and immunology topics. Stay abreast of the latest knowledge and trends and gain practical information that you can apply in your practice.
  Featuring: Erwin Gelfand, MD, Richard Martin, MD, and Harold Nelson, MD
  **February 2-5, 2011, Keystone, CO**

*This activity has been approved for AMA PRA Category 1 Credit.

For a complete list of live events, for more information, or to register go to njhealth.org/ProEd or call 800.844.2305
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