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LUNG CANCER
IASLCNEWS
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LUNG CANCER STAGING

Innovations in the 8th Edition of the TNM Classification of Lung Cancer Enhance Prognostic Capabilities

By Cynthia L. Kryder, MS, CCC-Sp, with Ramón Rami-Porta, MD

Clinicians around the world began implementing the 8th edition of the tumor, node, and metastasis (TNM) classification of lung cancer on January 1, 2017. There has been confusion, however, over when the 8th edition of the TNM staging system will be fully implemented in the U.S. While the staging system has been implemented by the Union for International Cancer Control (UICC) as of January 1, 2017, the U.S. American Joint Committee on Cancer (AJCC) has delayed implementation until January 1, 2018. The reason for this is to ensure that that all partners in U.S. patient care and cancer data collection are working in synchrony, which the time until January 2018 will allow.

The revisions included in the TNM staging classification update represent a data-driven approach to the staging of lung cancer that features several innovations that will enhance prognostic capabilities and enable improved tumor stratification in future clinical trials. These innovations were informed by an analysis of data from the International Association for the Study of Lung Cancer (IASLC) database that included 70,967 evaluable patients with non-small cell lung cancer and 6,189 with small cell lung cancer. In particular, the 8th edition reflects an increased recognition of tumor size as a relevant prognostic factor as well as the prognostic significance of tumor burden in hilar and mediastinal lymph nodes and the prognostic impact of the number and anatomic location of metastatic tumors. The table (page 3) summarizes the innovations introduced in the 8th edition of the TNM classification of lung cancer.


Ramón Rami-Porta

The T Component

Within the T component, new categories—adenocarcinoma in situ (Tis, AIS) and minimally invasive adenocarcinoma (T1mi)—were introduced based on tumor size and radiological and pathological features, endobronchial location < 2 cm from carina and total atelectasis/pneumonitis were downstaged from T3 to T2, and invasion of the diaphragm was upstaged from T3 to T4. In addition, visceral pleural invasion and its 2 categories (PL1: invasion beyond its elastic layer and PL2: invasion of the pleural surface) were confirmed as important prognostic factors.

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TOBACCO CONTROL

Is Tobacco-Free by 2030 a Realistic Goal? The Finnish Government Thinks So

By Cynthia L. Kryder, MS

Tobacco exposure remains one of the leading preventable causes of premature disease and death in the United States and abroad. Around the world, 6 million people die each year as a result of tobacco exposure, including 480,000 people in the United States. The global costs of smoking due to health problems and lost productivity are staggering and have been estimated to exceed USD$1 trillion annually.[1]

Not only is smoking a risk factor for lung cancer, the adverse effects of smoking continue even after a cancer diagnosis. Smoking and tobacco-related products promote more aggressive tumors through increased proliferation, angiogenesis, migration, invasion, and resistance to cytotoxic therapy, and they cause adverse outcomes in patients with cancer through increased overall mortality, cancer-specific mortality, risk for developing a second primary cancer, and strong associations with increased toxicity from cancer treatment.[2]

In an effort to improve population health, the Finnish government aims to make the country tobacco-free by 2030. With the ambitious goal of having fewer than 2% of adults using tobacco in any form by 2040, Finland enacted new measures in January 2017 to help its residents kick the habit.

Finland already had a reputation for being tough on smokers. As a pioneer in smoking-reduction efforts, Finland first introduced the Tobacco Act in 1976, which included measures to reduce the use of tobacco products. Initial efforts involved banning advertising and retail displays of nicotine products. Smoke-free workplaces were implemented in the mid-1990s, and smoking in bars and restaurants was banned in 2007.[3]

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MEETING PREVIEW

Societies Join Forces to Host Seventh European Lung Cancer Conference

For the seventh year, the world's leading societies in the field of thoracic oncology are collaborating to host the European Lung Cancer Conference (ELCC), a multidisciplinary event that aims to advance science, disseminate education, and improve lung cancer care worldwide. The conference, to be held May 5–8 in Geneva, Switzerland, will be hosted by IASLC and the European Society for Medical Oncology (ESMO), in partnership with the European Society for Radiotherapy and Oncology, European Society of Thoracic Surgeons, and European Thoracic Oncology Platform.

"I am excited to be involved in this partnership between IASLC and ESMO. It brings together the best healthcare specialists from around the world in order to present, discuss, and advance our understanding of thoracic malignancies," said IASLC's co-chair of the conference's Scientific Committee, Andrew Nicholson, Head of Diagnostic Thoracic Pathology at the Royal Brompton Hospital and Honorary Professor of Respiratory Pathology, National Heart and Lung Institute, Imperial College London. He shares leadership of the committee with ESMO's Martin Reck, Head of the Department of Thoracic Oncology and the Clinical Trial Department in the Department of Thoracic Oncology at the Lung Clinic Grosshansdorf in Germany.

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LUNG CANCER POLICY

Lung Cancer in the Context of a Precision Medicine Approach

By Giorgio Vittorio Scagliotti, MD, PhD

The ambition to personalize medicine is intrinsic to the mission of every individual physician with the twin goals of reducing drug-related toxic effects and improving treatment efficacy. Hippocrates first proposed a combined assessment of the 4 humors—blood, phlegm, yellow bile, and black bile—to determine the best course of treatment for each patient. Today, exploiting gene sequencing enables more accurate medical predictions for almost every disease. Personalized predictions include whether an individual is currently developing an illness or will develop it many years ahead, whether a patient will respond positively to treatment or will suffer a serious adverse reaction to a drug. Modern medicine—and the reason why the word "personalized" has been added for emphasis—offers technology that has brought us much closer to exquisite precision in disease diagnosis and treatment.

Lung cancer is the most frequent cause of cancer death in the world. Annually, 1.8 million people are diagnosed with this disease and 1.6 million die of it, making this disease a relevant global social problem. The 5-year survival rate for all stages combined varies from 4% to 17%, depending on regional differences.

Tobacco smoking remains the main risk factor for lung cancer, even if a rising incidence of the disease in never-smokers has been observed in the last two decades, and the vast majority of newly diagnosed lung cancers are metastatic or locally advanced.

In the last 15 years, a series of studies documented a potential role of low-dose computed tomography (CT) scan as an effective tool for early diagnosis. Cancer screening is a process chain, and each link in the chain needs to be performed correctly to maintain its significant but fragile benefit. While the primary goal in cancer screening is to achieve an objective reduction in cancer-related mortality, the utility of a screening approach is also defined by the extent of resultant harms, such as iatrogenic injury and psychological stress, from the execution of that process. At a time of profound financial stress on healthcare systems worldwide, if screening is to be delivered, then it is essential to ensure that it is of high quality and includes smoking cessation services so that harms and costs are minimized.

Nowadays, physicians are often making diagnoses using symptoms-based disease archetypes as opposed to underlying molecular patho-physiology. The growing concept of "precision medicine" addresses this challenge by recognizing the vast, yet fractured, state of biomedical data, and calls for a patient-centered view of data in which molecular, clinical, and environmental measurements are stored in large shareable databases. Such efforts have already enabled large-scale knowledge advancement, but they also risk enabling large-scale misuse.

> "The genomic revolution encompasses only a portion of the emerging hallmarks of cancer, which include delineating tumor characteristics and enabling better understanding of the tumor microenvironment."

With the completion of the human genome, we understand now that life is based on dynamic molecular networks rather than on a direct connection between genotype and phenotype.

The genomic revolution is still a "work in progress" and represents an unprecedented opportunity with regard to emerging cancer diagnosis and therapies. Advances in genomic technologies have made it possible to sequence candidate oncogenes in cancers, quickly and affordably; gene expression profiling and/or full genome sequencing will hopefully characterize a reasonably wide collection of tumors. These data provide critical information about the spectrum and frequencies of mutations in cancers and will facilitate the development of drugs against targets that are most frequently mutated.

Despite the early successes of targeted therapies, it is becoming evident that primary and acquired resistance will be major limitations. Most solid and liquid tumors will not be overcome by single-agent targeted therapies. Even in those cases in which a single agent dissolves the tumor, the victory is short-lived and the tumors re-emerge. More often, single-agent trials involving targeted therapies administered to solid tumors result in modest effects, or no responses, even when confined to patients who have mutations in the target oncogene. Clearly, there is much to learn about in vivo tumor biology, and exploring resistance mechanisms is essential to identify which combination of drugs will treat resistant tumors or prevent the emergence of resistance.

However, the genomic revolution encompasses only a portion of the emerging hallmarks of cancer, which include delineating tumor characteristics and enabling better understanding of the tumor microenvironment. In this context, an understanding of the immune landscape of cancers, including immune-evasion strategies, have led to breakthrough therapeutic advances for patients with non-small cell lung cancer and have created a platform for future therapeutic developments.

We are at the beginning of a creative period of bottom-up research activity, organized through pilot projects of increasing scope and scale, from which best practices will progressively emerge. In particular, given the size and diversity of the healthcare enterprise, a single approach to data gathering that will populate the space is probably not appropriate for all contributors. As in any initiative of this complexity, we will need the right level of coordination and encouragement of the many players who must cooperate to create a higher level of biomedical knowledge.

In this patient-centered context, patients and their advocates are and will be more critical, each and every day: first, to promote the right social pressure for the systematic implementation of the results of preclinical and clinical research and, second, to develop a work in progress and continuous discussion with the regulatory bodies and national healthcare systems in an attempt to guarantee drug accessibility to every patient as well as to help national authorities maintain the long-term financial sustainability of healthcare systems.✦

LUNG CANCER IASLC NEWS

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IASLC MISSION

To embrace the study of the etiology, epidemiology, prevention, diagnosis, treatment, and all other aspects of lung cancer and other thoracic malignancies; to provide education and information about lung cancer and other thoracic malignancies to IASLC members, to the medical community at large, and to the public; to use all available means to eliminate lung cancer and other thoracic malignancies as a health threat for the individual patient and throughout the world.

Updated TNM Staging from page 1

The analyses of tumor size in the IASLC database provided evidence to support further subclassification of tumors 3 cm or less in size (T1 category in the 7th edition) and those greater than 3 cm (T2 category in the 7th edition), and to distribute tumor size as a descriptor of all T categories. Consequently, precise tumor size measurement is now more important than ever before, as small changes in size mean important changes in prognosis. Although the 3-cm cutoff point separating T1 and T2 tumors remains valid, survival analyses according to 1-cm cutoff points showed that from 1 to 5 cm, every centimeter counts. Larger tumors were associated with a worse prognosis than determined in previous TNM classifications and are better aligned with either T3 (tumor size of more than 5 to 7 cm) or T4 (tumor size of more than 7 cm).

The N Component

There are no changes in the N categories; however, the analyses for the 8th edition explored the quantification of nodal disease and found that the number of nodal stations involved had prognostic implications. The more nodal stations involved, the worse the prognosis. In addition, the prognosis of tumors with involvement of multiple N1 stations was similar to that of tumors with single station N2 without concomitant N1 disease (skip metastases).

Nodal quantification is classified as:

- N1a: involvement of a single N1 nodal station
- N1b: involvement of multiple N1 nodal stations
- N2a1: involvement of a single N2 nodal station without N1 involvement (skip metastasis)
- N2a2: involvement of a single N2 nodal station with N1 involvement
- N2b: involvement of multiple N2 nodal stations

The M Component

Refinements to the M component include different categories for single and multiple extrathoracic metastases in one or in several organs. There is no change in the designation of metastasis within the thoracic cavity (M1a); however, since single extrathoracic metastases have better prognoses than multiple extrathoracic metastases in one or in several organs, different categories have been defined for them: M1b for single and M1c for multiple extrathoracic metastases. Prognosis is similar for M1a and M1b tumors. Nevertheless, they represent distinct forms of metastatic involvement that require different approaches to diagnosis and treatment, justifying the need to define them separately.

Stage Grouping

Some TNM subsets have moved from one stage to another, and new stages and substages have been created to accommodate groups of tumors with similar prognoses. Taxonomic changes, however, do not necessarily dictate an automatic change in therapy if the clinical trials performed to test therapeutic options did not originally include the tumors that are now included in the selected stages for study. In the absence of results from clinical trials, clinical judgment will determine the best therapeutic options for a given patient with a given tumor.

Clinicians should be aware of the following stage changes:

- Stage IA is now divided into stages IA1, IA2, and IA3 to include the new T1a, T1b, and T1c N0M0 tumors
- Stages IB and IIA now denote T2aN0M0 and T2bN0M0 tumors, respectively
- All N1M0 tumors are now stage IIB, together with T3N0M0 with one exception: T3-T4N1M0 tumors are now stage IIIA
- All N2M0 tumors are now stage IIIA, except for T3-T4N2M0 tumors, which are in stage IIIB, together with all N3M0 tumors, except for T3-T4N3M0 tumors, for which a new stage IIIC was created
- Stage IV is now divided into stage IVA to group M1a and M1b tumors and stage IVB to include M1c tumors

In summary, the 8th edition of the TNM classification of lung cancer introduces new groups based on tumor size, validates the prognostic importance of quantifying nodal disease, establishes a new category for single extrathoracic metastasis, and defines new stage groupings that more closely align with expected prognosis. These refinements enable a better understanding of the anatomic extent of the tumor and help clinicians refine both a clinical and pathologic staging. In so doing, these changes will require greater attention in measuring tumor size, determining nodal disease status, searching for metastases, and using clinical judgment to determine treatment. ✦

Table. Innovations Introduced in the 8th Edition of the TNM Classification of Lung Cancer

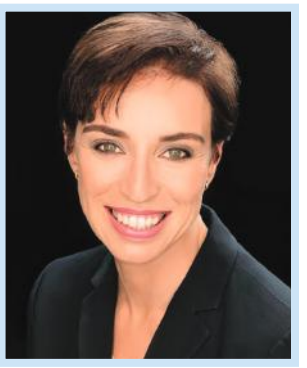
Descriptor	8th edition
T component	
0 cm (pure lepidic adenocarcinoma ≤ 3 cm total size)	Tis (adenocarcinoma in situ, AIS)
≤ 0.5 cm invasive size (lepidic predominant adenocarcinoma ≤ 3 cm total size)	T1mi (minimally invasive adenocarcinoma)
≤ 1 cm	T1a
> 1 – 2 cm	T1b
> 2 – 3 cm	T1c
> 3 – 4 cm	T2a
> 4 – 5 cm	T2b
> 5 – 7 cm	T3
> 7 cm	T4
Bronchus < 2 cm from carina	T2
Total atelectasis/pneumonitis	T2
Invasion of diaphragm	T4
Invasion of mediastinal pleura	-
N Component	
No assessment, no involvement, or involvement of regional lymph nodes	No change, but quantification by number of involved nodal stations is prognostic
M component	
Metastases within the thoracic cavity	M1a
Single extrathoracic metastasis	M1b
Multiple extrathoracic metastases	M1c
Other innovations	
Measurement of tumor size in part-solid non-mucinous adenocarcinomas	Only the size of the solid/invasive component counts for the determination of tumor size as a T descriptor
Classification of second primaries	One TNM for each tumor
Classification of separate tumor nodules	T3, T4, and M1a if in the same lobe of the primary tumor, in another ipsilateral lobe, or in the contralateral lung, respectively
Classification of multifocal adenocarcinomas with ground glass opacity/lepidic features	Highest T with number of lesions or 'm' for multiple in parentheses, with an N and an M that apply collectively to all tumors
Classification of pneumonic type adenocarcinoma	T3, T4, and M1a if in the same lobe of the primary tumor, in another ipsilateral lobe, or in the contralateral lung, respectively

mi=minimally invasive; Tis=tumor in situ

POINT/COUNTERPOINT

Should Physicians Recommend E-Cigarettes to Their Lung Cancer Patients Who Smoke? What About Their Family Members Who Also Smoke?

Opinion-No: Emily Stone, MBBS, MMed



Emily Stone

There is little doubt that lung cancer patients and the people around them who smoke need to stop. Smoking cessation can improve survival,[1] surgical outcomes,[2-4] and response to anticancer therapies[5] and can reduce the risk of recurrence.[6] However, many physicians feel poorly trained and unsure about providing smoking cessation advice; even if they advise their patients to quit, they often fail to follow through with specific measures.[7-9] There are many compelling arguments to include e-cigarettes in smoking cessation. They may give smokers autonomy. They may address the urgency of smoking cessation in lung cancer patients. They may be less dangerous than tobacco cigarettes although the data are not entirely clear.[10] If we could sell them under tight regulation, we could minimize the risks.[11] But these arguments carry inherent flaws with a profusion of contradictory evidence. We have plenty of access to effective, alternative forms of nicotine with a longer safety track record supported by evidence.[12] With good advice, smokers can exercise autonomy over their choice of nicotine replacement from the more established products. Regulatory frameworks may be harder to put in place than we think.

Although e-cigarettes have attracted significant support as smoking cessation tools from at least 1 major public health entity,[13] 2 recent systematic reviews cast doubt upon such claims. The first reviewed 38 studies and found that smokers who used e-cigarettes had lower rates of quitting than those who did not.[14] The second reviewed 12 studies, including 3 randomized trials and found only very limited evidence that e-cigarettes aided smoking cessation.[15] E-cigarettes may even have the potential to increase smoking rates in teenagers, with a recent study showing that e-cigarette use was associated with a 4-fold increase in tobacco cigarette smoking.[16] The marketing of e-cigarettes may undermine the smoking cessation message; advertisements recommend that smokers "switch," rather than "quit" and use familiar strategies to glamorize the smoking of e-cigarettes.[17]

Safety data on e-cigarettes are immature. Some studies suggest that e-cigarettes are better: in vitro data have shown reduced cytotoxicity[18]; exposure chamber data indicate lower levels of secondhand exposure to toxic combustion products.[19] However, other reports demonstrate that in vitro exposure to e-liquid results in reduced cell viability[20] and increased inflammatory responses.[21] Studies have also reported the presence of toxic aldehydes in e-liquids (particularly from flavorings)[22] and the potential for harm from passive exposure to e-cigarette vapor.[23] Other safety issues, such as leaks, fires, explosions,[24,25] and danger to children,[26,27] add to these concerns.

Does the urgency for smoking cessation in lung cancer patients make e-cigarettes a more necessary option? No—there are plenty of guidelines to smoking cessation, replete with information on nicotine replacement therapy, other pharmacotherapies such as varenicline and bupropion, appropriate behavioral strategies, and advice on combining approaches.[28-31] In many cases, these strategies are underused[32]—our need for "better smoking cessation" may simply reflect the need to use the tools we already have.

> E-cigarettes may even have the potential to increase smoking rates in teenagers, with a recent study showing that e-cigarette use was associated with a 4-fold increase in tobacco cigarette smoking.

How would tight regulation work for e-cigarettes? There may be potential for restrictions to minimize the risks of e-cigarettes. Suggested restrictions include selling them only to adult smokers, childproof containers, appropriate labeling, electrical safety, and consumer advice.[33,11] This would require vigorous oversight by agencies such as the FDA in the United States or the TGA in Australia. In August 2016, the FDA finalized a rule that extended its regulatory authority to cover a range of tobacco products, including e-cigarettes. Requirements include safety warnings and rules for retailers and manufacturers.[34] Criticisms of the rule have included concerns about obstruction to safety modifications, reduced product innovation, and protection of tobacco cigarette sales through grandfathering of tobacco cigarettes.[35] In Australia, e-cigarettes are currently unlawful for sale or personal use.[36] Comprehensive regulation of standardized e-cigarettes seems some distance away.

By recommending e-cigarettes to lung cancer patients as a strategy for smoking cessation, does the physician undermine robust tobacco control? Good tobacco control, which drives down smoking rates, depends on multipronged strategies such as the MPOWER measures recommended by the WHO.[37] Countries where these measures have been successfully introduced have shown a steady decline in smoking rates over the past few decades;[38,39] such countries include those without high rates of e-cigarette use.[38,40,41] E-cigarettes cannot be separated easily from the tobacco cigarette industry as the major international tobacco companies (including PMI, BAT, Lorillard, and Reynolds) have all purchased or developed e-cigarette brands since 2013.[42] Does this matter for the lung cancer patient who smokes? In the short term, probably not. They just want to stop smoking and we, their physicians, want them to stop, too. We should avoid, however, any strategies that empower the tobacco industry through profit and that distract us (by the complexity of introducing e-cigarette regulations) from the real game of helping our patients finally quit.

No one can argue against smoking cessation in lung cancer patients. Many strategies are available to physicians, particularly to those who feel up-to-date in the field. But until (1) the safety data are mature, (2) e-cigarettes conform universally to tight regulatory standards, (3) e-cigarettes are no longer made by companies whose primary interest is profit from tobacco, and (4) there are no better alternatives, physicians should not routinely recommend them to their patients.✦

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Opinion-Yes: K. Michael Cummings, PhD, MPH


K. Michael Cummings

Should clinicians recommend electronic cigarettes (e-cigarettes) to their lung cancer patients who continue to smoke? For many clinicians the answer to this question is a resounding NO WAY. However, I hope to persuade you that there are good reasons why clinicians should strongly consider recommending e-cigarettes to at least some of their patients who smoke.

It is not hard to understand why healthcare providers may be hesitant about recommending e-cigarettes to patients who continue to smoke, especially for those with a diagnosis of lung cancer. No e-cigarette has been officially licensed and marketed as an effective method to help someone stop smoking; in fact, some reviews suggest that e-cigarettes might actually hinder one's ability to stop smoking.[1,2] Additionally, it is hard to ignore the barrage of negative news stories about e-cigarettes: e.g., they can explode, there are cancer-causing chemicals in the vapor, the flavorings used in some of the products are attracting kids to use them, and big tobacco is pushing them as a way to keep people hooked and to attract a new generation of smokers.[3-5] Finally, for patients with lung cancer, it seems illogical to consider recommending a product that involves inhaling vapor particles into already sensitive and damaged lungs.

Patients expect treatment guidance from their doctor. For those who smoke, the standard of care should include firm advice to stop smoking along with the provision of evidence-based treatment methods to address their nicotine dependence.[6] Treating nicotine dependence is exceedingly inexpensive compared to treating the consequences of not quitting, especially in those with lung cancer where continued smoking is known to increase risks for treatment-related complications, recurrence, and mortality.[7-10] Individual, group, and telephone counseling combined with 7 government-licensed stop smoking medications (i.e., nicotine replacement medications: gum, lozenge, patch, inhaler, and nasal spray; and non-nicotine medicines: varenicline [Chantix, Champix] and bupropion [Zyban, Wellbutrin]) have been shown to reliably increase quit rates over and above quitting without support (i.e., "cold turkey").[11,12]

So why consider e-cigarettes as a treatment option? First, many patients have already tried the evidence-based methods and have found them to be unhelpful.[13-16] Indeed, even with the best combination of evidence-based treatments, only about 1 in 5 smokers will be abstinent 6–12 months later.[12] Most lung cancer patients do try to stop smoking when given the bad news about their cancer diagnosis, but a significant percentage relapse back to smoking.[7,8] Mostly, what clinicians tell patients who have relapsed is to try harder to quit, often recommending the same failed treatment options again. Rarely does this work. If a patient's cancer therapy fails to work, it would not be sound advice to recommend it keep being used; the same philosophy should apply to treating nicotine dependence.

> Nicotine seeking is the primary motivation for continued smoking, so providing addicted smokers with an alternative that delivers nicotine without most of the harmful toxins in smoke makes sense.

Second, nicotine seeking is the primary motivation for continued smoking, so providing addicted smokers with an alternative that delivers nicotine without most of the harmful toxins in smoke makes sense.[17] The problem with the licensed nicotine replacement medications is they provide too little nicotine too slowly to really satisfy smokers' craving for nicotine when they try to abstain from smoking. Newer model e-cigarettes can deliver nicotine in a way that more closely mimics the nicotine delivery from a tobacco cigarette, which makes them attractive substitutes for cigarettes.[18,19] The improved nicotine delivery of newer e-cigarette devices may help explain conflicting scientific evidence on the effectiveness of e-cigarettes in stopping smoking. Many of the early studies of e-cigarettes were evaluating products that did not deliver nicotine effectively. Smokers in these studies rarely used the products frequently enough to get any benefit, and most returned to smoking. Studies with newer model e-cigarette devices are showing greater frequency of use by smokers and improved effectiveness for smoking cessation.[20]

Third, e-cigarettes are not lit, do not burn, and do not produce cigarette smoke. While e-cigarette vapor does include some of the same chemicals found in cigarette smoke, the levels of these chemicals are many-fold lower than found in cigarette smoke.[21,22] So while e-cigarettes are not 100% safe, the risks are surely far lower than the alternative of inhaling cigarette smoke.[23-25] It is also worth noting that several studies have found that smokers who switched from cigarettes to an e-cigarette had significantly improved lung function and lower risk of airway infection, which would be clinically important for someone with lung cancer.[26-30]

Fourth, many smokers prefer e-cigarettes over other aids to quitting. In England, a study tracking the use of stop smoking methods found that e-cigarettes were the most popular method used.[14] There are several reasons for the popularity of e-cigarettes as a stop smoking method, including the behavioral and sensory similarity to cigarette smoking, access to products that can be purchased at retail and online often at a lower cost compared to nicotine medications, effective product marketing with appealing flavors, and word of mouth from those who have successfully switched from smoking to "vaping." The fact that e-cigarettes are not viewed as medicines and are used in much the same way as cigarettes may actually make them more attractive as substitutes for smoking compared, to licensed stop-smoking medicines. Additionally, with the wide variety of e-cigarette models now available, smokers have an opportunity to try different flavors and nicotine deliveries before settling on a device that best suits their needs. Two recent studies have found that smokers who purchased e-cigarettes from vape shops, where presumably they received some advice on the types of products available and how to vape, were more successful in quitting smoking compared to those who purchased e-cigarettes online or through a traditional tobacco selling retail outlet.[31,32] Given the wide range of e-cigarette devices available and complexities associated with using them properly, it is not surprising that those getting instructions on which device might best suit their needs would fare better than those left to figure this out on their own.[33] Currently, there are no standards for licensing vape shops or guidelines to ensure that the advice given to customers is accurate. However, unlike tobacco selling outlets that may also sell e-cigarettes, vape shops are in the business of selling only vaping products and are therefore motivated to help their customers switch away from cigarettes.

Given the evolving and sometimes confusing science on e-cigarettes and the rapidly changing marketplace of nicotine delivery products, it is understandable why clinicians are hesitant to recommend e-cigarettes as an option to their patients trying to stop smoking.[34] However, faced with the realities of nicotine addiction, the inadequacies of current evidence-based tobacco dependence treatments, and the dire consequences of continued smoking, uncertainty about e-cigarettes is no excuse for simply rejecting them. Clinicians have to make decisions based on the available evidence, which is nearly always incomplete. However, currently available evidence suggests a favorable risk-benefit profile for e-cigarette use in smokers who are otherwise unable to quit.[23-25] Useful and credible guidance on how to talk to patients about e-cigarettes can be found in medical journals and online.[35-39]

What is important to recognize is that e-cigarettes are not a fad. Millions of people (including many cancer patients) are using them daily, and the marketplace of products is continuing to evolve. It would be unwise for clinicians to ignore this new technology that offers the potential to make cigarette smoking obsolete.[40] ✦

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MEETING HIGHLIGHTS

17th Annual Targeted Therapies of the Treatment of Lung Cancer Meeting

By Kristina Wasson-Blader, PhD, ELS

For the 17th year, leading experts in the biology, diagnosis, and treatment of lung cancer convened in Santa Monica, California, from February 22nd to 25th to attend the Targeted Therapies of the Treatment of Lung Cancer meeting. "This important meeting brings lung cancer experts from around the world to exchange ideas and develop new clinical trials to improve the outcomes of patients with lung cancer," says Ramaswamy Govindan, MD.

Sponsored by the International Association for the Study of Lung Cancer (IASLC), the annual Targeted Therapies of the Treatment of Lung Cancer Meeting provides an informal setting to stimulate active discussions on data from studies that range from basic science to ongoing clinical trials for treating patients with lung cancer. "The Santa Monica meeting provides a unique opportunity for thoracic oncology investigators from around the world to informally discuss their latest research and network with colleagues," says Fred R. Hirsch, MD, PhD, IASLC Chief Executive Officer. "Many of the scientific presentations later made at larger meetings around the globe are first discussed at this event."

This year's meeting focused on new ideas and developments in lung cancer research, including the latest advances in immunotherapy, immunotherapeutic combinations, and biomarkers for immunotherapy as well as target-delineated therapies, including EGFR and ALK with an increasing focus on acquired resistance. Dr. Govindan notes, "Over the years, we have seen the Santa Monica meeting evolve from a meeting mainly focusing on targeted therapies to one that is increasingly allotting more time to discuss immunotherapy of lung cancer."

> Many of the scientific presentations later made at larger meetings around the globe are first discussed at this event.
>
> —**Fred R. Hirsch, MD, PhD**, IASLC CEO

Suresh Ramalingam, MD, a co-chair of this year's meeting, says, "The meeting highlighted all the exciting developments in immunotherapy, targeted therapy, and emerging new anticancer agents for lung cancer. The quality of presentations was outstanding and, most notably, the discussion sessions were deeply insightful. This year's meeting also had a fantastic session for fellowship trainees to guide them on various aspects of career development."

In attendance at this meeting were several IASLC fellows. This experience gives fellows the opportunity to interact with leading experts in lung cancer research. Kenichi Suda, MD, received one year of IASLC funding during 2015–2016, and he presented results from his study at the recent Santa Monica meeting. "It is very rare that we can meet so many researchers who work on the forefront in the field of lung cancer research. I received feedback from attendees after my presentation, and I also had the opportunity to discuss another research project with other attendees while at dinners. These communications will be helpful as I expand my research program and look to develop collaborations."

Kenichi Suda

By providing this early platform for data discussions and review, IASLC plays an important leadership role in advancing research. This meeting also serves as a setting to identify new opportunities for collaboration and to strengthen existing collaborations among investigators at various academic institutions and in industry. Through the combination of organized but informal networking gatherings and formal data presentation sessions, the Targeted Therapies Meeting and its increasing focus on immunotherapy helps to facilitate discovery in the thoracic oncology research community. "Coverage and summaries of scientific meetings around the globe throughout the world is a core content area of *IASLC Lung Cancer News*," notes Dr. Corey J. Langer, Editor. "The annual Targeted Therapies of the Treatment of Lung Cancer Meeting is comprehensive; it provides an important platform leading to continued international collaboration and scientific discovery so vital for the treatment of patients with lung cancer." ✦

Tobacco-Free Finland from page 1

These measures have deterred smoking to some degree. According to statistics reported by Finland's National Institute for Health and Welfare, cigarette smoking has steadily declined over the past 2 decades, at least among men. Still, in 2014 the prevalence of daily smoking was 17% for men and 14% for women, which represents 875,000 daily or occasional smokers among the 15- to 84-year-old population.[3]

Among Finland's latest efforts is legislation that increases the cost to retailers, who will likely pass these costs on to customers. Vendors who want to sell tobacco products are now required to pay a one-time licensing fee plus an annual surveillance fee that covers the cost of surveillance officers who ensure compliance. Surveillance fees, which are set by individual municipalities rather than by the state, are calculated per cashier and can cost as much as €500 (USD$536) annually per checkout.[4] Such fees may make it unprofitable for retailers to sell tobacco products. A ban on price rebates for tobacco products, tobacco substitutes, smoking accessories, tobacco imitations, electronic cigarettes, and nicotine-containing liquids may present further financial barriers for smokers.

> "The aim of Tobacco-Free Finland is ambitious, but obtainable. More and more emphasis is put ….into prevention of initiation of the use of tobacco products. In our opinion the main challenge is to be efficient in systematically offering enough help and support to our smoking patients in quitting smoking…"
>
> —**Annamari Rouhos, MD, PhD**, *Helsinki University Hospital Heart and Lung Center and the Finnish Respiratory Society in the working group of Tobacco-Free Finland 2030 network*
>
> —**Aija Knuuttila, MD, PhD**, *Helsinki University Hospital*

Finland also has moved from regulating tobacco use in public spaces into the private domain. Recent measures include a ban on smoking in private cars if passengers under the age of 15 years are present and the extension of smoke-free policies to residential properties. For example, Finland now permits housing companies to apply for a ban prohibiting residents from smoking on the balconies of individual apartments, if the smoke spreads from the private living space into other areas.[4]

In addition to getting smokers to give up the habit, Finland wants to reduce the number of people who start smoking in the first place by decreasing its appeal and availability. Consequently, it has put in place restrictions on the purchase of products that imitate tobacco or cigarettes, such as cigarette- or pipe-shaped candy. E-cigarettes also are strictly regulated; they are banned in venues where smoking is prohibited, regardless of whether or not they contain nicotine, and they may not be formulated with any flavors. Likewise, sale of smokeless tobacco products is prohibited.[4]

As the first country in the world to set the goal of ending the use of tobacco and other nicotine-containing products, Finland serves as a model for other countries seeking to take an aggressive approach to the elimination of products that are harmful to humans and cause addiction. Finland's multifaceted tobacco-control program should help to reduce tobacco-related disease and death.✦

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INTERVIEW WITH DARA CORRIGAN, JD*

FDA CORNER

United States to Implement Mutual Recognition Agreement with European Union

On March 2, 2017, the European Union (EU) and the US announced the Mutual Recognition Agreement to allow the FDA and the EU to accept one another's inspections of drug and pharmaceutical manufacturing facilities, a change intended to reduce duplicated effort with European inspectorates and to more efficiently monitor the global drug supply. Known as the 2017 Amended Sectoral Annex, this agreement grew out of the Mutual Reliance Initiative that launched in 2014 and allowed the FDA and EU to evaluate each other's drug inspection processes. Dara Corrigan, JD, the FDA's Acting Deputy Commissioner for Global Regulatory Operations and Policy described the purpose and potential impact of the Mutual Reliance for *IASLC Lung Cancer News* readers.

Dara Corrigan

Q: What need does the Mutual Reliance Initiative address?

A: Strengthening use of the FDA and EU drug inspection expertise and resources will result in greater efficiencies for both regulatory systems, and will provide a more practical means to oversee the large number of drug manufacturing facilities outside of the US and the EU. Until now, the EU and the FDA sometimes would, in the same year, inspect some of the same facilities, even when the facilities had a strong record of compliance. With the 2017 Amended Sectoral Annex, such duplication should be the exception. By utilizing each other's inspection reports and related information, the FDA and EU will be able to reallocate resources towards inspection of drug manufacturing facilities across the globe that have potentially higher public health risks.

The scope of the Amended Sectoral Annex covers a broad range of human drugs and biologics, as well as veterinary drugs, and does have specific exclusions. Current good manufacturing practices (GMPs) inspections of facilities that are manufacturing vaccines and plasma-derived products are not immediately included within the scope of the agreement. The possibility of including vaccines and plasma-derived products will be re-evaluated no later than July 15, 2022. Human blood, human plasma, human tissues and organs, and veterinary immunologics are not included within the scope of the Amended Sectoral Annex.

Q: How has the growth pattern of drug manufacturing affected the distribution of needed pharmaceutical agents?

A: The FDA inspects drug manufacturing facilities that make drugs for US consumers. Similarly, regulatory agencies in other nations inspect facilities that make drugs for their citizens. Currently, a large percentage of the FDA's foreign drug manufacturing facility inspections are conducted in the EU. Because the number of manufacturing facilities around the world is growing, the FDA uses a risk-based approach to focus inspection resources on those facilities with the highest potential risk.

This surging growth of foreign drug manufacturing facilities, particularly in China and India, has had ramifications for the FDA's approach to inspections of drug manufacturing facilities that are overseas. Within the current risk-based approach, the FDA has steadily increased foreign surveillance inspections overall. However, we can be more strategic and efficient in using our limited resources to manage this shift of drug facilities to foreign territories. One way of doing so is to identify partners with capable inspectorates so we can share the hard work of overseeing drug manufacturing for the global market, thus ensuring that our patients receive quality drugs that are safe and effective.

If the FDA is able to rely on inspections conducted by the EU regulatory agencies, then we can shift our drug inspection resources from the EU to other manufacturing locations and facilities and increase coverage of drug manufacturing facilities that pose a higher risk to US patients. This will allow the FDA to be better able to identify drug quality problems earlier and prevent poor-quality drugs from entering the US market.

Since 2012, an average of 41% of the FDA's inspections of foreign drug manufacturing facilities have been conducted in the EU, compared to 13% in China, 19% in India, and 27% in the rest of the world (excluding the US). Over 80% of drug ingredient manufacturers registered with the FDA are located outside of the US.

Q: What is the background to the Mutual Recognition Agreement?

A: The amended Sectoral Annex builds on the 1998 Agreement on Mutual Recognition between the European Community and the United States of America (U.S.-EU MRA), which included a Pharmaceutical Annex relating to GMP inspections. It benefits from the collaboration of the EU and the US in the past years through various pilot initiatives on GMP inspections.

In 2012, Congress passed the *Food and Drug Administration Safety and Innovation Act* (FDASIA). This law gave the FDA authority to enter into agreements to recognize inspections conducted by foreign regulatory authorities, if the FDA determines that these authorities are capable of conducting inspections that meet US requirements. This new law, combined with our previous experience, enabled us to successfully negotiate the amended Sectoral Annex.

The 2017 amended Sectoral Annex to the 1998 U.S.-EU MRA allows FDA and EU inspectorates to use inspection reports and other related information obtained during drug manufacturing facility inspections, whether conducted by an EU inspectorate or by the FDA, to help determine whether a facility is manufacturing high-quality drugs. Then, if necessary, the FDA or EU can require further inspections or take other action to protect the public.

Q: Why have previous efforts to reach this type of agreement failed and why did the present program succeed? Is this an accurate characterization?

A: The Pharmaceutical Annex of the U.S.-EU MRA was never fully implemented for various reasons, including lack of dedicated resources. There were outstanding information gaps regarding how the FDA and EU systems compared, and no clear path forward on how to implement the Annex.

Although the MRA was agreed between the US and the EU, the FDA will conduct an assessment of each EU country's regulatory authority individually. The FDA is currently assessing 5 regulatory authorities, and anticipates reaching a final decision on 8 EU regulatory authorities by November 1, 2017. The capability assessments of all EU countries' inspectorates are scheduled to be completed by July 15, 2019.

Q: What is the real or potential impact of the MRA on patient care?

A: This MRA will further enhance the FDA's ability to prioritize inspections of drug manufacturing facilities that may pose higher risks to public health. This prioritization will help the FDA to identify potential drug quality problems more quickly and prevent poor quality drugs from entering into the US market, thereby benefiting patients and reducing adverse public health outcomes.

Conclusion

Overseas pharmaceutical manufacturing presents a growing challenge to the FDA's capacity to monitor the quality and safety of imported drugs. The MRA represents a new strategy to find efficiencies in the inspection process so that more resources can be allocated to regions presenting greater risks. Although a first for the FDA, the EU already has MRAs in place with Australia, New Zealand, Japan, and Switzerland. Asked what the future holds now that the Pharmaceutical Sectoral Annex has been amended, Ms. Corrigan said that the FDA will implement the agreement and continue to work collaboratively with trusted regulators in non-EU nations to evaluate whether mutual recognition agreements will provide similar benefits to public health. ✦

**Erik T. MacLaren, PhD, is acknowledged for his editorial support of this article.*

MEETING HIGHLIGHTS

IASLC Small Cell Lung Cancer Workshop

By Kristina Wasson-Blader, PhD, ELS

From March 15 to 17, 2017, the International Association for the Study of Lung Cancer (IASLC) hosted the second Small Cell Lung Cancer Workshop at Memorial Sloan Kettering Cancer Center in New York, New York, which is held on an every-other-year basis. This focused meeting attracted more than 175 leading basic scientists and clinical investigators from around the world whose mission includes the treatment and eradication of small cell lung cancer (SCLC).

The most recent advances in SCLC research and clinical trials were discussed, including genomic studies on human tumors, the generation and analysis of novel models to study SCLC, the identification of biomarkers of cancer initiation and response to treatment, and the development of novel targeted therapies, including immunotherapies. Co-chair of the meeting, Julien Sage, PhD (Stanford University) indicated that "the main message was that the field is moving from a fairly 'homogeneous' view of SCLC to a recognition of genetic, histologic, and cellular heterogeneity." The other three co-chairs of the Workshop included Lauren Byers, MD (MD Anderson Cancer Center), Anna Farago, MD, PhD (Massachusetts General Hospital Cancer Center), and J.T. Poirier, PhD (Memorial Sloan-Kettering Cancer Center).

During this 3-day meeting, attendees listened to presentations grouped by topic into 9 separate sessions. Peter Ujhazy, MD, PhD (Translational Research Program, National Cancer Institute [NCI]) gave the opening talk on behalf of the NCI and discussed current NIH funding opportunities through the SCLC Consortium's U01 mechanisms. He also noted that Dr. Charles Rudin of MSKCC and others were recently awarded a U24 grant that will support their role as the Coordinating Center. SCLC pathology was also discussed on the first day. Dr. Julien Sage described a talk by Ignacio Wistuba, MD, (MD Anderson Cancer Center) as "one of the most thought-provoking because it raised the question of how small cell lung cancer initiates in the lungs of a patient. Small precursor lesions for SCLC are basically never seen in patients, and mouse models do not exactly recapitulate the lung microenvironment because SCLC patients are nearly always heavy smokers. Discussion of the possible existence of a cancer field effect for SCLC was of high interest."

On the second day of the meeting, six discrete sessions covered the topics of genomics and genetic models, developmental genetics and epigenetics, tumor heterogeneity, platforms for discovery, and targeted therapies. Paul Bunn, Jr, MD (University of Colorado) chaired the discussion of targeted therapies and summarized this session: "New targets in DNA repair pathways, cell cycle checkpoints, and stem cells all have the potential to be biomarkers for SCLC and may be useful in choosing therapy based on these targets as we get closer to providing patients with more personalized medicine. It is important to note that these targets are quite different than those found in lung adenocarcinomas."

The last day of the meeting included sessions on biomarkers, immunotherapy, and recent or ongoing clinical trials in SCLC. There were a number of new novel therapies covered (e.g., Rovapituzumab-tesirine [ROVA-T], PARP inhibitors, lubrenectidin, nano-lipo-irinotecan [nal-IRI] and others), for which there was considerable enthusiasm, based on the presentations. Suresh Ramalingam, MD, (Emory University School of Medicine) presented his work on PARP inhibitors. He noted that "Our work with PARP inhibitors has provided an important avenue to improve the efficacy of current treatment approaches."

In addition to targeted therapies, the meeting focused on new developments in immunotherapy for SCLC, including the recent addition of immunotherapy agents to the NCCN treatment guidelines for SCLC. "The activity of several immunotherapy agents in a subset of SCLC patients opens a new avenue for translational research in this field. Investigations into mechanisms of immune escape in SCLC, disease-specific biomarkers, and approaches to enhance clinical responses to immunotherapy represent important areas of opportunity," said Lauren Byers, Co-chair.

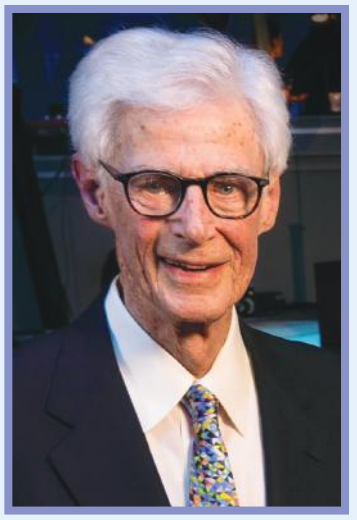
Reflecting on the meeting in general and the status of current research, Dr. Ramalingam added, "This is the second meeting fully dedicated to discussing research focused on SCLC. The topics spanned basic research to exciting novel approaches in the treatment of SCLC. The meeting left me with the hope that breakthroughs in the treatment of this lethal disease are imminent."✦

IN MEMORIAM

Charles M. LeMaistre (1924–2017)

Former MD Anderson President Dr. Charles A. LeMaistre Passes Away at 92

By Waun Ki Hong, MD



Charles A. LeMaistre, MD, past president of The University of Texas MD Anderson Cancer Center and a pioneer in cancer prevention and a strong advocate against tobacco use, passed away on January 28, 2017, in Houston at the age of 92. LeMaistre came to MD Anderson as President in 1978 after serving 7 years as Chancellor of The University of Texas System.

An Alabama native and graduate of the University of Alabama, Dr. LeMaistre earned his medical degree from Weil Cornell Medical College in 1947. After a medical residency at New York Hospital and an early career in infectious diseases at Cornell University, he left for Emory University in 1954, where he continued to work on infectious diseases and developed a particular interest in disease prevention. He helped set up a department of preventive medicine and served as its first chairman.

In 1959, LeMaistre left Emory University for The University of Texas Southwestern Medical School as a professor of internal medicine and went on to become associate dean and then Vice Chancellor for health affairs. In 1971, he was elected as Chancellor of The University of Texas System and directed a huge expansion of the UT system to include the creation of several medical schools in Houston and San Antonio, among others.

LeMaistre served as a young physician on the first US Surgeon General's Advisory Committee on Smoking and Health that, in 1964, issued its report identifying cigarettes as a major health hazard. In 1978, at age 54, he was named President of The University of Texas MD Anderson Cancer Center. During his 18-year tenure, MD Anderson became a world leader in outpatient care of cancer patients. He is credited for bringing a strong research focus to the center, and as volunteer and past president of the American Cancer Society, Dr. LeMaistre campaigned tirelessly for over 3 decades to disseminate information on the hazards of smoking.

One of the innovative programs he established at MDACC as President was the state-of-the-art comprehensive cancer prevention program, which is generally regarded as a role model worldwide.

LeMaistre retired in 1996, concluding a distinguished medical career after 18 years as President of MD Anderson Cancer Center.

In 2006, LeMaistre returned to MD Anderson part-time as a professor of behavioral science in the Division of Cancer Prevention and Population Sciences, which he founded years earlier. He spent the next 2 years writing about tobacco-related issues, including the evolution of public policies on tobacco control.

He was the recipient of many prestigious awards, including the President's Award from the American Lung Association and the Gibson D. Lewis Award for Excellence in Cancer Control as well as the Public Service and Humanitarian Award from the National Conference of Christians and Jews presented to him by the ACS. In 2015, LeMaistre was inducted into the Healthcare Hall of Fame. Dr. Ronald DePinho, the current President of MD Anderson, said, "Mickey LeMaistre was one of the great icons of 20th century medicine who pushed boundaries, drove innovation and positioned MD Anderson to be the world's most impactful cancer center." ✦

Note. *This article is an abridged version of Hong WK. Charles M. LeMaistre (1924–2017): former M. D. Anderson president Dr. Charles A. LeMaistre passes away at 92. J Thorac Oncol. 2017 Apr;12(4):597-598. Used with permission.*

ELCC 2017 from page 1

ELCC 2017 will convene medical oncologists, radiation oncologists, thoracic surgeons, respiratory physicians/pulmonologists, interventional radiologists, pathologists, and other medical professionals involved in the diagnosis, treatment, and follow-up of patients with lung cancer. Attendees will discuss multidisciplinary clinical practice, receive updates on how molecular biology and immunology are changing the tumor treatment landscape, and learn the latest advances in translational and clinical research in lung and other thoracic malignancies.

Keynote lectures will focus on "Genetic Profiling of Lung Cancer," "Molecular Clonal Development of Lung Cancer," and "The Implementation of Screening."

Other sessions will address:

- Staging and classification of lung cancer, including the new IASLC staging system
- ESMO recommendations for thoracic malignancies
- Immunotherapy: first-line treatment, biomarkers, and combination approaches
- Management of brain metastases
- Diagnosis and management of molecularly defined non-small cell lung cancer
- Small cell lung cancer and mesothelioma
- Rare thoracic malignancies
- Thymic tumors
- Management of dyspnea and cachexia
- Lung cancer presenting through the emergency room
- The role of the pathologist in guiding therapy
- Smoking prevention and cessation
- Screening and early detection
- Topics in chemotherapy and radiotherapy

In addition, the conference will feature poster presentations, best abstracts from ESMO-IASLC, and satellite symposia and exhibits supported by industry.

The educational programming has been submitted for accreditation through the Medical Oncologist's Recertification Approval program for medical oncologists to remain certified by ESMO as well as the European Accreditation Council for Continuing Medical Education (EACCME) for continuing medical education credits for medical specialists. Physicians may convert EACCME credits to an equivalent number of credits through the American Medical Association.

For more information and to register, visit ESMO.org/Conferences/ELCC-2017-Lung-Cancer or contact Pia Hirsch, IASLC, at pia.hirsch@iaslc.org. After the conference, webcasts of sessions will be available to IASLC and ESMO members. ✦

LUNG CANCER SCREENING

Speedbumps on the Road to Robust Low-Dose Computed Tomography Lung Cancer Screening National Implementation

By James L. Mulshine, MD, PhD and John K. Field, PhD, FRCPath

Recently a group of Veterans Health Administration (VHA) clinicians reported their experience in implementing low-dose computed tomography (CT) lung cancer screening at 8 VHA hospitals.[1] In this experience, 2,106 subjects were screened from July 2013 to June 30, 2015, which resulted in the diagnosis of 31 lung cancers (1.5%), but incurred considerable effort by the hospitals to implement the process. In a follow-up editorial, Drs. Redberg and O'Malley noted that the rate of incidental findings exceeded lung cancer diagnoses by 40 to 1.[2] Certainly these are interesting findings that merit more in-depth consideration.

The VHA experience started with an assessment of screening eligibility of 93,033 primary care patients, but smoking data were missing in 36,555 or 39.3% of the cohort. It is also notable that only 57% of the screening candidates offered participation agreed to join the study. In the VHA study, the Fleischer Society guidelines developed in 2005 to guide the work-up of symptom-detected lung cancer were used as a foundational tool to decide nodule management process. Based on that management approach, a false positive diagnosis rate of 26.6% was reported.[1] However, when the VHA authors reassessed their results using the more relevant screen-detected nodule management approach developed by the American College of Radiology, the false positivity rate was reduced to 12.8%.

The questions this experience raises are important and may reflect on issues beyond those related to the challenges of CT screening implementation. For example, why was the participation rate in the study so low? Were subjects concerned about the excessively high rate of false positivity that occurred as a result of not employing best screening practice? Did the informed decision-making tool reflect current realities about low-dose CT screening and relate how newer CT scanners required notably less medical radiation than the 4 detector scanners typically used in the National Lung Screening Trial? Consensus is now emerging that low-dose CT screening does not result in cumulative medical radiation doses that are predictably associated with measurable medical harms.[3]

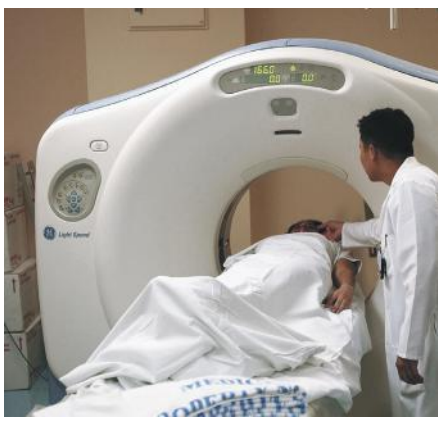
A growing number of screening studies, including ACR, I-ELCAP, NELSON, and the WellStar community program experience, have all reported markedly lower false positivity rates than the initial VHA finding.[4-6] Further, both the NELSON screening studies and the United Kingdom pilot CT screening trial not only documented very low rates of false positivity in the screening workup process, but also indicated that there was no significant persistence of distress from this screening process.[7,8]

Another common miscommunication about lung cancer screening that may be off-putting to potential screening subjects is the inappropriate conflation of the presence of lung nodules as being synonymous with the diagnosis of lung cancer.[2] Lung nodules are like colonic polyps as they are both age-related in frequency and generally benign; this observation should be conveyed as part of the informed decision-making discussion to avoid unduly distressing screening subjects.

Both the NELSON screening studies and the United Kingdom pilot CT screening trial not only documented very low rates of false positivity in the screening workup process, but also indicated that there was no significant persistence of distress from this screening process.

A further misconception about screening was communicated in the already-mentioned editorial by Redberg and O'Malley.[2] To designate other tobacco-related imaging findings identified in the thorax in the course of CT lung screening as "incidental findings" is an inaccurate characterization. There has been a considerable and rapidly growing literature involving thousands of screening subjects that documents both frequent and expected findings of radiologically significant but asymptomatic COPD as well as coronary calcification.[9-11] This situation is aligned with the long-established host response to the pleotrophic consequences of repeated tobacco combustion particulate exposure catalogued in the Surgeon General's multiple reports. A recent review highlighted the critical importance of finding frequent, asymptomatic COPD in the course of conducting lung cancer screening as a major opportunity to improve COPD outcomes.[12] A critical new finding in regard to COPD outcomes from a meta-analysis of 4 studies evaluating COPD mortality in a total of 88,767 participants found that cardiovascular patients on chronic statin therapy had a hazard ratio of 0.48 compared to COPD patients not on a statin.[13] This suggestion of potential benefit in patients taking statins relative to their COPD opens up a promising avenue of new drug intervention research to determine if individuals undergoing lung cancer screening but found to have asymptomatic COPD may benefit from receiving statin therapy for their COPD.

In conclusion, implementing screening is challenging, but many groups are now independently reporting high-quality, efficient lung cancer screening with good subject acceptance. Embedding best screening management practices in the process is critical to minimize harm while maximizing benefit. The Lung Cancer Alliance Framework for Screening Excellence provides an array of excellent resources to facilitate responsible screening implementation.[14] Lung cancer screening is also presenting new opportunities to find early asymptomatic COPD and coronary artery



diseases. Research is urgently needed to validate whether and how this approach can potentially extend the public health impact of CT screening to address other major tobacco-related, thoracic co-morbidities in the target screening population. ✦

James L. Mulshine

John K. Field

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MEETING HIGHLIGHTS

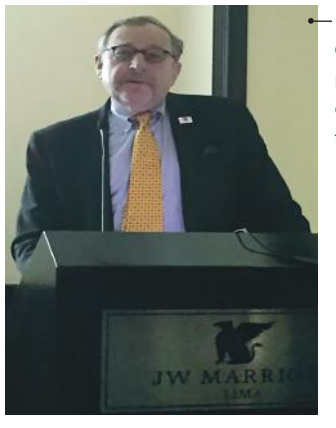
Best of the IASLC 17th World Conference on Lung Cancer in Lima, Peru, February 2017

By Luis E. Raez, MD

The International Association for the Study of Lung Cancer (IASLC) and the Peruvian Oncology Research Group (GECO) organized and hosted the "Best of the IASLC 17th World Conference on Lung Cancer (WCLC)" in Lima, Peru, on February 9–10, 2017. The conference was very successful; almost 200 doctors attended from several medical specialties, including medical oncology, surgery, pulmonology, and radiation oncology, among others. The meeting chairs were: Dr. Luis E. Raez from Memorial Cancer Institute (Florida, US) who is also Chairman of the IASLC Membership Committee, Dr. Luis A. Mass from the National Cancer Institute (Lima, Peru), and Dr. Denisse Bretel from GECO (Lima, Peru). We had the opportunity to have several IASLC speakers from the US: these included Drs. Fred R. Hirsch, Luis E. Raez, Edgardo Santos, Francisco Tarrazzi, and Ana Botero. We also had several other IASLC members from other countries speak: this included Drs. Carlos Vallejos (Peru), Ignacio Gil and Pilar Garrido (Spain), and Christian Rolfo (Belgium). They joined another 12 outstanding IASLC speakers from Peru.

The meeting featured a comprehensive review of lung cancer from epidemiology, tobacco control, and screening to the latest developments in diagnosis, surgery, and radiation, culminating in molecular diagnosis, immunotherapy, and targeted therapies. Many oncology fellows from several subspecialties attended. One of the major goals of WCLC meetings in Latin America is to motivate young oncologists training in these programs to join IASLC and the fight against lung cancer. IASLC has a well-established tradition of organizing successful meetings in Peru. In 2014, Drs. Raez and Vallejos organized the 6th Latin American Lung Cancer Conference (LALCA), the largest LALCA meeting ever conducted, with more than 750 doctors attending. This was followed by IASLC World Conference on Lung Cancer in 2016. We are looking forward to another successful meeting in Lima, Peru, in 2018. ✦

IASLC Speakers for the Best of World Conference of Lung Cancer in Lima, Peru, 2017. (From left to right: Drs. Mass, Rolfo, Hirsch, Bretel, Raez, and Vallejos)



Dr. Fred R. Hirsch, IASLC Chief Executive Officer, presenting the latest data on personalized therapy for lung cancer.

Dr. Luis E. Raez, IASLC Chairman of the Membership Committee, discussing immunotherapy developments.

E-cig Debate-Cummings from page 5

Kenneth Michael Cummings, PhD, MPH, is co-leader of the Tobacco Research Program at the Hollings Cancer Center, Medical University of South Carolina, US. A conflict of interest statement for Dr. Cummings is on file with the IASLC and available upon request.

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PATIENT CARE

Immunotherapy in Lung Cancer: How Can Nurses and Allied Health Teams Support Patient Care?

By Anne Fraser, Oncology Nurse Practitioner

Anne Fraser

Immunotherapy has changed the landscape of lung cancer treatment, offering hope to advanced lung cancer patients. Immunotherapy works by activating the patient's immune system, helping it to better fight and destroy the cancer cells. Cancer cells evade death from T cells by expressing PD-L1 (programmed death ligand 1), which then deactivates the T cell by binding to PD-1 on the surface of the T cell. Immunotherapies target PD-1 or PD-L1, preventing the tumor from suppressing T cells and allowing the T cells to kill the cancer cells (Figures 1 and 2).

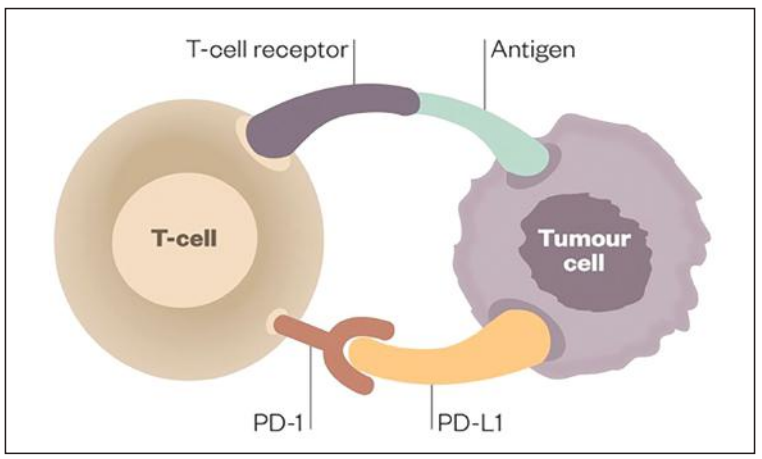

Figure 1. Tumor cells can evade the body's immune system by turning it off just as it begins to mount a response against them. However, scientists have discovered how to block this "immune checkpoint" and let the body continue its attack. Source. *The Pharmaceutical Journal*, 2014;293:7837/8. DOI: 10.1211/PJ.2014.20067127. Reprinted with permission.

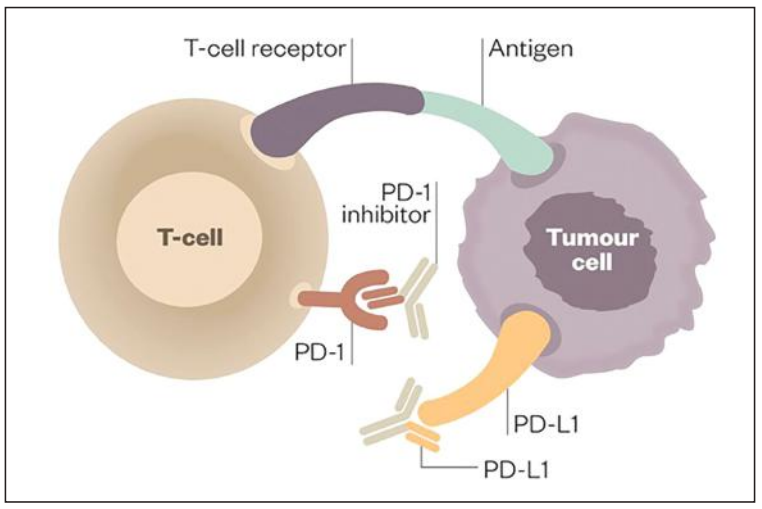

Figure 2. Deactivated T cell: When programmed death receptor (PD-1) on the T cell binds to programmed death ligand 1 (PD-L1) on the tumor cell, the T cell becomes deactivated, allowing the cancer cell to evade immune attack. Source. *The Pharmaceutical Journal*, 2014;293:7837/8. DOI: 10.1211/PJ.2014.20067127. Reprinted with permission.

Treatment with immunotherapies is not without risks, and patients may experience a wide range of side effects, including serious adverse events. Common patient-reported events include rash, fatigue, pruritus, diarrhea, arthralgia, nausea, vitiligo, asthenia, myalgia, headache, fever, decreased appetite, and cough. More serious immune-mediated adverse events include pneumonitis, endocrinopathies including hypothyroidism and hypophysitis, colitis, hepatitis, and nephritis. The key to managing such side effects of treatment is early recognition and close communication with the patient. Nurses and allied health staff play a key role in early intervention. Patients may require a break from therapy for many months and the use of high-dose steroids to manage Grade 2 or higher toxicities. In these situations, patients require close monitoring and support. Grading of toxicities should be done in conjunction with the NCI-CTCAE guidelines; the latest version can be found on this link: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

At the recent IASLC 17th World Conference on Lung Cancer, held in Vienna December 4-7, 2016, the Nurses and Allied Health (N&AH) Committee were kindly sponsored by IASLC to attend a workshop with the aim of developing clinical guidelines for the management of patients receiving immunotherapies (Figure 3). The group consisted of nurses from Australia, New Zealand, the United States, the United Kingdom, Hong Kong, and Denmark. Each regional group had completed work on clinical management prior to arriving in Vienna, and this was presented to the wider group for further discussion and consultation. There were lively debates as regional management proved to vary in some cases. One of the aims was to produce a guideline that would be useful in all clinical settings—for those countries with limited clinical resources and for those clinicians who do not have the support of a wider oncology team. This led to thoughtful discussion about clinical resourcing for lung cancer patients worldwide, with a particular focus on the lack of skilled nurses and the lack of utilization of allied health staff in the clinical setting. The N&AH Committee of IASLC intends to publish and disseminate these guidelines in 2017. ✦

Figure 3. IASLC Nurses and Allied Health Professionals Committee at WCLC workshop, with the aim of developing clinical guidelines for the management of patients receiving immunotherapies.

E-cig Debate-Stone from page 4

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BREAKING NEWS BRIEFS

- The global, randomized phase III ALEX study was announced to have met its primary endpoint, demonstrating that alectinib (Alecensa), as an initial (first-line) treatment, significantly reduced the risk of disease worsening or death (progression-free survival) compared to crizotinib in people with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). This is the second phase III trial to show the efficacy of alectinib as an initial treatment in this type of lung cancer. The safety profile of alectinib was consistent with that observed in previous studies, with no new or unexpected adverse events. (4/10/17)

- Afatinib (Giotrif) was granted marketing authorization by the European Commission for the treatment of patients with advanced squamous cell carcinoma (SqCC) of the lung whose disease has progressed on or after treatment with platinum-based chemotherapy. Afatinib is already approved for the treatment of patients with EGFR mutation-positive NSCLC. (04/07/17)

- Dabrafenib (Tafinlar) in combination with trametinib (Mekinist) was approved by the European Commission for the treatment of patients with BRAF V600-positive advanced or metastatic NSCLC. The approval marks the first targeted treatment approved for the patient population in the 28 member states of the European Union (EU), plus Iceland and Norway. (04/03/17)

- Osimertinib (Tagrisso) was granted full approval by the FDA for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive NSCLC whose disease has progressed on or after an EGFR tyrosine kinase inhibitor (TKI) therapy. Osimertinib is the first and only approved medicine in the US indicated for NSCLC patients who have tested positive for the EGFR T790M mutation. (03/31/17)

- Osimertinib was also approved by the China Food and Drug Administration (CFDA) as a second-line treatment for EGFR T790M mutation-positive metastatic NSCLC. Lung cancer is the leading cause of cancer-related deaths in China and approximately 30% to 40% of Asian patients with NSCLC have the EGFR mutation at diagnosis. (03/27/17)

- Ceritinib (Zykadia) was granted a Priority Review from the FDA for expanded use as a first-line treatment for patients with metastatic NSCLC whose tumors are anaplastic lymphoma kinase (ALK)-positive (ALK+). The FDA also granted Breakthrough Therapy designation to ceritinib for the first-line treatment of patients with ALK+ metastatic NSCLC with metastases to the brain. (02/23/17)

- Alectinib (Alecensa) was granted conditional marketing authorization by the European Commission as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced NSCLC previously treated with crizotinib. (02/21/17)

NCI CORNER

NCI Formulary Holds Promise to Speed Clinical Trials

By Erik T. MacLaren, PhD

On January 11, the National Cancer Institute (NCI) launched a virtual agent formulary (NCI Formulary): a new public-private partnership designed to speed access to targeted therapies and combinations of cancer-fighting drugs by oncology researchers at the 69 NCI-Designated Cancer Centers. *IASLC Lung Cancer News* discussed the details of the NCI Formulary with Sherry Ansher, PhD, Associate Chief of the Regulatory Affairs Branch, Cancer Therapy Evaluation Program, and Jason Cristofaro, JD, PhD, Intellectual Property Program Manager, Office of the Director, from the Division of Cancer Treatment and Diagnosis, NCI.

Negotiating agreements between individual investigators and drug companies to use proprietary therapeutic agents is complex and can take up to 18 months, which often delays the start of important pre-clinical and clinical trials. The NCI expects that such delays will become even more common, due to increased genetic testing as a standard part of cancer therapy as well as the greater use of targeted agents. The NCI Formulary was designed to mitigate such delays and to contribute to the goals of the Cancer Moonshot by increasing collaboration and speeding the development of new treatments.

"Many of these agents are not generally available for clinical studies that are not sponsored by the company or are only available to investigators after lengthy negotiations with the investigators' institutions," said Dr. Cristofaro. "The NCI Formulary eliminates the need for investigators to negotiate agreements independently, making the agents available for use."

In trials testing Formulary agents for unapproved purposes, an Investigational New Drug Application (IND) may be required, according to Dr. Ansher, who explained that this "…is a decision made by the FDA upon submission of the protocol/IND and is based on the patient population, dose and schedule of the agent, and potential of increased risk." Should an IND be required, it would be sponsored by the receiving investigator, he added, saying, "Industry partners have agreed to provide letters of cross-reference in support of approved studies."

At its launch, the NCI Formulary had Clinical Cooperative Research and Development Agreements (CRADAs) with 6 pharmaceutical companies that covered the use of 16 targeted drugs, and more are expected soon. Dr. Cristofaro noted that this response exceeded the NCI's original goal of 5 collaborators and 10 agents and that the number of agents is expected to double during the first year of the NCI Formulary.

Although the Formulary is open to trials in all cancer types, many of the agents available are known or suspected to be effective for treating thoracic cancers (agent list available at http://nciformulary.cancer.gov/available_agents/default.htm). Additionally, Dr. Ansher hoped that this new partnership would be especially helpful to investigators who want to test new combinations of targeted therapies manufactured by different companies and requiring multiple agreements, a problem neatly solved by the Formulary.

Participation in the NCI Formulary is open to NCI-registered investigators from NCI-Designated Cancer Center sites in good standing. However, agents from the Formulary may be tested in combination with other Formulary agents or marketed agents only; combinations with investigational agents from other sources are not permitted. Detailed information about the NCI Formulary can be found online.[1]

The NCI Formulary complements another planned public-private partnership in oncology called the Partnership to Accelerate Cancer Therapies (PACT), in which the National Institutes of Health and the FDA will work with foundations, advocacy organizations, and private sector biopharmaceutical groups to identify and validate biomarkers for use with cancer therapies.[2] PACT is expected to launch later in 2017. ✦

1. NCI Formulary website available at http://nciformulary.cancer.gov/.
2. New Drug Formulary Will Help Expedite Use of Agents in Clinical Trials. NCI Press Release. January 11, 2017. Available at http://www.cancer.gov/news-events/press-releases/2017/nci-formulary-launch.

PROFESSIONAL DEVELOPMENT

IASLC International Mentorship Program Boosts Early Careers, Fosters International Collaboration

By Keightley Amen, BA, ELS

To help ensure that high-quality thoracic oncology care is available throughout the world and well into the future, the IASLC offers an International Mentorship Program to support early-career physicians and researchers from economically developing countries. The competitive program provides each winner with a full scholarship to the IASLC 17th World Conference on Lung Cancer (WCLC), it matches each mentee with a well-established scientific or clinical mentor, and it arranges a weeklong visit at the mentor's institution, including coverage of all expenses.

Since the program's inception in 2013 with one mentee, 44 young thoracic specialists from 18 countries have participated. The program helps awardees develop their careers, learn new skills and treatments, experience an established department in action, and establish collaborative relationships—then bring the new information and ideas back to their home institutions.

Previous awardees lauded the opportunity to learn from experts about a wide array of topics, including immunotherapy, molecular testing, pathology, rare patient cases, subspecialization, imaging, personalized medicine, and the importance of multidisciplinary teamwork; many mentees also gleaned precious advice on their own specific areas of research and practice.

In a recent anonymous survey, one respondent described the meaningful impact of coming from an area that has little oncology infrastructure to see how an established program runs: "I have just started my new career as the first medical oncologist in my hometown. Everything in my hospital is new. When I went to my mentor's institution, I got lots of ideas to improve my oncology unit and team. I saw strong oncology teams, the importance of networking, the system of cancer research, and I saw what experts do in practice. All of these experiences make me really want to make something better."

IASLC's international perspective was a key to the program's success: "It is really interesting to see the way things are done elsewhere in the world. The US standard of care is not the same as the European standard or the Mexican standard. Now I realize how lucky I am to have the view from different parts of the world."

In a personal letter to IASLC, one participant marveled at how much knowledge could be fit into a short time. Chunxia Su, from Shanghai Pulmonary Hospital and Tongji University School of Medicine in China, met with a mentor throughout the 17th WCLC in Vienna, then was immersed at the mentor's institution in London, United Kingdom. "My schedule was quite full and busy. I received training lectures, participated in clinic with my mentor, attended lung cancer multidisciplinary meetings, as well as one-on-one meetings with my mentor. I also attended meetings in London on lung cancer prevention. There were patient review meetings, journal club and research meetings. My head was buzzing. This was a great opportunity to learn from my mentor and other outstanding lung cancer oncologists, and the process started on the very first day."

The two shared meals and walked many miles among the famous landmarks of London, all while discussing oncology, how to design a successful clinical trial, the most vital details related to inclusion and exclusion criteria, how to give interesting and informative lectures, and how to write high-quality papers, Su said.

Mentors and mentees responding to the survey reflected on the long-term effects the program would have after the return trip home:

> Said a mentee: "Winning the IASLC mentorship award will impact my career. … My mentor and I are planning to establish collaboration both in basic and clinical research. … We will get in touch with each other and look for potential collaborations in the future."

A program mentor echoed the hope for future collaboration: "It was my pleasure to be a mentor for the IASLC program and to host an intelligent and warm-hearted mentee who proved to be a very skilled pathologist and researcher. I have much enjoyed our discussions on difficult pathology cases, molecular pathology, and lung cancer research, and I believe the two weeks together formed a base for future collaborations and friendship."

Participants and IASLC believe the program will affect not only individual careers, but the entire field. "Interaction with the scholars enriches you with newer thoughts and ideas for future collaborative research in thoracic oncology," answered one mentee. "I sincerely believe that such kind of collaborative research is necessary for eradication of lung cancer."

➲ For further information about IASLC International Mentorship Program, email Pia Hirsch, IASLC pia.hirsch@iaslc.org. ✦

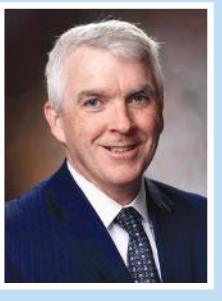
Participants in the IASLC Mentorship Program, Vienna 2016.

Names and News

Vinicius Ernani, MD, has been appointed Assistant Professor at the Fred and Pamela Buffett Cancer Center of the University of Nebraska, Omaha, NE. Previous to this appointment, Dr. Ernani completed a hematology/oncology fellowship at Emory University, Atlanta, US.

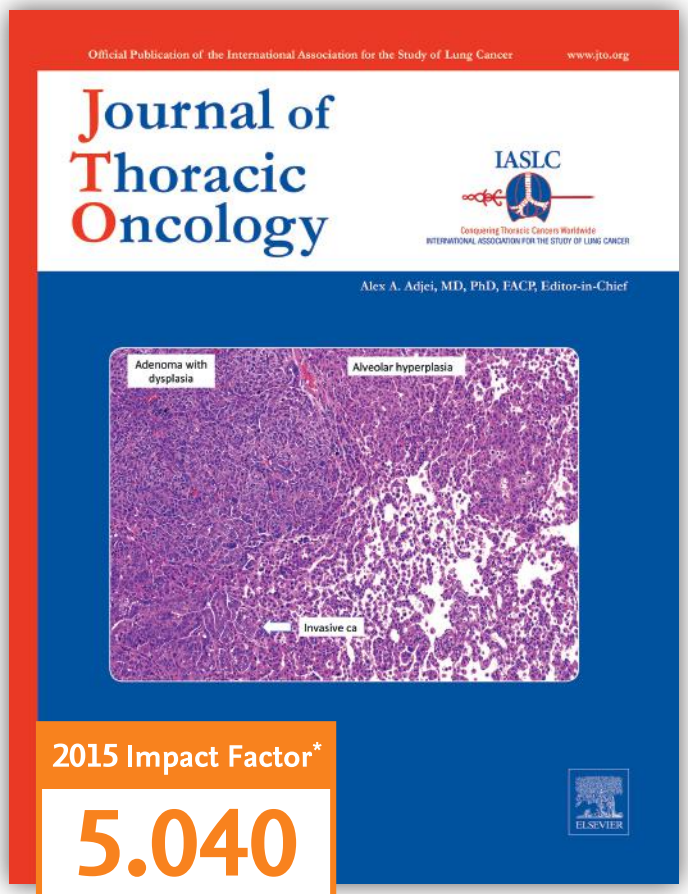
Shirish M. Gadgeel, MD, has been appointed Professor, Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan as of May 1, where he will be Leader of the Thoracic Oncology Research Program. Dr. Gadgeel will hold the Mary Lou Kennedy Research Professorship in Thoracic Oncology. Previous to this appointment, Dr. Gadgeel was Professor and Leader of the Multidisciplinary Thoracic Oncology Team at the Karmanos Cancer Institute/Wayne State University.

Mary Hesdorffer, RN, Nurse Practitioner, will retire as Executive Director of the Mesothelioma Applied Research Foundation (Meso Foundation) in July 2017. Prior to being Executive Director, Ms. Hesdorffer held several roles with the Mesothelioma Foundation since its inception and following her retirement will continue in an advisory role. She also will also continued to serve on a number of IASLC committees and Mesothelioma Taskforce.



Thomas J. Lynch Jr, MD, was appointed executive vice president and chief scientific officer of Bristol-Myers Squibb. Previous to this appointment, Dr. Lynch served as chairman and chief executive officer of Massachusetts General Physicians Organization and as a member of the MGH Board. Prior to that Dr. Lynch was the director of Yale Cancer Center and was the Richard and Jonathan Sackler Professor of Internal Medicine at the Yale School of Medicine.

Journal of Thoracic Oncology



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