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

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Bronchial Carcinoid Tumors: Diagnosis and Management

By Zoran Lesic, MD and Laurie L. Carr, MD

Carcinoid tumors are rare neuroendocrine tumors that arise from enterochromaffin cells found throughout the gastrointestinal and bronchopulmonary systems.[1] Carcinoids are predominantly found in the gastrointestinal tract, most commonly in the small intestine, but the lung is the second most common site of disease. Bronchopulmonary carcinoid tumors comprise 0.5 to 2% of all lung cancers.[2] The diagnosis is made histologically, based on positive immunohistochemical staining with neuroendocrine markers, such as chromogranin A or CD56 (neural cell adhesion molecule).[3]

Diagnosis

Proliferation of bronchial neuroendocrine cells can be divided into several categories according to WHO criteria (***Table 1***).[1] The spectrum of disease ranges from relatively indolent, well-differentiated neuroendocrine cell hyperplasia to aggressive, often metastatic carcinomas that include large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung cancer (SCLC). Neuroendocrine cell hyperplasia confined to the bronchial epithelium can arise in response to chronic pulmonary diseases such as bronchietasis.[4] Recently, neuroendocrine cell hyperplasia without underlying chronic lung disease has been identified and labeled as diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH).[5] In DIPNECH, the cellular hyperplasia is associated with obstructive lung disease, often with fibrosis of the involved airways. DIPNECH is thought, though not proven, to be a pre-neoplastic condition, as these cells often break through the basement membrane and begin to form carcinoid tumorlets (carcinoid tumors <5 mm in size) or carcinoid tumors. It is common for entities on this spectrum of disease to be seen together, as peripheral carcinoid tumors are often associated with areas of hyperplasia or carcinoid tumorlets, suggesting progression. In a retrospective study of bronchial carcinoid tumors resected at a large cancer center, 28 of 294 resection

In this issue

Bronchial Carcinoid Tumors: Diagnosis and Management

continued from page 1

Table 1. Characteristics of bronchial neuroendocrine tumors

	Neuroendocrine Cell Hyperplasia and Tumorlets	Typical Carcinoid	Atypical Carcinoid	Large-Cell Neuroendocrine Carcinoma	Small-Cell Lung Carcinoma
Mitosis*	<2	<2	2-10	>11 (usually up to 70-80)	
Necrosis	Absent	Absent	Present	Present (more extensive than atypical carcinoid)	
Other Features	Includes diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH)		More commonly peripheral	Morphology more closely resembles large cell carcinoma than a carcinoid tumor	Displays histologic heterogeneity with other types of lung carcinoma (e.g., squamous cell carcinoma)
		Readily diagnosed with light microscopy No histologic heterogeneity			
Smoking History	Frequently found in non-smokers	Found in only 60-80% of patients with a smoking history		Virtually all patients have significant smoking history	

** Mitotic counts per 2 mm² of viable tumor (10 high-power fields)[7]*

samples were found to contain multiple carcinoid tumors or tumorlets.[6] Overall, these patients had a good prognosis, with several having persistent but stable disease.

Bronchopulmonary carcinoid tumors are further divided according to their morphologic appearance into typical carcinoid (TC) (low-grade neuroendocrine carcinoma) and atypical carcinoid (AC) (intermediate-grade neuroendocrine carcinoma). Compared to TCs, AC tumors are more commonly found in patients ≥50 years old and are typically located in peripheral lung fields.[7] An initial diagnosis based on small tissue samples or cytology can frequently lead to misdiagnosis of AC. Final classification should be made only after careful review of pathologic specimens from surgical resection.

Little is known about the genetic changes that underlie the tumorigenesis of bronchial carcinoids. Chromosome 11q losses are the predominant change in TCs and ACs, although other alterations have been detected less frequently.[8,9] Small-cell lung cancer and LCNEC display different patterns, including losses in 13q. These losses of genetic material may be related to differences in progenitor cells, or varying types of carcinogen exposure, such as cigarette smoke.

Although the majority of bronchial carcinoid tumors are not associated with paraneoplastic syndromes, these tumors can produce various hormones and neuropeptides. These may cause carcinoid syndrome, with classic symptoms of diarrhea, flushing, and bronchoconstriction, Cushing syndrome through ectopic ACTH production, and acromegaly.[10,11]

Bronchial carcinoids are predominantly located centrally in the lung and often have an endobronchial component. Carcinoid tumors can be visualized easily on CT scans, and because of their increased vascularity, they often demonstrate contrast enhancement.[1] They usually appear as well-defined nodules and are frequently calcified.[12] Cavitation, irregular margins, and pleural effusions are rarely seen in association with carcinoid tumors.

Few studies have examined the value of fluorodeoxyglucose positron emission tomography (FDG-PET) in the diagnosis and staging of bronchial carcinoids. A single-site, retrospective study demonstrated FDG-PET specificity of 75% in carcinoids that presented as a solitary pulmonary nodule.[13] Additional small studies of FDG-PET consistently demonstrated that TCs fail to show significant uptake on FDG-PET.[14] Available evidence does not support the use of FDG-PET to evaluate

Bronchial Carcinoid Tumors: Diagnosis and Management

continued from page 2

lymph node involvement or distant metastatic disease. Because FDG-PET scans can be misinterpreted and lead to confusion about the diagnosis and staging of bronchial carcinoid tumors, their routine use is not recommended at the time of diagnosis. Novel radiotracers that are more specific to neuroendocrine cell metabolism, such as ^{18}F- DOPA, are being developed to improve PET imaging for this disease.[15]

Because over 80% of bronchial carcinoids have surface somatostatin receptors, radiolabeled octreotide, a somatostatin analog, has been used in nuclear medicine imaging (somatostatin receptor scintigraphy, or octreoscan) to detect metastatic disease.[16] However, because patients with bronchial carcinoid tumors rarely have metastatic disease, the routine use of octreoscans is not recommended unless metastatic disease is suspected. In the setting of metastatic disease, an octreoscan may also help determine if therapy with somatostatin analogs will be effective.[17] Studies have demonstrated that CT and MRI are more sensitive than octreoscan for identification of metastatic lesions, and often a combination of imaging modalities is needed to fully evaluate metastatic carcinoid tumors.[18]

Management

The majority of bronchial carcinoids are fairly indolent, and they are most often treated with complete surgical resection. However, some bronchial carcinoids are relatively more aggressive and require additional therapy. Characteristics associated with more aggressive bronchial carcinoids include features of AC (high mitotic rate, necrosis), the presence of lymph node metastases, and multifocal lesions at the time of diagnosis. All of these features are associated with unfavorable outcomes.[19]

Retrospective case analyses have consistently shown a higher recurrence rate and worse overall survival for AC compared with TC (***Table 2***).[21,22] Recently, certain prognostic markers, such as Ki-67 (a cellular marker of proliferation), gastrin-releasing peptide, and low expression of CD44 (a cell-surface protein involved in cell-cell interactions) were associated with poor outcomes.[20] These markers are not currently used on a widespread basis. Although the prognosis for TCs is better than for ACs, TCs may recur following surgical resection. Most TCs recur within 10 years after surgery. Prolonged follow-up is therefore recommended for both TCs and ACs.[19]

Table 2. Lymph node involvement and prognosis of bronchial carcinoid tumors

Author	Year	Number of Patients	Lymph Node Involvement (%)		5 Year Survival (%)		10 Year Survival (%)	
			TC	AC	TC	AC	TC	AC
Travis et al.[21]	1998	113	NA		87	56	87	35
Soga et al.[23]	1999	1875	NA		93	69	82	59
Ferguson et al.[24]	2000	139	8	30	NA		NA	
Thomas et al.[25]	2001	34	100%*				95	54
Cardillo et al.[26]	2004	163	12	64	N0: 100 N1: 90 N2: NA	N0:100 N1: 79 N2: 22	NA	
Kyriss et al.[27]	2006	111	27	21	94	82	92	62
Garcia-Yuste et al.[28]	2007	661			N0: 97 N1-2: 100	N0: 78 N1-2: 60	NA	
Rugge et al.[20]	2008	67	5	50	NA		NA	

**Only subjects with lymph node involvement were analyzed. TC: typical carcinoid. AC: atypical carcinoid. NA: not available.*

Bronchial Carcinoid Tumors: Diagnosis and Management

continued from page 3

Recent studies demonstrate that systematic nodal dissection at the time of initial diagnosis may potentially reduce the risk of recurrence, and surgical removal of any lymph node metastases is recommended.[29] It is clear that patients with AC and mediastinal lymph node (N2) involvement have high recurrence rates and poor overall survival with surgical resection alone.[26] This finding raises the question of the role of adjuvant therapy, particularly in this high-risk group. Although no formal randomized studies have evaluated the efficacy of adjuvant therapy in bronchial carcinoid tumors, there have been case reports that adjuvant radiation decreases local recurrence in patients with AC with and mediastinal lymph node metastases.[30] Because of these findings, the National Comprehensive Cancer Network guidelines recommend that adjuvant chemotherapy, with or without radiation, be considered for patients with AC with nodal involvement.[31] In this setting, adjuvant chemotherapy known to be active in SCLC (e.g., cisplatin, etoposide, doxorubicin) is recommended.

While surgical resection alone has been associated with good outcomes in bronchial carcinoids, distant metastatic disease develops in a minority of patients. Because advanced disease is rare, there are no randomized studies of standard chemotherapy for treating advanced bronchial carcinoid tumors. Often, cytotoxic chemotherapeutics active in SCLC are used to treat advanced bronchial carcinoid tumors. In patients with advanced disease complicated by carcinoid syndrome or with positive octreoscans, somatostatin analogs, such as octreotide, have been shown to improve symptoms and slow progression.[32,33] For patients with a small number of metastases in the liver (the most common site of metastatic disease), liver-directed therapies, such as chemoembolization or ablative therapy, may be possible options.

Recently, a stage III randomized study of advanced carcinoid tumors (gastrointestinal and bronchial) compared therapy with everolimus, an oral inhibitor of the mammalian target of rapamycin (mTOR), given with placebo or octreotide long-acting release (LAR).[34] Previous studies had shown that overactivity of the mTOR pathway, which is involved in cellular growth, proliferation and metabolism, was common in neuroendocrine tumors. Of 429 subjects studied with low- or intermediate-grade neuroendocrine tumors (carcinoid) and metastatic disease, 44 had primary lung carcinoid tumors. Regardless of the primary site of the carcinoid, patients who received combination therapy with everolimus and octreotide LAR had longer progression-free survival. In the everolimus plus octreotide LAR group, the median progression-free survival was 16.4 months (95% CI, 13.7-21.2 months) vs. 11.3 months (85% CI, 8.4-14.6 months) for the placebo plus octreotide LAR group. The most common drug-related adverse events were stomatitis, rash, and diarrhea. Among those treated with everolimus, 8% developed pneumonitis leading to drug discontinuation in 2% (4 patients). An assessment of overall survival was confounded by crossover of patients from the placebo arm to everolimus upon disease progression.

In summary, bronchial carcinoid tumors are generally indolent tumors with an excellent prognosis following surgical resection. Tumors with necrosis and/or high mitotic count (AC) are less common, but they carry a higher risk of disease recurrence and are associated with worse overall survival. Patients with AC tumors and mediastinal lymph node involvement should be considered for adjuvant therapy with radiation and chemotherapy. Metastatic disease treatment options include liver-directed local therapy, cytotoxic chemotherapy, somatostatin analogs, and more recently, the mTOR inhibitor everolimus.

Disclosures

Drs. Carr and Lesic submitted ICMJE Disclosure Forms to ***Lung Cancer Frontiers***. No significant conflicts of interest exist with any companies or organizations whose products or services are discussed in this article.

Bronchial Carcinoid Tumors: Diagnosis and Management

continued from page 4

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Selections from the Peer-Reviewed Literature

By Ali I. Musani, MD, FACP, FCCP

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Simultaneous isolation of total RNA, DNA, and protein using samples obtained by EBUS-TBNA

Nakajima T, Anayama T, Koike T, Waddell T, Keshavjee S, Kimura H, Yoshino I, Yasufuku K. *J Bronchology Interv Pulmonol* 2011; 18:301-5.

BACKGROUND: Samples obtained by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) have been shown to be useful for molecular analysis.

METHODS: The purpose of this study was to evaluate the feasibility of simultaneous isolation of DNA, RNA, and protein using EBUS-TBNA samples. We extracted DNA, RNA, and protein from 59 archived samples obtained by EBUS-TBNA. All samples were mixed with DNA, RNA, and protein-protective solution immediately after taking the biopsy and stored in –80°C for at least 1 year (range, 12 to 30 mo). We used QIAzol Lysis Reagent for the sequential isolation of total RNA, DNA, and protein. The concentration of RNA and DNA was measured and the quality of RNA was evaluated. The concentration of protein was measured using the Bradford protein assay.

RESULTS: Total RNA was successfully isolated in all 59 samples. DNA was isolated in 58 of 59 (98.3%) samples and protein was isolated in 57 of 59 (96.6%) samples. On average, 7.18 µg of total RNA, 7.79 µg of DNA, and 3.96 mg of protein were isolated. RNA integrity number (RIN) was measured in 32 samples and the average RIN number was 6.2 (range, 2.7 to 7.3). Twenty of 32 total RNA samples (62.5%) showed a RIN of >6.

CONCLUSIONS: DNA, RNA, and protein can simultaneously be isolated from archived samples obtained by EBUS-TBNA. This method facilitates direct comparisons of alterations in the genome, transcriptome, and proteome within metastatic lymph nodes through a minimally invasive approach.

EDITORIAL COMMENT: Over the last five to seven years, EBUS-TBNA has been shown to be superior in yield, cost effectiveness, and efficiency to mediastinoscopy and other surgical procedures for the diagnosis and staging of lung cancer. Debates about its efficiency and cost-effectiveness were largely settled just a few years after its introduction.

Recently, multiple studies, including this one, demonstrated that EBUS-TBNA has the potential to provide tissue not only for histopathological diagnosis, but also for genetic profiling of lung cancer. Nakajima et al. report success isolating high-quality RNA and DNA that could potentially allow RNA- or DNA-based molecular testing for certain oncogenes, including endothelial growth factor receptor (*EGFR*), Kirsten rat sarcoma (*KRAS*), and likely anaplastic lymphoma kinase (*ALK*) mutations in the future.

For this initial feasibility study, samples were collected and stored in RNA/DNA/protein extraction media. Although the specimens were not processed to detect molecular changes, enough DNA was recovered to analyze. However, DNA and RNA were extracted from the entire specimen that contains both malignant and non-malignant cells. The relative proportion of malignant cells was not determined. Consequently, the amount of normal vs. tumor DNA

Selections from the Peer-Reviewed Literature

continued from page 6

was not known. The proportion of malignant cells in the sample is critical because during mutation analysis, both mutant and wild-type DNA will be identified. Enough DNA that contains the mutation of interest must be present to be detected over the background of the wild-type gene. This study raises two important questions. First, can these results be duplicated using standard processing of formalin-fixed, paraffin-embedded specimens? Second, what are the characteristics of the optimal sample for molecular analysis? Is the number of cells, number of nuclei, number of malignant cells, proportion of malignant to normal cells, or some other factor strongly associated with accurate molecular testing results?

EBUS-TBNA is rapidly gaining wide acceptance. This study shows that proper technique and adequate sampling by EBUS-TBNA can easily be learned and adopted by general pulmonologists and thoracic surgeons alike as a minimally invasive diagnostic, staging and molecular profiling modality.

Molecular profiling allows for targeted chemotherapy with improved tolerance, decreased toxicity and better prognosis. Further discoveries of more genetic variations and more specific therapies will undoubtedly change the way we treat lung cancer.

Electromagnetic navigation bronchoscopy (ENB): Increasing diagnostic yield

Lamprecht B, Porsch P, Wegleitner B, Strasser G, Kaiser B, Studnicka M. *Respir Med* 2012; 106:710-5.

OBJECTIVES: To determine factors associated with diagnostic yield of ENB.

METHODS: In 112 consecutive patients referred to our department between March 2010 and December 2010 the diagnostic work-up for solitary pulmonary lesions included a FDG-PET-CT scan, and ENB in combination with ROSE. The final diagnosis was confirmed by histopathological evaluation of specimen obtained either by ENB, or, if ENB was not diagnostic, by CT-guided fine needle aspiration or surgery.

RESULTS: Thirty-seven (33%) subjects were female, mean age was 66.7 (±1.04) years. The mean diameter of lesions was 27 mm (range: 6-46 mm). In 83.9% the combination of PET-CT, ENB, and ROSE established a correct diagnosis, as defined by the definite histopathological result. 15.2% (17/112) of lesions were benign, and 84.8% (95/112) were malignant. For 112 procedures we observed a steep learning curve with a diagnostic yield of 80% and 87.5% for the first 30 and last 30 procedures, respectively. The diagnostic yield in lesions ≤20mm and >20mm in diameter was 75.6% and 89.6% (p=0.06), respectively. No significant difference in diagnostic yield was seen depending on lung function, and the localization of the lesions. Two cases (1.8%) of pneumothorax were seen during and up to 24h after bronchoscopy, none of them required a chest tube.

CONCLUSION: Diagnostic yield increased with experience but was independent from the size of the lesion, the localization in the lungs, and lung function. The diagnostic yield of ENB can be as high as for CT-guided transthoracic biopsies but carries a significantly lower complication rate.

EDITORIAL COMMENT: The diagnostic approach to pulmonary nodules has gained renewed interest in recent years due to an ever-intensifying focus on lung cancer screening. The National Lung Cancer Screening trial (*N Engl J Med* 2011; 365:395-409) showed a 20% relative reduction in lung cancer mortality in high-risk patients screened with low-dose computed tomography of the chest. Such trials and the increasing use of chest CTs are expected to result in a several-fold increase in the number of pulmonary nodules detected. Currently, more than 150,000 patients present to their physicians with solitary pulmonary nodules every year in the U.S. (*Chest* 2003; 123:89-96S). The demand for nodule biopsies to rule out lung cancer will certainly grow.

Modalities for lung nodule biopsy that are now available include CT- or fluoroscopically-guided transthoracic needle aspiration (TTNA), transbronchial biopsy (TBBX) via the bronchoscope, and surgical biopsy. Of the two non-surgical modalities, TTNA is only practical for peripheral lesions and carries a substantial risk of pneumothorax. Transbronchial biopsy, on the other hand, has traditionally resulted in a very poor diagnostic rate for multiple reasons, including inaccurate localization on two-dimensional fluoroscopy and three-dimensional body CT, as well as the inability of biopsy instruments to reach lesions in the outer third of the lungs. CT-guided transbronchial biopsy has fallen out of favor for several reasons, including very high radiation exposure for

Selections from the Peer-Reviewed Literature

continued from page 7

patients, logistical problems associated with performing CT imaging and bronchoscopy in the same room, and poor three-dimensional accuracy.

Novel navigation technologies that enable electromagnetic and real-time guidance during bronchoscopy have significantly improved the yield of TBBX. The technology discussed in this study is Super Dimension.™ This modality uses a high-resolution CT of the chest to construct a virtual map of the patient's airways with patented software. Once the user selects the target, the software finds the easiest path to the target using air columns in the airways. This modality has been rapidly adopted in many centers and has shown great promise.

In this study from Austria, the authors evaluated 112 patients with pulmonary nodules of varying size and location. The study was a prospective, observational trial. In all cases in which navigation-guided TBBX did not result in a diagnosis, TTNA or surgical biopsy was performed. The authors noted very high diagnostic yields for navigation-guided TTBX: 75.6% for nodules ≤2 cm in size, and 89.6% for nodules >2 cm. These yields are greater than those reported in most previous studies. The authors admit that there was a steep learning curve, and that they observed a significant improvement in the yield with practice.

This study adds to a growing literature supporting the use of navigation-guided bronchoscopy for the efficient and minimally invasive work up of pulmonary nodules.

The utility of interventional pulmonary procedures in liberating patients with malignancy-associated central airway obstruction from mechanical ventilation

Boyd M, Rubio E. *Lung* May 30, 2012 [Epub ahead of print].

PURPOSE: Utilization of intensive care services by patients with malignancy has risen during the past several decades. Newer cancer therapies have improved overall survival and outcomes. Patients with respiratory failure from central airway obstruction related to tumor growth were previously viewed as inappropriate candidates for ventilator support. However, an increasing number of reports suggest that interventional pulmonary (IP) procedures may benefit such patients.

METHODS: We reviewed the literature for case reports or case series from the past 20 years regarding the use of IP procedures for the treatment of respiratory failure from malignancy-associated central airway obstruction.

RESULTS: As a whole, IP procedures were greater than 60% successful in liberating patients from mechanical ventilation. Moreover, IP procedures served to palliate respiratory symptoms, prolong overall survival, allow for additional cancer treatments, and reduce hospitalization costs. Nevertheless, it remains unclear who may benefit the most from these procedures.

CONCLUSIONS: Although data are limited, IP procedures are generally safe and should be considered for appropriate patients with respiratory failure from malignancy-associated central airway obstruction as a potential means of liberation from mechanical ventilation.

EDITORIAL COMMENT: Patients with large, central, obstructing malignant lesions are considered to be in the terminal stages of illness because the vast majority of these patients have advanced disease. Hence, they are considered poor surgical candidates. When they develop respiratory failure related to the obstruction itself, or to post-obstructive pneumonia leading to sepsis and atelectasis, they are thrown into an even worse prognostic category. These patients may end up on a ventilator where they usually succumb to complications of central airway obstruction.

Approximately 10 years ago, IP focused primarily on recanalizing airways obstructed by malignant and, less commonly, benign masses. Flexible and rigid bronchoscopic procedures, in concert with laser, electrocautery and other ablative modalities, were the cornerstone of the IP approach. Metallic self-expandable stents and silicone stents were also used sparingly, when indicated. Many patients were relieved of their airway obstruction, allowing better pulmonary toilet for post-obstructive pneumonia, successful treatment of sepsis, and improved ventilation. This often led to liberation of these patients from the ventilator and discharge from the hospital for chemotherapy, radiation and even surgery.

In spite of this limited success, the utility of IP procedures for these patients was often questioned. However, many of the

Selections from the Peer-Reviewed Literature

continued from page 8

obstructing cancers were newly diagnosed and many of these patients had not received any therapy. Liberating these patients from the ventilator in order to receive definitive treatment meant a fair shot at cancer therapy and extended life -- months to years of life in many cases. Prognosis is, of course, a relative term. Does three or four months of hospital-free life with friends and family constitute a good or a bad prognosis?

In this paper, Boyd et al. reviewed 12 studies published between 1991 and 2011 identified in a Medline search. They reviewed reports of 323 patients with central airway obstruction, 112 of whom underwent IP procedures for central airway obstruction that had caused respiratory failure and ventilator dependence. The review included patients from 12 centers and bronchoscopists with different levels of experience using varying ablative modalities. The modalities included neodymium:yttrium-aluminum garnet laser, electrocautery, argon plasma coagulation and rigid bronchoscopic debulking. Despite all these variables, the majority (71 of 112; 63.4%) of patients with malignancy-related central airway obstruction were successfully liberated from the ventilator. One important point to notice is that these procedures did not just provide palliation, as we all were led to believe in the past, but they also improved survival and quality of life, and decreased intensive care unit and hospital stays. Obviously, there is a potential selection bias in these reports that come from selected centers with a high level of IP expertise. In addition, it is likely that cases in which IP was felt to be beneficial would be more likely to be reported in the literature.

With the rapid growth of IP and an increasing number of interventions for central airway obstruction available for patients both on and off the ventilator, randomized controlled studies are needed to evaluate improvements in survival, quality of life, and other parameters of performance. Further studies are also needed to help physicians and surgeons improve patient selection and the timing of IP interventions, and to optimize cost-effectiveness.

Disclosures

Dr. Musani reported to ***Lung Cancer Frontiers*** that he has received a research grant from Aeris Medical. He has served on speakers bureaus for superDimension, Carefusion, Olympus, Covidien, Boston Scientific, and Intuitive Surgical. With National Jewish Health, he holds a patent for a tracheal stent anchor and an instrument holding device for bronchoscopy equipment. He has received royalties for bronchoscopy forceps from Boehringer Ingelheim and travel support from Olympus, Boehringer Ingelheim, Carefusion and Intuitive Surgical.

Lung Cancer Meetings and Symposia

5th Asia Pacific Lung Cancer Conference

November 26-28, 2012
Fukuoka, Japan
Information: aplcc2012.org

European Multidisciplinary Conference in Thoracic Oncology

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

15th World Conference on Lung Cancer

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

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