Abstract
This 3-part Lung Cancer Supplement highlights progress in the management of lung cancer on the one hand, while reminding us of established challenges on the other. Ming-Sound Tsao, MD, FRCPC, sets the scene with a review of how molecular characterization has become the standard of care in non-small cell lung cancer. The molecular classification of solid tumours has been a recurring theme in the vision of personalized medicine in oncology. While estrogen and progesterone receptor analysis has been a basic part of breast cancer management for 3 decades, it is only recently that we have seen this paradigm achieve a sound basis in other tumours. Having lung cancer lead the way in this approach is simultaneously gratifying and surprising. In a succinct review of paraneoplastic neurologic syndromes, Nafisha Lalani, MD, and Anthony Brade, MD, FRCPC, shift the focus to small cell lung cancer. Again we are reminded that while progress is made on one front, much remains to be learned about other aspects of the illnesses — the interaction between malignancy and the immune system being one key area. Dale Dirkse, BA (Hons), and Janine Giese-Davis, PhD, address the issue of shame and guilt in lung cancer. They remind us of how these nebulous, easily dismissed clinical concepts have very specific, mainly negative, consequences for our patients.

Keywords
lung cancer, pulmonary cancer, small cell lung cancer, pathology, molecular biology, paraneoplastic syndromes, distress, stigma, shame, guilt
LUNG CANCER PATHOLOGY
Changing paradigm and priorities

Ming-Sound Tsao, MD, FRCPC

ABSTRACT
The last decade has witnessed the dramatic coming of age of targeted therapy in lung cancer. Several new targeted drugs have been approved but only for use in a subgroup of patients whose tumours harbour the genetic/molecular aberrations targeted by these drugs. In addition, several drugs are used only in lung cancer patients with specific histologic subtypes, as the latter may define efficacy or risk of toxicity. These recent developments have required pathologists to provide a more precise diagnosis of the tumour type, as well as additional molecular data on the presence or absence of the targetable molecular aberrations. Thus, pathology practice is not just diagnostic for cancer, but has to provide information on predictive biomarkers to guide drug selection. As more and more drugs and treatment options will be based on the molecular characteristics of the tumour, pathology practice must also embrace and adopt the new advances being achieved in molecular medicine and targeted therapy. The ability to meet the challenges presented by the changing paradigm in cancer treatment will define the future role of pathologists and pathology departments.

INTRODUCTION
Lung cancer is the leading cause of cancer-related death worldwide among males, and the second leading cause among females. In 2008, it accounted for 13% (1.6 million) of all cancer deaths worldwide. Despite recent data showing decreasing incidence in developing countries and notable advancements in its early detection and treatment, lung cancer is still projected to be the sixth leading cause of death in 2030, advancing from the ninth position in 2002. In North America and Canada, the mortality rate of lung cancer is greater than the next 3 most common cancers combined: colorectal, breast and prostate cancer. Currently as many as half of new lung cancer patients are former smokers who had quit for more than 10 years. This is due to significant lag time between carcinogenic initiation and development of invasive cancers, such that the benefits of smoking cessation take approximately 20 years to realize. Importantly, lung cancers of never-smokers demonstrate distinct clinical features and associations when compared to those of smokers, accounting for at least 20% of lung cancer cases worldwide and being more common among females. Thus, lung cancer will remain a major health burden worldwide for many years to come.

Currently, the overall 5-year survival rate for all lung cancer patients is approximately 15%. This poor overall rate reflects largely the fact that around two-thirds of patients are initially diagnosed with advanced stage disease with very little possibility of cure by surgery. The treatment of lung cancer patients is based primarily on the histologic diagnosis of the tumour and the stage of the disease. Two major histologic types with different biology and therapeutic responses are recognized: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC is a highly aggressive cancer with almost all patients presenting with advanced loco-regional or systemic metastases at diagnosis. Therefore, SCLC patients are rarely treated by surgery but mainly by chemotherapy, to which it is highly sensitive. Yet, despite the high initial response rate, very few SCLC patients are curable and their median survival time is approximately 18 months.

In contrast, NSCLC is a very heterogeneous disease with approximately 80–85% being represented by adenocarcinoma (ADC) and squamous cell carcinoma (SCC). Importantly, about one-third of NSCLC patients present with tumours that are still localized to the lung or immediate local lymph nodes, and thus can potentially be cured by complete surgical resection.
However, even for patients who are initially treated by surgery, there is a 30–60% risk of death from tumour recurrence. Clinical trials conducted in North America, Europe and Japan during the last 2 decades have demonstrated that for a subgroup of patients, especially Stage II patients, adjuvant chemotherapy is effective in significantly increasing survival. Currently, there is an intensive effort to identify additional molecular biomarkers that could further stratify patients at high risk of developing postsurgical metastatic recurrences, and thus who are most likely to benefit from adjuvant chemotherapy. Equally important is to identify patients who have inherently good-prognostic tumours, are at low risk for developing metastasis, and thus could be spared from the toxicity of adjuvant chemotherapy.

RECENT DEVELOPMENTS IN LUNG CANCER PATHOLOGY

For advanced NSCLC patients, the last 5–6 years have witnessed the availability of several novel drugs, some having been developed to target molecules/pathways that are crucial for the growth and survival of cancer cells. Most importantly, these targeted therapies have demonstrated safety or effectiveness in specific subgroups of patients, thus requiring selection of patients suitable for the use of these agents (Table 1). The fact that these therapy-related biomarkers include both tumour histologic typing and molecular aberrations highlights the importance of greater precision in histologic classification of the tumours, and the necessity of acquiring and preserving tissues for molecular testing to be performed after the initial histology-based diagnosis and classification. Furthermore, new efforts or strategies need to be developed for ensuring that minimal biopsy materials (e.g. from fine needle aspiration biopsy) are processed such that sufficient material would be available not only for the diagnosis of malignancy, but also for biomarker testing.

Consistent with this concept, a recently published report developed by multidisciplinary experts representing the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS) provided some “good pathology practice” guidelines on diagnostic pathways for the handling and diagnosis of small or minimal biopsy specimens, including the panel of immunohistochemical (IHC) markers that are recommended for more accurate histologic typing of lung carcinomas. An algorithm for determining the type of specimens that should be subjected to molecular testing has also been proposed, as certain tumour types appear to demonstrate greater association with specific molecular aberrations.

ROLE OF PATHOLOGISTS IN THE AGE OF PERSONALIZED MEDICINE

With the new developments described above, pathology has assumed even greater responsibilities in the diagnostic and therapeutic pathways of patient care. Aside from its traditional role in diagnostic pathology to identify and classify cancer and/or cancer cells based on histology and cytology, pathologic reports also need to include predictive pathology elements that are essential for selecting specific treatments for the patients. Importantly, such responsibility goes beyond deciding what markers to assay for or molecular tests to perform, and also includes many aspects of good laboratory practice and scientific knowledge associated with the performance of these tests. These include ensuring that: 1) adequate specimens are obtained during the biopsy procedure for both diagnostic and “predictive” molecular

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment setting</th>
<th>Patient cohort</th>
<th>Selection marker</th>
</tr>
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<tbody>
<tr>
<td>Gefitinib/erlotinib</td>
<td>first line</td>
<td>ADC</td>
<td>EGFR mutation*</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>≥ second line or maintenance</td>
<td>NSCLC</td>
<td>none</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>first line with chemotherapy</td>
<td>NSCLC</td>
<td>none (potentially EGFR protein level by IHC)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>first line with chemotherapy</td>
<td>non-squamous NSCLC</td>
<td>non-squamous histology</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>all</td>
<td>NSCLC</td>
<td>non-squamous histology</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>all</td>
<td>NSCLC (ADC)</td>
<td>rearranged ALK gene</td>
</tr>
</tbody>
</table>

ADC=adenocarcinoma; ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; IHC=immunohistochemistry; NSCLC=non-small cell lung carcinoma

*Improvement in progression-free survival
testing; 2) samples are appropriately processed such that molecular assays will not be compromised; 3) appropriate samples (e.g. paraffin block) with sufficient tumour cellularity are selected for molecular testing; 4) the areas of the tumour with greatest tumour cellularity are identified and chosen for molecular testing (e.g. sequencing or fluorescent in situ hybridization [FISH] analyses; and 5) molecular test results are integrated and correlated with the histopathologic diagnoses.

As genetic aberrations may occur in specific tumour types and tissue may be limited to perform multiple independent tests, the histologic evaluation may be used to streamline ordering of molecular tests, in order to conserve tissue and shorten the time for reporting the diagnostic results. As an example, mutations on the epidermal growth factor receptor (EGFR) gene are known to occur predominantly in ADC (~40–60% among East Asians and 15–20% among Caucasian lung cancer patients) and have been found much less frequently (2–4%) in SCC. Thus, for economic and practical reasons, EGFR testing is commonly limited to non-squamous NSCLC or ADC samples only. However, ADC is a highly heterogeneous tumour with multiple differentiation lineages. It is known that ~80% of lung ADC also stain positive for the nuclear marker thyroid transcription factor 1 (TTF-1), while SCC very rarely stains for TTF-1. Furthermore, mucinous ADC is mostly TTF-1 negative and is associated more commonly with the presence of v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation.\textsuperscript{10,13}

It is also known that, except in very rare cases, the occurrence of EGFR and KRAS mutations are mutually exclusive. Therefore, while current practice tends to use histology (non-squamous) as the first criterion for ordering EGFR mutation testing, emerging evidence suggests that perhaps TTF-1 positivity could potentially be a better selection marker for testing.\textsuperscript{14}

While TTF-1 is an IHC test that is routinely and extensively used in histopathology practice at relatively low cost, DNA sequence analysis used in EGFR mutation testing takes more time to complete and costs at least ten times more. Pending further confirmation of the low frequency of EGFR mutation being present in TTF-1 negative tumours, the adoption of TTF-1 as a selection marker could potentially reduce EGFR mutation testing volume by 20–30%. A similar algorithm could potentially be applied to the testing of anaplastic cell lymphoma kinase (ALK) gene rearrangement, as this genetic aberration has been reported to have a high association with a specific but rare histologic type of ADC with "signet ring" appearing tumour cells.\textsuperscript{15,16} Therefore, by integrating histopathology into a molecular-marker testing algorithm, pathologists have the opportunity to develop diagnostic algorithms that could make molecular testing more cost-effective, resulting in shortened turnaround times and increased efficiency for the molecular testing laboratory.

**CHALLENGES FOR PATHOLOGISTS AND PATHOLOGY DEPARTMENTS**

In the current era of greater societal expectation for better and more effective healthcare in the face of limited healthcare budgets and continuing increases in the costs of laboratory procedures and tests, pathologists face significant challenges to deliver their professional mandate. This means not only greater precision in their diagnoses but also greater information content necessary for the delivery of personalized medicine. Pathology reports will require molecular information about the tumour that is necessary for oncologists to tailor treatment with the most effective and/or best tolerated therapies. As the amount of biopsy tissues may be limited, especially in advanced cancer patients, strategic institu-

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**Table 2. Histochemical/immunohistochemical markers useful for more precise classification of NSCLC without definitive histologic evidence of differentiation\textsuperscript{7,8}**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Tumour type</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td>Mucin</td>
<td>ADC</td>
<td>23%</td>
<td>100%</td>
</tr>
<tr>
<td>TTF-1</td>
<td>ADC</td>
<td>54.84%</td>
<td>97.100%</td>
</tr>
<tr>
<td>P63</td>
<td>SCC</td>
<td>92.100%</td>
<td>68.74%</td>
</tr>
<tr>
<td>CK5/6</td>
<td>SCC</td>
<td>84.98%</td>
<td>79.82%</td>
</tr>
</tbody>
</table>

ACC=adenocarcinoma; CK=cytokeratin; SCC=squamous cell carcinoma, TTF=thyroid transcription factor

\textsuperscript{7}Mentioned in Table 2. Histochemical/immunohistochemical markers useful for more precise classification of NSCLC without definitive histologic evidence of differentiation.\textsuperscript{7,8}
tional protocols with multidisciplinary inputs should be developed to prioritize the marker studies that are required for the initial accurate diagnosis, to ensure tumour samples are available for necessary molecular testing, and conserve samples for future tests that may as yet be identified and developed.

The field of molecular oncology, targeted therapy and predictive biomarkers is rapidly evolving. Every year we are witnessing reports on positive clinical trials involving new targeted therapies in patients whose tumours harbour specific molecular aberrations. The responsibility for the development and rapid clinical implementation of assays for these predictive markers falls within the professional responsibilities of pathologists, who increasingly need to keep abreast of new advances in the molecular pathology of cancers, especially those relevant to novel therapeutics being tested in clinical trials. This requires greater participation of pathologists in multidisciplinary rounds that allow them to interact closely with their clinical oncologist colleagues. Working closely with interventional radiologist colleagues to obtain adequate first biopsy specimens may also spare patients the need for repeat biopsies, thus reducing morbidity and cost, and at the same time shortening the time for treating physicians to obtain all diagnostic information necessary to make treatment decisions. Last but not least, pathologists should continue to strive to make their diagnostic algorithm more efficient and cost-effective by exploiting the association between specific histomorphologic and IHC features of tumours with molecular markers, as discussed above.

COSTS OF MOLECULAR DIAGNOSTICS AND PREDICTIVE PATHOLOGY
Current histopathology and cytopathology involve routine dye-based staining as well as IHC. The low material cost and high throughput of these techniques render their unit cost relatively low. When it comes to molecular assays such as mutation analysis by polymerase chain reaction (PCR) and sequencing or by FISH, the cost of the reagents and low throughput may make each test appear to be “expensive” (in the hundreds of dollars per test). As more and more markers become available, development of multiplex testing will be required due to the limited amount of biopsy materials available for testing. However, it is important to note that predictive marker testing tends to be a one-time cost, as the molecular marker relevant for treatment is either present or absent in the tumour. This is in contrast to imaging studies or blood tests, which tend to be performed multiple times during the course of patient treatment or care to track clinical progression.

The real cost of a test to a healthcare system should be measured based on the frequency of positive test results. For each EGFR mutation-positive patient identified, the overall cost of testing would be approximately 5 times the unit cost of the test, as only ~15–20% of non-squamous NSCLC patients tested would be positive. For targeted drugs with lower target prevalence, e.g. ALK gene rearrangement that is reported in only ~5% of lung ADC patients, the effective cost of the test by FISH would be substantially higher, at 20 times the unit cost. Fortunately, antibodies specific to mutant EGFR or fusion (aberrant) ALK proteins have been developed.17,18 Once their sensitivity and specificity have been determined and validated, their application in routine histopathology laboratory may further streamline the molecular testing algorithm.

PERSONAL PERSPECTIVE AND CONCLUDING REMARKS
Pathology has traditionally been the medical science discipline that focuses on recognizing pathologic changes occurring in diseases and on understanding the mechanism of disease development. Pathologists have been accustomed to adopting new technologies to enhance their diagnostic accuracy, such as electron microscopy and IHC. However, pathologists are currently facing a new challenge in continuing this traditional role in the age of molecular medicine, targeted therapy and personalized medicine. To meet these challenges, pathologists must continue to equip themselves with new knowledge and expertise in molecular biology and pathology, their clinical impacts, and technologies to detect and measure clinically relevant molecular changes. The challenge is unprecedented, as in all areas the
advances are very rapid and exponential. More resources need to be devoted to continuing education for the pathology community on advances in targeted therapies and biomarkers, which may enhance the accuracy of their histologic or cytologic diagnoses and provide critical information for patient treatment. In the conflicting world of less tissue for greater information, pathologists need to develop protocols for processing biopsy samples and ordering tests, with clear priorities to provide the most diagnostic content, lowest turnaround time and greatest cost-effectiveness. Rapid advances in functional imaging and nanotechnologies will further accelerate the development of new methods for diagnosis using minimal or noninvasive approaches. While morphologic diagnoses currently remain, in most instances, the accepted “gold standard,” this may shift as one day the accuracy and reliability of these new technologies may potentially supersede the relative subjectivity of microscopic morphologic assessment. As pathologists and laboratory physicians have the unique responsibility to issue diagnostic test results for clinical use, the ability of pathologists to continue their mandate rests with their ability to adapt, prioritize and adopt the rapid advances that are occurring in the field of molecular medicine.

REFERENCES

Acknowledgement
The author wishes to thank Dr. David H. Hwang for valuable input and editorial assistance.

Disclosure
The author reports no conflicts of interest pertaining to this article.
SMALL CELL LUNG CANCER
Paraneoplastic neurologic syndromes

Nafisha Lalani, MD; Anthony Brade, MD, FRCPC

ABSTRACT
Paraneoplastic neurologic syndromes (PNS) are a rare manifestation of cancer, are thought to be the result of immune responses and have been associated with the presence of onconeural antibodies. “Classical” PNS are those with well-documented associations to onconeural antibodies. The majority of patients diagnosed with PNS initially present with a neurologic complaint, with subsequent evaluation leading to a diagnosis of lung cancer. A high level of suspicion is required for the appropriate diagnosis and management of the underlying malignancy. To date, a paucity of knowledge regarding PNS may lead to delayed diagnosis with a subsequent impact on prognosis. This review will provide a discussion of the prevalence, clinical presentation, diagnostic assessment and management considerations for patients with PNS in small cell lung cancer (SCLC).

INTRODUCTION
PNS are a rare group of conditions affecting less than 1 out of every 10,000 patients diagnosed with cancer.1 SCLC is the most common malignancy associated with PNS.2 PNS occur as a result of neoplastic mechanisms that are not related to the tumour, metastatic disease, infections, ischemia or metabolites. These syndromes are thought to occur due to immunologic mechanisms. A number of studies have confirmed the presence of onconeural antibodies in patients with PNS and suggest that the neurologic manifestations stem from an antibody-induced inflammatory reaction.3 The neurologic presentation varies depending on the site of the lesion. PNS can affect one or multiple regions of the nervous system, resulting in a variety of clinical manifestations.4 A number of classical PNS found in SCLC have known associations with particular antibodies (Table 1). These associations may have prognostic importance. For example, the presence of anti-Hu antibodies in SCLC has been shown to be a predictor of treatment response; patients who are positive for the antibodies show longer survival.3

PRESENTATION AND DIAGNOSIS
The majority of patients diagnosed with PNS initially present with a neurologic complaint, with subsequent evaluation leading to a diagnosis of malignant disease.5 Due to the rarity of PNS, a delay in diagnosis of the primary malignancy is not uncommon and may lead to poor outcomes. Any patient presenting with a neurologic complaint should undergo investigation, starting with a thorough history and physical examination to determine the etiology of the deficit, first ruling out nonmalignant etiologies. In the event of an unexplained neurologic abnormality and the presence of risk factors for malignancy, the diagnosis of PNS should be further investigated.

A definite diagnosis of PNS requires one of the following criteria:4
1. A classical syndrome and a documented malignancy within 5 years of the onset of the syndrome
2. A nonclassical syndrome that (a) shows some resolution after treatment for a known malignancy, or (b) is present within 5 years of a cancer diagnosis and a presence of onconeural antibodies
3. Any neurologic syndrome in the presence of well-characterized onconeural antibodies, regardless of a cancer diagnosis

When a clinical abnormality leads to the suspicion of PNS, an initial screen should be performed to identify the presence of onconeural antibodies. Early screening used immunohistochemistry techniques to identify known patterns. This also required immunoblotting with recombinant proteins to confirm their specificities. In recent years, serum testing has been developed as an effective tool to
identify onconeural antibodies in the blood. Because many PNS are related to a number of antibodies, it is recommended to screen the serum using a panel of common onconeural antigens. Well-characterized antibodies may provide the most reliable, evidence-based, diagnostic information since they have:

1. Recognizable patterns on routine immunohistochemistry (using earlier detection methods);
2. Well-characterized neurologic syndromes associated with the antibodies;
3. Reproducible validation within the literature;
4. A lower frequency of these antibodies in patients without cancer.

Currently, well-characterized antibodies include anti-Hu, Yo, CRMP5/CV2, Ri, Ma2 and amphiphysin. Commercial immunoblots containing panels of the corresponding onconeural antigens are now readily available.

Table 1: Major paraneoplastic neurologic syndromes and antibodies associated with small cell lung cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical presentation</th>
<th>Associated antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraneoplastic encephalomyelitis</td>
<td>Epileptic seizures or epilepsy partialis continua, extrapyramidal symptoms, sensory neuropathy and autonomic dysfunction, often presenting as gastrointestinal dysmotility</td>
<td>Hu, CRMP5*, PCA2, Amphiphysin*</td>
</tr>
<tr>
<td>Limbic encephalitis</td>
<td>Epileptic seizures, depression, personality changes and cognitive dysfunction</td>
<td>Hu, CRMP5*, ANNA-3*, VGKC*</td>
</tr>
<tr>
<td>Brainstem encephalitis</td>
<td>Gaze palsy, diplopia, reduced consciousness and central sleep apnea</td>
<td>Hu, Mo2*</td>
</tr>
<tr>
<td>Extrapyramidal syndromes</td>
<td>Extrapyramidal features such as chorea, ballistic movements and dystonia</td>
<td>Hu, CRMP5*</td>
</tr>
<tr>
<td>Paraneoplastic cerebellar degeneration</td>
<td>Severe pancerebellar involvement, with ataxia of the limbs and trunk, dysarthria, dysphagia and nystagmus</td>
<td>CRMP5*, Hu, Zic4, ANNA-3*</td>
</tr>
<tr>
<td>Paraneoplastic opsoclonus-myoclonus</td>
<td>Multidirectional saccades</td>
<td>Hu</td>
</tr>
<tr>
<td>Visual syndromes</td>
<td>Progressive retinopathy, usually bilateral</td>
<td>Recoverin CRMP5</td>
</tr>
<tr>
<td>Sensorimotor peripheral neuropathy</td>
<td>Mixed axonal and demyelinating sensorimotor neuropathy, optic neuritis, cerebellar dysfunction and extrapyramidal symptoms</td>
<td>Hu, Amphiphysin CRMP5*</td>
</tr>
<tr>
<td>Subacute sensory neuropathy</td>
<td>Paresthesia, hypoesthesia, proprioceptive loss and sensory ataxia; usually asymmetrical upper limb involvement</td>
<td>Hu, Amphiphysin ANNA-3*, CRMP5*</td>
</tr>
<tr>
<td>Paraneoplastic peripheral nerve hyperexcitability</td>
<td>Spontaneous and continuous twitching and painful cramps; often accompanied by various combinations of stiffness, pseudomyotony, pseudotetany and weakness</td>
<td>VGKC*</td>
</tr>
<tr>
<td>Lambert–Eaton myasthenic syndrome</td>
<td>Proximal muscle weakness and generalized fatigue, with a sparing of the ocular and bulbar muscles; autonomic dysfunction, often presenting as dry mouth</td>
<td>VGCC</td>
</tr>
</tbody>
</table>

ANNA-3=antineuronal nuclear autoantibody type 3; CRMP5=collapsin response mediator protein 5; PCA-2=Purkinje cell antibody; VGCC=voltage-gated calcium channel; VGKC=voltage-gated potassium channel

*Antibodies may be associated with other malignancies in addition to SCLC.
available, which allows for easy serum analysis. As the immune response is made in proximity to the tumour, antibodies are at highest concentration in the serum, rather than the central nervous system. The presence of onconeural antibodies can then guide further diagnostic evaluation aimed at locating the primary malignancy. Computed tomography (CT) and positron-emission tomography (PET) can be recommended to aid in the detection of the primary tumour as well as providing information on extent of disease. Sensitivity of CT-thorax has been estimated in the range of 80–85% for the detection of SCLC in PNS. In the event that a tumour is identified but is of a different type than what would be expected, it is recommended to continue investigations in the case of a second malignancy. It should be noted that onconeural antibodies are not always present in PNS, while conversely, they have been detected in patients with neurologic complaints in the absence of malignancies. Because of this, the presence or absence of antibodies in a patient with a classical PNS should not dissuade the clinician from investigating for malignancy.

MULTIDISCIPLINARY MANAGEMENT

Once a diagnosis of PNS is made, strong interdisciplinary communication is required to ensure adequate care of patients. A multidisciplinary care plan should be created with cooperation between the medical oncologist, radiation oncologist, thoracic surgeon (if required) and neurologist. Early detection offers the greatest advantage to the patient, as the primary malignancy may have a more favourable prognosis. The associated neurologic deficits may also be more manageable with earlier intervention.

The management of PNS has 3 main components: treatment of the underlying malignancy, treatment of the PNS and long-term followup. Treatment of the underlying malignancy comprises the mainstay of management in PNS. This may remove autoantibody activity and improve PNS symptoms. For example, 30% of patients with paraneoplastic limbic encephalitis showed some symptom resolution with treatment of the SCLC. Treatment of the PNS may also include immune therapy and symptomatic treatment. Immune therapy consists of steroids, plasma exchange or intravenous immunoglobulin. These therapies may be of benefit to certain subgroups of patients with PNS, including those with Lambert-Eaton myasthenic syndrome and paraneoplastic peripheral nerve hyperexcitability and pediatric patients with paraneoplastic opsoclonus-myoclonus. In patients with other PNS, a clear benefit of immune therapy has not yet been shown. All patients should also be considered for other symptomatic treatment to improve quality of life, including cognitive and/or physical rehabilitation.

A delay in the diagnosis of PNS is a common occurrence due to the vague nature of the presenting symptoms and the often unusual constellation of neurologic findings. Early identification and the use of diagnostic and management algorithms may lead to an improved prognosis in this patient population. Multimodality therapy is required to promote continuous symptomatic improvement throughout the treatment of the primary tumour/metastases and PNS.

REFERENCES


Disclosure
Drs. Lalani and Brade have no disclosures/conflicts of interest to declare pertaining to this article.
SHAME AND GUILT IN LUNG CANCER
The stigma of lung cancer

Dale Dirkse, BA (Hons); Janine Giese-Davis, PhD

ABSTRACT
Lung cancer patients report higher levels of distress than patients in all other cancer groups. The stigma of lung cancer’s association with smoking, recognized by the public and healthcare professionals alike, contributes to patients’ feelings of shame and guilt, and in turn, their illness burden. Only a limited number of studies examine shame and guilt in lung cancer patients. This article summarizes literature investigating whether patients’ shame, guilt and experience of social stigma perpetuate their distress. Research could make possible a deeper understanding of the effects of shame and guilt in the journey for lung cancer patients, as well as lead to effective interventions.

INTRODUCTION
Lung cancer patients report the highest burden of distress of all cancer groups.\(^1\)\(^-\)\(^7\) Despite evidence that interventions may improve quality, and possibly quantity of life,\(^8\)\(^-\)\(^11\) they access healthcare professionals for help less often than other cancer groups.\(^12\)\(^-\)\(^14\) Experiencing distress at diagnosis may be normal since lung cancer patients have a poor prognosis,\(^7\) and receive their diagnosis at an advanced stage.\(^15\) However, newly diagnosed patients report more psychosocial than physical concerns, and these concerns remain throughout their cancer journey.\(^16\) This pattern of distress combined with lack of help-seeking has led researchers to look for explanations and seek ways to improve quality of life.

Due to the link between smoking and a later lung cancer diagnosis, current and former smokers may feel responsible for their cancer\(^17\) and hide from others due to their shame and guilt.\(^18\)\(^-\)\(^21\) SHAME AND GUILT
Though only a few published studies examine shame and guilt in lung cancer patients,\(^15,17,18,22,23\) they indicate that social stigma and feelings of guilt may lead lung cancer patients to blame themselves. When they blame something about their character that is enduring, researchers define this as shame. When they blame an activity or behaviour that can change, researchers define this as guilt. People who attribute their disease to internal causes regardless of cancer type report poorer self-esteem, higher anxiety, depression and anger.\(^17\) Several qualitative studies indicate that these feelings of shame and guilt negatively influenced patients’ lives. In one study, experiencing uncertainty, thoughts of death, and shame and guilt were the 3 themes endorsed as reducing quality of life.\(^24\) Shame and guilt together led patients to feel a sense of social anguish,\(^22\) which is physical and mental distress that has a significant impact on interpersonal interactions.

Because feelings of shame lead people to hide from others, it also negatively influences lung cancer patients’ relationships, with individuals withdrawing from social activities and friendships as well as failing to seek out support from friends or family.\(^18,22,24\) Patients may also avoid disclosing their diagnosis,\(^19\) resulting in financial difficulties and less support.\(^18\) Feelings of shame and guilt can affect medical treatment by delaying symptom reporting,\(^16,22\) increasing false reporting or non-disclosure to doctors about smoking habits,\(^25\) and in addition to poor prognosis and advanced state of disease, may in part account for a lack of success...
in creating lung-cancer support groups/advocacy. Feelings of shame and guilt can cause emotional suffering that may increase the illness burden, lead to social isolation, and contribute to ongoing distress. Social isolation not only affects their quality but also quantity of life.

STIGMA
Smokers and nonsmokers alike experience and fear the stigma associated with lung cancer. A large population-based survey examined respondents’ willingness to attribute blame across cancer groups. Although their sample consisted of women, who generally hold positive attitudes towards individuals in need of support, 70% attributed blame to lung cancer patients, as opposed to 9% blame attribution for leukemia and 15% for breast cancer. The blame attributions for lung cancer were similar to conditions more widely seen as a matter of individual responsibility, such as chlamydia and obesity.

Healthcare professionals and the lay public recognize the stigma lung cancer patients experience. In an interview study, 18 oncology social workers reported that stigma related to cigarette smoking was a principal reason for patients’ emotional burden. Six focus groups made up of healthcare professionals and members of the public identified shame and blame as a main impediment to lung cancer patients’ coping. This stigma is also present in the news. In a study of all cancer-related stories presented on Australian television news, only 2% related to lung cancer although it is the leading cause of cancer death. Furthermore, 62% of these reports addressed lung cancer in nonsmokers.

Both this underrepresentation of the disease and the portrayal of mainly nonsmokers as deserving of sympathy may perpetuate the stigma and shame among patients with lung cancer, especially in those who have smoked. Anti-smoking campaigns, which are important in order to prevent young people from starting smoking and encourage smokers to quit, can also have an unintended consequence of upsetting those with smoking-related illness and perpetuating stigmatization.

FUTURE DIRECTIONS
The majority of studies on shame and guilt in lung cancer have used qualitative methodology and have highlighted the prevalence and debilitating consequences. These studies are a starting point for future research to understand how these emotions affect patients and to test ways to combat these emotions so patient care can be improved.

Past research has uncovered several areas that need attention. Teaching lung cancer healthcare teams to recognize the signs of shame and guilt in their patients may empower them to reach out more empathically to their patients and refer them more often for psychosocial care. Healthcare professionals play a large role in alleviating distress by being aware of the high psychosocial needs of this population. There is room for improvement when it comes to physician-patient communication. In a study of oncologists’ and surgeons’ responses to lung cancer patients’ concerns in consultations, they responded empathically to only 10% of patients’ concerns, emotions or mention of a stressor. Empathy in physician-patient communication has been associated with patient satisfaction and improved adherence to treatment, and need not delay consultations.

There is also a need for research to evaluate interventions that target shame and guilt and interrupt the cycle of distress. A more sensitive approach to anti-smoking campaigns using nonjudgmental and nonblaming material that acknowledges how hard it is to change health behaviour might reduce the stigma. Not so long ago, smoking was pervasive, acceptable and encouraged by tobacco advertising. Education about this might

Approach to addressing shame and guilt in lung cancer patients

- Recognize the signs of shame and guilt (e.g. social withdrawal/isolation; physical and verbal cues including a head-down, gaze-down position often occurring with pauses or breaks in speech)
- Inquire about emotional state
- Administer a form of distress screening
- Refer to counselling services
alter the judgmental attitude experienced by lung cancer patients who smoked. If reducing the shame experienced by patients can decrease the delay in reporting symptoms, diagnosis and access to more treatment options may occur earlier.

In summary, this developing literature offers important clues to the cycle of distress lung cancer patients experience. Cancer patients at any stage are susceptible to guilt and shame and research should examine if there is a different effect based on disease stage. More research is crucial to understand these patterns, intervene more effectively and improve quality of life for lung cancer patients.

REFERENCES

Disclosure
The authors report no conflict of interest pertaining to this article.