Ready or not? Lung cancer diagnosis in 2015

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Lung cancer remains a significant health issue in Canada, with more than 26,000 new cases reported in 2014. The disease also unfortunately remains the cause of the greatest number of cancer-related deaths, at more than 20,000 annually. That toll is attributed in part to half of all patients presenting upfront with metastatic disease. Of those diagnosed, approximately 85% have non-small-cell lung cancer (NSCLC). In that subgroup, approximately 40% have adenocarcinoma histology; 10%–15%, squamous cell carcinoma; and 5%–10%, neuroendocrine carcinoma; the rest are classified as not otherwise specified (NOS). Recent developments in the therapy and understanding of the pathobiology of lung cancer have triggered a refinement of the histologic classifications to take into account the advent of novel targeted therapies and chemotherapeutic agents. Most importantly, the new classifications have been based on a multidisciplinary collaborative effort that has included clinicians, pathologists, radiologists, and molecular biologists—underscoring the exciting revolution underway in the field of lung cancer management.

Although platinum doublets have been standard in the therapy of advanced NSCLC across all histologies, more recent studies have demonstrated the importance of histology in determining optimal therapy. Pemetrexed has demonstrated the differential effect of histology on treatment response, with survival benefit restricted to those with adenocarcinoma histology. Conversely, regimens incorporating bevacizumab have been associated with significant toxicity in patients with squamous histology, leading to the development and use of that agent in non-squamous NSCLC.

The discovery of molecular biomarkers such as EGFR gene mutations and ALK gene rearrangements have triggered the era of targeted therapy in lung cancer. Those molecular targets are both strongly associated with adenocarcinoma histology and are highly predictive of response to tyrosine kinase inhibitors, with better outcomes than are seen with conventional chemotherapy. The pivotal Iressa study, which compared gefitinib with conventional chemotherapy in never- or light-smoking Asian patients with metastatic adenocarcinoma, served to highlight the importance of ascertaining the molecular status of patients before initiating therapy. Patients with activating mutations experience better response, better quality of life, and better progression-free (and likely even overall) survival with initial targeted therapy. By contrast, those with wild-type EGFR or ALK adenocarcinoma experience better outcomes with initial chemotherapy.

In light of the foregoing advances, the American Society of Clinical Oncology, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association of Molecular Pathologists recommend routine testing for EGFR mutations and ALK rearrangements and accurate pathologic subtyping in all patients with advanced-stage adenocarcinoma, regardless of clinical characteristics, before first-line therapy.

Furthermore, current guidelines recommend turnaround times of 5–10 days maximum for the results, so that clinicians and patients have the information necessary to make optimal treatment decisions. Those recommendations underscore the importance of prompt and accurate histologic subtype and molecular diagnosis of NSCLC, a clear mandate for our pathology colleagues. However, given that most patients (approximately 70%) present with unresectable disease, pathologists are faced with an increasing number of small diagnostic samples that occasionally limit a definitive diagnosis and more often limit successful molecular testing.

In this issue of *Current Oncology*, VanderMeer et al. highlight some of the challenges facing clinicians given these recent advances in the field of lung cancer. In a retrospective study of lung cancer patients diagnosed in 2007 and 2008 at a single Canadian cancer centre, they report that only 77% of cases had a sufficient pathology diagnosis for histology-directed treatment. In particular, they highlighted that 18% of the patients had been diagnosed with NSCLC NOS. Those results might partly be a result of the historical nature of the cohort, diagnosed using the 2004 World Health Organization schema of lung tumours, which endorsed the classification of nondefinitive specimens as non-small-cell carcinoma. The 2011 revision offers clear guidance on the importance of routine immunohistochemical (IHC) staining to further differentiate the pathologic subtypes. The authors do not report the use of IHC in their cohort, although other Canadian academic centres were using it in approximately half the cases being managed at that time.

How does the proportion of samples reported as NSCLC NOS compare with that in similar series? An analysis of 8117 *de novo* stage IV NSCLC patients in the Cancer Care Ontario Registry diagnosed between 2005 and 2009 indicated that 43% were reported to have NSCLC NOS. Other series from the Ottawa Regional and the Princess Margaret cancer centres included 739 advanced NSCLC patients treated between 2007 and 2010, 16% of whom were reported to have NSCLC NOS. Similarly, 19% percent of 238 NSCLC cases diagnosed...
at an academic cancer centre between 2007 and 2009 were reported as nos\textsuperscript{19}. The latter two reports highlighted that, although \textit{hnc} staining might not always be required for \textit{nsclc} subtyping, it clearly lowers the rate of \textit{nsclc} nos diagnoses. The results reported by VanderMeer \textit{et al.}\textsuperscript{17} are consistent with those from other academic centres and suggest the use of \textit{hnc} in their cohort, compared with the larger provincial study in which more than 40% of cases were signed out without a pathologic subtype\textsuperscript{4}.

The authors also report that 24% of pathology reports used terminology that either was not definitive or was ambiguous in the diagnosis of malignancy, and that another 2% of patients lacked a confirmed pathology diagnosis from their diagnostic sample. Those findings suggest an important challenge for clinicians and pathologists, because small biopsy and cytology samples can be inadequate for complete diagnosis. Cancer Care Ontario has introduced synoptic pathology reporting, which might alleviate the problem posed by ambiguous terminology in reports. Recently Cancer Care Ontario’s Program in Evidence-Based Care published best practices for secondary review of oncologic pathology in lung cancer\textsuperscript{20}. Although secondary pathology review is not required for samples that are unsatisfactory or insufficient for diagnosis or have cellularity termed “atypical,” clinicians should ensure repeat biopsy for diagnosis. Secondary review is recommended for samples without a complete work-up, those considered suspicious, those deemed “atypical” or nondiagnostic despite adequate cellularity, and those with morphology that lacks material for \textit{hnc} or other studies (or where such studies are inconclusive), especially when additional tissue cannot be collected and therapeutic decisions are reliant on the final diagnosis (for example, small-cell or \textit{nsclc} subtype). All final diagnoses of \textit{nsclc} without \textit{hnc} (including adenocarcinoma and squamous cell carcinoma) are recommended to undergo secondary pathology review, as are diagnoses of undifferentiated or poorly differentiated \textit{nsclc} nos, mesothelioma, neuroendocrine tumours nos, or other rare tumour types. Secondary review should be performed by a pathologist or cytopathologist with subspecialty expertise in pulmonary pathology. When resection is planned, further review of the larger sample is recommended, and secondary review should be conducted if the results are inconsistent with an earlier diagnosis from a smaller biopsy sample.

Consistent with other reports from Canadian centres\textsuperscript{3,19}, 22% of patients in the VanderMeer cohort had undergone surgical resection. Those patients had better outcomes than did the patients diagnosed with \textit{de novo} late-stage disease, likely because of inherent biologic differences and a better prognosis.

Almost two thirds of patients in the cohort, 61%, underwent bronchoscopy as the initial investigation for lung cancer diagnosis. But bronchoscopy led to definitive diagnosis in only half the patients (32% of the total), similar to results in other Ontario reviews. That finding speaks to an urgent need to better define the role of bronchoscopy in the current era of lung cancer diagnosis. The types of samples collected for diagnosis are also less clear in the VanderMeer report: How many were diagnosed on exfoliative cytology (for example, from pleural effusions)? How many were diagnosed based on endobronchial biopsy compared with bronchial brushing or bronchoalveolar lavage alone? How many were diagnosed by image-guided biopsy (computed tomography– or ultrasound-guided)? Compared with numbers reported from other centres, the number diagnosed from core needle samples (approximately 30%) as opposed to fine-needle aspirations (approximately 6% reported) appears disproportionate. In reports from Ontario and Toronto, 25%–50% of cases were diagnosed using transthoracic image-guided biopsies, and two thirds of advanced \textit{nsclc} diagnoses were based on cytology samples from a variety of invasive procedures. Conventional bronchoscopy remains a widely used diagnostic procedure, endorsed for central tumours and associated with a low complication rate\textsuperscript{21}, but the resulting biopsy specimens tend to be small (fewer than 300 malignant cells per sample), and the diagnostic yield is low for peripheral lesions. Bronchoalveolar lavage and bronchial brushings offer even poorer yields, with diagnostic sensitivity of 43% and 54% respectively. Those poor yields pose major challenges in the diagnosis of lung cancer, because, on top of necessary material for diagnosis, standard molecular testing currently requires 100–300 cells to perform \textit{egfr} genotyping, plus additional material to test for \textit{alk} rearrangement and to perform relevant \textit{hnc} staining for subtyping\textsuperscript{22,23}.

Endobronchial ultrasound-guided (ebus) transbronchial needle aspiration is emerging as an increasingly popular minimally invasive diagnostic modality for both pathology diagnosis and mediastinal staging\textsuperscript{24}. Radial-probe \textit{ebus} transbronchial needle aspiration has been demonstrated to offer better diagnostic yields for peripheral nodules\textsuperscript{25,26}. A recent study also demonstrated that, compared with conventional diagnostic procedures, linear \textit{ebus} with systematic examination of all mediastinal and hilar lymph node stations reduced time to treatment decisions\textsuperscript{27}. Furthermore, \textit{ebus} was shown to be a useful modality to obtain tissue for mutation analysis\textsuperscript{28}. For those reasons, \textit{ebus} is becoming an increasingly common primary diagnostic procedure. In addition, the adequacy of samples acquired by \textit{ebus} and fine-needle aspiration using other methods such as image-guided sampling or bronchoscopy can be evaluated in real time using the technique of rapid on-site evaluation.

Unfortunately, the article by VanderMeer \textit{et al.} does not address the impact of current diagnostic sampling on the success of molecular testing for driver mutations in \textit{nsclc}. The current movement toward the use of minimally invasive procedures can lead to insufficient tissue being gathered for molecular testing. The key factor for testing success is sample cellularity\textsuperscript{29}. A recent study looking at \textit{egfr} testing in Canada found that 12% of samples were not tested for \textit{egfr} mutations because of insufficient tissue or specimens not being sent to the testing laboratory\textsuperscript{30}. A review at the Princess Margaret Cancer Centre revealed that tissue from 10% of patients was insufficient for molecular testing and that half the group required a second biopsy\textsuperscript{31}. The result was treatment delays and an increased risk of additional procedure-related complications.

With each passing year, new targets in lung cancer are emerging, with active therapies available. Examples include \textit{ros1}–, \textit{braf}–, \textit{ret}–, \textit{met}–, and \textit{her2}-aberrant
Additional predictive biomarkers on the horizon in NSCLC include EGFR T790M and KRAS mutations and, potentially, programmed death–ligand 1 expression. Although multiplex genomic and protein expression testing offers the possibility for genotype-directed and other personalized therapy, tissue sampling issues remain a major obstacle. To exclude patients from promising treatments because of insufficient tissue acquisition, processing, or testing contributes to worse outcomes and tremendous lost opportunity for progress in lung cancer. To keep pace with the rapid evolution of personalized therapy in lung cancer, future guidelines must address testing for the new predictive markers and how best to diagnose the disease.

In the 21st century, management of lung cancer has witnessed remarkable progress in both diagnostic testing and options for treatment. Increased knowledge of the pathophysiology of lung cancer has led to the development of targeted therapies that have ushered in the era of personalized medicine. However, as VanderMeer and colleagues show, considerable logistical obstacles remain to be overcome. The Canadian consensus guidelines offer recommendations for histopathologic and molecular testing but a national consensus for diagnostic testing in lung cancer is urgently needed to accommodate the need for better lung cancer diagnostic tissue samples in this current era of personalized medicine. Such a consensus will require thoughtful discussion by the various pertinent specialties—radiologists, respirologists, surgeons, pathologists, and medical oncologists—across the country. The ultimate goal is to optimize current lung cancer diagnostic efforts so that patients can be provided with the most appropriate, timely, and efficient diagnostic testing that allows them to benefit from a growing number of novel therapies and that improves patient outcomes.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare the following interests: NBL holds the combined hospital–university OSI Pharmaceuticals Foundation Chair in Cancer New Drug Development.

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REFERENCES


