Cancer pathology

Challenges and opportunities in the era of personalized medicine

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“As is your pathology, so goes your clinical care” — Sir William Osler

ABSTRACT

Pathology is vital to cancer diagnosis, treatment and research. However, in most institutions, pathology is ill equipped to take on the augmented role required to fulfill the promises of personalized cancer care. This article outlines how pathology has evolved in recent years and challenges that have accompanied this evolution, and looks to initiatives that will help to fully integrate advances in pathology into a new era of cancer care.

Pathology offers a window into the damage different disease processes inflict on our bodies. Histologic examination of tumours that began with the naked eye came to benefit from optical microscopes and then sophisticated electron microscopes with ever-greater resolution. These advances brought about a paradigm shift in the way we define cancer and in our understanding of cancer biology. In the late 19th and early 20th centuries, cancer was defined by the demonstration of invasion and metastases based on gross findings at surgery or autopsy.1 Developments in pathology during the 20th century enabled more precise concepts to evolve and be adopted in clinical practice: cancer grading and staging, carcinoma in situ, cytopathology in screening and diagnosis, immunohistochemistry and biomarkers.

As we enter the 21st century, cancer is acknowledged as a genetic disease that can be diagnosed and treated using molecular/genomic approaches in addition to traditional surgery, radiotherapy and chemotherapy. Another wave of technologic advances in digitization, telepathology, molecular diagnostics and genomic screening marks the latest paradigm shift in cancer pathology. Figures 1 and 2 illustrate the increasing complexity and importance of pathology in targeting treatment based on molecular pathology diagnosis. However, pathology departments working to meet these new expectations face important challenges, not least in limited staffing and budget resources. This article provides insight into how these challenges can be overcome to enable pathology to fulfill its increasingly vital role in cancer research, diagnosis and treatment.

Pathology within the hospital

More than 70% of all clinical decisions regarding diagnosis and treatment, hospital admission and discharge rest on medical test results that are the sole responsibility of pathologists.2 However, pathology is unique as a clinical specialty in that pathologists do not have direct contact with patients. As such, it tends to be perceived as a commodity rather than a knowledge-based professional service. Pathology is the place where physicians drop off a specimen and pick up a report. Expectations are for fast and accurate reports, and accuracy is seen in black and white terms. If there is an error, pathologist incompetence is always to blame, as we have seen in all-too-frequent news reports over the last decade.3

Subspecialization

Medical errors can lead to adverse patient outcomes. Today, however, an error in cancer pathology is no longer as simple as identification of a benign lesion as cancerous or vice versa. More frequently, a pathologist may miss or misinterpret an important predictive or prognostic marker. The one-line diagnosis of “breast carcinoma” 20 years ago has today become a full-page report with detailed information on grading, staging, and predictive and prognostic markers. In this era of “precision medicine,” a general surgical pathologist cannot be expert in all organ systems.

In response to the knowledge revolution of the past 3 decades and in conjunction with the subspecialization of surgical disciplines, pathology departments in many large institutions, including the McGill Department of Pathology, have moved to organ-based subspecialized practice.4 In most cancer centres, pathologists with subspecialty expertise are core members of multidisciplinary cancer teams who work closely with surgeons and medical and radiation oncologists to provide personalized care to cancer patients. Subspecialization has increased the experience and skill...
of pathologists in interpreting challenging cases in their specialty area and has reduced interpretive errors. It has also enhanced communication between the members of clinical subspecialty groups and facilitated the optimization of teaching and research activities. However, subspecialization can only succeed in large departments where there are enough pathologists to cover all specialty areas. Challenges arising from subspecialization include workload distribution that considers the volumes in different specialty areas, handling of frozen sections, on-call coverage and concerns over job mobility.

Centralization and telepathology

The knowledge explosion and subspecialization significantly increase the intellectual demands on pathology practice and challenge the existence of small pathology laboratories in peripheral hospitals. On the one hand, there is a need for local pathologists who can facilitate clinicopathologic correlation and on-site communication; on the other, the need is for expert subspecialized opinion. Whole-slide imaging and telepathology have rendered it possible for a large diagnostic centre to provide subspecialty diagnostic services in the setting of frozen sections, second opinion consults and even routine service coverage to a huge geographic region with a low population density.7,8 The Eastern Québec telepathology project led by the Department of Pathology at Laval University has been successful in using telepathology to improve patient care in that region. Virtual slides have become a viable tool in the classroom, for clinical decision making and in research. We can now seek or provide expert pathology opinion globally through web-based telepathology.9 After acquiring experience with whole-slide imaging and digitization, the McGill University Health Centre (MUHC) installed its telepathology centre in the summer of 2013. Soon, pathologists will be able to make diagnoses remotely through their iPhone, iPad or other electronic devices. However, these exciting possibilities raise new challenges in quality assurance.

Molecular pathology

Molecular pathology now makes it possible to

- identify an etiologic factor such as human papillomavirus (HPV) testing
- reclassify an entire entity such as soft-tissue tumours
- provide prognostic information, such as microsatellite instability, gene amplification, etc.
- predict a response to therapy, such as anti-HER2 (human epidermal growth factor receptor 2) and anti-EGFR (epidermal growth factor receptor) therapies
- adjust the dosing of critical medications, such as warfarin
- identify minimal residual cancer
- suggest preventive therapy, such as prophylactic gastrectomy in family members with CDH1 (epithelial [E]-cadherin) mutation gastric cancers.10

The task of providing clinically relevant information on morphologic, genetic, proteomic and epigenetic alterations will fall to surgical pathologists. Most of the current population of practising pathologists lack sufficient training in molecular pathology, making continuing education an urgent priority.

Pathology departments also need to constantly update their molecular test menu in order to meet new clinical practice standards. They require a pathologist trained in bioinformatics to appropriately process the massive quantities of genomic and proteomic data and ensure that all the relevant clinical information is harnessed for clinical application. Banking fresh tumour tissue will likely become a necessity.

The molecular laboratory should have PhD-level scientists to develop and validate new molecular tests on an ongoing basis. The McGill Department of Pathology has established one of the nation’s best molecular pathology centres at the Jewish General Hospital (JGH) under the leadership of Dr. Alan Spatz. With the help of Dr. Spatz and Dr. Leon Van Kempen, and support from the Cedars Cancer Foundation, the MUHC’s molecular pathology laboratory is scaling up its development of molecular tests to complement those under development at the JGH, specifically in areas such as sarcomas, breast cancer, prostate cancer, ovarian cancer, pediatric tumours, brain tumours, etc.

Workload and staffing

The workload in pathology has been increasing consistently due to population growth and aging, expansion of the types of services made possible by scientific advancement, and increasing complexity as new patterns of clinical pathologic correlation require the incorporation of serologic, genomic, proteomic, immunohistochemical, flow cytometric and morphologic information.11 In Canada, the annual number of new cancer cases increased from 129,300 in 1999 to 171,000 in 2009. This represents an increase of 17.1% in cancer cases per pathologist.12 The Canadian Association of Pathologists estimates that about 500 new pathologists will be needed over the next 10 years to keep up with demand at the current trend.11 In Québec, the government has exacerbated the situation by imposing a greater number of work units per year on pathologists.13 These combined pressures have a direct impact on stress, fatigue...
and risk of error, and also prevent pathologists from undertaking and providing the professional development and research activities that will enable our labs to meet the expectations of new clinical models in precision care.

**WORKFLOW EFFICIENCY**

Between 2006 and 2013, the workload at the MUHC increased 65%, while the pathology budget and number of pathologists remained essentially unchanged. In order to stay competitive locally and globally, pathology laboratories have to radically change their work concepts and adopt new technologic approaches to improve their efficiency. These include: 1) considering cost effectiveness in providing care and changing the concept from “at any cost” to “appropriate, affordable care;”14 2) using a “lean approach” to remove non-value-added activities; 3) standardization to reduce variations; 4) consolidation; and 5) full automation.15,16

**QUALITY ASSURANCE**

Quality in cancer pathology is defined as accurate, timely and complete reporting that can guide patient management.17 We now have a better-informed population with high expectations regarding access to quality diagnostic services. We also know the full impact of medical incidents (including those arising from pathology errors) on the patient, pathologist, hospital reputation and public confidence in our health system, along with, of course, their legal and financial consequences. Errors can occur at any step in the work process: pre-analytical, analytical and post-analytical.18,19

A number of factors that increase the risk of error have been identified:

- pathologist fatigue due to high workloads and staff shortages
- variability in practice
- subjectivity and lack of gold standards
- inadequate culture of quality improvement
- lack of resources for ongoing professional development
- lack of designated quality monitors
- lack of standard policies and procedures to cope with medical incidents when they do arise

Healthcare administrators recognize the importance of pathology in cancer care and have started to invest in quality improvement initiatives. Quality standards and guidelines have been put in place by the College of American Pathologists, the Association of Directors of Anatomic and Surgical Pathology and other professional bodies.23,24 Canadian national and provincial accreditation bodies require that pathology departments have a structured and active program of quality assurance (QA) and quality improvement (QI), with the goals of enhancing patient safety, minimizing error, ensuring timely delivery of reports and monitoring physician competence.

In 2012, the McGill Department of Pathology conducted a gap analysis against best practice guidelines and identified areas that needed improvement such as turnaround time, specimen grossing and synoptic reporting. In 2013, the department began benchmarking our laboratory processes against those of the Mayo Clinic, Johns Hopkins Hospital and Massachusetts General Hospital. The goal of all these efforts is to ensure that our cancer patients receive the highest-quality diagnostic service.

**CANCER RESEARCH**

Pathology is both a medical specialty and an investigative scientific discipline, encompassing the etiology, mechanism, progression and prognosis of human disease. Pathologists in cancer research facilitate the banking of fresh tumour tissue and control tissue, as well as subsamples of the full spectrum of all progressive neoplastic states. They establish databases that include clinical information and pathology materials (the “gold mine” for current clinical research) and refine tumour tissue for research. They analyze and interpret genomic and molecular testing data using pathbioinformatics, assess the safety and efficacy of chemicals or other substances used in cancer prevention and therapy, and provide clinical researchers with information on tumour cell proliferative activity, steroid receptor status, occult distant micrometastasis, immunologic phenotypes,
gene amplifications and molecular classification.\textsuperscript{23,24} For pathologists to be effectively involved in basic science, translational and clinical research, we must liberate some of their time and increase academic support for and recognition of research excellence in a clinically focused environment.

At a 2012 retreat, the McGill Department of Pathology established a department-wide strategic research plan and defined signature research programs. To support the research community, the pathology departments at both the JGH and MUHC have established a core research facility. The Molecular Pathology Centre at the JGH and the Molecular Pathology Laboratory at the MUHC have each developed platforms to support research initiatives. To facilitate collaboration, the department launched its scientific lecture series with speakers from both inside and outside McGill. These strategic initiatives demonstrate the institution’s support for all collaborative research activities where pathology can make a positive contribution.

**MEETING THE CHALLENGE**

The service provided by pathology departments to cancer patients incorporates making a definitive diagnosis of disease, guiding selection of the most appropriate therapy, predicting a patient’s response to a specific therapy and prognosis, and identifying familial/hereditary cases to institute preventive measures for healthy family members. Pathology also plays an important role in researching the cause and mechanism of disease, discovering new therapeutic and preventive measures for patients, educating staff and the public, predicting trends, auditing health care and establishing health policy. Pathology practice will become more integrated into clinical care. Digital imaging, telepathology and computer-assisted information assembly of clinical, radiologic, histologic and molecular testing data will become routine practice in providing diagnostic information and supporting research. In the near future, we anticipate that pathology departments will have pathologists with specific areas of expertise providing patient consultations.

**GAME CHANGER**

National pathology leaders such as Dr. Sylvia Asa have introduced the concept of “pathology clinics” in the Toronto University Health Network, where pathologists meet with patients to explain the biochemical, immunologic, morphologic, molecular and proteomic changes identified in their specimens, and to reinforce the direction of care required.\textsuperscript{25} However, before they can take on such an augmented role, pathologists will require training in communicating with patients directly, and interdepartmental efforts will be needed to ensure that pathology clinics complement oncology and surgery clinics and reinforce each others’ messages. For the moment, most pathology departments are struggling with overwhelming workloads and severe staff shortages, and this next step in realizing pathology’s new promise to improve patient care in cancer remains far beyond reach.

**References**