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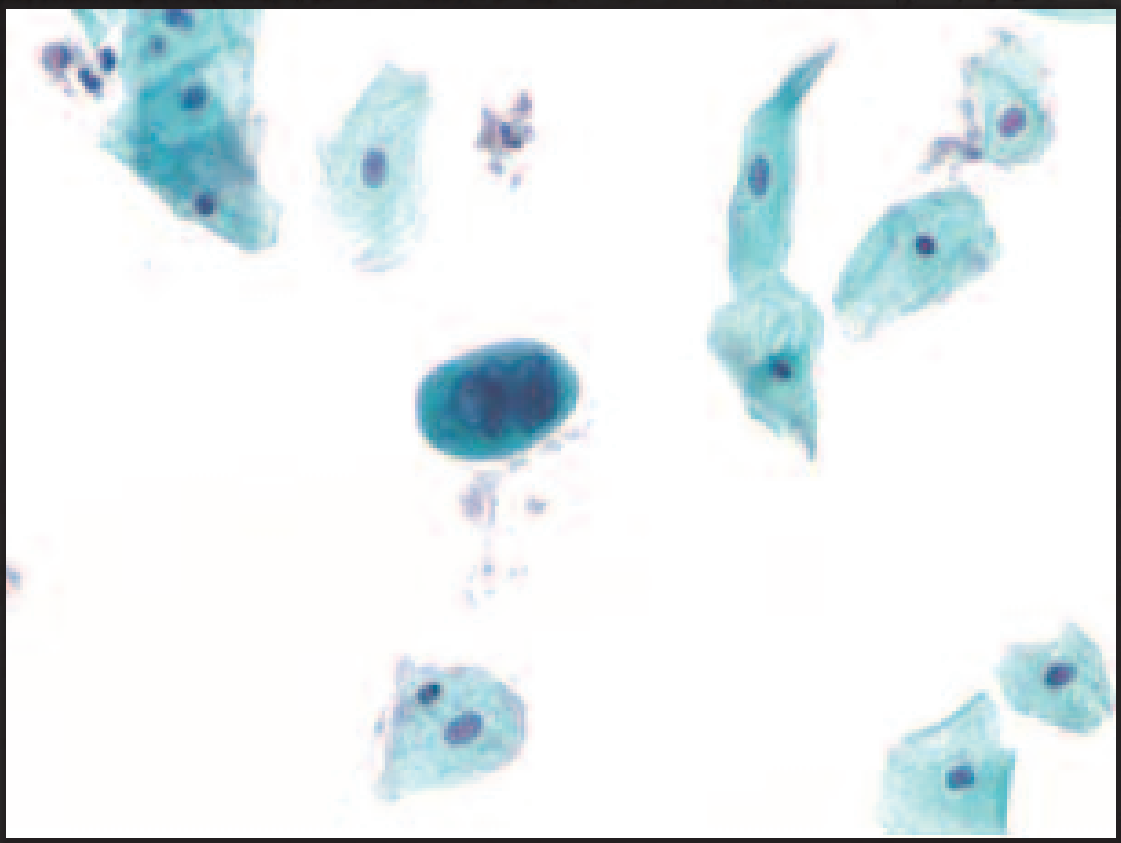

Kulcsar Lecture 2012: Technologic Advances in Cytology

Who Owns Diagnostic Specimens?

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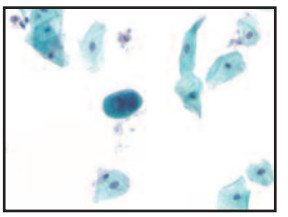

The cover image shows low-grade squamous intra-epithelial lesion with rare diagnostic cells (Papanicoloau stain).

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Recognition of Advanced Cytopathology Training in Canada

In this issue of the *Canadian Journal of Pathology*, Drs. Michele Weir and Karim Khetani[1] outline the diploma program of the Royal College of Physicians and Surgeons of Canada (RCPSC) and the pathway to official recognition of cytopathology as an area of focused competence (AFC).

The application process has been an arduous one and has been a work in progress for almost two decades. In their article, these authors note that diploma programs are for those areas that do not meet the criteria for a subspecialty status. This point may be puzzling to many practising in this field since cytopathology is recognized as a subspecialty in many countries, including the United Kingdom, the United States, and Australia. Over the years, many members of the executive committees of the Canadian Society of Cytology (CSC) have worked to attain the same status for Canadian cytopathology fellows training in Canada. However, the RCPSC was very reluctant to increase the number of recognized subspecialty programs and was moving more toward diploma programs. Persistence of the CSC executive has now paid off with this accomplishment of diploma status for cytopathology, the first diploma program in the field of pathology.

The creation of this new status of AFC in cytopathology comes at an opportune time as cytopathology is facing a number of new challenges, among them, the increasing use of endoscopically guided fine-needle aspirates (EUS), endobronchial ultrasound-guided fine-needle aspirates (EBUS), cytological specimens for targeted therapy decisions for lung cancer, automated cytology screening, and more complex, stringent quality assurance and quality improvement requirements. Those trainees who will obtain a diploma in AFC in cytopathology will be better equipped to face these current challenges, as well as those that will undoubtedly come in the future.

Many Canadian pathology leaders in the area of cytology have contributed to this successful application, and their countless hours of work preparing various iterations of the required application documents over the years are finally recognized. The success of this final application is a considerable achievement that will benefit our Canadian-trained fellows, our cytopathology community at large, and ultimately our patients.

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Reference

1. Weir M, Khetani K. A new era for advanced cytopathology training: The Royal College Diploma Program. Can J Pathol 2013;5(3):117–8.

Reconnaissance de la formation spécialisée en cytopathologie au Canada

Dans le présent numéro de *Canadian Journal of Pathology*, Michele Weir et Karim Khetani[1] offrent un aperçu du programme d'études menant à un diplôme dans un domaine de compétence ciblée du Collège royal des médecins et chirurgiens du Canada (CRMCC) et la voie de la reconnaissance officielle de la cytopathologie comme domaine de compétence ciblée.

Le processus de demande de reconnaissance, parsemé d'embûches, s'est échelonné sur près de 20 ans. Dans leur article, les auteurs précisent que les programmes de domaines de compétence ciblée s'appliquent à des disciplines qui ne correspondent pas aux critères d'une surspécialité. Cet aspect peut en laisser plus d'un perplexe étant donné que la cytopathologie est une surspécialité établie dans de nombreux pays, dont le Royaume-Uni, les États-Unis et l'Australie. Depuis longtemps, le comité de direction de la Société canadienne de cytologie fait des pieds et des mains pour que la formation en cytopathologie soit attestée officiellement. Cependant, le CRMCC, réticent à la perspective d'augmenter le nombre de surspécialités reconnues, a opté pour des programmes de domaines de compétence ciblée menant à un diplôme. La persévérance de la Société canadienne de cytologie a été récompensée puisque la formation en cytopathologie conduit désormais à l'obtention d'un diplôme en bonne et due forme à l'issue du premier programme de domaines de compétence ciblée relié à la discipline de la pathologie.

La reconnaissance de la cytopathologie comme domaine de compétence ciblée arrive à point nommé alors que la discipline connaît un essor marqué par l'usage de plus en plus répandu de pratiques jusque-là inédites, comme la cytoponction endoscopique, la cytoponction guidée par échographie endobronchique, le prélèvement cytologique en vue du choix de la thérapeutique sélective dans le cancer du poumon et le dépistage cytologique automatisé, et par les exigences de la procédure de plus en plus complexe et stricte d'assurance et d'amélioration de la qualité. Les médecins titulaires du diplôme de domaine de compétence ciblée en cytopathologie seront aptes à relever haut la main ces défis et ceux qui se présenteront inévitablement à l'avenir.

De nombreux pathologistes canadiens chefs de file dans le domaine de la cytologie ont participé à cette entreprise de reconnaissance de cette formation spécialisée; ils n'ont rien ménagé, ni les heures, ni l'énergie, dans la préparation et l'acheminement des documents nécessaires pour aboutir à cette reconnaissance tant attendue. Tous autant que nous sommes, médecins spécialisés dans ce domaine et communauté de la cytopathologie, nous pouvons être fiers de la réussite de cette démarche de reconnaissance, qui rejaillira sur nos patients au bout du compte.

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Référence

1. Weir M, Khetani K. A new era for advanced cytopathology training: The Royal College Diploma Program. Can J Pathol 2013;5(3):117-8.

Who Owns Diagnostic Specimens in the Era of Personalized Medicine?

Ubaka Ogbogu, LLB, BL, LLM, Michael Mengel, MD, on behalf of the Canadian Chairs of Pathology and Laboratory Medicine

The Canadian Chairs of Pathology and Laboratory Medicine read with great interest the article by Cheung and colleagues published earlier this year in the *Canadian Medical Association Journal*.[1] In that opinion piece, the authors addressed the very important issue of ownership, stewardship, and accessibility of diagnostic specimens for research, teaching, and quality assurance purposes. We applaud the authors for tackling this complex and still unresolved issue, which for us stimulated a lively discussion with our academic colleagues from health law research groups. With this commentary, we would like to contribute to this important discussion by giving the academic perspective (i.e., a perspective with a major focus on maintaining and facilitating reasonable access to human diagnostic specimens for teaching and research).

As a general practice, the collection of specimens for diagnostic purposes usually does not require consent for research use. However, widespread current practice is that institutional research ethics boards permit "secondary" research use of archived or excess diagnostic specimens and derivatives without specific consent for such use, subject to rules that protect donor and patient privacy in accordance with health information protection legislation (specifically, if the specimens are de-identified).

Cheung and colleagues take a strong position that because diagnostic specimens and derivatives are a component of the patient record, they are owned by the institution that collects them.[1] We think that this interpretation overstates the law by comparing tissue to a physical medical record. Questions regarding tissue ownership remain unsettled in both Canadian jurisprudence and elsewhere, and the case law discussed by Cheung and colleagues does not definitively address or decide the issue. A better view may be that the law is presently unclear on who owns excised tissue, whether classified as diagnostic tissue or as research tissue. One thing is clear: once a diagnostic specimen is excised, the donor has rights founded in consent (at least to the procedure of removing the tissue) and privacy law (and in some situations, fiduciary law), but it is not clear whether this extends to an ownership interest.[2] In our opinion, it is not legally established that ownership of tissue specimens lies with the collecting institution. It is possible that derivatives from the specimens belong to the collecting institution or to the person who derived it. In any event, the ownership question should not be our priority because from a donor rights perspective, access to specimens for research and teaching (i.e., purposes other than rendering diagnoses) should not depend on ownership but primarily on consent rules and privacy protections. The ownership question is perhaps only important in determining who (between the collecting institution and researchers) should benefit financially from exploiting the specimens and derivatives.

Therefore, in our opinion the most relevant question is whether the academic community can use diagnostic tissue and derivatives for research and teaching without specific (prospective or retrospective) consent. Pathology archives across the world – and particularly in Canada – contain unprecedented amounts of human tissue specimens that were virtually all procured, stabilized, refined, and stored through public resources (i.e., a public health care system). Such public

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support indicates that it is in the public interest to facilitate widespread but regulated access to these specimens for use in research. We suggest that the term *ownership* does not properly describe the role of the institutions in which these tissue archives are housed and is inconsistent with this concept. Ownership of these specimens by an institution that may be private or become private in the future could imply that the institution has the legal right to sell these specimens to the highest bidder; they would cease to be a public resource for research, teaching, and quality assurance. We therefore recommend that the term *ownership* be abandoned in this context and replaced with the term *stewardship* to more accurately describe the role of the institution as custodian of these tissue archives.

If researchers are seeking to use a tissue specimen collected for diagnostic purposes, then current legal and ethical rules require specific consent for research use. It is possible that these rules do not apply to derivatives from the diagnostic specimens, particularly if the derivatives are classified as data or information. The reason for this is that health information legislation throughout Canada provides that one does not need consent to use or disclose health information if it has been de-identified or (if identifiable) a research ethics board has approved such use or disclosure. Therefore, the most important question to us is, at what stage does a human tissue specimen procured for diagnostic purposes become "data or information"? One can postulate that it becomes so once it is manipulated or altered to create a "research-specific" derivative (e.g., when fixation and tissue processing is applied to the otherwise unmodified specimen). This becomes even more obvious if true derivatives that fundamentally alter the original diagnostic specimen are generated, such as stained histological sections or extracted ribonucleic acid. Cheung and colleagues take the further step of characterizing the diagnostic tissue specimen as part of the health record and therefore "data/information." To our knowledge, no legal clarity has been established in regard to this question in Canada. In the era of personalized diagnostics – with archived specimens becoming accessible to "omics" technologies even after formalin fixation and paraffin embedding – it is crucial to address this unmet need. To this end, a concerted response by health care providers, academia (medical, legal, and ethical), and legislative bodies is required.

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Frequency of Upgrading to Carcinoma at Final Excision in Biopsy-Diagnosed Benign Papillary Lesions of the Breast

Stephanie Petkiewicz, MD, CM, PhD, Shahidul Islam, MD, PhD, FRCPC

ABSTRACT

Purpose: To determine the frequency of carcinoma in final resections of biopsy-diagnosed benign papillary breast lesions and to determine the radiological and pathological features associated with increased likelihood of carcinoma.

Methods: Hospital pathology records were searched for biopsies of benign papillary lesions of the breast with subsequent excisions. Radiological and histological characteristics that may have increased suspicion of carcinoma were sought. Histopathological sections from the biopsy and resection material were examined for features suggestive of underlying malignancy.

Results: Of the 41 biopsy-diagnosed papillary lesions, 41% harboured malignancy at final excision. Ductal carcinoma in situ was the most common finding, but invasive carcinoma was also diagnosed. Lesion size was significantly associated with risk of malignancy. Re-examination of the histological sections confirmed that in most cases the carcinoma was not present within the biopsy material.

Conclusion: At our institution, 41% of biopsy-diagnosed papillary lesions of the breast were malignant at resection, larger lesions being at greater risk. Our data indicate that the most common cause of this discrepancy is sampling error (with carcinoma not present within the biopsy material). This suggests that women diagnosed with papillary lesions on biopsy should undergo local resection.

RÉSUMÉ

But : Établir la fréquence du carcinome papillaire du sein dans des tissus mammaires excisés en raison de la présence de lésions papillaires bénignes détectées à la biopsie et déterminer les traits radiologiques et pathologiques laissant entrevoir une probabilité accrue de carcinome.

Méthodologie : Recherche de cas de lésions papillaires bénignes du sein détectées à la biopsie et excisées dans des dossiers du service de pathologie; relevé des caractéristiques radiologiques et histologiques pouvant étayer la suspicion de carcinome; examen des coupes histologiques du tissu prélevé à la biopsie et du tissu excisé en vue de cerner des traits indicateurs d'une tumeur maligne.

Résultats : Dans une proportion de 41 % des 41 cas de lésions papillaires détectées à la biopsie que nous avons recensés, une tumeur maligne est présente dans le tissu excisé. Le carcinome canalaire in situ est le plus courant, quoiqu'il y ait des cas de carcinome invasif. La taille de la lésion est un indicateur prévisionnel important du risque de malignité. Le réexamen des coupes

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histologiques confirme que, dans la plupart des cas, le carcinome est absent dans le tissu prélevé à la biopsie.

Conclusion : À notre établissement, une tumeur maligne est présente dans le tissu mammaire excisé de 41 % des cas de lésions papillaires du sein détectées à la biopsie, les lésions les plus grandes posant le plus grand risque de malignité. Selon nos données, la disparité des diagnostics tient à une erreur de prélèvement (carcinome absent dans le tissu prélevé à la biopsie). En conclusion, la résection locale est indiquée en présence de lésions papillaires du sein détectées à la biopsie.

Papillary breast lesions are a frequent finding in breast biopsies and include intraductal papillomata, papillary lesions with or without atypia, and papillary carcinomas. Whether or not to excise benign papillary lesions diagnosed on core biopsy is controversial because only a fraction of lesions are later found to contain malignancy.[1] The risk of finding malignancy at resection varies by study and ranges from 6.3% to 67.0%.[1–15] Several authors have suggested that core needle biopsy can be used to accurately diagnose papillary lesions of the breast,[16–18] and stereotactic vacuum-assisted biopsy was supported by Mercado and colleagues.[7] Others have suggested that neither method is consistently reliable,[12,19] likely because of the histological heterogeneity of papillary lesions.[20] A recent study demonstrated that papillomata can be adequately followed by regular imaging and that there is a low risk of progression.[2] However, many reports recommend excision of any papillary lesion after biopsy diagnosis,[1,8,15] whereas others suggest excision of only those lesions showing atypia.[3,9,14,17]

Radiological features associated with malignancy include dilated ducts, intracystic masses, and well-circumscribed solid masses.[21] However, several studies have demonstrated that radiological examination cannot reliably distinguish between benign and atypical papillary lesions of the breast.[3,17,22]

In this study, we compared biopsy-diagnosed benign papillary breast lesions with their paired final resection specimens from the pathology database of The Ottawa Hospital (Ottawa, Ontario) to determine the frequency of malignancy at resection. We also reviewed radiology reports for information that could increase the level of suspicion when the biopsy specimen is examined.

Materials and Methods

Case Selection

This research was completed in compliance with The Ottawa Hospital Research Ethics Board under protocol #2010274-01H. The pathology database of The Ottawa Hospital was searched between January 2005 and March 2010 for all breast lesion diagnoses containing the terms *papillary* or *papilloma*, yielding 300 papillary lesions and 101 papillomata. From these, all biopsy specimens containing any malignancy (including ductal carcinoma in situ) were eliminated, leaving 54 papillary lesions and 85 papillomata. Only specimens from those biopsies with subsequent resection were retained, resulting in a total of 22 papillary lesions and 19 papillomata. The use of the term *papillary lesion* or *papilloma* reflected the personal choice of the reporting pathologist.

Data Collection

Full pathology reports and all associated imaging reports for the biopsy and resection specimens were retrieved from the hospital's electronic database. From these reports, we obtained each patient's age at the time of biopsy and resection, laterality, details of the histopathological findings, lesion size, method of biopsy used, and radiological descriptors.

Pathology

All tissue samples were fixed in 10% neutral buffered formalin and processed according to the standard protocol of the Department of Pathology at The Ottawa Hospital. Sections of 3 μm thickness were stained with hematoxylin and eosin. Immunohistochemical studies for myoepithelial

Table 1. Characteristics of Paired Biopsy (Needle Core and Vacuum-Assisted) and Resection Specimens

	Papilloma	Papillary Lesion
Biopsy diagnosis	19 cases	22 cases
Age at biopsy*	59 (43–89) y	60 (44–80) y
Age at resection*	60 (43–89) y	61 (44–80) y
Laterality	12/19 left	14/22 left
Imaging technique†		
Ultrasound	17 (89%)	18 (82%)
Mammography	6 (32%)	13 (59%)
MRI	1 (5%)	4 (18%)
Biopsy technique		
Core needle	9 (47%)	14 (64%)
Vacuum-assisted	10 (53%)	5 (23%)
Stereotactic	0 (0%)	3 (14%)
Excision technique		
Lumpectomy	15 (79%)	16 (73%)
Mastectomy	2 (11%)	6 (27%)
CDE	2 (11%)	0 (0%)

*Age at biopsy and at resection is listed as mean age, with range in parentheses.
†Imaging techniques exceed 100% because more than one modality was utilized for each breast lesion.
CDE = central duct excision; MRI = magnetic resonance imaging.

cells or deeper levels were obtained at the discretion of the reporting pathologist.

Slide Review

Available slides from biopsies and resections were reviewed by two surgical pathologists for possible causes of discrepancy. Of the 41 paired biopsy-resections, 35 sets of slides were available for microscopic examination. A discrepancy was designated a sampling error if the malignancy present in the final resection specimen was not present in the biopsy material. A discrepancy was designated an error of interpretation if there was atypia or malignancy in the biopsy material that was not commented on in the original pathology report. Only the material available to the reporting pathologist was reviewed; no additional sections or ancillary studies were ordered.

Results

Population Characteristics

The age of the patients at the time of biopsy ranged from 43 to 89 years among the papillomata group and 44 to 80 years in the papillary group, with a mean of 60 years (Table 1). Multiple imaging techniques were utilized in the assessment of the breast lesions; ultrasound was used most frequently in over 80% of women. Magnetic resonance imaging (MRI) was used least frequently (in only five women) (see Table 1). Biopsy technique varied. Ultrasound-guided core needle biopsy was carried out on 94% of the radiologically solid lesions whereas vacuum biopsy was used for all of the intraductal lesions and for 57% of the lesions with calcifications. Stereotactic biopsy was used for two lesions with microcalcifications. Information on the needle gauge used for the biopsy was provided for 5 of 19 papillomata and 17 of 22 papillary lesions. Most of the core needle biopsies were performed with a 14-gauge needle; a 10- or 11-gauge needle was used for the vacuum biopsies. Fifty-three percent of the vacuum-biopsied lesions and 35% of the core-biopsied lesions were subsequently upgraded to carcinoma at final excision.

The most common excision technique was lumpectomy; greater than 70% of masses were removed by this method in both groups. Central duct excision was performed on two patients following a core biopsy diagnosis of papilloma. Mastectomy was carried out on six patients following a biopsy diagnosis of papillary lesion (27%) and on two patients following a biopsy diagnosis of papilloma (11%). The rationale for using one excisional technique over another was not available.

Diagnoses on Biopsy

The lesions grouped as papillomata included those diagnosed as "papilloma" and "favor papilloma." If the diagnosis contained the term *papillary*, the lesion was designated as a papillary lesion, even if papilloma was considered. The use of the terms *papilloma* and *papillary lesion* was decided by the original reporting pathologist. Of the three papillary lesions in which a benign papilloma was considered, two were upgraded at resection and one was diagnosed as papillomata with atypia. A substantial fraction of both papillary lesions (13 of 22) and papillomata (7 of 19) contained areas of atypia either within the papillary lesion itself or in adjacent breast tissue. Of the lesions that were upgraded at resection, 67% had shown atypia at biopsy; however, 48% of the lesions that were not upgraded also showed atypia at biopsy.

1A

	Papillary	Papilloma	Total
Nodule/solid	12/22 (55%)	6/19 (32%)	18/41 (44%)
Cystic	5/22 (23%)	6/19 (32%)	11/41 (27%)
Calcifications	4/22 (18%)	3/19 (16%)	7/41 (17%)
Intraductal	1/22 (5%)	4/19 (21%)	5/41 (12%)

1B

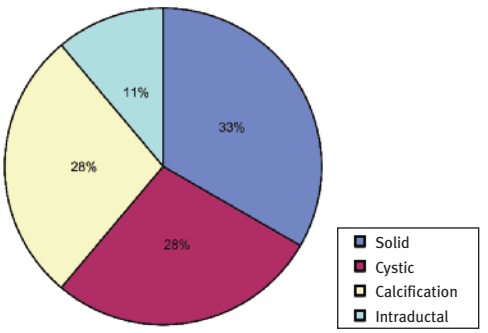

Figure 1. Radiological features of papillary breast lesions. *A,* Percentages of lesions described as solid/nodule, cystic, intraductal, or calcifications. *B,* Radiological description of benign lesions that contained carcinoma at final resection.

Table 2. Average Diameters of Lesions by Radiological and Gross Pathological Assessment

	Papilloma		
	Benign	Malignant	*p* Value
Radiological	0.9 cm	1.1 cm	.5946
Gross	1.2 cm	1.8 cm	.215

	Papillary Lesion		
	Benign	Malignant	*p* Value
Radiological	1.2 cm	1.6 cm	.1603
Gross	1.2 cm	2.1 cm	.1496

	Total		
	Benign	Malignant	*p* Value
Radiological	1.1 cm	1.6 cm	.0354*
Gross	1.2 cm	2.1 cm	.0221*

*Statistically significant as determined by unpaired student *t*-tests.

Diagnoses on Resection

Half of the malignant diagnoses at resection were ductal carcinomas in situ whereas the other half were carcinomas, three of which were papillary carcinomas. A second biopsy was performed prior to resection in seven cases – six papillary lesions and one papilloma. Carcinoma was identified in five of the seven follow-up biopsy specimens; in one, papilloma was diagnosed, and one showed only inflammation. All resulted in definitive excision.

Correlation with Radiological Findings

Reports from the various imaging modalities were reviewed for information on the appearance and size of the breast lesions. Lesions described as "solid" or "nodular" were grouped as solid lesions. Those with any cystic component (whether or not there was also a solid component) were grouped as cystic lesions. The remaining lesions were grouped as those containing calcifications and those described as "intraductal."

A solid mass was the most common radiological finding (18 of 41 lesions); intraductal lesions was the least common (5 of 41) (Figure 1A). Among lesions that were upgraded, intraductal lesions were the least common (11%) and solid masses were the most frequent (see Figure 1B).

The size of the lesion – as determined by radiology and by gross examination at final excision – was one feature that significantly correlated with the likelihood of subsequent malignancy. Lesions that were upgraded were significantly larger than those that were not upgraded (Table 2). This difference was not apparent when the lesions were separated into papillary lesion and papilloma subgroups. Data on lesion size were not available for all lesions, either because lesion size was not stated in the available radiology reports or because no mass was apparent in the specimen on gross examination.

Review of Slides

Of the 41 cases, 35 paired biopsy and resection sets were available for comparison (Table 3). Examination of the histopathological sections allowed determination of the likely cause of the discrepancy between the biopsy sample and the final resection. In the concordant cases, the material in the biopsy sample was histologically similar to that in the final resection (Figure 2). In the discordant cases, however, 10 biopsy specimens did not contain the areas of carcinoma that were present in the final resection, and the discordance was attributed to a sampling error. In 8 of the 10 sampling error cases, local excision was performed. Mastectomy was performed in 2 of the 10 cases; in both of these cases, a second intervening biopsy had demonstrated the presence of carcinoma. Sampling error was considered a minor discrepancy since the pathologist was not responsible for the sampling and the discordance was unavoidable. Any significant misinterpretation of the biopsy sample would

Table 3. Slide Review – Benign Biopsies with Carcinoma at Final Excision

Sample*	Error Cause	Type of Error	IHC†	Explanation
O-3	Sampling	Minor discrepancy	No	N/A
O-6	Sampling	Minor discrepancy	Yes	N/A
O-12	Sampling	Minor discrepancy	Yes	N/A
O-17	Sampling	Minor discrepancy	Yes	N/A
A-1	Sampling	Minor discrepancy	Yes	N/A
A-2	Sampling	Minor discrepancy	Yes	N/A
A-17	Sampling	Minor discrepancy	Yes	N/A
A-3	Sampling	Minor discrepancy	No	N/A
A-4	None	None	Yes	Bx report suggests excision
A-5	Sampling	Minor discrepancy	No	N/A
A-7	Sampling/time	Minor discrepancy	Yes	Resection 3 years after bx. DCIS not in bx
A-9	None	None	No	Bx report suggests excision
A-10	None	None	No	Bx report suggests re-bx or excision
A-12	None	None/sampling	No	Bx report suggests excision
A-13	Sampling	Minor discrepancy	No	Bx report suggests re-bx or excision
A-14	None/sampling	None	Yes	Bx report suggests re-bx or excision

*Samples coded "O" are papillomata; samples coded "A" are papillary lesions.
†Whether immunohistochemistry for myoepithelial markers was utilized in the interpretation of the initial biopsy.
bx = biopsy; DCIS = ductal carcinoma in situ; IHC = immunohistochemistry; N/A = not available.

have been classified as a major discrepancy; however, after a review of the sections, it was determined that there were no such errors.

Rebiopsy or excision was recommended in the pathology reports of six of the biopsies in the discordant cases. These cases were classified as having no cause or type of discrepancy because the pathologist's comments indicated a level of uncertainty about the nature of the lesion and concern for the presence of an underlying malignancy. Appropriate management of the case was suggested. Of these six cases, one patient had a fine-needle aspirate that was read as ductal carcinoma on the same date as the core needle biopsy, resulting in a subsequent mastectomy. A second patient also underwent mastectomy and had a final diagnosis of multifocal ductal carcinoma in situ (DCIS).

A final case of discordance was potentially attributable to the time between biopsy and resection. The biopsy indicated a sclerosing papillary lesion, and the final mastectomy 3 years later again showed the sclerosing papillary lesion but also showed the presence of DCIS. There was no hospital record of investigations between these two events. In only one case, a papillary lesion, was there a possible interpretation error in the examination of the biopsy material. This material contained several ducts filled with

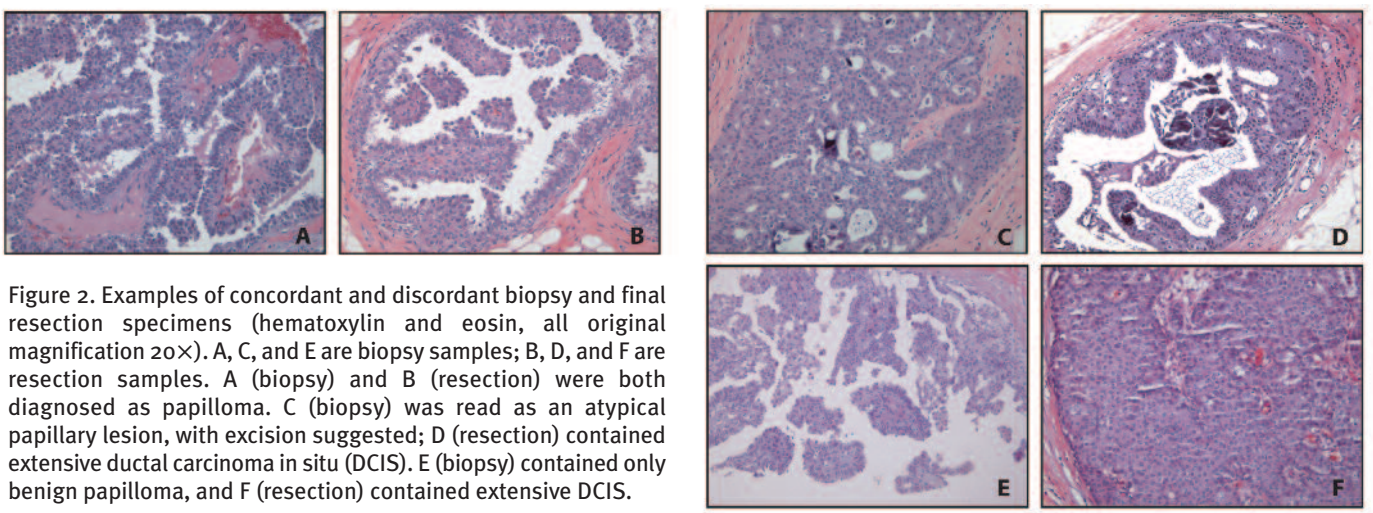

Figure 2. Examples of concordant and discordant biopsy and final resection specimens (hematoxylin and eosin, all original magnification 20×). A, C, and E are biopsy samples; B, D, and F are resection samples. A (biopsy) and B (resection) were both diagnosed as papilloma. C (biopsy) was read as an atypical papillary lesion, with excision suggested; D (resection) contained extensive ductal carcinoma in situ (DCIS). E (biopsy) contained only benign papilloma, and F (resection) contained extensive DCIS.

atypical cells that in aggregate measured 3.3 mm in diameter. Because the diameter of the involved area is not a universally agreed-upon criterion for DCIS, this specimen was also coded as a sampling error.

As mentioned above, eight women underwent mastectomy. From these, four specimens were found to contain papillary lesions; three of these were associated with DCIS, and the remaining specimen contained an atypical papilloma. In total, six cases were diagnosed as DCIS as the highest grade of lesion. Only one mastectomy specimen contained an invasive ductal carcinoma; this tissue had been biopsied subsequent to the diagnosis of papilloma and was known to contain DCIS. One mastectomy specimen contained only benign changes and no evidence of a papillary lesion.

Discussion

Despite the number of studies examining the management of papillary lesions of the breast, there is still no consensus on whether or not all biopsy-diagnosed papillary lesions require excision.[2,3,9,16,22–24] In our study, we used both the radiological findings and the final excisional diagnoses to determine whether or not all papillary breast lesions should be excised.

Because papillary lesions are heterogeneous, an important factor in making a correct diagnosis is the amount of tissue available in the biopsy specimen for study.[20] We examined material from both core needle and vacuum-assisted biopsies. The amount of tissue obtained by each method varies greatly, and the number of cores taken can be of importance. Studies of nonpapillary breast lesions demonstrated that core needle biopsy could have high diagnostic accuracy if at least four cores were taken with a 14-gauge needle.[25,26] However, another study demonstrated that for papillary lesions, even three or more cores result in a high rate of false-negative biopsy results.[15] In our study, information on the number of cores taken was rarely available and thus was not included.

Despite the difference in tissue volumes between core needle and vacuum-assisted biopsies, there was no significant difference between the groups in the frequency of subsequent diagnosis of malignancy ($p = 0.2186$, Fisher exact test, two-tailed).

Our results demonstrated a relationship between the size of the papillary lesion and the risk of subsequent carcinoma. For lesions with a subsequent diagnosis of malignancy, the average diameter was 1.6 cm by radiological assessment and 2.1 cm on gross examination, whereas for those whose diagnosis remained benign, the gross and radiological diameters were both 1.1 cm. These results are consistent with those of a study by Chang et al. that demonstrated a greater risk of malignancy for lesions greater than 1.5 cm in diameter.[3]

The rate of upgrading in our study was higher than that in most other studies. Even among studies that selected papillary lesions with atypia, the rates of malignancy at resection ranged from 11.4% to 26%[11,13,24] whereas our overall malignancy rate was 41%. As mentioned above, 23 of the 41 biopsy samples were reported as containing areas of atypia. Of those 23 samples, 12 (52%) were later found to harbour malignancy. Of the 18 nonatypical biopsy samples, six were subsequently upgraded. Our higher rate of malignancy may reflect our small sample size, since the rate of resection at our institution was low during the study period. Only 41% of papillary lesions and 22% of papillomata were resected. Why these were selected for resection is unknown, but of 18 patients with discordant cases, four had a subsequent biopsy whose sample contained malignant tissue, likely prompting the resection. Two patients with concordant benign biopsy/resection diagnoses also had repeat biopsies with maintained benign diagnoses; yet the patients still underwent resection.

In summary, 41% of biopsy-diagnosed papillary breast lesions at our institution were upgraded to malignancy at resection. The most frequent cause of discordant biopsy/resection was the absence of malignant tissue in the biopsy material. The rate of subsequent malignancy was greatest for those lesions that were on average 1.6 cm in diameter by radiological assessment. Our data suggest that owing to the high rate of carcinoma, all biopsy-diagnosed papillary lesions should be excised.

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ORIGINAL ARTICLE

Technology, Education, and Society in the Transformation of Canadian Pathology: The Department of Pathology at the Winnipeg General Hospital, 1936–1972

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ABSTRACT

During the middle two quarters of the twentieth century, Canadian pathology evolved into a modern specialty by incorporating new technology to satisfy surgical demands, among others, and by institutionalizing research and teaching. This essay describes developments at the Department of Pathology of the Winnipeg General Hospital in Manitoba that illustrate such an evolution. Frequent references to events at the national level support the thesis that occurrences in Winnipeg were not unique. Economic support by provincial and federal governments, participation by the administrations of the hospital and the Faculty of Medicine, supervision by the Royal College of Physicians and Surgeons of Canada, and the enthusiastic contribution of pathologists were the factors responsible for the transformation of pathology in Winnipeg. One can induce from this analysis that events were similar in other Canadian provinces.

RÉSUMÉ

Au Canada, la pathologie s'est transformée au milieu du siècle dernier en une spécialité moderne en adoptant de nouvelles technologies pour satisfaire les besoins de la chirurgie notamment et en établissant la recherche et l'enseignement sur une assise institutionnelle. L'article illustre cette évolution en décrivant le parcours du service de pathologie de l'Hôpital général de Winnipeg au Manitoba. L'exemple de Winnipeg n'est pas unique, l'essor de la pathologie était manifeste un peu partout au pays. L'appui économique des gouvernements provincial et fédéral, la participation de la direction de l'hôpital et de la faculté de médecine, la supervision du Collège royal des médecins et chirurgiens du Canada et l'apport de pathologistes enthousiastes ont favorisé la transformation de la pathologie à Winnipeg. L'on peut facilement imaginer qu'il en a été de même ailleurs au pays.

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The transformation to the modern practice of pathology occurred in Canada during the middle two quarters of the twentieth century. This transformation can be traced in the history of the Department of Pathology at the Winnipeg General Hospital (WGH), an institution affiliated to the University of Manitoba. After the departure of then-chairman William Boyd for Toronto in 1936, the department went through a series of innovations introduced by enthusiastic young physicians in a period that lasted until 1954. From 1954 to 1972, the department continued expanding in service, teaching, and research and became a modern institution.

This essay shows that the transformation resembled the evolution of the specialty in Canada. Primarily, the transformation was made possible by the introduction of new technology to satisfy surgical demands, among others, and by the influence of the Faculty of Medicine. Secondarily, the transformation had the economic support of the hospital through private contributions and public health insurance, the influence of the Royal College of Physicians and Surgeons of Canada, and the professional interaction of its members with the national and international communities.

Department Conditions Resulting from the Economic Depression (1938–1944)

In the 1930s, the Depression sharply curtailed economic support to the WGH, and hospital beds became occupied mainly by nonpaying patients.[1–3] Under these conditions, the hospital's pathology department changed little for the first 4 or 5 years after Boyd's departure. The staff was stable and consisted of Daniel Nicholson, Sara Meltzer, and a new recruit, John McDonald Lederman. The same stability was true of the technical and clerical staffs. Senior interns spent 1 year in the department. The same laboratory tests were offered, but publications fell dramatically to one article. Working conditions, however, seemed to be satisfactory; for technologists in particular, conditions appeared not to be different from those described in the Maritimes.[4]

The economic situation was reflected in the departmental facilities. Hoogstraten commented that in 1940 to 1941 (the year he was a junior rotating intern), autopsies were performed with instruments and other items discarded by the operating room; these included rubber gloves that were patched and inelastic.[5] There were no photographic facilities; if photographs were needed, the specimens had to be transported to the medical school. There were also chronic complaints about inadequate laboratory space. Hoogstraten also confirmed that the pathology staff of the whole department, the hospital, and the university consisted of three individuals (Nicholson, Lederman, and Meltzer) apparently working from 8 a.m. to 4 p.m. Monday through Friday.[5]

The pathology department therefore suffered the same economic limitations as the WGH, and a hospital prepayment plan (Blue Cross) was the response. As confirmed by the president of the hospital's board of directors in 1940, the budget in those years was provided by the provincial and municipal governments and by private sources (i.e., by prepaid plans of insurance companies).[6] Nevertheless the hospital still functioned largely as a private institution delivering a public service and, in contrast to early years, without federal funds.[7]

In spite of these conditions, new recruits came to the department. Donald Willis Penner was incorporated as a resident in 1942, and he and Lederman (the assistant pathologist) carried out the workload of the department.[8] Meltzer died in October of 1942 after 15 years of service, and Thomas Harry Williams replaced her as associate pathologist that same year. Williams was an expert in parasitology who taught this subject to prepare future physicians for eventual enlistment in the army.[9] In March 1943, Penner left for New York for a year of training at Memorial Hospital; on his return to Winnipeg in April 1944, he was appointed assistant pathologist of the hospital and demonstrator to the Faculty of Medicine.[10,11] Georgina Ruth Hogg came in 1943 as a junior rotating intern. She devoted her professional life entirely to the department, following closely in Meltzer's footsteps.

Creation of a Blood Bank, Control of Infection, and Expansion of Surgical Pathology (1942–1954)

Three scientific discoveries were applied in the department after 1940 to support demands of surgery: blood banking, technical advances in microbiology, and the microscopic examination of tissues. The first blood bank in North

America was established at the Cook County Hospital in Chicago in 1937.[12] In Winnipeg a blood bank was established under the leadership of Penner and Lederman, the guidance of Nicholson, and the strong support of private companies, community organizations, and hospital authorities. However, physical facilities, resources, and personnel soon became insufficient. A shortage of blood donors led to reliance on medical students as donors. The hospital closed the blood bank on January 30, 1950, when the Canadian Red Cross Donor Service took control of blood supply for Manitoba hospitals.[13,14] This transfer coincided with the government's creation in 1947 and 1948 of a voluntary donor system that was run by the Red Cross.[15]

The bacteriology section of the department developed further under the leadership of John Charles Wilt and was part of the so-called "therapeutic revolution" that emerged after the end of World War II.[16] The bacteriology section had traditionally been the section that produced the highest number of tests, but the increment appeared to be exponential during this period. Cultures and tests for bacterial sensitivity to antibiotics represented the greatest portion of this increment.[17] New techniques for culturing bacteria were simultaneously introduced, and for the first time, samples taken directly from patients could be tested to determine bacterial sensitivity. Attention was also directed to the culture of viruses. Infection control therefore became one of the main responsibilities of the department.[18]

Another technical advance was microscopic examination of tissues and cells. The quality of biopsy reports was significantly improved with the arrival of Penner. In contrast to biopsies, autopsies were not finalized promptly due to the reduced number of pathologists. Autopsies were losing relevance, as is evident from the efforts of hospital accreditation agencies such as the Royal College of Physicians and Surgeons of Canada, which demanded them for a hospital's accreditation.[19] Cytopathology was also introduced by Penner in the mid-1940s at a time when there was skepticism about its value as a diagnostic procedure. Its practice, however, increased rapidly.

Expansion of the Department and a New Orientation for Pathology (1954–1957)

Optimism prevailed in the department in the early 1950s. The atmosphere at the Medical College was described as peaceful, in part because the core activities were carried out at the hospital. The teaching of pathology to medical students was essentially unchanged from the curriculum introduced by Boyd. Nicholson and Lederman were professors. Lederman was secretary of the faculty, a member of the Medical Faculty Council Executive, and the faculty representative in the university senate. Meanwhile, Penner was an assistant professor and Hogg was demonstrator. Clearly there was an inversion in importance of the kind of appointments of these individuals that reflected the relationship between the hospital and the university departments.

Optimism was the evident result of the department's important contribution to the practice of surgery. However, unexpected events dampened that optimism. In April 1953, Nicholson took a leave of absence due to illness,[20] and the consequences of his departure would affect the department for the next 20 years, partly owing to personalities. Penner was promoted to acting director of the hospital's laboratories whereas Lederman was appointed acting chairman of the university department. In 1954, the section of bacteriology became an independent department under the leadership of Wilt, reducing the hospital's pathology department to anatomical pathology and hematology, a unique combination.[21] The same year, Lederman was appointed chairman of the university department, replacing Nicholson, who resigned at the end of his term; Penner was appointed medical director at the hospital. In the Faculty of Medicine's annual report of 1955, Lederman is mentioned as retiring from the active staff of the WGH and being appointed "Honorary Consultant Pathologist." The promotions were the natural consequence of the efforts made by these three individuals in their respective areas of interest in the previous decade. The most important consequence was that the hospital department administration became independent of the college.

In the following 3 years (1955–1957), the hospital department established itself as a strong and independent entity that fulfilled the functions of service, clinical research, and teaching. This was made possible in part by the collaboration of a group of pathologists – Georgina Ruth Hogg, H. M. Ross, H. T. G. Strawbridge, and B. Wolanskyj –

under the leadership of Penner. Lederman and Williams acted as consultants in hematology and parasitology, respectively. A strong clinical orientation was given to the department in response to health issues prevalent in Winnipeg in those years. Programs such as the cervical cancer screening program and research in cardiovascular diseases exemplified the orientation. Longitudinal studies in perinatal mortality were also contributing to an understanding of the new causes of death at that age in Manitoba. The incorporation of John Suddaby as an efficient coordinator of the department in 1957 contributed significantly to maintaining stability in spite of continuous limitations in technical personnel.[22]

In general, the conditions that were shaping the evolution of pathology as a specialty at the WGH in the 1940s and 1950s were similar to those at other centres in North America. Such conditions demanded more economic resources, which were beyond the existent provincial support provided to the hospital. This produced a political response by the federal government that would dominate health care for the rest of the twentieth century.

Conditions in the Department as a Result of New Federal Support (1958–1964)

The federal government was to become the main patron of the hospital's department. In 1955, five provinces (excluding Manitoba) that already had universal hospital insurance plans pressed the federal government to honour its 1945 hospital insurance offer to share hospital costs. As a result, the Hospital Insurance and Diagnostic Services Act was passed by Parliament and adopted by Manitoba on July 1, 1958.[23]

The introduction of the federal act favoured the implementation of Penner's vision for the department, and he had the collaboration of Hogg, Ross, Strawbridge, and L. S. McMorris. (Later, S. C. Lauchlan, J. E. Arnott, D. S. Horoupian, J. Taylor, C. Merry, and N. Shojania joined the team. D. Buntine and F. William Orr arrived in the last 2 years of the WGH's existence.) The vision was based on the principle that university hospital pathology departments must provide service, teaching, and research in an integrated manner but that patient care, not teaching and research, was the essence of their existence. The vision is clearly stated in the annual reports of the department.[24,25]

What were the results of the implementation of this vision? Analysis of the service component indicates that the total number of tests increased by 500% during this period. Although it is undeniable that the federal plan was partly responsible (as it covered not only ward care but also diagnostic laboratory services), additional explanations are also possible. Visibility of pathologists in the hospital might have played a role, as was recognized by the department heads of several specialties in their annual reports. An increase in the number of surgical operations by around 34% was another factor. Finally, the introduction of automation and a new style of reporting the annual number of tests may have also contributed. This work overload favoured subspecialization not of organs but of clinical specialties.

The introduction of cytopathology was another result at a time when its value was underestimated and when it was not seriously considered by the majority of practising pathologists in North America. Fine-needle aspiration biopsies, a novelty, were initiated in 1959, and the first provincial screening program in cytology for cancer of the cervix (one of the first such programs in Canada) was introduced in 1963. On January 1, 1961, the first Canadian school of cytotechnology opened in the hospital department.[26]

Teaching is the second area that permits evaluation of the vision. By this time, the department had been recognized as a centre of training for candidates planning to take the Royal College and American Board of Pathology examinations. However, some residents were recruited directly from abroad, so numbers declined when there were immigration problems.[27] These recruits became necessary for the functioning of the autopsy service, so the section suffered with such problems; in reality, the recruits were cheap labour.[28]

Teaching also played a pivotal role in the training of allied health professionals. In 1963, the Province of Manitoba initiated a laboratory technologist training program in coordination with the Manitoba Institute of Technology and the WGH to provide training in cytology, histology, and hematology[29]; The Canadian Medical Association approved the program in 1967. In 1965, the department began to

develop a new concept of "tissue diener." The initial idea was to train a technician expert in the flow of information. This was the beginning of pathologists' assistants, a new model of professional work that the department was one of the first institutions in North America to implement.[30]

Research and development was the third component of the vision. All staff members were participants in this domain, frequently as supervisors of residents and medical students. The number of papers published surpassed that of any previous period. Penner remained the most visible member in local, national, and American publications whereas Lederman's participation in these activities at the hospital was minimal.

Yet, some factors limited the implementation of the vision. Perhaps the most visible were the poor physical environment and additional demands without compensation in resources. In addition, there was a shortage of technical and clerical personnel due to high turnover, which reached almost 50% in some years. The introduction of the 5-day 48-hour shift on October 1, 1958, also created an additional strain on personnel resources.[31] This was the situation of the department in 1964.

New Relationship of the Hospital Department with the Faculty of Medicine (1964–1968)

Since 1954, the hospital department had been only nominally related to the university department. Drummond Bowden confirmed this when he arrived in 1964; they were two independent units.[32] However, in the 1960s, events that are more evident in retrospect were occurring in the hospital and at the college, along with an evolving mindset in the professional and managerial staffs of both institutions. At the hospital, the new mentality embraced the possibility of significantly improving the WGH as an affiliated university teaching hospital by bringing it closer to the university. Surprisingly, since its beginnings, the hospital had had no formal agreement of cooperation with the University of Manitoba. The need for an agreement was based on the acceptance that both institutions had the same interests (i.e., education and research). An agreement was formalized on April 26, 1967, maintaining the hospital as an independent institution. The plan evidently was to establish an ambitious larger facility as in other jurisdictions in North America.

At the Medical College, the administration was also interested in becoming closer to the hospital, and new events (both incidental events and those resulting from Lederman's death) fitted the mood in the hospital. These events came in 1964 with the appointment of John P. Wyatt as professor and chairman of the department and with the appointment of Drummond H. Bowden as associate professor. One of the main reasons for Wyatt's appointment was the intention to modernize undergraduate instruction in pathology, as teaching still followed the curriculum introduced by Boyd in the 1920s.[32] There was also need to introduce basic science research, which had been practically non-existent.[32] Otherwise, the university had no impact on postgraduate education, which was designed and directed by the hospital pathologists. In Wyatt's opinion, the university department needed the structural changes that had already been implemented in the hospital department.[33] He came to Winnipeg with the idea that the most important functions of an academic department of pathology were teaching and research.

Under these conditions, what was the impact of the university-hospital agreement on the hospital's pathology department? The most visible effect was the effect on teaching. Undergraduate and postgraduate education became demanding and led pathologists to participate less in extra-departmental activities. Claims for financial support and more professional staff were frequently heard. The situation became so critical that the personnel department of the hospital conducted a job analysis in the department.[34] Residents were now admitted to be taught rather than to expand resources for service, and other departments utilized the facilities for supplemental training for their residents. Approval of the program by the Royal College of Physicians and Surgeons of Canada in 1967 supported that integration and recommended that it be strengthened. As a result, although initially the hospital administration appointed interns and the hospital department heads appointed residents, a committee with representation from the hospital and the university came to appoint both. In this manner, the university department progressively took control of postgraduate education.

How did the agreement affect clinical research? One of the intentions of the affiliation was to expand research in the

hospital. However, it had the opposite effect. When comparing the academic production of the department before and after 1967, one should note that it decreased by almost 50%.

One might conclude that the agreement's consequences for the hospital department were the result of distinct conceptualizations of pathology. Penner and Wyatt disagreed about the philosophy of the department. Bowden described their relationship: "At a personal level, continuing battles between Penner and Wyatt did little to create an atmosphere conducive to developing a co-operative plan" (Ian Adamson, personal communication).[32] On balance, however, long-term results were positive in spite of the problems. In particular, training of new pathologists reached a high level of sophistication under a new educational philosophy, subspecialization in practice improved the quality of service, and basic research supplemented the reduction in clinical research.

The Final Years: Medicare and the Creation of the Health Sciences Centre (1969–1972)

The introduction of medicare by the federal government on April 1, 1969, also generated rapid and constant change in patient care at the WGH. The practice of medicine had become more complex and sophisticated as a result of new scientific and technological advances, and the medical personnel of the hospital increased by approximately 70% between 1964 and 1970. However, no funds were available to support the medical staff in spite of negotiations carried out over several years to secure funds for such activities.[32]

In the pathology department, annual workloads increased by approximately one third between 1964 and 1970. The most evident increases were in histopathology and cytology. In histopathology, the increment was more than 40% and was mainly due to work in surgical pathology, as the number of surgical operations had increased by around 18%. The workload in cytology, on the other hand, had increased by about 75% as a consequence of the provincial screening program for cervical cancer. This volume was among the largest of any cytology laboratory in North America. There were also requests for more technically complex tests. The professional staff of the department was insufficient to cope with the demand. The situation was made acute by small salaries paid to the pathologists, who had to supplement their income with fees derived from medico-legal autopsies and private laboratories. Undoubtedly, the introduction of medicare and the new practice of medicine had only increased demand on services. These were the conditions in the department in 1972.

The 1960s was a decade of change.[35] It was in this decade that the idea of creating a "megacentre" – the future Health Sciences Centre – appeared. It was a consequence of a general trend in Canada toward organizing health services on a regional basis.[36] On January 1, 1972, the WGH ended its existence as an autonomous institution, and a new medical administration was formally created.[37] On that date, the pathology department became the Department of Pathology of the Health Sciences Centre.

Summary

The Department of Pathology of the Winnipeg General Hospital (WGH) evolved in parallel with the specialty in Canada during the middle two quarters of the twentieth century. New technology was introduced to satisfy surgical demands, among others, in accord with similar developments in other provinces. Experts recruited from abroad initiated basic research, and the Royal College of Physicians and Surgeons of Canada monitored the quality of teaching. This evolution was supported by the administrations of the WGH and the Faculty of Medicine with the economic participation of the provincial and federal governments.

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Rapid Rescreening of Papanicolaou Tests: Comparison with 10% Rescreening

Harkiran Kaur, MB, BS, MSc, FRCPC, Aaron Haig, MD, FRCPC, Alison Nell, MLT, Michele M. Weir, MD, FRCPC

ABSTRACT

Purpose: The aims of this study were to (1) assess the effectiveness of 100% rapid rescreening (RR) compared with 10% random and targeted rescreening (RATR) of Papanicolaou (Pap) tests, (2) examine reasons for significant discrepancies at RR, and (3) examine the outcomes of significant discrepancies at RR.

Methods: A comparison of the time taken for RR and RATR and the proportion of false negatives (FNP) was made. Follow-up of significant discrepancies at RR was performed by chart review. Pap tests identified at RR with a significant discrepancy were retrospectively examined by two reviewers to identify reasons for the difference between initial and rapid rescreening interpretations.

Results: The FNP by RATR was 0.9% (2004–2005) and by RR was 1.5% (2006–2007). The time needed was 1.5 hours per day (one cytotechnologist) for RATR and 4 hours per day (two cytotechnologists) for RR. Reasons for significant discrepancies at RR included screening errors (32%), interpretive errors (23%), and both screening and interpretive errors (45%). Follow-up of significant discrepancies in 31 cases resulted in confirmation of a squamous intraepithelial lesion (SIL) or malignancy in 10 cases.

Conclusions: The FNP with RR was higher than that with RATR. The time involved for RR was two to three times greater than for RATR. Analysis of significant discrepancies at RR revealed SIL or malignancy in some cases.

RÉSUMÉ

But : Les buts de l'étude consistent (1) à évaluer l'efficacité comparative du réexamen rapide de 100 % des tests de Papanicolaou et du réexamen sélectif d'un échantillon aléatoire de 10 % des tests, (2) à cerner les motifs des constatations différentes au réexamen rapide et (3) à examiner les répercussions de la des constatations au réexamen rapide.

Méthodologie : Comparaison entre le réexamen rapide et le réexamen sélectif et aléatoire des points de vue du délai d'exécution et de la proportion de résultats faux négatifs; examen du dossier médical en cas de divergence importante des constatations au réexamen rapide. Revue rétrospective des frottis vaginaux pour lesquels il y a divergence des constatations au réexamen rétrospectif par deux examinateurs pour cerner les motifs de divergence de l'interprétation initiale et de l'interprétation au réexamen rapide.

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Competing interests: None declared

Résultats : La proportion de faux négatifs est de 0,9 % (2004-2005) au réexamen aléatoire et sélectif et de 1,5 % (2006-2007) au réexamen rapide. La durée d'exécution est de 1,5 heure par jour (un cytotechnologiste) dans le cas du réexamen aléatoire et sélectif et de 4 heures par jour (deux cytotechnologistes) dans le cas du réexamen rapide. Les motifs de divergence notable des constatations au réexamen rapide sont l'erreur au dépistage (32 %), l'erreur d'interprétation (23 %) et la conjugaison des deux types d'erreurs (45 %). La révision de 31 cas de divergence des constatations aboutit à la confirmation d'une lésion intraépithéliale malpighienne ou d'une tumeur maligne dans 10 cas.

Conclusion : La proportion de faux négatifs au réexamen rapide est plus élevée qu'au réexamen aléatoire et sélectif. Le délai d'exécution du réexamen rapide va du double au triple de celui du réexamen aléatoire et sélectif. La divergence des constatations au réexamen rapide s'explique dans certains cas par la présence d'une lésion intraépithéliale malpighienne ou d'une tumeur maligne.

The Papanicolaou (Pap) test has been an effective, low-cost, reliable screening tool for cervical precancer that aids in the identification of squamous intraepithelial lesions (SILs) and has led to a steady decline in mortality due to cervical cancer in the last five to six decades.[1,2] However, false-negative results on Pap tests do occur, which may have significant implications for patients. As a result, quality assurance procedures (including rescreening) are essential to minimize false-negative results.

Different methods used to address Pap test false-negatives include 10% random and targeted rescreening (RATR), 100% rapid rescreening (RR), and prescreening (PS), all of which are used in different institutions around the world. The technique of RR was first described in 1957 in the United States,[3] although it gained more widespread acceptance in the United Kingdom, where it is the quality assurance method of choice.[4,5] Various studies have shown a higher percentage of false-negative results identified by RR than by random rescreening (RAR).[6,7] PS has also been shown to be superior to 10% RAR in a few studies and to have a higher sensitivity than RATR.[8]

The aims of this study were to (1) assess the effectiveness of 100% RR compared to 10% RATR in regard to Pap tests, (2) examine reasons for significant discrepancies at RR, and (3) examine the outcomes of the significant discrepancies identified at RR at our institution.

Materials and Methods

We compared the time required for rescreening and the proportion of false-negative test results (FNP) between RR (2006–2007) and RATR (2004–2005) at our institution. For both the RR and RATR groups, the Pap tests were from colposcopy clinics, obstetrics and gynecology outpatient clinics, and the offices of family physicians.

In 2004–2005, after primary screening, 10% of negative cases (5% targeted and 5% random) were rescreened. The samples for 2004 were conventional smears whereas those for 2005 were mostly liquid-based samples (ThinPrep) with a few conventional smears. One cytotechnologist daily rescreened the entire slide by using the Turret screening method.[9]

In 2006–2007, all negative cases after primary screening were rapidly rescreened prior to sign-out. All samples were liquid based. Two cytotechnologists were on the daily schedule for rapid rescreening; a maximum of 40 slides was allotted to each. As much of the ThinPrep slide as possible was rapidly rescreened in 1 minute, with attention paid to the clear areas between cells to identify small immature cells. If any abnormal cells were identified, the slide was assigned to a full rescreening by a third cytotechnologist and was subsequently reviewed and reported on by a pathologist, regardless of the rescreening cytotechnologist's opinion.

For this study, a significant discrepancy was defined as a case that had an initial diagnosis of negative for intraepithelial

lesion and malignancy but was found on rescreening to be a low-grade squamous intraepithelial lesion (LSIL), a high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells, cannot exclude HSIL (ASC-H), atypical glandular cells (AGC), adenocarcinoma in situ, carcinoma, or any other condition that led to a significant management difference.

Cases with significant discrepancies at RR were examined in blinded fashion by two reviewers (the authors) to identify reasons for the difference between the initial and rapid rescreening interpretations. The reasons were classified into screening errors (cells not seen), interpretive errors (cells seen but not interpreted correctly), or both, with further categorization of each error.

Follow-up of the significant discrepancies was performed by chart review to determine if there was any clinical impact. Pap tests with concurrent abnormal biopsies were not counted among cases with significant clinical impact unless the Pap test diagnosis was more significant than the biopsy diagnosis and would have changed management. Only cases in which management was changed exclusively because of the cytology diagnosis were counted as having a clinical impact.

Results

By RATR, only one significant discrepancy (LSIL) was detected (1,871 screened cases, 1,061 abnormal cases, FNP 0.9%): one per 413 abnormal cases (FNP 3.3%) in 2004 and none per 648 abnormal cases in 2005 (Tables 1 and 2). In contrast, RR detected 57 significant discrepancies (32,254 screened cases, 3,938 abnormal cases, FNP 1.5%): 37 per 1,953 abnormal cases (FNP 1.9%) in 2006 and 20 per 1,985 abnormal cases (FNP 1.0%) in 2007 (see Tables 1 and 2). The time needed for RATR was 1.5 hours per day (one cytotechnologist); that needed for RR was 4 hours per day (two cytotechnologists).

The significant discrepancies with RR had the following diagnoses: ASC-H (51%), LSIL (31%), AGC (9%), HSIL (7%), and malignant cells (2%) (Figure 1). The discrepancies resulted from screening errors (30% of cases), interpretive errors (24%), or both (46%) (Figure 2). The causes of the screening errors were the following: few abnormal cells (42%), obscuring inflammation (22%), small cells (19%), abundant immature metaplasia (12%), abundant glycogenated cells (3%), and confounding *Candida* effect with perinuclear inflammatory halos (2%) (Figure 3). The interpretive errors were the result of the underinterpretation of a few abnormal cells (35%), cells associated with inflammation (27%), immature metaplasia (16%), small cells (14%), glycogenated cells (4%), and *Candida* effects (4%) (Figures 4–6).

Follow-up of significant discrepancies at RR was available

Table 1. Comparison of False-Negative Proportion, Number of Significant Discrepancies, and Cytotechnologist Time Requirement for Random and Targeted Rescreening versus Rapid Rescreening

	RATR (2004–2005)	RR (2006–2007)
FNP	0.9% (1 case)	1.5% (57 cases)
Cytotechnologists required	1	2
Time (h/d)	1.5	4.0

FNP = false-negative proportion; RATR = random and targeted rescreening; RR = rapid rescreening.

Table 2. Comparison of Significant Discrepancies and False-Negative Proportion in Screened and Abnormal Cases, by Year

Year	Cases Screened	Abnormal Cases	Significant Discrepancies	FNP (%)
		RATR		
2004	778	413	1	3.3
2005	1,093	648	0	0.0
2004–2005	1,871	1,061	1	0.9
		RR		
2006	15,118	1,953	37	1.9
2007	17,136	1,985	20	1.0
2006–2007	32,254	3,938	57	1.5

FNP = false-negative proportion; RATR = random and targeted rescreening; RR = rapid rescreening.

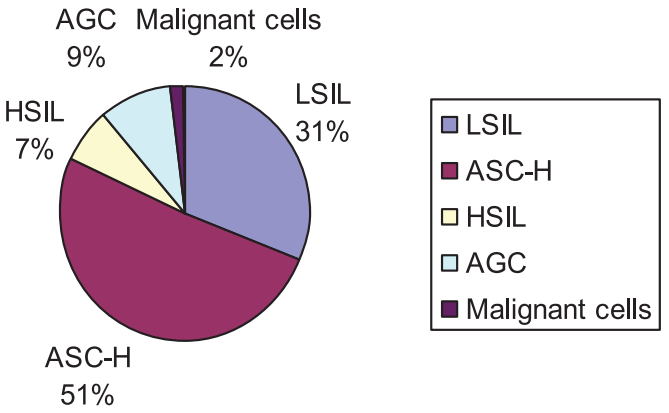

Figure 1. Pie chart illustrating significant discrepancies (n = 57) and their distribution. AGC = atypical glandular cells; ASC-H = atypical squamous cells, cannot exclude HSIL; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.

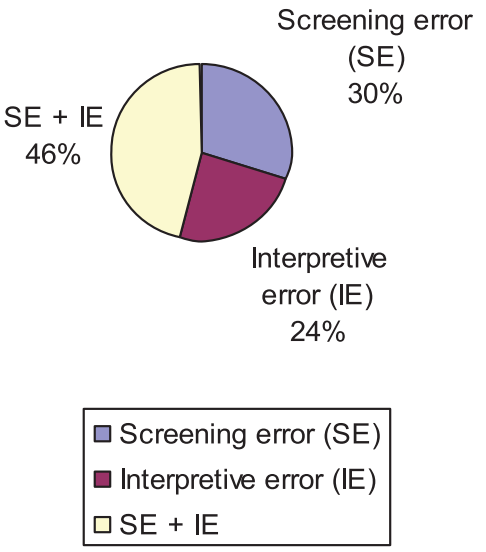

Figure 2. Pie chart illustrating reasons for significant discrepancies identified by rapid rescreening (n = 57).

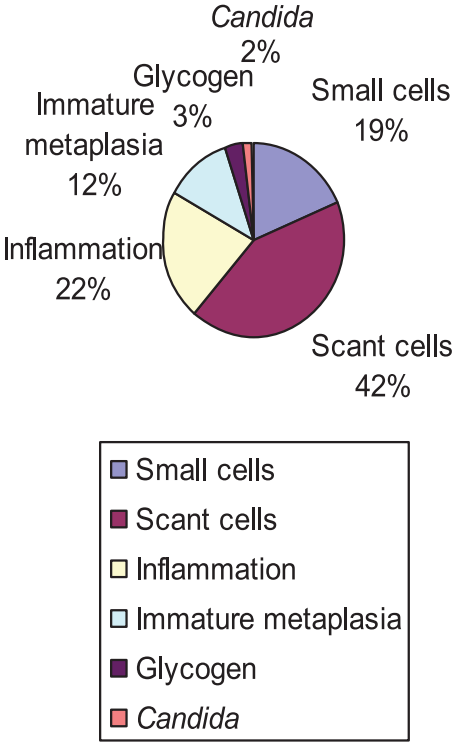

Figure 3. Pie chart illustrating reasons for significant discrepancies with screening (n = 43).

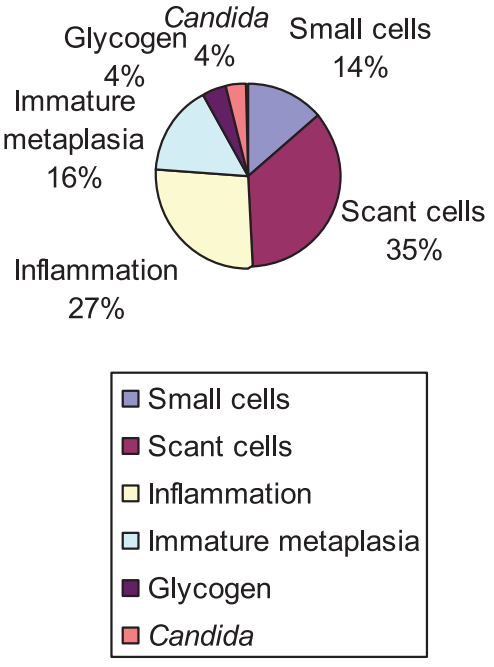

Figure 4. Pie chart illustrating reasons for significant discrepancies in interpretation (n = 40).

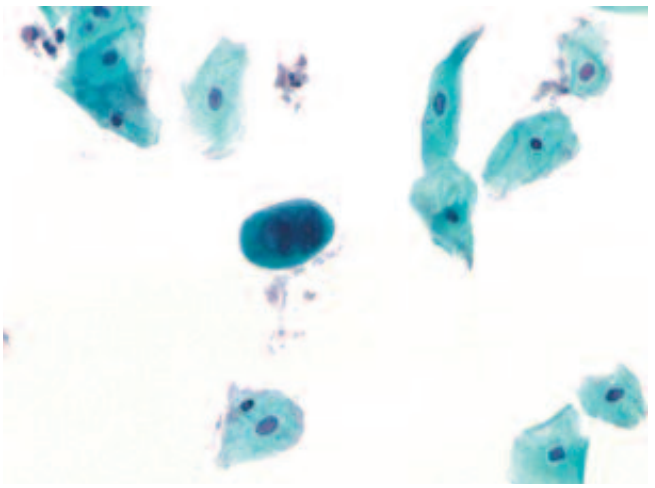

Figure 5. A case of low-grade squamous intraepithelial lesion screening error due to rare diagnostic cells is shown here.

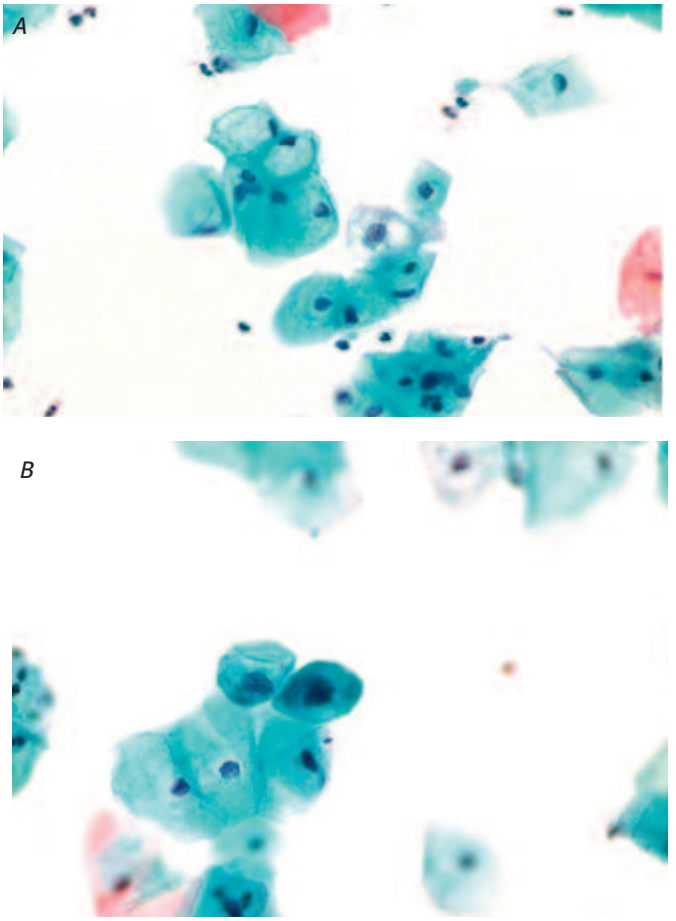

Figure 6. Examples of significant errors of interpretation. *A*, Glycogenated cells. *B*, Reactive cells, which can mimic a low-grade squamous intraepithelial lesion and lead to interpretive difficulties.

in 37 of 57 cases (65%), with confirmation of a SIL or malignancy in 22 (60%) by chart review. The cases with available follow-up included those with LSIL (8), HSIL (3), ASC-H (21), AGC (4), and malignant cells (1). RR had a clinical impact in 10 of 37 cases (27%), all of which were ASC-H.

Discussion

The identification of the precursor lesions of cervical cancer (i.e., SILs) is important to lessening the mortality and morbidity associated with the disease. Missed SILs (false-negatives) may also be a source of litigation. (Not surprisingly, the small abnormal cells found on rescreening negative tests have been called "litigation cells.")[10] As a result, quality assurance measures are essential to increasing the sensitivity of the Pap test. The different methods may include RR, RATR, PS, and automated rescreening. The purposes of our study were to compare the effectiveness of 100% RR compared to 10% RATR and to examine the reasons for (and outcomes of) significant discrepancies at RR.

Our study showed results similar to those of other studies for RR and RAR, with FNPs of 1.5% by RR and 0.9% by RATR of 10% of Pap tests. However, RR was two to three times more time consuming and required more personnel. Various studies have shown a higher sensitivity for RR than for RAR. Lemay and Meisels showed that RR identified more false-negative results than did RAR.[11] The FNP with RAR was 0.7% as compared to 13.1 % with RR. RAR involved the examination of 160 negative cases for one false-negative case (all atypical squamous cells of undetermined significance [ASCUS] in that study) to be detected, whereas RR involved the examination of eight negative cases for one false-negative case (either ASCUS or LSIL) to be detected.[11] Amaral et al. showed that RR identified 69.9%, 95.7%, and 100% of ASCUS, LSIL, and HSIL cases, respectively, with a sensitivity of 73.5% and a specificity of 98.6%, compared with RAR, which had a sensitivity of 40.9% and a specificity of 98.8%.[12] The false-negative cases were mostly cases of ASCUS. These authors also concluded that 1 minute is probably a reasonable time for a well-trained cytotechnologist to identify false-negative cases by RR. Arbyn and Schenck showed similar results and suggested that RR is

also a more cost-effective method than RAR.[13]

Suelene et al. showed that PS detected 132 false-negative cases as compared to 7 cases using RATR and 32 cases using RAR with a targeted approach. PS required twice the time of RAR but had a sensitivity (74.9%) superior to that of RAR (53.8%). The specificity of PS (96.7%) was lower than that of RAR (99.3%).[8] Arbyn and Schenck showed that rapid prescreening has a high diagnostic yield for severe dysplasia and is comparable to RR in sensitivity.[14] One study reported a 54–92% sensitivity for high-grade abnormalities and a 33–75% sensitivity by rapid prescreening, with cytotechnologists showing a wide range of performance levels.[15] Various studies have shown that PS is superior to RAR and equivalent to (or perhaps better than) RR.[14] Djemli et al. established a 43.5% sensitivity for PS with 17 cases that included diagnoses of LSIL and HSIL detected only on PS.[16] A recent study by Brimo et al. showed that PS aided in improving the overall sensitivity of routine screening, increased the performance of cytotechnologists, and standardized the laboratory by bringing the sensitivity of individual cytotechnologists into a similar range. It also helped in monitoring screening performance in a real-life practice setting.[17] Another study demonstrated that the assessment of the ratio of atypical squamous cells to squamous intraepithelial lesions (ASC/SIL ratio) during prescreening could be used as a quality control tool for gauging the performance of cytotechnologists. The authors correlated the ASC/SIL ratio with screening accuracy and concluded that an ASC/SIL ratio of less than 1.5 may suggest inadequate screening sensitivity for a cytotechnologist.[18] In a different study, based on their prescreening data, they also suggested that the screening sensitivity of individual cytotechnologists did not appear to be related to experience or workload, contrary to general belief.[19]

Other approaches to reducing false-negative results include seeding abnormal slides into the routine workload to increase the sensitivity of the screening procedure.[20,21] Automated cervical cytology screening also has been suggested as an alternative.[22,23] Renshaw showed that automated rescreening reduced the overall FNP by 5.7% as compared to 1% by manual rescreening. The FNP for ASCUS was 34% by automated rescreening versus 73% by manual rescreening.[22] The false-positive rate was also significantly lower. Other studies have shown that automated rescreening reduces case backlog, turnaround time, and the need for overtime and additional staff.[23] However, it may not be cost-effective for some laboratories. Analysis of significant discrepancies in our study gave insight into the problematic diagnoses and their mimics. Not surprisingly, ASC-H was a challenging diagnosis. Usually the cells of interest were small, few in number, and lying in the clear spaces between the cells. Distinguishing immature metaplasia from ASC-H and HSIL also was difficult in some cases. The presence of reactive atypia, glycogenated cells, and Candida effect led to difficulty in the diagnosis of LSIL. Part of the difficulty in some diagnoses may have been the transition in our practice from conventional smears to liquid-based preparations. The FNP did decrease from 1.9% in 2006 to 1.1% in 2007, which may have been related to increased experience in screening with liquid-based preparations. Moreover, the recognition of difficult diagnoses and potential pitfalls has aided in focusing education at our institution on challenging areas for cytotechnologists as well as pathologists. We have also found the FNP of RR to be a good tool with which to compare the performance of individual cytotechnologists. Another benefit from RR is that there is increased standardization among our cytotechnologists in the interpretation of reactive cellular changes, which is the trigger for the case to be passed on to a pathologist for sign-out. RR did have a significant clinical impact. All the significant discrepancies were ASC-H, a diagnosis requiring colposcopic examination and sampling. Based on the above observations, our institution will continue to use RR.

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ORIGINAL ARTICLE

Kulcsar Lecture 2012: Technological Advances Changing the Practice of Cytology – Liquid-Based Cytology, Automation, Human Papillomavirus, and Lean-Sigma

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ABSTRACT

The implementation of liquid-based cytology at Calgary Laboratory Services and its application to cervical screening in the province of Alberta are described. The advantages of liquid-based cytology compared with conventional cytology are discussed. Advances in human papillomavirus (HPV) testing and developments in immunocytochemistry are reviewed. Finally, the authors discuss their experience in the application of Lean Six Sigma principles to the cytopathology laboratory.

RÉSUMÉ

L'article porte sur l'adoption de la technique de cytologie en milieu liquide par les Services de laboratoire de Calgary et son utilisation dans le dépistage du cancer du col de l'utérus dans la province de l'Alberta. Il examine les avantages de la technique par rapport à la méthode classique, les avancées dans le dépistage du virus du papillome humain et les faits nouveaux en immunocytochimie. Enfin, les auteurs présentent leur initiative de mise en application des principes Lean Six Sigma au laboratoire de cytopathologie.

Since its introduction, the Papanicolaou (Pap) smear has been the most successful cancer screening test, resulting in reductions of up to 70% in the incidence of cervical cancer in areas where it has been adopted.[1] This fact is even more remarkable when one considers that the Pap test suffers from notoriously low sensitivity.[2] With recent advances in technology, ancillary testing, and methods involving the organization of cytology laboratories, all aimed at improving the detection of cervical cancer and precancerous lesions, there is tremendous potential for improving practice. This review attempts to address some of these advances and their potential impact on screening and diagnosis.

Despite the success of Pap test screening, the most important factor is the patient presenting for testing. No test is worth offering if a patient will not present for initial testing, treatment, and follow-up. It is well recognized that in jurisdictions where Pap testing is available, the majority of women who present with cervical cancer will not have had a recent Pap test. For this reason, two key elements of a cervical cancer screening program must be recruitment and regular participation.

This review will discuss the adoption of liquid-based cytology (LBC) and automated screening in the authors' laboratory in Calgary. A discussion of ancillary testing, such as human papillomavirus (HPV) testing, the use of p16, Ki67, and ProEx C immunostaining, will be covered. The concluding portion relates to the role of Lean Six Sigma in the cytology laboratory. Technological advances aside, it is important to remember the

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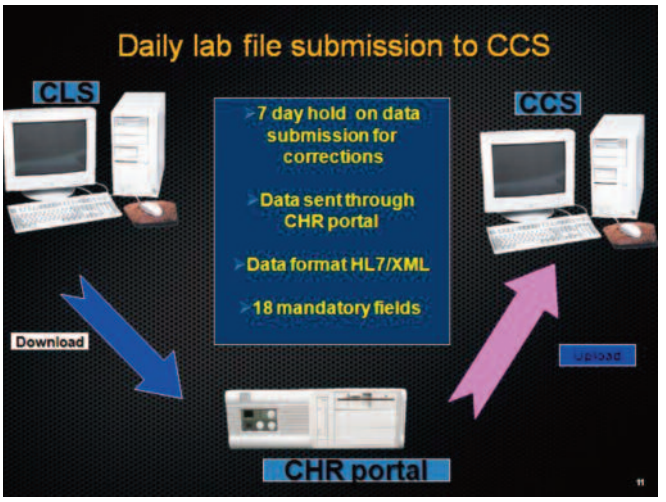

Figure 1. A model of laboratory data transfer between Calgary Laboratory Services (CLS) and the Alberta Cervical Cancer Screening (CCS) program database. CHR = Calgary Health Region.

Figure 2. ThinPrep Imaging System imager.

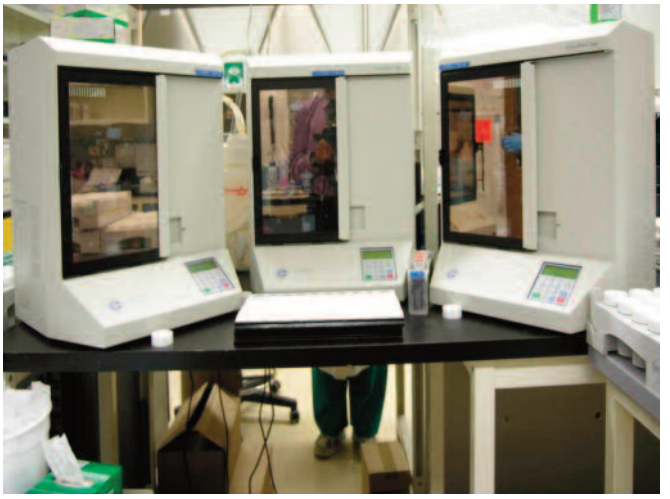

Figure 3. T2000 analyzer bank.

Figure 4. Review Scope Manual Plus (Hologic Inc., Bedford, MA).

Figure 5. T5000 automated processor.

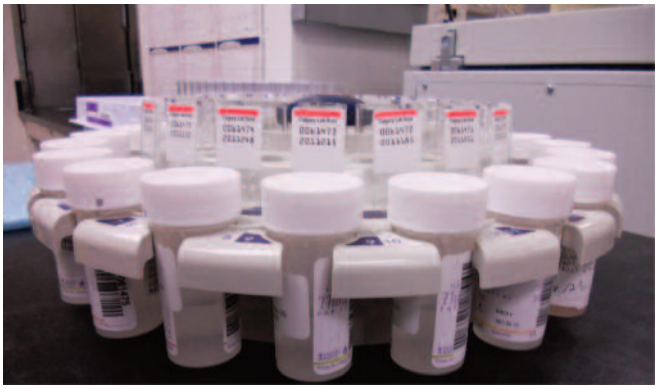

Figure 6. Carousel of specimens for processing by the T5000 processor.

role of the laboratory in patient care. In cervical cancer screening, the participation of the laboratory is crucial in the development of guidelines and test protocols and in providing patient results to the screening program for follow-up and recall. Figure 1 demonstrates a model of laboratory data communication between Calgary Laboratory Services and the Alberta Cervical Cancer Screening program database.

Historical Background

Calgary Laboratory Services (CLS) is a regional medical laboratory serving a population of 1.3 million in southern Alberta. CLS performs >23 million tests per year and operates as a multisite model having laboratories at five acute care sites and a central laboratory (Diagnostic & Scientific Centre [DSC]), where the centralized cytopathology laboratory is located. The centralized cytopathology laboratory started operations in May 2004. In August 2006, CLS Cytopathology opted to adopt LBC testing for gynecological cytology; the preferred vendor was Cytyc Corporation (developer of the ThinPrep system). In January 2007, automated screening was implemented with the ThinPrep Imaging System (Cytyc Corporation [now Hologic, Inc.]) (Figure 2).

The Alberta Cervical Cancer Screening Program (ACCSP) was initiated in 2000 under the umbrella of the Alberta Cancer Board. The ACCSP and CLS worked closely to ensure that laboratory results pertaining to all eligible women in the Calgary zone were placed in the Cervical Cancer Screening (CCS) database by 2003. This database now contains Pap smear results, colposcopy findings, and HPV data on all eligible women in Alberta and manages follow-up and recall.

In 2006, the cytopathology laboratory at CLS acquired six T2000 analyzers (Figure 3) for the specimen processing of roughly 240,000 Pap tests. Four ThinPrep Imaging System (TIS) imagers were used to prescreen the slides, which then went to the primary screeners, who used the imager scopes (Figure 4) to view the 22 fields of view. If all 22 fields of view revealed no abnormal cells, the slide was verified as "negative for intraepithelial lesion or malignancy" (NILM) by the primary screener. If any abnormal cells were found, a full review of the slide was conducted, and the slide with the abnormality would be passed on to a postscreener before it was reviewed and verified by a cytopathologist. This hierarchical screening remains the standard of practice at CLS today.

With respect to processing, the T2000 analyzers have been replaced by four T5000 automated instruments that process the Pap test samples directly from vials, eliminating the need for manual uncapping and specimen transfer (Figure 5). The T5000 (Hologic, Inc.) is a walk-away capable closed instrument that takes one 20-specimen carousel at a time, processing the specimens directly from the vial to the slide (Figure 6). Bar-coded specimen vials and slides are matched, reducing the risk of error. The automation also eliminates repetitive strain injury of the wrist that may result from opening the LBC vials. Staff operating the instruments can perform other duties while the instrument is processing the samples in the carousel. At the end of the cycle (approximately 40 minutes), the 20 slides are ready to be stained.

When screening guidelines were updated at the ACCSP and provincial practice guidelines (Toward Optimized Practice) were introduced, screening of women under the age of 21 years was deferred. This resulted in decreasing Pap test numbers. In December 2010, CLS acquired the Roche cobas 4800 for polymerase chain reaction–based high-risk HPV testing. The province adopted reflex HPV testing for women aged 30 years or older whose Pap test results indicate atypical squamous cells of undetermined significance (ASCUS) and for women aged 50 years or older with a low-grade squamous epithelial lesion (LSIL). If the HPV test result is positive, the recommendation is to refer the woman for colposcopy. When the result is negative, the recommendation is to repeat the Pap test in 3 years. This protocol has eliminated frequent and repeated screening of women who have borderline abnormalities identified on the Pap test who are at risk for overinvestigation.

Liquid-Based Cytology

In our opinion, LBC is the single most significant innovation in cytology. This technology has many advantages over conventional cytology despite literature reports that the performance of LBC is equivalent to conventional cytology in disease detection. A meta-analysis performed from 1991 to 2007 found only eight studies with data that could be considered of moderate quality.[3] In that analysis, the performance of LBC was found to be equivalent to that of conventional cytology. In another randomized control trial, the equivalent performance of LBC and conventional cytology was again demonstrated; however, it was found that there were significant reductions in unsatisfactory samples with LBC.[4] With LBC performing only as well as conventional cytology, the increased cost becomes more difficult to justify, although we still advocate the adoption of LBC by cytology laboratories. LBC eliminates the problems inherent in the conventional

smear. The entire sample obtained with the spatula or brush is captured in the liquid medium, the cells are immediately fixed (avoiding air-drying and other preparation artifacts), and the "noise" from blood and inflammatory cells is eliminated. The sample is spread in a small (13 mm or 20 mm) circle in a thin layer, avoiding dense overlaps and layers of cells. The resulting slide is "clean," facilitating the identification of abnormal cells with proprietary stains (Figure 7). In some instances in which the liquid-based sample is contaminated with abundant lubricant, which can lead to an artifact that may mask cell morphology.

Awareness of this potential complication and avoidance of excessive use of lubrication will limit this effect. There are some lubricant products available that are not as likely to lead to this problem.

The reader should be aware that two systems are dominant in the marketplace: ThinPrep (Hologic) and SurePath (Becton, Dickinson). The literature evaluating LBC has tended to consider them to be equivalent, and no direct comparisons are available to demonstrate differences between the two platforms. There are subtle differences between the platforms with respect to proprietary media, and there are technical differences in sample preparation. These considerations need to be assessed for each individual cytology laboratory with regard to workflow and specific laboratory needs. For expansion of the differences between the platforms, the reader is advised to consult specific product information brochures.

Problem of False-Negative Smears

The greatest liability of the Pap smear is false-negative cases. These may arise from three scenarios: sampling errors, screening errors, and interpretation errors.

With sampling errors, the great difficulty is cells not being collected properly from the cervix, in which (regardless of the method of examination) the cells are not present for detection. To this end, when CLS was converting to LBC, the vendor spent time collecting samples with each physician so as to ensure that proper collection techniques were followed. Specimen transfer can also contribute to sampling errors. An adequate sample can be lost if the cellular material from the collection device is not transferred for examination; this was demonstrated in earlier studies.[5] A study by Bigras et al. also demonstrated that the number of rinsing rotations may result in further loss of sample on collection devices.[6]

Screening errors are encountered when technologists do not identify abnormal cells on preparations. The reasons for this

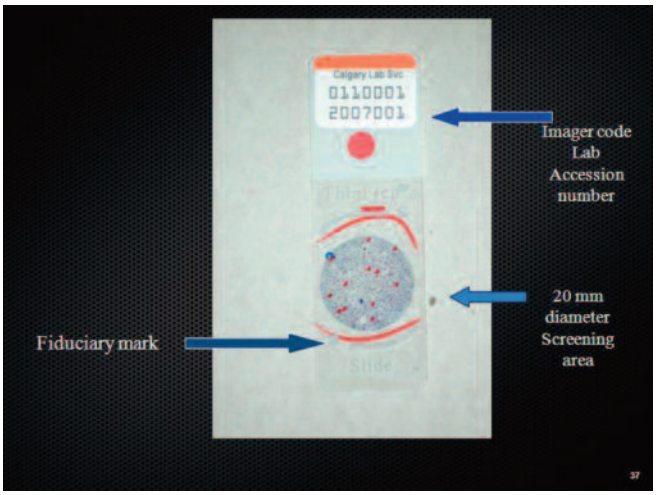

Figure 7. A ThinPrep-processed liquid-based cytology slide.

are many but may include obscuring elements that make the identification of abnormal cells difficult. With LBC, the removal of these potentially obscuring elements allows better visualization of the abnormal cells. The application of automated screening devices can further facilitate the identification of abnormal cells. Another possible factor is screener fatigue. This is minimized with the removal of obscuring elements with better preservation, fewer cells to examine, and the potential to avail of computer-assisted screening.

Interpretation errors may result from inadequate fixation leading to artifacts that may be misclassified as abnormalities; interpreting gynecological LBC preparations requires training and certification. However, LBC facilitates standardized fixation and allows ancillary HPV testing or other immunocytochemical assays to aid with interpretation on the residual material in the liquid medium.

Automation

Each of the commercial vendors has an automated platform that can offer computer-assisted screening. ThinPrep has the ThinPrep Imaging System (TIS) while SurePath has the FocalPoint Slide Profiler and the FocalPoint Guided Screen (FPGS) imaging system (Beckton Dickinson, Franklin Lakes, New Jersey). Again, there are differences among the platforms. FP is capable of removing up to 20–25% of negative smears without human review. It can also identify samples for quality assurance review, stratifying 10–15% of the highest index of abnormality in the scanned slides. The TIS and FPGS require a technologist to review each slide with assigned field of view;

Table 1. Changes in Diagnostic Detection after Implementation of Liquid-Based Cytology in 2006

	% of Total Diagnoses, by Year						
Diagnosis	2006	2007	2008	2009	2010	2011	2012
Unsat	1.9	2.6	2.6	2.6	3.0	3.2	1.9
NILM	93.3	91	91	91	90	90	91.3
ASCUS	1.9	2.3	2.3	1.9	2.1	1.9	1.9
LSIL	2.3	2.9	3.0	3.5	3.8	3.7	3.8
ASC-H	0.1	0.3	0.2	0.2	0.2	0.3	0.1
HSIL	0.4	0.8	0.8	0.7	0.8	0.8	0.67
AGC	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Total cases (× 1,000)	230	240	237	235	206	215	209

AGC = atypical glandular cell; ASC-H = atypical squamous cells (cannot exclude high-grade squamous intraepithelial lesion); ASCUS = atypical squamous cells of undetermined significance; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; NILM = negative for intraepithelial lesion or malignancy; Unsat = .

if the screening technologist sees no abnormality, the case is signed out as NILM if permissible by history. A recent study in the United Kingdom found these devices to have lower sensitivities (−8%) for disease detection at a threshold of a histological diagnosis of CIN 2+.[7] However, an independent study of the TIS found increased detection of atypical squamous cells, and a study on the FPGS found an increased detection of high-grade squamous intraepithelial lesion (HSIL).[8,9] It is interesting that Davey et al. showed that LBC is not cost-effective in comparison to conventional cytology unless combined with automated screening.[10,11] It remains to be seen whether automated screening is a reasonable alternative for cervical cancer screening in the future in terms of cost-effectiveness and disease detection. The issue of safe workload limits remains an area of uncertainty; we have seen a 50–70% increase in HSIL diagnoses in comparison with the retrospective historic cohort since adopting the TIS at CLS (Table 1).

Human Papillomavirus

HPV was recognized by the World Health Organization as a necessary cause of cervical cancer in 1999.[12] More than 120 HPV types have been reported. These are separated into high- and low-risk types (although occasional intermediate types are recognized). Infection with high-risk HPV (hr-HPV) types is responsible for the development of cervical cancer. However, not all women infected with hr-HPV will go on to develop cervical carcinoma. The majority of women who are infected will typically be clear of the virus within 1 to 2 years of acquiring it. Those in whom hr-HPV types persist after the age of 30 years are at greatest risk for development of carcinoma. For some women with persistent infections, the virus may become "dormant" in the cells only to become reactivated at a later time. Progression to cervical carcinoma is considered a chronic process typically requiring 8 to 12 years; for this reason, recognition of individuals with a persistent infection is ideal for screening. Most commercially available HPV tests have been based on deoxyribonucleic acid (DNA), which detects only the presence of the virus and gives no indication as to how long the virus has been present. The testing cannot separate an acute infection from a chronic one, nor can it distinguish a transcribed DNA compared with an episomal DNA. Several DNA-based HPV tests are commercially available (Hybrid Capture 2 [Qiagen], Cervista [Hologic], and cobas 4800 [Roche]); readers are advised to consult product information because the companies offer different platforms and detection methodologies. Despite the excellent sensitivities of these tests, there are problems with their specificities. The recently introduced messenger ribonucleic acid (mRNA) tests Proofer (NorChip) and APTIMA (Hologic Gen-Probe) offer the potential to facilitate the detection of infection that may create a higher risk for the development of cervical cancer.[13,14] The benefit here is that detection targets mRNA transcripts of E6 and E7 proteins from the hr-HPV DNA, proteins responsible for the interruption of cell cycle regulators p53 and retinoblastoma protein. Preliminary data have shown sensitivities similar to those of the DNA assays and an increased specificity (although not as high as that seen with Pap test cytology).

Many studies have compared primary HPV screening tests, with results demonstrating performance superior to that of Pap test cytology.[15,16] These studies have tended to focus on women over the age of 30 years and have been compared to conventional cytology. Another variable to be considered is the use of hr-HPV vaccines (types 16 and 18) from Merck and GlaxoSmithKline. There are differences between the two vaccines, and readers are advised to consult the literature for comparisons.

p16, Ki67, and ProEx C

As LBC provides a residual sample, a tremendous amount of literature has been generated around immuno-cytochemistry as applied to LBC. The protein p16 is a member of the INK family, which is a surrogate marker for the dysregulation of p53. The protein is up-regulated and considered as a surrogate marker for hr-HPV infection. In the past, p16 cytology suffered from a problem of standardized interpretation. How to interpret findings in gynecological cytology was unclear because of variability in cytoplasmic and nuclear staining, compounded by issues of intensity of staining.

More recently, combined staining with Ki67 (CINtec [Roche]) has been developed with standardized interpretation.[17] This combined staining requires that only one cell demonstrate dual staining for the specimen to be interpreted as positive. Recent studies are encouraging, with good reported specificities and with the potential of reducing colposcopy referrals by up to 50%.[18]

ProEx C (Becton Dickinson) is a marker of aberrant S-phase induction.[19] It is a "cocktail" of minichromosome maintenance protein 2 and topoisomerase 2α. The presence of nuclear staining in an abnormal nucleus is interpreted as positive. There is, however, a tendency for normal endocervical and squamous metaplastic cells to demonstrate focal positive nuclear staining. Performance in triaging cytological preparations has been variable, with sensitivities varying from 71–98% and specificities of 70–75%.[20,21]

Lean Six Sigma

"Lean" is a process strategy that focuses on creating "value" by the elimination of "waste" or non-value-added items. It has been used for decades in the manufacturing industry, and the Toyota Production System is deeply rooted in the principles of Lean. This has only recently been adapted for use in health care and has shown significant benefits; reduction in surgical wait times, smooth turnover of patient handling in the emergency room, and improvements in laboratory test turnaround times are a few good examples. Other applications can be found in the finance, hospitality, and sales and marketing industries and in government organizations.

Lean has several tools, including value stream mapping, 5S, kaizen (continuous improvement), poka yoke (error proofing), takt time, cause and effect tree, visual management, and standard work. The seven "wastes" to be eliminated are commonly recognized as defect, overproduction, transportation, waiting, excess inventory, motion, and overprocessing. An additional waste is underutilization. Successful utilization of the Lean strategy depends upon judicious selection of the right tools and applications in order to eliminate the most significant wastes that cause poor performance in the system. As in medicine, a "shotgun" approach to treatment without establishing a diagnosis may temporarily reduce symptoms but will not treat the root cause of the illness.

When properly applied, Six Sigma is another process strategy that decreases the variation in a process, thereby significantly improving the consistency and quality of the work or product and increasing customer satisfaction. Some of the many tools and methods in Six Sigma are DMAIC (define, measure, analyze, improve, control), root cause analysis, SIPOC (supplier, input, process, output, customer), RACI (responsible, accountable, consulted, informed), ANOVA (analysis of

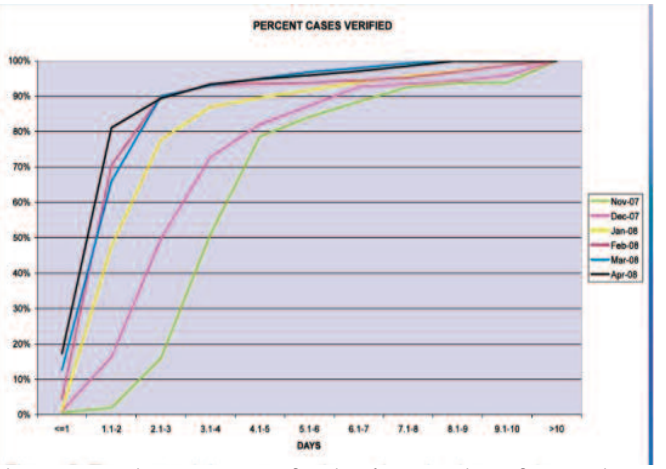

Figure 8. TAT improvement after implementation of Lean-Sigma process.

Pathologist slide delivery

Figure 9. Visual management of workflow as part of Lean-Sigma process.

variation), and FMEA (failure mode effect analysis). Many organizations have combined Lean and Six Sigma synergistically to improve efficiencies in their systems and have managed to turn their businesses around in a highly competitive environment.

CLS introduced Lean Six Sigma processes in the cytology laboratory and initiated three projects soon after the implementation of LBC. Outcomes of the projects included the following:

1. Workflow was organized by elimination of bottlenecks in the pre- and analytical areas. Requisitions received in data entry were matched and colour-coded for arrival time so that the slides and requisitions were available for screening in a timely manner.
2. Management of time-sensitive duties was optimized, with breaks for staff scheduled to ensure that peak work times were well staffed.
3. Elimination of bottlenecks improved turnaround times (Figure 8).
4. Primary screening targets were established based on duties, available screening time, and elimination of interruptions.
5. Visual management of workflow was done with easily identifiable colour-coded flags showing which work required attention first (Figure 9).
6. Organization of each area eliminated clutter and created smoother flow between stations.
7. Staff was designated to handle external requests by rotation, with fewer interruptions for the remaining staff so that they could focus on the work at hand.

Conclusion

Despite all of the discussions about the potential demise of Pap test cytology, we still maintain that the field of gynecological cytology is expanding and full of potential. The conversion to LBC represents an opportunity to move forward and explore new frontiers. Table 1 shows the change in detection of both LSIL and HSIL in our laboratory with the adoption of LBC and automation. Improved test performance will support a change to longer screening intervals. Further, patients who are hr-HPV negative can also benefit from longer screening intervals. New technology does not always offer cost-effective value at the beginning; one has to look at all the potential benefits rather than rejecting it outright. With the advent of ancillary testing and molecular techniques, the opportunities for better care and patient management are at our disposal. We know that cervical cancer screening in the future will not look like it does now, but the only way to shape our future is to be part of it, and we can continue to reduce the burden of cervical cancer.

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A New Era for Advanced Cytopathology Training: The Royal College Diploma Program

Michele Weir, MD, FRCP, Karim Khetani, MBBS

ABSTRACT

Residency programs provide basic training in cytopathology. The Royal College of Physicians and Surgeons of Canada has accepted an application from the Canadian Society of Cytopathology to establish a diploma in cytopathology. The diploma will be awarded on the basis of ongoing competency assessment during a 1-year period of advanced training at a university centre.

RÉSUMÉ

Les programmes de résidence offrent une formation de base en cytopathologie. Le Collège royal des médecins et chirurgiens du Canada a accédé à la demande d'attestation sous forme de diplôme de la formation dans cette discipline présentée par la Société canadienne de cytologie. Le diplôme viendra couronner l'évaluation continue des compétences durant un an d'études supérieures à un centre universitaire.

Something historic happened in April 2012, and we have been smiling ever since. After 18 years of hard work and persistence, the Canadian Society of Cytopathology (CSC) finally succeeded in convincing the Royal College of Physicians and Surgeons of Canada (RCPSC) that the field of cytopathology should have a route for advanced training. Although the CSC's cytopathology subspecialty application had previously been turned down several times, its last application was successful because of a new opportunity – the Areas of Focused Competence (Diploma) program. The program was created by the RCPSC to address the need for additional training among graduates of pathology residency programs in Canada. Such additional training would focus on supplemental competencies specific to a relatively narrow area of expertise that does not meet the criteria for a subspecialty. To clarify, in order for a discipline to be formally recognized by the RCPSC as a subspecialty, it must have a more advanced scope that builds on much broader knowledge within a parent specialty and not be as highly focused as in the case of an area of focused competence. The Areas of Focused Competence (AFC) Program mainly differs from the subspecialty route for certification in that (1) training is based on competency assessments rather than time-dependent goals and a final examination, (2) assessment is through a summative portfolio, (3) accreditation is granted by new standards and a different process, and (4) financial support comes from the universities and candidates rather than from the RCPSC itself. Additionally, the new credential – the Diploma of the Royal College of Physicians and Surgeons of Canada (DRCPSC) – is internationally recognized.

With these changes in mind, the CSC submitted an application form along with training requirements and competency assessments in September 2011 after consultation with the CSC executive (Dr. J. Benoit, Dr. S. Islam, and Ms. P. Francis) and other pathologists (Drs. M. Auger, S. Boerner, T. Colgan, M. Duggan, L. Kapusta, and C. M. McLachlin). There were five main criteria for recognition: (1) evidence of need, (2) a defined scope

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of practice, (3) a relationship to other disciplines (cannot replace practice in an existing discipline), (4) no adverse impact on an existing specialty, and (5) sustainability and an appropriate available infrastructure. The arguments used to promote our application included (1) a societal and specialty need in Canada for experts with advanced training in cytopathology and (2) a societal and specialty need for Canadian cytopathology laboratory directors with training in leadership, resource management, and quality assurance. The intention of diploma recognition in cytopathology is not to undermine what currently exists in cytopathology practice in Canada but rather to further strengthen the structure in the current environment of increasingly complex patient samples, litigation in cytology, and stricter quality assurance and licensing standards. Pathologists without diploma training and recognition would still practise cytopathology and would not be excluded from the field. Diploma-trained cytopathologists would be added to the pool of experts who would act as diagnostic consultants, teachers, and leaders in the field of cytopathology.

Our application noted that current residency training programs in anatomical and general pathology provide a mandatory, dedicated, 3-month rotation in basic cytopathology in which the trainee is expected to achieve a working competence in regard to exfoliative samples and fine-needle aspiration biopsies. The level of training is enough to achieve basic competence in cytopathology, and the trainee usually functions at an advanced novice level. The Diploma program builds on these competencies and provides in-depth and longer training (12 months) with a higher volume of cases, more complex cases, and performance feedback. This additional focused training would deliver the level of expertise and excellence in diagnostics, laboratory management, quality assurance, and risk management required for advanced cytopathology practice in Canada. The trainee would be able not only to serve as a consultant cytopathologist but also to undertake a leadership role in a laboratory.

We also showed that the CSC would stand as the professional organization capable of advancing the field of cytopathology in Canada through the annual meeting of the Canadian Association of Pathologists, the *CSC Bulletin*, the *Canadian Journal of Pathology*, and the CSC's work on guidelines and reporting standards. A high-quality educational experience would be provided by a group of cytopathology experts at several Canadian universities that have the appropriate program infrastructure.

The one-time application fee ($12,500) was expensive for the CSC, an organization primarily supported by annual dues from its members. The CSC has been requesting monetary donations from its members who are issued charitable tax donation receipts and from university pathology department chairs to recoup its costs. As RCPSC dues are not used to finance the Diploma programs, each program pays a $2,000 fee for accreditation per year, and candidates would have to pay a $350 credentialing fee, a $500 assessment fee, and annual dues of $425 to the RCPSC. Other financial hurdles include the university programs' source for the Diploma candidate's salary, in contrast to the subspecialty fellowship route.

In October 2012, the working group for the AFC Program in cytopathology convened to further refine and consolidate the training requirements and competency assessments for the program. The working group included Drs. M. Auger, S. Boerner, M. Duggan, S. Islam, and A. Shawwa and was chaired by Dr. M. Weir. Expert administrative and educational support was prospectively provided by Ms. C. Morgan and Dr. J. Franks. In contrast to the traditional fellowship training assessment, which is dependent on a final examination, the Diploma training assessment is based on a variety of competency assessments throughout the period of training, standardized for all training programs in Canada. The competencies are at an advanced level above and beyond the basic competencies acquired during residency and cover all of the CanMEDS categories. Future work by the group includes the development of the program's application form and practice eligibility route (PER) requirements. The PER will allow current cytopathologists to apply and possibly be eligible for the DRCPSC on the basis of their cytopathology practice experience.

On behalf of the CSC, we would like to acknowledge and thank all of the prior CSC executive members who contributed to the previous subspecialty and Diploma applications. As well, special appreciation goes to Drs. M. Auger, J. Benoit, S. Boerner, M. Duggan, S. Islam, L. Kapusta, C.M. McLachlin, and A. Shawwa for contributing their time and expertise. Let us all celebrate the final arrival of an advanced training route in Canada that will increase the number of experts in the field of cytopathology and that is comparable to cytopathology training programs in the United States, the United Kingdom, and Australia.

Practice and Leadership Opportunity

Medical Director - Laboratory Services

Interior Health Authority, Kelowna, Southern British Columbia, Canada

Interior Health Authority (IHA) is seeking an experienced physician leader to join its medical leadership team. Interior Health is one of five regional health authorities in British Columbia serving a population of 740,000 and covering a geographic area of 216,000 sq. km. We employ approximately 18,666 staff with over 1,500 physicians privileged in our acute care facilities.

As the Medical Director – Laboratory Services, reporting to the Executive Medical Director, you will be responsible for the provision of clinical leadership, ongoing network development, and medical oversight of laboratory services across Interior Health. You will provide leadership in the development and alignment of laboratory medicine standards, policies and processes—including direct leadership of the Divisional Directors, performance improvement monitoring and research activities. In addition to the leadership role, you will provide clinical pathology services.

The service level expectation for the Medical Director, Laboratory Services will be a range of one day of fitted time and one-and-a-half days flexible time per week (1.0 – 2.5 FTE), plus Clinical Services for four days a week (0.8 FTE), for forty-six weeks per year.

The ideal candidate is currently licensed, or eligible to be licensed to practice medicine in BC; is a Pathologist duly recognized under the Royal College of Physicians and Surgeons; has a minimum of five years recent experience in Laboratory Medicine; has Certification and/or experience in administrative leadership and in quality management; and has a current valid BC Driver's License.

Applications will be accepted until suitable candidates are identified. Start date is flexible. If interested, please email **physicanrecruitment@interiorhealth.ca**.

Detailed job posting information can be found on the IHA physician website **www.betterhere.ca**.

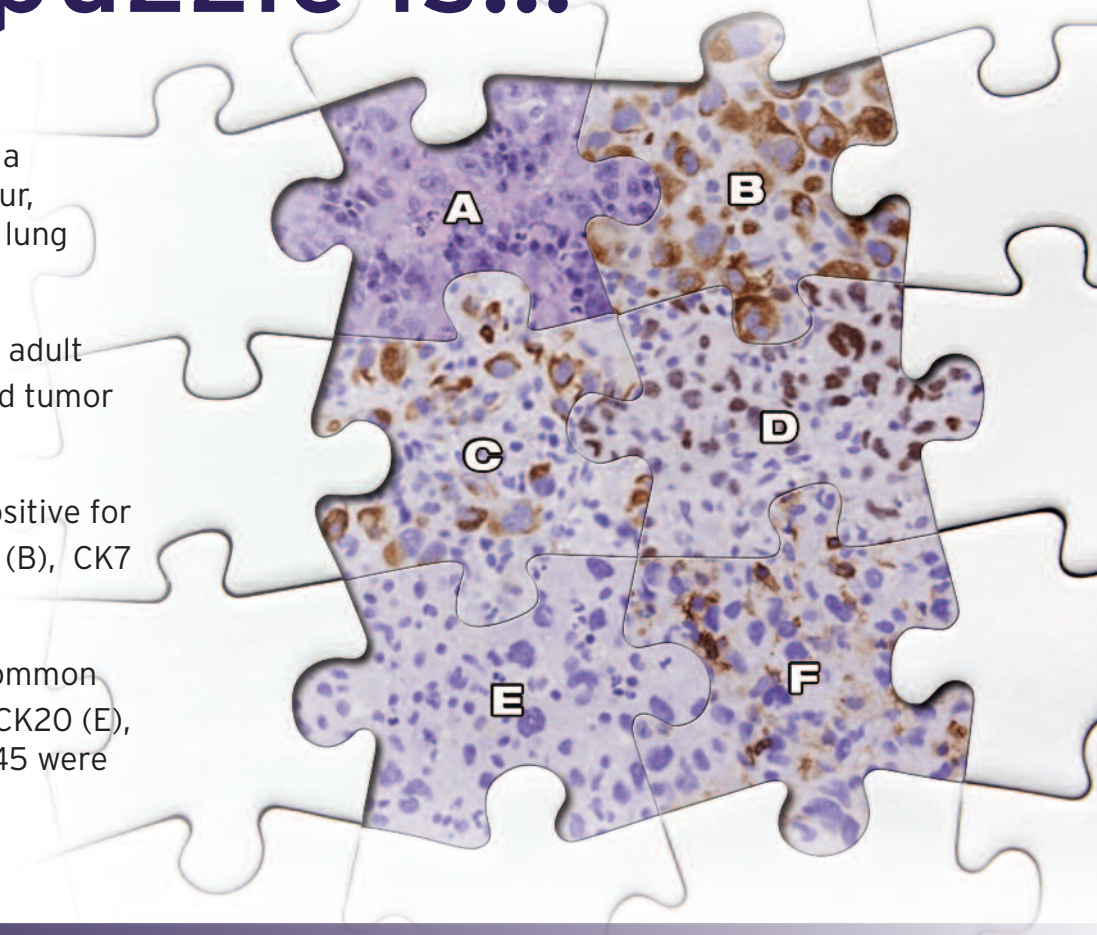
Interior Health

betterhere.ca

The correct diagnosis to the puzzle is...

CK7 and TTF-1 positivity in a poorly differentiated tumour, consistent with metastatic lung adenocarcinoma.

- (A) Rectal biopsy from an adult shows an undifferentiated tumor (H&E)
- (B, C, D) The tumour is positive for Pan-cytokeratin AE1/AE3 (B), CK7 (C), and TTF-1 (D)
- (E,F) CD45 (Leukocyte Common Antigen; F), CK5/6, p63, CK20 (E), S100, Melan-A, and HMB45 were negative in tumour cells



Congratulations to **Dr. Daniel Gervais** for giving the right diagnosis!

Gamma-Dynacare now offers:

- A comprehensive menu of Immunohistochemistry (IHC) tests including:
  - Estrogen Receptor
  - Progesterone Receptor
  - Her2/neu for breast cancer

  The IHC service can be technical only or include interpretation.
- Whole Slide Imaging (where results can be provided remotely over a secure internet connection)

For more information, visit us at our booth or email immunohistochemistry@gamma-dynacare.com.

Gamma-Dynacare Medical Laboratories

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