Encapsulated Follicular-Patterned Tumours of the Thyroid

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About the Cover

The cover image shows follicular variant of papillary carcinoma. Note the irregularity of the follicles, with dense, scalloped colloid and rare intrafollicular giant cells, lower right.

For Instructions to Authors, please visit http://www.andrewjohnpublishing.com/CJP/instructionstoauthors.html
The authors of an article in the Canadian Journal of Pathology are asked to declare any competing interests before publication. Following correspondence with one author, I thought it might be worthwhile to review what we mean by competing interests and why we require such a declaration.

“The whole world runs on trust.”¹ This statement, from a recent essay by cryptographer and computer security expert Bruce Schneier, may sound rather trite, but Schneier goes on to examine the societal forces that encourage trust and discourage behaviour whereby an individual gains the benefits of a cooperative system, while simultaneously exploiting it to further his or her own self-interest. In the medical world, the principal societal influences that ensure trustworthy behaviour are morals and reputation. Morals may well reflect character and upbringing and almost certainly depend on the viewpoint of the beholder. Reputation is based on medical skill, administrative or academic accomplishments, and the credibility of an individual’s public utterances, both verbal and written. One does not have to look far in the medical press to discern that some physicians and scientists are poor at recognizing their conflicts of interest and reputations suffer accordingly when these conflicts are uncovered. A recent example is the correction notice issued for four articles on asbestos in the journal Inhalation Toxicology following the revelation that some of the authors were employees or expert witnesses for an industrial company that sold asbestos and was engaged in litigation over the mineral’s health effects.² The influence of pharmaceutical companies and manufacturers of medical devices on the decisions of doctors is a topic of frequent discussion and debate in the medical press. Although this may not appear to be a major issue for pathologists and laboratory physicians and scientists, it is clearly a matter of significant concern in some specialties, such as psychiatry. The size of this problem was well illustrated a few years ago by the announcement from GlaxoSmithKline that the company was intending to limit the size of payments and honoraria to individual physicians to $150,000 USD per annum.³ I do not think that anyone would seriously dispute that the pharmaceutical and medical device industries have contributed enormously to the well-being of countless patients, yet there is clear evidence that financial ties with industry influence the views and practices of physicians.⁴ For this reason, medical scientific societies and journals require declarations of financial relationships from their speakers and authors.

Nevertheless, conflicts of interest may have little to do with financial gain. Stossel and Lee defined conflicts of interest as occurring “when clinicians or researchers have personal, professional, or financial interests that could interfere with, or be perceived to interfere with, their professional obligation to act in the best interests of patients or objectively conduct, present, review or publish research.”⁵ According to this definition, with its emphasis on objectivity, a declaration of competing interests should include background information relevant to the author’s opinions. If an article contains guidelines or specific recommendations that could have far-reaching implications for medical practice, then it is particularly important for the readership to learn of the author’s experiences and what biases, if any, may have influenced the formulation of the recommendations. Such statements enhance the credibility of the published material. These matters were nicely summarized by the editorial team at CMAJ a few years ago.⁶ In this issue of Canadian Journal of Pathology, Drs. Sidhu and Duggan have reported a critical assessment of the legal protections of laboratory quality assurance committees and make a number of recommendations that all laboratory medical directors need to consider. These recommendations are accompanied by a brief but helpful statement of competing interests.

Many of the major medical journals associated with the International Committee of Medical Journal Editors (ICMJE) now use a specific form for the disclosure of competing interests that can be accessed through the ICMJE website (www.icmje.org). Although we do not propose to insist on the use of this form at Canadian Journal of Pathology, it does provide a comprehensive example of the type of background information that all authors need to consider as they prepare manuscripts for publication.

J. Godfrey Heathcote
Editor-in-Chief

References are listed on page 49

Competing Interests: The author has been an avid reader of BMJ (formerly British Medical Journal) for 44 years, and many of his views on publication ethics have been formed by successive editors of that journal.
ÉDITORIAL

Les intérêts concurrents ou le conflit d’intérêts

La revue Canadian Journal of Pathology a pour principe de demander aux auteurs de divulguer tout conflit d’intérêts avant d’autoriser la publication de leurs articles. À la suite de la correspondance avec un auteur, j’ai eu le sentiment qu’il était pertinent de revoir la notion d’intérêts concurrents à l’origine du risque de conflit d’intérêts et la nécessité de les dévoiler le cas échéant.

« Tout dans le monde repose sur la confiance »1. C’est par cette phrase qui a l’apparence d’un lieu commun que le cryptographe et expert en sécurité informatique Bruce Schneier aborde, dans un essai publié récemment, le sujet des forces vives de la société qui tendent à promouvoir la confiance et à décourager l’envie de retirer des avantages d’un système commun tout en l’exploitant à son profit dans la poursuite de ses propres buts. Dans l’univers médical, les éléments sociétaux les plus influents s’agissant de motiver un comportement digne de confiance sont la moralité et la réputation. La moralité relève sans doute du tempérament et de l’éducation et elle est assurément propre à chacun. La réputation, quant à elle, tient à la compétence médicale, aux réalisations administratives ou scientifiques et à la crédibilité des déclarations publiques de la personne, verbales comme écrites. Inutile de chercher beaucoup dans la presse médicale pour constater que des médecins et des scientifiques omettent de divulguer leurs intérêts concurrents, et des réputations sont ternies à la découverte de conflits d’intérêts. Citons à titre d’exemple l’errata au sujet de quatre articles sur l’amiante qui ont paru dans Inhalation Toxicology publié à la suite de la révélation selon laquelle des auteurs étaient soit des employés, soit des témoins experts d’une société industrielle faisant le commerce de l’amiante et étant partie prenante d’un litige à propos des effets du minéral sur la santé².

L’influence des sociétés pharmaceutiques et des fabricants d’appareils médicaux sur la prise de décisions des médecins est un sujet débattu fréquemment dans la presse médicale. Bien que cette question ne soit pas un problème majeur pour les pathologistes, les médecins et les scientifiques du domaine de la biologie médicale, elle constitue assurément une préoccupation de taille dans certaines spécialités, notamment la psychiatrie. GlaxoSmithKline qui annonçait il y a quelques années son intention de limiter les honoraires versés aux médecins à la somme de 150 000 dollars américains par an chacun illustre parfaitement l’ampleur de cette problématique³. Je suis certain que personne n’aurait l’idée de contester la contribution énorme de l’industrie pharmaceutique et l’industrie du matériel médical à l’amélioration de la santé d’innombrables patients, pourtant il est évident que des liens financiers avec l’industrie influent sur le point de vue et la pratique des médecins⁴. C’est pourquoi les sociétés savantes et les revues médicales exigent la divulgation des relations de nature financière qu’entretiennent les conférenciers et les auteurs.

Néanmoins, les conflits d’intérêts peuvent être étrangers au gain financier. Pour Stossel et Lee, le conflit d’intérêts risque de se produire « lorsque les intérêts personnels, professionnels ou financiers du clinicien ou du chercheur l’empêchent potentiellement, réellement ou en apparence de remplir son obligation professionnelle d’agir au mieux des intérêts du patient ou compromettent sa capacité d’effectuer de la recherche ou d’en présenter, diffuser, examiner ou publier les résultats avec objectivité »⁵. Selon cette définition qui met l’accent sur l’objectivité, la déclaration des intérêts concurrents devrait renfermer des renseignements sur les antécédents de l’auteur qui ont participé à façonner son opinion sur le sujet en question. Si l’article propose des lignes directrices ou des recommandations précises susceptibles d’avoir une vaste portée dans la pratique médicale, il est alors particulièrement important que le lectorat connaisse les antécédents de l’auteur et les aspects de son expérience qui biaisent le cas échéant ces recommandations. La déclaration des intérêts concurrents rehausse la crédibilité de la publication.

L’éditeur du Canadian Medical Association Journal a exposé sa position à ce sujet voilà quelques années⁶. Dans le présent numéro de Canadian Journal of Pathology, les docteurs Sidhu et Duggan rendent compte de l’évaluation critique de la protection législative accordée aux renseignements découlant des activités du comité d’assurance de la qualité des services de laboratoire et ils formulent des recommandations pertinentes pour les

Continued on page 49
Venous invasion (VI) is an independent predictor for disease recurrence and survival in colorectal cancer. Its detection is of particular importance in stage II tumours, since it may encourage oncologists to offer adjuvant chemotherapy. There is wide variation in the reported incidence of VI. The most recently published dataset for colorectal cancer from the Royal College of Pathologists (RCPath) in the United Kingdom states that extramural VI should be detected in at least 25% of all specimens. However, anecdotal reports suggest that the actual reported rate may be closer to 10%.

Standardized, synoptic reporting of colorectal cancer resections has been adopted across the Province of Ontario and is based on the checklist set up by the College of American Pathologists (CAP). Currently, VI (or large-vessel invasion) is not recorded separately from lymphovascular (or small-vessel) invasion. Instead, these two elements have been incorporated under the single heading “lymph-vascular invasion” in the most recent CAP protocol. This lack of distinction between venous invasion and lymphatic invasion may not be appropriate, since there is evidence that they provide differing prognostic information, with the presence of VI more likely to be associated with the development of visceral metastases.

We recently performed a population-based survey of Ontario pathologists to investigate the reasons for the variability in VI detection rates and to clarify the current practice patterns among Ontario pathologists with respect to the detection of VI. The practice patterns of Ontario pathologists are likely to reflect those of Canadian pathologists in general. As such, we would like to draw the attention of the broader Canadian pathology community to the findings of this survey.

This 15-item survey, designed to assess practice patterns with regard to diagnostic criteria for VI, the use of special stains, and demographic information, was mailed to 361 Ontario pathologists. The corrected response rate was 64.9%, which compares favourably with previous surveys of pathologists within Ontario. The full details and results of the survey have recently been published, but the important findings of the survey are summarized here.

The majority of pathologists (70.2%) reported that they detected VI in less than 10% of resection specimens, with only 9.1% reporting VI detection rates above 20%.

With regard to the criteria for the diagnosis of VI by pathologists,

- 89.4% would diagnose VI if tumour were present within an endothelium-lined space surrounded by a rim of muscle;
- 74.7% would diagnose VI if a tumour nodule were present adjacent to an artery (“orphan arteriole” sign) if smooth muscle or elastin could be demonstrated within the nodule by routine or special stains; and
- 51.5% considered tumour within an endothelium-lined space containing red blood cells sufficient evidence to record the presence of VI.

Practice in a university-affiliated centre, a subspecialist interest in gastrointestinal (GI) pathology (as declared by
participants), and the acceptance of the “orphan arteriole” sign were all independently associated with a self-reported VI detection rate above 10% on multivariate analysis. Special stains (e.g., for elastin) were employed by 57.6% of pathologists if VI was suspected on hematoxylin and eosin (H&E)–stained sections. However, only 11.1% routinely used special stains (i.e., irrespective of the presence or absence of suspected VI on H&E-stained sections). Pathologists who routinely use a special stain were more likely to report detection rates above 10%, although this association was not significant on regression analysis. Pathologists who reserve special stains for equivocal cases on H&E staining reported detection rates similar to those of pathologists who relied on H&E stains alone. Supplementary provincial data from pathology reports submitted to Cancer Care Ontario during the period over which the study was conducted (April to July 2010; 1371 cases) revealed that VI was reported in only 14.4% of cases. Pathologists practising in university-affiliated centres reported a higher VI detection rate (20.8%) compared with their counterparts in community-based centres (11.4%). Provincial data on the subspecialist interest of reporting pathologists were unavailable, but a recent study at Mount Sinai Hospital, Toronto, revealed that specialist GI pathologists reported the detection of extramural VI more than twice as frequently as nonspecialist GI pathologists (24.4% versus 10.2%). This observation has been confirmed by a follow-up study on a predefined slide set, with GI pathologists (n = 6) reporting VI three times more frequently than did non-GI pathologists (n = 6; R. Kirsch,

Figure 1. Morphological clues to venous invasion: “Orphaned artery” sign: a thick walled artery with an adjacent nodule containing tumour (inset) but no normal vein (a, b); delicate concentric elastin fibres (arrows) surround tumour (b). “Protruding tongue” sign: a round to oval smooth contoured protrusion of tumour into pericolic fat adjacent to an artery; delicate concentric elastin fibres (arrows) surround the tumour nodule (d). A = artery; V = vein. (a, c: hematoxylin and eosin; b, d: Movat pentachrome stain).
unpublished data, May 2012). Importantly, an elastin stain more than doubled the rate of VI detection overall (with a 3.5-fold increase among non-GI pathologists). In these studies, GI pathologists were defined as “anatomical pathologists whose scope of practice includes a significant volume of GI pathology as a subspecialty focus (including provision of consultation/second opinions) and whose research interests are in GI pathology.”

Figure 2. a–f, Subtle examples of VI easily missed on hematoxylin and eosin–stained sections (a, c, e) but readily identified with an elastin stain (b, d, f). Note the presence of an artery adjacent to the tumour nodule (a–d). Elastotic change following radiation (e, f, arrows) may make veins difficult to recognize on hematoxylin-stained sections (e), but vessels are highlighted by an elastin stain (f). A = artery; V = vein. (a, c, e: hematoxylin and eosin; b, d, f: Movat pentachrome stain)
We conclude that self-reported VI detection rates are low among most pathologists reporting colorectal cancer resections in Ontario. If the RCPath’s guidelines for detection of 25% were to be taken as a reference standard, only a small minority of pathologists would be close to achieving this target. However, even among specialist GI pathologists in university-affiliated practice, only 25% reported detection rates in excess of 20%, highlighting the fact that even among pathologists who could be considered “experts,” the RCPath standard seems to be rarely achieved.

Strategies to improve VI detection by pathologists may be warranted. Knowledge transfer may be facilitated by issuing explicit guidance on the application of reporting criteria, the use of special stains, and, perhaps, specimen preparation techniques. An awareness of the benchmark rate of VI detection and recognition of specific morphological clues for VI (e.g., “orphan arteriole sign” and smooth-contoured tongues of tumour protruding into pericolic fat; Figure 1), coupled with the judicious use of special stains (Figure 2), may bring VI detection rates closer to current benchmarks.

We also recommend that venous and lymphovascular invasion be recorded separately, as they provide differing prognostic information.

References

The Canadian Society of Cytopathology (CSC) celebrated its 50th year at the recent CSC Symposium during the Canadian Association of Pathologists Annual Meeting held in Vancouver, British Columbia, on June 6, 2011. Dr. S. Swiggum from the Canadian Medical Protection Association gave an outstanding and well-received Kulcsar Lecture on Risk Management and Cytopathology. This was followed by a synopsis of the practice of cytology in Canada over the past 50 years, given by past, current, and future CSC chairs. The following review highlights the CSC chairs’ presentations.

The 1960s–1980s (Drs. V. Chen and M. Weir)
The CSC was officially formed in 1961 from the previous Canadian Cytology Council, and the first CSC chair was Dr. J. Penistan. Subsequently, there have been thirty-five CSC chairs, including some nationally and internationally recognized cytopathologists (Table 1). Throughout the past 50 years, many monumental events related to cytopathology have taken place. The CSC’s strength is its members, who have dedicated their time and talents not only to the CSC but also to the general cytopathology community. Some examples of their achievements and contributions follow. Dr. David Kulcsar was one of the founding members of the CSC. Dr. Kulcsar was a gynecologist from Montreal with a special interest in gynecologic (GYN) cytopathology and a major benefactor of the CSC. Dr. Kulcsar’s donation allowed the CSC Executive in the late 1980s to establish an annual lecture in his honour (Table 2). The first Kulcsar lecturer in 1990 was Dr. Alex Ferenczy from Montreal, another gynecologist with a special interest in cytopathology.

The CSC Executive members have worked on quality assurance issues since the mid-1970s. The first CSC quality assurance guidelines document was published in 1978.

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This article has been peer reviewed.

Competing interests: None declared.
Major revisions and additions, including non-gynecological specimens and the use of point systems, were undertaken in 1989 by the CSC Executive led by Dr. Michael Lipa. In the 1970s, Ontario introduced a Laboratory Proficiency Testing Program (LPTP) to promote quality assurance in laboratories through education and maintenance of competence. The main CSC members involved were Drs. Hugh Curry, Don Thompson, and Michael Lipa. The first 15 years’ experience of LPTP was published in 1987; this was followed by an informative booklet, “Adequate ‘Pap’ Smear for Clinicians” in 1989. In the mid 1980s, Dr. Khan Nguyen obtained an International Standard Serial Number (ISSN) so that a copy of the CSC Bulletin can be kept at the National Library in Ottawa. The CSC symbol designed by Dr. Ian Turnbull from Victoria Hospital, London, Ontario, has been used on the Bulletin since 1988.

In the late 1980s, shortly after the death of Dr. Hugh Curry, the CSC Executive created two Hugh Curry Awards for the best papers in cytology, one by a cytotechnologist and one by a resident, presented each year at the annual meeting of the CAP-ACP.

**The 1990s (Dr. M. A. Duggan)**

This was a productive 10-year period, during which the CSC continued to support and advance its projects and undertook some important new initiatives. The vision and energy of the CSC chairs and executive members resulted in a number of important publications. A position statement entitled “The Adequacy of the Papanicolaou Smear” was pivotal at a time when a standardized and consistent definition of adequacy did not exist. The CSC also created a mission-and-goals statement, which is still applicable today. It states: “The Canadian Society of Cytology (CSC)... is a group of pathologists and cytotechnologists with an interest in cytopathology. The Society’s purpose is to promote the health and safety of all Canadians by achieving and maintaining a high standard of practice within the discipline of cytopathology and to foster continued growth and development of cytopathology in Canada.”

The CSC also focused on the development of practice guidelines. Drs. Máire Duggan and Manon Auger updated the 1978 “Guidelines for the Establishment of Quality Assurance Programs in Cytology.” The update, completed in 1995–1996, was renamed “Guidelines for Practice and Quality Assurance in Cytopathology” and reflected new approaches and evidence in cytopathology, quality assurance, and laboratory management practices. Guidelines on fine-needle aspiration of breast and thyroid tissue and the review of Papanicolaou (Pap) smears in the context of litigation were later developed by other executive members.

Discussions regarding an application to the Royal College of Physicians and Surgeons of Canada (RCPSC) for the recognition of cytopathology as a subspecialty began around 1996. Progress was initially slow because the College introduced a moratorium on new applications. However, when this was finally lifted, the application for subspecialty recognition, written by Dr. Máire Duggan and Manon Auger updated the 1978 “Guidelines for the Establishment of Quality Assurance Programs in Cytology.” The update, completed in 1995–1996, was renamed “Guidelines for Practice and Quality Assurance in Cytopathology” and reflected new approaches and evidence in cytopathology, quality assurance, and laboratory management practices. Guidelines on fine-needle aspiration of breast and thyroid tissue and the review of Papanicolaou (Pap) smears in the context of litigation were later developed by other executive members.

Table 1. Canadian Society of Cytopathology Chairs (1961–2011)

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<th>Decade</th>
<th>Chair 1</th>
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<tr>
<td>1960s</td>
<td>Dr. Penistan</td>
<td>Dr. Meisels</td>
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<td>Dr. Boakes</td>
<td>Dr. Kulcsar</td>
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<td>Dr. Waugh</td>
<td>Dr. Thompson</td>
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<td>1970s</td>
<td>Dr. Boivin</td>
<td>Dr. Anderson</td>
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<td></td>
<td>Dr. Worth</td>
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<td>Dr. Steele</td>
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<td>Dr. Marshall</td>
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<td>Dr. Ramzy</td>
<td>Dr. Qizilbash</td>
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<td>1980s</td>
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<td>Dr. Ahmed</td>
<td>Dr. Lipa</td>
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<td>Dr. Nguyen</td>
<td>Dr. Chen</td>
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<td>1990s</td>
<td>Dr. Anderson</td>
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<td>Dr. Colgan</td>
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<td>Dr. Yazdi</td>
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<td>2000s</td>
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<td>Dr. Auger</td>
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<td>Dr. McLachlin</td>
<td>Dr. Khetani</td>
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2010–2011 | Dr. Weir | Dr. Khetani |

Table 2. Canadian Society of Cytopathology Kulcsar Lecturers (1990–2010*)

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<th>Year</th>
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<tr>
<td>1990</td>
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<td>Dr. Voojis</td>
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<td>1992</td>
<td>Dr. LeRiche</td>
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<td>1994</td>
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<td>Dr. Dawson-Hayes</td>
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<td>2005</td>
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<td>2008</td>
<td>Dr. Colgan</td>
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<td>2009</td>
<td>Dr. Auger</td>
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<td>2010</td>
<td>Dr. DeMay</td>
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*The Kulcsar lecture was not given in 2007, the year that the CSC hosted the International Congress of Cytology.
specialties selected by the Royal College to provide input on the application were not fully supportive.

The 2000s (Dr. C. M. McLachlin)
The first decade of the new millennium saw significant changes in terminology for GYN cytology. The second iteration of the Bethesda System was published in 2001 following a consensus conference. The CSC was represented by Dr. Meg McLachlin at this conference and several other Canadian cytologists attended as well. The changes included (1) refinement of the ASC (atypical squamous cells) and AGC (atypical glandular cells) categories; and (2) recommendations for women over the age of 40 years with endometrial cells identified on the Pap smear. These changes led to improved reporting consistency, although reporting of benign endometrial cells remains controversial. The much anticipated results of the ASCUS/LSIL (atypical squamous cells of uncertain significance/low-grade squamous intraepithelial lesion) Triage Study (ALTS) suggested that women with ASCUS should have a test for human papillomavirus (HPV) to determine referral for colposcopy. Despite these results, HPV testing has yet to be introduced widely in Canada. Interestingly, the ALTS trial also highlighted the tremendous interobserver variability for both Pap tests and cervical biopsies.

In January 2005, the third revision of the “Guidelines for Practice and Quality Assurance in Cytopathology” was published. This version updated terminology and definitions, including those for liquid-based preparations. As well, the CSC endorsed guidelines for non-gynecological cytology, including breast and thyroid specimens. A second submission of the application to the RCPSC for the recognition of cytopathology as a subspecialty was led by Dr. Manon Auger. However, the application was again unsuccessful.

The crowning achievement for the CSC in this decade was hosting the 16th International Congress of Cytology in Vancouver in May 2007. Delegates from around the world were in attendance. A broad range of topics were presented, including HPV testing in screening programs, HPV vaccines, cervical cancer management in developing countries, in vivo cytology, and the impact of genomics and proteomics on diagnostic cytology and screening programs.

2010–2011 (Dr. M. Weir)
Although only two years of activity are reported here, they were busy years for the CSC Executive. The CSC website had some update of the guidelines section to include (1) new thyroid terminology to reflect the Bethesda system by Dr. M. Auger and Dr. M. Weir; (2) urine sample terminology by Dr. L. Kapusta; and (3) respiratory terminology by Dr. K. Khetani and Dr. M. Weir. An exciting change to the website was finally initiated, which will allow our members to access a members only area. The CSC Executive also revisited the subspecialty recognition issue. At the time of writing this synopsis, the CSC has submitted an application to the RCPSC for recognition of cytopathology as a Diploma program.

The outgoing CSC Chair, Dr. M. Weir, presented honorary memberships to Dr. Ken Suen and Ms. L. MacDonald in recognition of their contributions to the CSC. These cytologists join a select group of honorary members (Table 3). As well, Dr. L. Kapusta, past-chair of the CSC, was recognized for her contributions to the Society over the last decade.

The Future (Dr. K. Khetani)
In the decades since cytopathology has been practised as a subspecialty, we have become proficient at recognizing cytological features of disease processes. Going forward, however, most new developments are likely to be beyond the realm of morphology. We now receive several new types of specimens obtained through developments in endoscopic and radiological procedures. The role of digital imaging and ancillary studies in cytopathology will continue to grow, and electronic medical records will provide access to accurate, relevant information more efficiently. There will be greater emphasis on standardized reporting and cost-effectiveness of laboratory procedures. In gynecological cytology, revision of screening guidelines, HPV testing, HPV vaccination, and automated screening have already had a significant impact on human resources. These developments will need to be considered as we plan for the future so that talented, skilled

Table 3. Canadian Society of Cytopathology Honorary Members (1968–2011)

<table>
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<tr>
<th>Year</th>
<th>Members</th>
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<tbody>
<tr>
<td>1968</td>
<td>Dr. Fidler</td>
</tr>
<tr>
<td>1978</td>
<td>Dr. Kulcsar</td>
</tr>
<tr>
<td>1981</td>
<td>Drs. Gray, Ross, Penner</td>
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<tr>
<td>1987</td>
<td>Dr. Boyes</td>
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<tr>
<td>1998</td>
<td>Drs. LeRiche, Lipa</td>
</tr>
<tr>
<td>2000</td>
<td>Dr. Paraskevas</td>
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<tr>
<td>2002</td>
<td>Drs. Chen, Nguyen</td>
</tr>
<tr>
<td>2005</td>
<td>Drs. Bedard, Yazdi</td>
</tr>
<tr>
<td>2011</td>
<td>Dr. Suen, Ms. Macdonald</td>
</tr>
</tbody>
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individuals continue to practise cytopathology as a challenging, yet rewarding, profession.

References

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ABSTRACT

Purpose: Statutory protection of quality assurance (QA) committee activities exists in Alberta under Section 9 of the Alberta Evidence Act. Similar statutes exist across Canada. The current state of judicial interpretation and application of this statutory protection to QA data was examined. Statutory compliance of the QA committees of Calgary Laboratory Services was then evaluated.

Methods: Section 9 of the Alberta Evidence Act was interpreted per accepted practices and the Interpretation Act of Alberta. Calgary Laboratory Services QA committee structure and terms of reference were reviewed. Case law research was conducted through three legal databases.

Results: Compliance with the statutory requirements of a QA committee is narrowly interpreted by Canadian courts and was endorsed by the case law search. Alberta Health Services QA committees are in compliance with Section 9 of the Alberta Evidence Act; however, Calgary Laboratory Services internal QA committees fail the requirements of Section 9 with respect to their constitution, and consequently, their quality data are not protected.

Conclusions: A review of QA committee structure in laboratories and other health care institutions in Canada to assess statutory compliance is recommended. If not in compliance, restructuring is encouraged. Otherwise, de-identification of performance data pertaining to individual physicians and gathered as part of the QA committee activities should be adopted as standard practice.

RÉSUMÉ

But : L'article 9 de la Loi sur la preuve de l'Alberta prévoit que les communications et les renseignements relevant des activités des comités d'assurance de la qualité bénéficient d'une protection. Les autres provinces et territoires se sont dotés d'une législation semblable. Les auteurs examinent l'interprétation judiciaire et l'application de cette protection de l'information sur la qualité des soins. Puis, ils évaluent le respect des exigences législatives par le comité d'assurance de la qualité des Services de laboratoire de Calgary.

Méthode : L'interprétation de l'article 9 de la Loi sur la preuve de l'Alberta repose sur les normes de pratique et la Loi d'interprétation de la province. Nous avons examiné la structure et le mandat du comité d’assurance de la qualité des Services de laboratoire de Calgary. Nous...
Physicians have an ethical and legal duty to disclose medical error. This obligation arises from informed consent and fiduciary principles inherent in the patient–doctor relationship. Failure to disclose may vitiate patient consent and create health care provider liability in negligence and/or battery. Hospital and laboratory institutions across Canada embrace principles of continuous quality improvement. These principles are translated into quality control (QC), quality assurance (QA), and quality improvement (QI) practices, which collectively can be referred to as a quality program.

Legislation exists in all jurisdictions across Canada to provide statutory protection of QA data from being disclosed in legal proceedings. In Alberta, this statutory protection is enshrined in Section 9 of the Alberta Evidence Act. The intent of the legislation is twofold. First, it is designed to encourage free and full disclosure of individual or systemic errors in order to identify and address those issues. Second, it prevents the information gathered from being used against institutions and individuals in future litigation. It balances the interests of litigants in obtaining all relevant evidence in support of their case against the public interest in conducting QA practices. It is incumbent on every institution to constitute their quality programs and committees and keep data in precise adherence to the statutory guidelines in order to claim the protection they afford.

All physicians participate in a variety of QC, QA, and QI practices leading to the accumulation of identifiable quality data. The Canadian Medical Protective Association (CMPA) encourages its members to take part in “quality assurance reviews anchored in a properly constituted quality assurance committee.” However, it is not always clear if the QA data being generated are collected by a properly constituted QA committee. The analytical phase of laboratory testing performed by pathologists and other laboratory physicians is quality controlled and forms part of any laboratory quality program. These individualized data can generate a discoverable record for litigation of a culpable act. Risk of litigation exists for laboratory physicians because their lack of direct patient contact decreases the chances for timely disclosure, explanation, apology, and mitigation of error. The risk of potential discovery of their QA records is higher, however, because of their frequent voluntary and mandatory participation in more quality practices compared with other specialties. Although many provincial medical error disclosure guidelines suggest no intent to ascribe blame, disclosure of “laboratory error” by someone other than a laboratory physician often implies laboratory error, and blame is inherent in the context of the disclosure. All physicians and laboratory physicians, in particular, should therefore be knowledgeable about provincial statutory protections which exist to encourage quality practices but at the same time limit their liability exposure.

Objectives
The current analysis was carried out to clarify the statutory
and common law protections of QA data in Alberta and across Canada. We examined Section 9 of the Alberta Evidence Act and reviewed Canadian case law to show the current state of judicial interpretation and application of the statutory protection. Adherence by the QA committees of Calgary Laboratory Services to statutory requirements was then investigated to assess the existing liability exposure. Calgary Laboratory Services is a large, full-service laboratory serving Calgary and its environs. It is a wholly owned subsidiary of Alberta Health Services (AHS), which is the provider of health care services in the Province of Alberta.

Materials and Methods
Section 9 of the Alberta Evidence Act was deconstructed and interpreted according to accepted practices of statutory interpretation8 and the Interpretation Act9 of Alberta. Independent legal opinion was provided by the CMPA. The AHS and the Calgary Laboratory Services QA committee structures and terms of reference were reviewed.10 Both organizations were consulted for information regarding Section 9 protection of the QA committees and the existing Calgary Laboratory Services QA data. The QA data retention policy of Calgary Laboratory Services was reviewed,11 and its past response to requests for QA data for litigation, media, and research purposes was also examined. Case law research was conducted through three legal databases; Westlaw (www.westlawcanada.com), Quicklaw (www.lexisnexis.ca/en/quicklaw) and Canlii (www.canlii.org) to assess the current judicial interpretation of the statutory protection and common law privilege related to QA data.

Statutory Protection in Canada
The general evidentiary rule in civil litigation is that all relevant information is admissible in legal proceedings. Alberta, like all other Canadian jurisdictions, has passed legislation12 that creates an exception to this general rule by providing statutory protection for proceedings before, and records of, statutorily defined “quality assurance committees” in Subsection 9(1) of the Alberta Evidence Act (Figure 1). The Act relates to all quality data, including laboratory data. Subsection 9(2) of the Act generally grants the protection and provides that a witness in a legal action cannot be asked to provide information regarding proceedings before a “quality assurance committee” or be asked to produce “quality assurance records.” The Alberta Evidence Act’s protection is limited to proceedings of
properly constituted “quality assurance committees.” Thus, the Act’s protection will only provide protection from disclosure in legal proceedings if the QA committee has as its primary purpose the carrying out of “quality assurance activities,” which are defined as “a planned or systematic activity the purpose of which is to study, assess, or evaluate the provision of health services with a view to the continual improvement of the quality of health care or health services, or the level of skill, knowledge, and competence of health service providers” and is either duly appointed by one of the entities listed in Section 9(1)(b)(i), established by another Alberta statute or regulation, or designated by order of the minister of health (see Figure 1). Notably, this definition of “quality assurance activities” underscores a role for individuals.

Laboratory QA committee activity in Alberta is broadly divided into external AHS committees and internal laboratory committees. The AHS committees are properly constituted under Section 9 of the Alberta Evidence Act and conduct quality improvement reviews. Responsibilities include patient safety concerns, system improvement, performance measurement or evaluation, communication and promotion of safety culture.13 The Calgary Laboratory Services’ internal QA committees monitor the day-to-day operation and performance of laboratories, which are required to meet accreditation standards and contractual requirements. The internal committees consist of 1 central, 12 divisional, and 3 support committees, which work to implement quality systems and key quality metrics, policy development, document and information management, patient safety, data analysis, process improvement, accreditation readiness, and audits.14 The 12 divisional committees report their data in aggregate form, which ensures anonymity of the individuals participating in the QA activities. It is important to note that the aggregate is based on the sum of performance results from participating individuals. However, an individual’s results, for example, pathologists’ error correction reports and proficiency testing results, are not consistently de-identified and anonymized as a standard practice. This creates a repository of performance data on identifiable individuals.

The internal Calgary Laboratory Services committees fail the constitution requirements outlined in Sections 9(1)(b)(i),(ii), or (iii) of the Act (see Figure 1). The internal committees are not appointed by a health region, hospital, legislative act, or the health minister. Examination of past practices revealed that internal QA documentation at Calgary Laboratory Services was subpoenaed and accessed under the Freedom of Information Act15 and the Health Information Act.16 The internal document retention guidelines of Calgary Laboratory Services require maintenance of QC data for 2 years, maintenance of QA records for 5 years, and maintenance of performance indicator reports for 10 years. This, together with the inconsistent practice of de-identification, creates significant retrospective liability exposure for the laboratory and individuals, such as pathologists, laboratory physicians, or technologists.

**Case Law in Canada**

Review of the legislative debate in the introduction of the Alberta Evidence Act statute17 shows clear recognition of the vital role of QA practices and the need for confidentiality to encourage free participation and full disclosure to facilitate improved quality of health care in Alberta. In Dawe v. Evans18 in 2009, the plaintiffs requested access to neonatal mortality and morbidity committee notes that had been referred to by the treating physician in a letter to the plaintiffs. The judge in the case deemed the committee to be properly constituted, and thus, the information was protected as an “absolute prohibition” even if previously disclosed. Also in 2009 in Foresberg v. Naidoo,19 the defendant physicians and hospital asserted privilege over records citing Section 9. The judge found the QA committees had been constituted properly as defined under the act, and protection was granted as an “absolute prohibition.”

In a well-known decision in Eastern Health Integrated Health Authority v. Newfoundland and Labrador (Commission of Inquiry on Hormone Receptor Testing: the Cameron Inquiry),20 the health region was denied statutory protection on the grounds that no QA committees or policies even existed at the time the data regarding breast cancer hormone receptor testing were generated. The court went further and also denied any common law or public interest privilege of the Health Region’s records that were requested by the Public Inquiry. Several other cases have reiterated the need for narrow interpretation of the statutes to prevent abusive or arbitrary assertion of statutory protection to avoid litigation.21 Thus, case law in this area demonstrates that
courts will make determinations about statutory protection on the basis of the strict definition of “quality assurance committee” and “quality assurance record” in the relevant provincial acts.

Common Law Privilege in Canada
If an institution’s QA committees and program do not fit within the definition of “quality assurance committee” of the provincial acts, the data may, nonetheless, be protected against production in legal proceedings by common law privilege. The Supreme Court of Canada examined the issue of common law privilege in its 1976 decision, Slavutych v. Baker. In that case, the Supreme Court recognized that for communications made in the context of certain relationships based on an expectation of confidentiality, which are also of a nature that benefits society, the confidentiality of the communication should be respected. Courts in Canada have subsequently relied on common law privilege to protect the disclosure of QA records when they are not protected by the existing statutory guidelines. However, reliance on common law privilege carries risk, since it is determined on a case-by-case basis using the Slavutych test, and there is no guarantee of protection, unlike that afforded by the statutory protections available. A legal analysis of similar case law on behalf of the CMPA concurs.5

Conclusions and Recommendations
All laboratories, other health care institutions, and physicians participating in quality programs should be aware of the legal provisions available to protect the data collected. Statutory protections across Canada require strict adherence to the regulations to claim protection. Organizations might consider engaging legal counsel to address issues of committee constitution and terms of reference. Individual physicians should know and understand the potential liability exposure associated with engaging in quality practices. Based on this analysis, to increase the likelihood that information maintained by laboratories and other health care institutions in Canada for quality purposes will be protected in any subsequent legal proceedings, we would make the following recommendations:

- QA committees should be properly constituted in adherence to provincial statutory legislation that protects the confidentiality of the data collected.
- Operating policy and procedures for properly constituted quality programs, and terms of reference for properly constituted QA committees, should be documented and periodically updated.
- These documents should make it clear that all data acquired must be maintained in absolute confidence and should specify those persons who may have access to the data and how long the data will be stored.
- If protection under an evidence act is not available, coding, that is, de-identification and anonymization of quality data collected on individuals, should be adopted as a standard practice.

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11. CLS Retention Guidelines, Attachment to CLS Administrative Policy IV 3.010 Records/Materials Retention
13. AHS Laboratory Services Provincial Quality Council Quality Assurance Committee Terms of Reference; www.albertahealthservices.ca.
15. Freedom of Information and Protection of Privacy Act, R.S.A. 200 c.
Sebaceous Carcinoma of the Eyelid: An Elusive Diagnosis

Joshua S. Manusow, MD, Seymour Brownstein, MD, FRCSC, Navdeep Nijhawan, MD, FRCSC, W. Bruce Jackson, MD, FRCSC, Dan D. DeAngelis, MD, FRCSC

ABSTRACT
Sebaceous carcinoma is difficult to diagnose clinically and histopathologically and thus is frequently mistaken for other entities. We report the case of a man with sebaceous cell carcinoma of the eyelid misdiagnosed multiple times by several health care providers over many years and highlight the importance of being aware of this potentially lethal malignancy.

RÉSUMÉ
Le diagnostic de l’adénocarcinome sébacé sur la foi des aspects cliniques et histopathologiques n’est pas chose aisée, et l’on se méprend souvent sur sa nature. Nous présentons le cas d’un homme atteint d’un carcinome sébacé palpébral qui a consulté plusieurs médecins durant de nombreuses années avant que l’un d’eux pose le diagnostic juste de la maladie. Nous terminons en soulignant l’importance de connaître ce cancer parfois mortel.

Case Description
A 62-year-old man was referred to the University of Ottawa Eye Institute for a dry right eye. His history revealed that following 2 years of unsuccessful treatment for red eye by his family physician, an oculoplastic surgeon was consulted who identified an inflamed nodular lesion on the right upper eyelid (Figure 1A). Over the next 2 years, recurrent right upper eyelid lesions were biopsied and excised on four different occasions, and diagnoses of squamous cell carcinoma were made three times and basal cell carcinoma once by four different pathologists at two different institutions. The patient’s history included two previously excised specimens of basal cell carcinoma on the abdomen and back and a family history of pancreatic cancer in his mother.

Our review of all four previous eyelid biopsy specimens revealed in each specimen histological evidence of sebaceous carcinoma, including large lobules of foamy, vacuolated, pleomorphic, atypical cells with frequent mitoses, involving the section margins (Figures 1B–D). Prominent pagetoid invasion (see Figure 1D) of the epidermis and the adjacent conjunctival epithelium was noted. Lobules of neoplastic cells were seen in the tarsus. Immunohistochemical examination disclosed positive staining for epithelial membrane antigen and cytokeratin-7 in the tumour cells (see Figure 1D).
Our patient subsequently was diagnosed with an inoperable cholangiocarcinoma, with a suggested prognosis for survival of 18 months and eventually underwent right orbital exenteration. The exenteration specimen histopathologically showed residual eyelid sebaceous carcinoma with tumour-free resection margins. The patient eventually succumbed to his abdominal malignancy and died 1 year after the exenteration.

Discussion
Clinically, adnexal sebaceous carcinoma is frequently mistaken for chalazion, blepharitis, blepharoconjunctivitis, conjunctivitis, keratoconjunctivitis, superior limbic keratoconjunctivitis, sarcoid/pemphigoid/basal cell carcinoma, squamous cell carcinoma, melanoma, Merkel cell carcinoma, lymphoma, and sweat gland neoplasms, hence the term “masquerade syndrome.”1–3 Owing to its varied clinical presentations, the diagnosis may be delayed by more than 3 years.1,4 This is important clinically because sebaceous carcinoma is an aggressive tumour that spreads via local extension and may produce regional or, less frequently, distant metastases.3 Among ocular adnexal
neoplasms, only invasive melanoma has a greater potential morbidity and mortality.\(^5\) Alarmingly, up to 75% of cases of sebaceous carcinoma also are misdiagnosed initially on histopathological examination by an inexperienced pathologist, usually as squamous or basal cell carcinoma\(^3\); as exemplified in our case, it was misdiagnosed on four occasions over a 2-year period.

The Muir-Torre syndrome is an autosomal-dominant condition consisting of cutaneous neoplasms, primarily sebaceous and visceral malignancies.\(^5\) Our patient’s diagnosis of inoperable cholangiocarcinoma, along with his sebaceous carcinoma of the eyelid and a family history of pancreatic cancer, is highly suggestive of Muir-Torre syndrome. Rare cases of Muir-Torre syndrome presenting as periorcular sebaceous carcinoma have been reported.\(^2\) The earlier diagnosed “basal cell carcinoma” on his trunk, which was unavailable for our examination, could also have been misdiagnosed sebaceous cell carcinoma because of the unusual, relatively less sun-exposed location, and this makes Muir-Torre syndrome an even more likely diagnosis.

Our patient was not diagnosed correctly until 5 years after he initially presented with a red eye, despite having multiple biopsies examined by four different anatomical pathologists. It is important that pathologists and ophthalmologists have a high index of suspicion for sebaceous carcinoma in patients presenting with recurrent or chronic benign or malignant eyelid lesions.

**Acknowledgements**

Drs. Hatem Krema and Rand Simpson of the Department of Ocular Oncology, Princess Margaret Hospital and the University of Toronto, provided clinical information for this report.

**References**


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**HUMANITIES**

**POEM**

**Romancing the Disease**

Diabetes is drowning in sanguin syrup,
Nerve endings floating like poisoned fish given up,
Moanings of sludge from seeping veins and muscles,
While great vessels pulse with drunken corpuscles.

Diabetes is protein pouring like dark rich coffee beans
From bursting kidney sacks peddled in street market scenes,
Platelets in orgy in narrow alleys, neutrophils strewn
Over coliforms in a secluded downtown ruin.

---

Diabetes is a filthy avenue of funeral marches,
Grieving for loved ones, the toes and fingers and heart and senses,
Which bid farewell in spontaneous adventures,
Or linger their goodbyes in pain-faced embraces.

2010

Robert Ferrari, MD
Department of Medicine
University of Alberta
Edmonton, Alberta
CURRENT REVIEW

Encapsulated Follicular-Patterned Tumours of the Thyroid: Diagnostic Controversies and Evolving Concepts

Martin J. Bullock, MD, FRCPC

ABSTRACT
The assessment of encapsulated thyroid tumours with a follicular architecture has been a source of controversy and debate among thyroid pathologists and of diagnostic difficulty for surgical pathologists in general. This article discusses the differential diagnosis of the major entities in this category: hyperplastic or adenomatoid nodules, follicular adenoma, minimally invasive follicular carcinoma, and the encapsulated follicular variant of papillary carcinoma. The criteria for three proposed categories of tumour of “uncertain malignant potential” are also explained. The immunohistochemistry and molecular pathology of follicular-patterned thyroid tumours are briefly summarized, with particular emphasis on the similarities between the genetic abnormalities found in such tumours.

RÉSUMÉ
L’évaluation des tumeurs thyroïdiennes encapsulées d’architecture vésiculaire soulève la controverse et les débats dans la communauté des pathologistes de la thyroïde, et ces tumeurs posent des problèmes d’interprétation diagnostique aux spécialistes de la pathologie chirurgicale. L’article aborde le diagnostic différentiel des entités majeures : le nodule hyperplasique ou adénomatoïde, l’adénome vésiculaire, le carcinome vésiculaire d’invasion minime et la variante vésiculaire encapsulée du carcinome papillaire. Il précise également les critères des trois catégories proposées de tumeurs de « potentiel de malignité incertain ». Enfin, il résume les aspects immunohistochimiques et la pathologie moléculaire des tumeurs thyroïdiennes vésiculaires en insistant sur les anomalies génétiques communes de ces tumeurs.

The evaluation of thyroid nodules is a frequent source of difficulty for surgical pathologists and a common reason for consultation with colleagues and for requests for an expert opinion. The difficulties we face would not be suspected by a naïve first-year pathology resident “nodding off” over the Endocrine chapter of “Robbins,” having encountered a thyroid nodule during his or her first autopsy. Encapsulated versus unencapsulated, clear nuclei, grooves…it all seems pretty obvious at first glance. However, the reality of thyroid pathology is quite different and, for many pathologists (the author included), it can become a source of frustration and worry. Pathologists are aware of the interobserver variability associated with the diagnosis of the follicular variant of papillary carcinoma, as well as with differing interpretations of the criteria for capsular and vascular invasion.1–4 This is coupled with an evolving nomenclature for thyroid tumours – including the promotion of categories of tumour with “uncertain malignant potential”5 – and a greater

Martin J. Bullock, MD, FRCPC

This article has been peer reviewed.
Competing interests: None declared.
understanding of their molecular biology. The media attention in recent years to errors by anatomical pathologists and in our laboratories has made us more cautious, with a seemingly greater reliance on ancillary tests and consultation. This article will review the fundamentals of the diagnosis of encapsulated thyroid tumours with a follicular architectural pattern, evolving concepts regarding their diagnostic criteria and nomenclature, and adjuncts to histological diagnosis. The major tumours in this group are “adenomatoid” nodules in a nodular goiter, follicular adenoma, follicular carcinoma, and the encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC). The diagnostic criteria for papillary carcinoma will be discussed later, and this review will concentrate first on a discussion of the other “follicular” tumours and their capsules and vessels.

**Follicular Adenoma versus Hyperplastic Nodule**

Frequently, a nodular thyroid contains one or more encapsulated nodules that compress the adjacent thyroid parenchyma. When a nodule retains the typical internal features of a hyperplastic nodule, such as considerable variability in the sizes and shapes of follicles, pseudopapillae, uniform round nuclei in a “honeycomb” arrangement, and degenerative changes, the diagnosis is not usually an issue. However, other encapsulated nodules in multinodular goiter are truly “adenomatoid,” with uniform, microfollicular architecture that is quite distinct from the surrounding gland. In these cases, assuming PTC-like nuclear features are not present, the pathologist may be tempted to diagnose a follicular adenoma.

Approaches differ as to the designation of these cellular nodules. Any dispute usually relates to the appearance of the surrounding thyroid, specifically whether an adenoma should be diagnosed in the context of multiple nodules. The approach recommended by Suster for the diagnosis of follicular adenoma is to require the following: (1) a complete capsule, and (2) the absence of nodular hyperplasia elsewhere in the gland. A similar approach is suggested by DeMay. Neither of these authors specifically mentions how to deal with a lobectomy in which there is a single, encapsulated microfollicular nodule replacing most of the lobe. This is not an uncommon situation, as lobectomy would be the typical surgery for a nodule that, by fine-needle aspiration, would be diagnosed as “follicular lesion of undetermined significance” or “follicular neoplasm.” Most pathologists would probably diagnose this type of lesion as a follicular adenoma.

Realistically, the morphological criteria for distinguishing an adenoma from a hyperplastic nodule are artificial. Even many morphologically hyperplastic nodules are monoclonal (especially larger ones), and a thyroid may contain both polyclonal and monoclonal nodules with similar histology. While pathologists typically equate monoclonality with neoplasia, some evidence suggests that monoclonality in endocrine organs does not necessarily imply a monocellular origin. This is due to the presence of “clonal cell patches” that may be present even in adult tissues. More than one cell within a “patch” may proliferate autonomously, or following stimulation by trophic hormones, but still create a monoclonal nodule. These pathogenetic issues blur the boundaries between hyperplasia and neoplasia and are beyond the scope of this article, except to further emphasize the limitations of conventional histopathology. Ultimately, if one can reasonably exclude malignancy, the distinction is of little clinical relevance, other than to create havoc with cytological–histological correlation! Implicit in our understanding of multinodular goiter is the concept that one or more nodules may be monoclonal and neoplastic.

**Follicular Adenoma versus Minimally Invasive Follicular Carcinoma**

The incidence of thyroid carcinoma is increasing in many countries, and this can be attributed to a larger number of papillary carcinomas, particularly papillary microcarcinoma and the follicular variant of papillary carcinoma. Meanwhile, the relative incidence of follicular carcinoma among all thyroid malignancies has declined. The World Health Organization (WHO) Classification Tumours of Endocrine Organs (2004) puts the figure at 10–15% of “clinically evident” thyroid malignancies, but this may be a reflection of worldwide incidence and is higher than many Western studies would indicate. The figures vary for many reasons, including the use of dietary iodine supplementation, different application of diagnostic criteria for FVPTC, and the inclusion or exclusion of papillary microcarcinomas. Iodine deficiency is an important etiological factor in the development of follicular carcinoma, and supplementation in areas with iodine-deficient diets has resulted in a lower incidence of follicular thyroid cancer in many countries.
Recent studies from Europe and Japan indicate that follicular carcinoma typically accounts for only 5–10% of well-differentiated cancers of follicular cell origin. Often, the relative incidence is even lower in North American centres, mainly due to a greater tendency to diagnose EFVPTC. As an example, a review of cases from the University of Chicago Medical Center from 1994 to 1998 found that follicular carcinoma accounted for only 1% of all thyroid malignancies, compared with 86% for papillary carcinoma. In contrast, in iodine-deficient areas, follicular carcinoma comprises about 25–40% of all thyroid cancers.

Follicular carcinomas have a broad spectrum of histological appearance, from minimally invasive tumours (in which a diagnosis of malignancy is often in question), to widely invasive, clearly malignant tumours with a differential diagnosis of poorly differentiated carcinoma or papillary carcinoma. These tumours may lack a capsule entirely. Our main concern here is with minimally invasive follicular carcinoma, a tumour which, by definition, has a complete capsule and a prognosis that, in the absence of vascular invasion, is generally excellent.

Follicular carcinomas typically have a thicker capsule compared with follicular adenoma, and Sobrinho-Simoes even cautions against making a diagnosis of minimally invasive follicular carcinoma in a thinly encapsulated tumour. The definition of capsular invasion is debated, but most authorities only accept complete transgression of the capsule as confirmatory of malignancy. Invasive foci penetrating through the capsule may or may not be associated with a rim of fibrous tissue at the advancing front. Invasion is usually identified in multiple sites, although, in some cases, only a single invasive focus will be identified. LiVolsi requires a microscopically visible connection between suspicious areas and the main tumour mass to be certain of invasion. Disruption of a tumour capsule at the periphery of a gland (without invasion into surrounding tissue) should be disregarded, as should “pseudoinvasion” at the site of a prior fine-needle aspiration biopsy. All solitary or encapsulated thyroid tumours need to be adequately sampled, and the entire tumour capsule should be submitted, when feasible. The diagnosis of vascular invasion is also subjective, but adherence to conservative criteria is suggested to avoid overdiagnosis. In those follicular carcinomas with minimal capsular invasion, it is the additional presence of vascular invasion which adversely influences metastatic potential. About 50% of patients with angioinvasive follicular carcinoma have some form of recurrence. Vascular invasion must be identified within or outside the tumour capsule, not within the tumour itself. Numerous vessels of varying sizes and wall thicknesses are typically present in the capsule of thyroid tumours, so an intimate association is commonly seen between these vessels and the tumour abutting, or within, the capsule. This is why, in the author’s opinion, immunostains for the identification of endothelial cells are often unhelpful.

The diagnosis of vascular invasion requires, at a minimum, the identification of an intravascular tumour plug or polyp that is predominantly covered by endothelial cells or is associated with thrombus. Simple “bulging” of the tumour into a vessel is not sufficient. Mete and Asa have proposed stricter criteria for vascular invasion, requiring tumour cells invading through the vessel wall and thrombus adherent to intravascular tumour. They have shown that this definition more accurately predicts those tumours in which distant metastases will occur.

There are some follicular tumours without PTC-like nuclei, in which the diagnosis of vascular or capsular invasion is equivocal. In these cases, the designation “follicular tumour of uncertain malignant potential” (FT-UMP) has been proposed as a way of conveying the diagnostic uncertainty. The treatment for such a tumour would likely be partial thyroidectomy (lobectomy or hemithyroidectomy), as for follicular adenoma. The value of this designation might be to ensure closer clinical follow-up of the patient, to “cover” the pathologist in the very rare circumstance of such a tumour metastasizing, or as an aid to research into the natural history of such tumours. One could argue that, especially for thinly encapsulated tumours in which only capsular invasion is in question, the likelihood of metastases is so low that it would be safe to render a “benign” diagnosis. However, rare instances of metastases from apparently noninvasive tumours do occur (Figure 1A and B).

In the end, nothing should substitute for proper examination of the tumour, and it would be unwise to render the diagnosis...
of FT-UMP unless the tumour capsule has been completely submitted and thoroughly evaluated, with deeper sections of blocks with questionable findings. The author’s experience has been that use of this terminology is resisted by clinicians, as it creates a dilemma for treatment. If used at all, it is advisable to restrict it to cases with other worrisome features, such as high cellularity, uniform microfollicular architecture, and a thick capsule.

The term “atypical adenoma” has been used to refer to follicular tumours without capsular or vascular invasion but which exhibit a variety of atypical features, such as high cellularity, unusual patterns (e.g., spindle cell fascicles), numerous mitoses, or necrosis. Nevertheless, these tumours behave in a benign fashion.16,21 “Atypical” does not refer to the bizarre “endocrine-type” atypia that one might see on occasion. Use of the term is discouraged by the authors of the WHO Classification,15 likely because of the broad, rather nonspecific definition, lack of prognostic importance, and the potential for confusion among clinicians.

**Encapsulated Follicular Variant of Papillary Carcinoma**

Follicular variant of papillary carcinoma can be subdivided into encapsulated and nonencapsulated forms. In addition to having the characteristic nuclear abnormalities of PTC, nonencapsulated FVPTC invades the surrounding thyroid, and therefore, the diagnosis of malignancy is not problematic. In contrast, EFVPTC is an important and controversial diagnosis in which capsular and/or vascular invasion – while they may occur – are not necessary criteria. Rather, the diagnosis can be made solely by finding characteristic nuclear features of papillary carcinoma, without any evidence of invasion at all.13,25 The nuclear abnormalities can be diffuse or can be identified as multiple discrete foci, surrounded by cells with bland nuclear features. EFVPTC often occurs on a background of multinodular goiter.16 Among thyroid pathology experts, opinions vary considerably as to the extent and degree of PTC-type nuclear atypia (and/or other features) required to make the diagnosis of EFVPTC, and this subject has been the topic of many research studies and editorials.1-5,7,8,13,16,18,20,26-32 Some have suggested that EFVPTC is often overdiagnosed.14,29,33

The “true” incidence of EFVPTC is elusive because it is often not separated from the nonencapsulated form when incidence figures for FVPTC are reported and because of the lack of strict, widely-agreed-upon diagnostic criteria. Rosai has suggested that is has become “one of the most common diagnoses in thyroid tumour pathology,”32a statement which may certainly be true for North America. Estimates of the combined incidence of nonencapsulated FVPTC and EFVPTC vary widely, from 15% to greater than 40% of papillary carcinomas.13,34 A recent study from Memorial Sloan-Kettering Cancer Center (MSKCC) of FVPTC cases,
ENCAPSULATED FOLLICULAR-PATTERNED TUMOURS OF THE THYROID

diagnosed between 1980 and 1995, found that encapsulated tumours outnumbered nonencapsulated ones by about 4:1. EFVPTC generally has an excellent prognosis, particularly in the absence of invasion. In the same MSKCC study, there were no metastases or recurrences after nearly 11 years follow-up in 42 patients with noninvasive EFVPTC. Nearly 75% of these patients were treated by lobectomy alone.18 Similarly, Piana et al. found no fatalities among 66 cases of EFVPTC diagnosed over a 15-year period, with a mean follow-up of 11.9 years. Their data included many cases with capsular invasion and three with vascular invasion.20 In addition to PTC-type nuclei, nonencapsulated FVPTC commonly exhibits a variety of additional architectural features, including frequent elongated or irregularly shaped follicles, “abortive” papillae (short, without well-developed fibrovascular cores), dense eosinophilic colloid, and intrafollicular multinucleated histiocytes (Figure 2A and B).15 It would seem reasonable to expect similar features in EFVPTC if one assumes (perhaps incorrectly) that nonencapsulated and encapsulated tumours are subtypes of the same PTC variant. Rosai, in particular, has called into question the concept that classic nuclear abnormalities alone are pathognomonic of EFVPTC and has suggested that characteristic “background” features (such as those listed above) should be taken into consideration.31 The use of “strict criteria,” requiring a constellation of both nuclear and other features to make the diagnosis of EFVPTC, was also recommended by Chan in 2002.27 Chan’s diagnostic algorithm for EFVPTC would exclude from this category many tumours with widespread PTC-like nuclear changes. The reason is that in the absence of psammoma bodies, tumours with PTC-like nuclei require four additional (subsidiary or minor) criteria to be present for the diagnosis to be made. Choices include the architectural features listed in the previous paragraph, and rare intranuclear pseudoinclusions. Psammoma bodies are so seldom seen in EFVPTC that the criteria are quite exclusive – which is presumably the intention. The author would agree with Fonseca et al. that “additional morphological features...are only of crucial importance when one is dealing with a thyroid tumour with less than typical PTC nuclei.”35 Of course, “typical PTC nuclei” are in the eye of the beholder, so the goal of developing reproducible morphological criteria for EFVPTC is crucial for further discussion and research. Williams has proposed the term “well-differentiated tumour of uncertain malignant potential” (WDT-UMP) for those encapsulated tumours with equivocal nuclear features of PTC and no convincing evidence of capsular or vascular invasion (Figure 3A and B). He argues that this term is preferable to arbitrarily designating a tumour as benign or malignant.5 One would like to believe that pathologists do not classify tumours arbitrarily (i.e., based on random choice or a whim) but,
admittedly, different pathologists do have considerably different criteria for what is considered diagnostic of EFVPTC, and these criteria are often based on personal experience and bias. These criteria may evolve over time for an individual pathologist, as they do for the group, and may be influenced by “nonpathological” factors, such as fear of litigation, philosophy of the most appropriate treatment, or concerns over the psychological impact on patients when they are labelled with the cancer. The author would argue that the accepted “indeterminate” categories in surgical pathology (such as ovarian tumours of borderline malignancy) have diagnostic categories on either side that are clearly defined and accepted by experts in the field. Unfortunately, the same cannot be said for EFVPTC, so one can only expect that the WTD-UMP diagnosis will also be inconsistently applied. Parenthetically, Williams et al. also proposed the term “well-differentiated thyroid carcinoma, not otherwise specified” (WDTC-NOS) as an indeterminate category for tumours which present difficulty distinguishing between clearly invasive EFVPTC and follicular carcinoma. This designation would not typically affect treatment under current guidelines. As noted above, the natural history of EFVPTC does not lend itself well to identifying which “borderline” lesions should genuinely qualify as malignant, as, in general, they are indolent tumours. The rare cases in which “noninvasive” tumours metastasize are likely those in which vascular invasion has been missed, which may occur despite assiduous sampling. In comparison with both encapsulated classic PTC and nonencapsulated FVPTC, when EFVPTC metastasizes, it does so to distant sites and infrequently to lymph nodes. As discussed below, EFVPTC has been shown to have molecular attributes and behaviours more akin to follicular tumours (adenoma or carcinoma) than to classic papillary carcinoma.

Adjuncts to Diagnosis
It is clear that conventional H&E microscopy is fraught with interpretational difficulties and controversies and that, even if interobserver agreement were possible, categorization of thyroid tumours by conventional nomenclature may not accurately predict behaviour in any individual case. Fortunately, our knowledge of the molecular alterations in thyroid tumours is growing rapidly. The classification of thyroid tumours will likely evolve to incorporate molecular information more intimately into the definition of specific entities. Any discussion of this topic must be prefaced with the statement that nearly all immunohistochemical or molecular studies of thyroid tumours still regard the histological diagnosis as the “gold standard,” and this forms the basis for interpretation of the experimental results. Thus, the interobserver variability and bias that pervade histopathology
is transferred to these studies. As others have commented, if routine histology is the “gold standard” for the investigation of new technologies, only classic examples of tumours should be included.2,28

**Molecular Abnormalities**

The vast majority of molecular abnormalities in well-differentiated thyroid carcinomas fall into one of four categories: (1) *BRAF* point mutations, (2) *RET/PTC* rearrangements, (3) *RAS* point mutations, and (4) *PAX8/PPARgamma* rearrangements. The first three genotypical abnormalities account for more than 70% of mutations in papillary carcinoma, whereas one of the latter two is found in about 75% of follicular carcinomas.6 *RAS* mutations are also common in non-oncocytic follicular adenomas (20–40%), as well as in some nodules morphologically classifiable as hyperplastic.36,37 Most studies, to date, have not subdivided nonenapsulated FVPTC and EFVPTC in their analyses, but several recent studies suggest a closer molecular kinship between EFVPTC and the follicular adenoma or carcinoma group of tumours, than with nonencapsulated FVPTC and other variants of PTC.36-39

While specific for papillary carcinoma, both *BRAF* mutations and *RET/PTC* rearrangements are uncommon in FVPTC, whereas *RAS* mutations are frequently identified.39,40 Zhu et al. found an *RAS* mutation frequency of 43% in FVPTC, but the cases were not subdivided by encapsulation.39 Rivera et al. analyzed FVPTC according to subtype – encapsulated or nonencapsulated. They found a 36% frequency of *RAS* mutations in EFVPTC, compared with only 10% in nonencapsulated FVPTC. No *BRAF* or *RET/PTC* abnormalities were found among their cases of EFVPTC. However, nonencapsulated FVPTC had *BRAF* mutations or *RET/PTC* rearrangements in 26% and 10% of cases, respectively.36

*PAX8/PPARgamma* rearrangement is the second commonest abnormality in conventional follicular carcinoma (30–40%), but it is generally thought to be uncommon in follicular adenoma and FVPTC.6 In contrast to other studies, Castro et al. found a *PAX8/PPAR* rearrangement rate of 37.5% in FVPTC (not subdivided by encapsulation) and 33.3% in follicular adenoma. The rate in follicular carcinoma was 45.5%.38 *PAX8/PPAR* rearrangement was significantly associated with vascular invasion and multifocality in malignant cases, a finding which agrees with other studies.9 As such, the presence of *PAX8/PPAR* rearrangement in a follicular adenoma should prompt a diligent search for invasion. Of note, Castro et al. also found cases of follicular adenoma, follicular carcinoma, and FVPTC in which there was both *RAS* mutation and *PAX8/PPAR* rearrangement, more often in younger patients.38

In two other studies of *BRAF* mutations in FVPTC, the prevalence of mutation was low (10% or less) and was of a different type than in classic and tall-cell-variant PTC (*BRAF* K601E versus the more common V600E).38,41

**Immunohistochemistry**

Numerous immunohistochemical markers have been proposed as aids in the diagnosis of malignant thyroid tumours, and the topic is broad and complex. The reader is, therefore, referred to more comprehensive reviews.21,42 No individual antibody has been found to be completely specific or sensitive for malignancy, even for classic papillary carcinoma. However, a panel of antibodies may be helpful in correctly classifying follicular-patterned tumours.21,42 Suggested panels typically include some combination of HBME1, galectin-3, CK19, and fibronectin-1, among others.43-47 Two (HBME1, galectin-3) or three (HBME1, galectin-3, fibronectin-1) antibody combinations may be as effective as broader panels, as negativity for any pair of these markers is uncommon in thyroid malignancies.46,47 The results of individual immunohistochemical studies are often contradictory, for several reasons, including the following: (1) differing thresholds for the diagnosis of EFVPTC versus follicular adenoma, (2) methodological differences, and (3) differing criteria for interpreting the staining patterns. Several of the antibodies, particularly CK19 and galectin-3, may stain normal, inflamed, or otherwise altered benign thyroid tissue.16,42 Immunostaining for the RET protein is theoretically of value in detecting those papillary carcinomas with *RET/PTC* rearrangements (about 20–25% overall), as the protein is not normally expressed in thyroid follicular cells. C-cells are normally RET-positive. The results of immunohistochemistry are highly dependent on the antisera and methodology used and have been inconsistent. As such,
molecular testing for RET/PTC rearrangements is preferable.42

Conclusion
Encapsulated thyroid tumours with follicular architecture cause considerable diagnostic difficulty for many pathologists. When assessing capsular or vascular invasion, conservative criteria should be applied to avoid overdiagnosing malignancy in these generally indolent tumours. Adequate sampling is crucial and is the most reliable way of rendering a confident diagnosis. Advances in our knowledge of the molecular biology of these tumours may change the way we approach them. Studies of the behavior of follicular-patterned tumours indicate that EFVPTC shares many attributes with encapsulated “conventional” follicular tumours (i.e., follicular adenoma or minimally invasive follicular carcinoma), specifically a tendency to remain indolent in the absence of invasion, a low frequency of lymph node metastases, and the possibility of distant, blood-borne metastases in those tumours with vascular invasion. The molecular profiles of EFVPTC and other encapsulated follicular tumours are similar, with a high rate of RAS mutations and much lower rates of BRAF mutations and RET/PTC rearrangements compared with noninvasive FVPTC and other types of PTC. If borne out, these findings may lessen the relative importance of PTC-type nuclei in encapsulated tumours, and an argument could be made for treating many noninvasive EFVPTC with lobectomy alone.

References
Dr. Antoinette Day is a pathologist in a small Idaho town. Life for Dr. Day gets interesting when a less-than-pleasant new surgeon arrives in town. Then her life gets even more interesting when the new surgeon’s less-than-alive body ends up in Dr. Day’s office. “Toni” must then prove her innocence and sort out the surgeon’s ties to other staff, all the while dealing with her crazy ex-boyfriend.

Like all of us, I read a lot for work. An author has one chapter to convince me that I should spend my downtime reading a book. Dr. Munro’s first lines made me smile: “There was a dead body in my office. It wasn’t mine and I didn’t put it there.” I finished the book with no hard feelings about the book review I had promised to write. I also quite loved the last few lines. I would like the book even more if it were longer or shorter. It could tell a fast-paced story well without the ex-boyfriend subplot. As a longer book, it could give more details about the characters and their backgrounds. While the book is enjoyable, many of the characters are forgettable.

I do wonder how a reader without an MD would fare with the casual use of terms such as “pleural fluid,” “four-unit crossmatch,” and “hyaline membrane disease of newborns.” Sentences such as “I embedded, cut and stained my own surgicals” require a residency in pathology to truly comprehend. Personally I enjoyed a story set in familiar territory, free of awkward definitions and explanations, and overall I recommend Murder Under the Microscope as a fun read.

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