Endoscopic Mucosal Resection in Barrett’s Esophagus
Associated Neoplasia: Recommendations For Pathological
Evaluation And Reporting
The CAP-ACP Annual Meeting consists of two days of workshops (Saturday and Sunday) followed by two days of symposia. There is a half day with proffered paper/posters and a half day of CAP-ACP specific awards lectures. There are two evenings of special interest group and specialty network meetings. The overall meeting is under the supervision of the Annual Meetings Committee with subcommittees including the LOC, CPD Committee, CAP-ACP Sections and the CAP-ACP Awards Committee.

The Local Organizing Committee, under the direction of Chair, Dr. Martin Trotter have confirmed that the President’s Reception will be held at the Museum of Anthropology, UBC (transportation is provided) and that they will be assisting with the PA program to include a wet-lab on Sunday morning at St. Paul’s Hospital.

Confirmed speakers to date:

Dr. Mary Bronner is our invited Cam Coady Slide Seminar speaker and will be giving a talk titled: "GI Tract Mucosal Biopsy" on Tuesday, July 12, 1400-1700.

The Forensic Pathology section has invited Dr. C. Paul Johnson, a Forensic Pathologist from the UK (Liverpool). He has a research interest in, and will be presenting on "Traumatic Subarachnoid Haemorrhage and the Mechanisms of Vertebral Artery Trauma".

The Humanities/International Health Symposium speakers will be Dr. Maadh Aldouri, from the Royal College of Pathologists, UK, sharing a talk on his “Experience with Labskills Africa Project”, and Dr. Phil Clement, who will be giving a talk on “The History of Endometrial Carcinoma”.

Program to include:

- Pathologist Assistants Program
- Junior Scientist Award Lecture
- Cam Coady Slide Seminar
- William Boyd Lecture
- Awards Banquet
- Special Interest Groups
- President’s Reception
- Workshops
- Poster Presentations
- Satellite Symposia
- Networking
- Industry Partners

See www.cap-acp.org/2016meeting.php for more information
on Sunday morning at St. Paul’s Hospital.

with the PA program to include a wet-lab of Anthropology, UBC (transportation is

Reception will be held at the Museum in the direction of Chair, Dr. Martin Trotter

Specialists (UEMS) physicians may convert Royal College MOC credits to ECMEC

Through an agreement between the Royal College of Physicians and Surgeons of Canada and the European Union of Medical

physicians may convert Royal College MOC credits to AMA PRA Category 1 Credits™.

Through an agreement between the Royal College of Physicians and Surgeons of Canada and the American Medical Association,

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification program of the

CAP-ACP Annual Meeting

CAP-ACP Awards Committee.

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CAP-ACP Scientific

Hyatt Regency, Vancouver, BC

July 9-12, 2016

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Endoscopic Mucosal Resection (EMR) In Barrett’s Esophagus
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About the Cover
Omental cholelithiasis and bile granuloma with surrounding decidualized cells (H&E).

Submission of manuscripts
The manuscript must be sent by e-mail attachment to the Editor-in-Chief, Dr. George Yousef at: info@cap-acp.org Only electronic submissions will be acknowledged and sent out for peer review.
Screening for Prostate Cancer Risk: Fantasy or Reality

Prostate cancer is the most commonly diagnosed malignancy worldwide, affecting 233,000 men annually in the US alone. While the 5-year survival rate for localized disease approaches 100%, extraprostatic invasion results in a poor prognosis, thus early diagnosis to improve overall mortality is the goal. Prostate-specific antigen testing has been used to screen prostate cancer and has led to reduction in prostate cancer–related mortality over the last two decades. However, use of a single threshold of PSA has been criticized, as approximately two-thirds of men with elevated serum PSA levels will not have cancer on biopsy.

Recently, two large studies on PSA screening efficacy have been published: in the European trial (ERSPC) it reduced mortality by ~20-30 %, while in the US-based trial (PLCO), no reduction in mortality was observed. Both studies showed that PSA testing leads to over-diagnosis by ~50 %, which leads to overtreatment and associated co-morbidities, causing unnecessary costs and reduced quality of life. It should be also noted that US Preventive Service Task Force (USPSTF) recommends against prostate cancer specific antigen screening for prostate cancer. Moreover, recent clinical trials show that the outcome of active surveillance is comparable to radical prostatectomy for patient with low risk disease. Thus, the value of screening for prostate cancer risk has been recently challenged identifying a critical need for new diagnostic biomarkers that could minimize over detection by reducing the number of false-positive results, and which can distinguish indolent and aggressive disease.

Derivatives of PSA have been suggested in an attempt to improve its performance. Additional novel approaches include the PCA3-based urine test, Circulating Tumor Cells, circulating miRNAs, and 4K score as well as multiparametric magnetic resonance imaging. Changes to epigenetic patterns are also emerging. Similarly, common genetic variants have the capacity for differentiating patient risk. For instance, Nam et al. developed a nomogram that, by combining four identified SNPs, can predict an individual’s risk of developing prostate cancer. In a recent study, genetic scoring has been shown to be a better measurement of inherited risk of prostate cancer than family history. In a study by Kader et al., addition of 33 genetic markers to the classification of prostate cancer risk resulted in 33% of men reclassified into a different risk quartile with the net reclassification benefit of 10% (p=0.002).

Since a single marker is unlikely to suffice, multi-modal strategies look more promising. In our effort to develop new “genomic” screening tests for prostate cancer risk, the accepted WHO criteria for screening should be fulfilled, including the presence of an agreement on policy of whom to treat and also the presence of scientific evidence for screening program effectiveness. Identifying reproducible, robust biomarkers will require large combined efforts from multiple disciplines and implementation strategies to be adopted in clinics.


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Le dépistage des risques de cancer de la prostate : rêve ou réalité?

Le cancer de la prostate est le type de tumeur maligne le plus souvent diagnostiqué dans les pays développés; il touche chaque année 233 000 hommes aux États-Unis seulement. Lorsque la maladie est localisée, le taux de survie après cinq ans est de presque 100 %. Le pronostic est cependant moins bon en cas d’extension extra-prostatique; l’objectif est donc d’obtenir un diagnostic précoce afin d’améliorer le taux de survie 1. On utilise le test de l’antigène prostatique spécifique (APS) pour dépister le cancer de la prostate, ce qui a entraîné une réduction de la mortalité au cours des deux dernières décennies. Cependant, l’utilisation d’un seul unique d’APS est remise en question, car chez environ deux tiers des hommes dont le niveau d’APS est élevé, la biopsie ne révèle pas de cancer.

Deux grandes études sur l’efficacité du dépistage par l’APS ont été publiées récemment : selon l’étude européenne (ERSPC), ce test réduit la mortalité d’environ 20 à 30 %2–3, avec que selon l’étude américaine (PLCO), on ne constate aucune réduction du taux de mortalité 4. Selon les deux études, le test d’APS mène à un surdiagnostic d’environ 50 %5, et à un surtraitement et à des comorbidités connexes, ce qui entraîne de coûts inutiles et réduit la qualité de vie. Il faut également souligner que le Groupe de travail américain sur les services de prévention (USPSTF) s’est prononcé contre l’utilisation du test de l’antigène prostatique spécifique pour dépister le cancer de la prostate. De plus, de récents essais cliniques ont montré que les résultats d’une surveillance active se comparaient à ceux d’une prostatectomie radicale pour les patients ayant une maladie de la prostate à faible risque6. On a donc récemment remis en question la valeur du dépistage des risques de cancer de la prostate et mis en lumière l’urgence de trouver de nouveaux biomarqueurs afin de minimiser la surdétection, de réduire le nombre de faux positifs et de distinguer les formes indolentes des formes agressives de la maladie.

On a suggéré l’utilisation de dérivés de l’APS pour améliorer le rendement du test7. Parmi les approches novatrices, il faut aussi compter le test d’urine basé sur le PCA3, les cellules tumorales circulantes (CTC), le micro-ARN circulant, et la cote 4K, de même que l’imagerie à résonance magnétique multiparamétrique 8. Les changements au profil épigénétique présentent aussi un potentiel important. De la même façon, des variantes génétiques courantes peuvent permettre une différenciation du risque9. Par exemple, Nam et coll. ont mis au point un nomogramme clinique combinant quatre SNP connus pour prédire le risque de développer un cancer de la prostate10. Une étude récente a montré que l’évaluation génétique était une meilleure mesure du risque héréditaire de cancer de la prostate que l’histoire familiale11. Dans une étude menée par Kader et coll., on a ajouté 33 marqueurs génétiques à la classification des risques de cancer de la prostate, ce qui a entraîné une reclassification de 33 % des hommes dans un quartile de risque différent, avec un avantage net de 10 % (p = 0,002)12–13.

Comme il est peu vraisemblable qu’un seul marqueur suffise, les stratégies multimodales sont les plus prometteuses. Lorsqu’on cherche à créer de nouveaux tests « génomiques » de dépistage du risque de cancer de la prostate, il faut respecter les critères reconnus de l’OMS pour la prévention (USPSTF) s’est prononcé contre l’utilisation du test de l’antigène prostatique spécifique pour dépister le cancer de la prostate. De plus, de récents essais cliniques ont montré que les résultats d’une surveillance active se comparaient à ceux d’une prostatectomie radicale pour les patients ayant une maladie de la prostate à faible risque. On a donc récemment remis en question la valeur du dépistage des risques de cancer de la prostate et mis en lumière l’urgence de trouver de nouveaux biomarqueurs afin de minimiser la surdétection, de réduire le nombre de faux positifs et de distinguer les formes indolentes des formes agressives de la maladie. 

Omental Cholelithiasis: A Histologic Correlation

We read with great interest the recent article by Noy and Dupré, *Omental Cholelithiasis: A Potential Mimic of Peritoneal Carcinomatosis.* The article provides macroscopic images of omental cholelithiasis. We would like to report a recent similar case of omental cholelithiasis and provide histologic images to complement the gross images provided by the previous authors.

The case is that of a 35-year-old woman who underwent cesarean section for an abnormal fetal heart rate. At the time of surgery, inspection of the vesicouterine peritoneum revealed several small firm nodules that were clinically suspected to be endometriosis or an inflammatory reaction surrounding surgical clips from a previous operation. Gross examination showed diffuse submillimeter yellow gritty nodules.

Microscopic examination revealed cystically dilated spaces within the peritoneal tissue, many of which contained yellow, filamentous, refractile, non-polarizable material with a crystalline appearance. The cystic spaces were lined by a thin layer of histiocytes and multinucleate giant cells (Figures 1 and 2). In keeping with the recent pregnancy, decidualized stromal cells were focally identified in the background tissue (Figure 1).

On review, this patient had undergone a laparoscopic cholecystectomy 2 years prior for acute cholecystitis and gallstone pancreatitis. Gross examination of the gallbladder had revealed a small mural defect, more than 100 luminal stones and several spilled stones in the specimen container. These findings are consistent with a diagnosis of omental cholelithiasis secondary to gallbladder perforation and intra-abdominal spillage of gallstones at the time of laparoscopic cholecystectomy. As stated in the previous article, this can occur in up to 16% of cholecystectomies and more than one third of the spilled stones are not retrieved.1,2

Omental cholelithiasis/peritoneal bile granulomas can be mistaken for a malignant or other process.1,2 Pathologists and surgeons should be aware of this entity as it is a potential diagnostic pitfall, especially at frozen section/intraoperative consultation.

**References**


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Statutory and Common Law Protection of Laboratory Quality Assurance Data in Canada

In the article entitled Statutory and Common Law Protection of Laboratory Quality Assurance Data in Canada, the judicial interpretation and application of the statutory protection from disclosure of laboratory quality assurance (QA) were examined by Singh D and Duggan M.A. (Canadian Journal of Pathology 2012; 4: 54-58). They found that compliance with statutory protection was narrowly interpreted by Canadian courts and that the quality assurance committees (QACs) of Alberta Health Services (AHS) were compliant with the protection afforded by section 9 of the Alberta Evidence Act. However, the QA groups or committees formed locally within the provincial laboratories (internal QACs) were not eligible for protection. Consequently, laboratory QA data were not legally protected from disclosure to any party or individual who might request access to it. This would include access to the QA data of individual and identifiable laboratory professionals. Of note, simply naming an internal laboratory committee a QAC does not ensure legal protection; the committee must be officially constituted in compliance with the provincial Act that provides the protection. The purpose of this letter is to provide a brief update to that publication on the steps taken in Alberta to establish eligibility for and implementation of section 9 protection of QA data gathered by provincial laboratories for the mandated AHS Anatomical Pathology Quality Assurance Plan (AHS AP QA Plan). The Plan is province wide and includes both public and private laboratories. It is governed by the AHS Anatomical Pathology Quality Assurance Implementation Strategy Development Team (AHS AP Quality Team).

Eligibility for Section 9 protection of the internal laboratory QACs engaged in the AHS AP QA Plan was awarded in March 2014 by the AHS Quality and Safety Committee approximately 27 months after the request was initiated by the co-chairs (MAD and TT) of the AHS AP Quality Team. Sponsorship of the request by the Provincial Medical/Scientific Director of AHS Laboratory Services (Dr. James Wesenberg) and the AHS Vice President Quality and Chief Medical Officer (Dr. Verna Yiu), and a strategic alliance with the executive director of AHS Patient Safety (Ms. Paula Beard) were critical in moving the request forward and in achieving success. The delay in gaining eligibility was mainly due to debate amongst AHS key stakeholder services including legal services as to whether source data for the AHS AP QA Plan from individual and identifiable laboratory professionals should be protected from disclosure. The opponents argued that if the data was protected it could not be used to identify underperforming individuals. The proponents counter-argued the AHS AP QA Plan was designed to monitor and evaluate laboratory performance at a systems level using aggregate data and not at an individual level using identifiable data. Since this was the scope the provincial laboratories supported when they agreed to implement it, broadening the scope after the fact would jeopardize its full implementation and implementation of any future AHS QA Plans in the Pathology and Laboratory Medicine sphere. Since the safety afforded patients by the province wide implementation of the AHS AP QA plan was of paramount importance to the stakeholders, and the dependence of the Plan’s aggregate data on the collection of QA data from individuals was understood, eligibility for section 9 protection of internal laboratory QACs engaged in AHS AP QA Plan activities and any future AHS Pathology and Laboratory Medicine Plans was agreed upon. Central to the agreement was the reassurance that AHS and the College of Physicians and Surgeons of Alberta had other systems in place to assess the performance of individual laboratory professionals and these systems would be triggered should underperformance by an individual be highlighted by the Plan’s data.

Implementation of section 9 protected internal laboratory QACs was completed over the ensuing months principally by restructuring and rebranding the existing QACs as subcommittees of the pre-existing section 9 protected AHS QAC structure. They are now fully operational and engaged in the monitoring and evaluation of the AHS AP QA Plan data. Any data from an identifiable laboratory professional is now legally protected from disclosure. On a cautionary note however, section 9 protection does not extend to every QA activity performed by an individual. It only extends to those which are prescribed by AHS Pathology and Laboratory Medicine QA Plans.

We hope that by sharing this account, others may benefit from our experience.

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Tamara Trotter MLT, Co-Chair Alberta Health Services Anatomical Pathology Quality Assurance Implementation Strategy Development Team and Provincial Anatomical Pathology Quality Lead.
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Standard Terminology and Nomenclature for Pancreaticobiliary Cytology: A Review of the Guidelines from the Papanicolaou Society

Malcolm Schinstine, PhD, MD

Introduction

In anatomic pathology, the fruit of the pathologist’s labors is the diagnosis. Most of the time, the diagnosis is clear and understood by the intended audience, i.e., the ordering clinician or radiologist. Unfortunately, sometimes the diagnosis is misinterpreted or misunderstood leading to inappropriate treatment, including unnecessary surgery. Although a variety of circumstances can lead to misunderstanding, the use of descriptive or otherwise non-definitive diagnosis is a major cause of clinician confusion.

One way to reduce misunderstandings is to standardize the terms and nomenclature used by cytopathologists to make a diagnosis. The Bethesda Systems for cervical and thyroid cytopathology for example, are two such systems designed to standardize diagnoses. The use of these standardized systems has reduced diagnostic variability between cytopathologists and allows clinicians to be more confident in the treatment regimens they pursue subsequent to a particular diagnosis.

Recently, the Papanicolaou Society introduced diagnostic guidelines for the standardization of terminology and nomenclature for pancreaticobiliary cytology specimens. The categories suggested by the guidelines are listed in Table 1. In this review, the terms nomenclature and diagnostic categories for pancreaticobiliary cytology are briefly summarized and explained, including example diagnoses. The Papanicolaou Society has also published guidelines for the use of ancillary studies, indications for cytologic studies of pancreatic lesions, techniques for cytologic sampling of the pancreas, and treatment options. These subjects are not covered in the present manuscript.

Table 1.

Proposed Terminology Classifications for Lesions of the Pancreaticobiliary System

1. Nondiagnostic
2. Negative (for malignancy)
3. Atypical
4. Neoplastic: benign and other
5. Suspicious (for malignancy)
6. Positive/Malignant

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Competing interests: None declared.
This article has been peer reviewed.
Introduction

En anatomopathologie, le pathologiste cherche à produire un diagnostic; la plupart du temps, ce diagnostic est clair et bien compris par son destinataire, c’est-à-dire le clinicien ou le radiologiste qui a demandé l’examen. Malheureusement, le diagnostic est parfois mal interprété ou mal compris, ce qui peut mener à un traitement inadéquat, voire à une chirurgie inutile. Diverses circonstances peuvent mener à ce type d’erreur, mais le recours à un diagnostic descriptif ou à un autre diagnostic non définitif est une cause importante de confusion chez les cliniciens.

L’un des moyens d’éviter ce type d’erreur est de normaliser les termes et la nomenclature utilisés par les cytopathologistes pour établir un diagnostic. C’est l’objectif des systèmes de Bethesda employés pour la cytopathologie du col utérin1 et de la thyroïde,2 par exemple. L’utilisation de ces systèmes a réduit la variabilité des diagnostics entre les cytopathologistes et a permis aux cliniciens de choisir un traitement avec davantage de confiance.

Récemment, la Papanicolaou Society a publié des lignes directrices sur la normalisation de la terminologie et de la nomenclature des diagnostics établis à partir de prélèvements cytologiques pancréatique biliaires.3 Le tableau 1 dresse la liste des catégories suggérées dans ces lignes directrices. Nous résumons et expliquons ici brièvement les termes, la nomenclature et les catégories de diagnostics en cytopathologie pancréatique-biliaire, avec des exemples de diagnostics. La Papanicolaou Society a également publié des lignes directrices sur l’utilisation d’exams connexes,4 les indications de l’examen cytologique de lésions pancréatiques,5 les techniques de prélèvement cytologique du pancréas6 et les possibilités de traitement,7 mais ces sujets ne sont pas couverts dans le présent article.

Category I. Nondiagnostic

Similar to other classifications schemes, a category is needed to describe the situation where a specimen lacks the cellularity and/or cytologic integrity to achieve a diagnosis. Issues obfuscating diagnoses may be technical or involve sampling. In order to utilize the “Nondiagnostic” category, radiographic and clinical data must be considered in addition to the findings, or lack thereof, gleaned from the cytology slide. A specimen is not necessarily Nondiagnostic just because there is a lack of epithelial cells to adequately assess for dysplasia or malignancy. For example, epithelial cells would not be expected in an aspirate of a pseudocyst and the lack of epithelial cells in this case does not make the aspirate Nondiagnostic. Similarly, abundant mucin may be the only evidence for sampling of a mucinous cyst and the lack of epithelial cells in this aspirate does not necessarily render the specimen Nondiagnostic. Cyst fluid containing elevated carcinoembryonic antigen (CEA) may be sufficient to render a diagnosis of a neoplastic mucinous cyst, even in the absence of an epithelial component. Importantly, the presence of atypia (dysplasia) always precludes the use of the “Nondiagnostic” category.

Definition

The “Nondiagnostic” category is defined by a specimen where there is no diagnostic information regarding the nature of the solid or cystic lesion sampled. For example, a mucinous cyst where there is no evidence of background mucin, an epithelial component, elevated fluid CEA, or KRAS/GNAS mutation may be classified as “Nondiagnostic”. A specimen containing epithelial cells may also be rendered “Nondiagnostic” if the epithelial cells are obscured by blood or if the cells are poorly preserved severely limiting interpretation.
**Example Diagnoses**

1. Evaluation limited by scant cellularity
   Nondiagnostic
   Insufficient cell content or cyst fluid levels for cytologic or ancillary testing.

2. Evaluation limited by preparation artifact
   Nondiagnostic
   Cells entrapped and obscured by blood clot and fibrin.

**Category II. Negative (for Malignancy)**

The negative category implies the absence of malignant cells or any cytologic atypia (dysplasia). A descriptive negative interpretation without a specific diagnosis, e.g., chronic pancreatitis or pseudocyst, is not synonymous with a benign lesion. A descriptive negative diagnosis implies the sample is sufficiently cellular and no cytologic atypia is identified. This may include the presence of normal pancreatic tissue in the setting where the radiologic findings are unclear or nebulous, i.e., no definitive mass lesion. In the situation where a radiographic or clinically distinct mass is present and interpreted as adenocarcinoma, the presence of only normal pancreatic tissue should be considered as a false negative. The false negative rate for aspiration of solid pancreatic masses averages 15%. For cystic lesions, the false negative rate is as high as 60% and is usually due to scant specimen cellularity. The lack of high-grade epithelial atypia in an aspirate of a pancreatic cyst has a high negative predictive value for malignancy.

Pancreaticobiliary brushings offer special diagnostic challenges often due to known, or unknown, underlying disease(s), e.g., primary sclerosing cholangitis, and/or the presence of a stent. The latter circumstance is frequently associated with marked reactive change requiring the implementation of strict cytologic criteria to arrive at a malignant diagnosis. Another factor contributing to the high false negative rate for pancreaticobiliary brush specimens is the difficulty of obtaining sufficient, well preserved diagnostic cells.

**Definition**

The definition of a “negative” cytology specimen is one with adequate cellularity and/or extracellular material that correlates with radiographic and/or clinical findings. A specific diagnosis should be rendered when possible (see Table 2).

**Table 2. Specific Benign Diagnoses That Should Be Rendered When Possible**

1. Benign pancreaticobiliary tissue in the setting of vague fullness with no definitive pancreatic mass
2. Autoimmune pancreatitis
3. Chronic pancreatitis
4. Acute pancreatitis
5. Pseudocyst
6. Lymphoepithelial cyst
7. Splenule/accessory spleen

**Example Diagnoses**

1. Satisfactory for evaluation
   Negative for Malignancy
   Benign and reactive ductal epithelium, acinar tissue, mixed inflammation, and background necrotic and calcific debris; compatible with chronic pancreatitis.

2. Satisfactory for evaluation
   Negative for Malignancy
   Nonmucinous cyst fluid with no epithelial cells and numerous hemosiderin-laden macrophages, suggestive of serous cystadenoma (see comment). Comment: Low CEA and amylase fluid levels support the diagnosis (if the information is available).
3. Satisfactory for evaluation
   Negative for Malignancy
   Cyst fluid with inflammation and histiocytes, amorphous yellow pigment, and no cyst lining epithelial cells; suggestive of a pseudocyst (see comment).
   Comment: Low CEA and markedly elevated amylase levels support the diagnosis (if the information is available).

Category III. Atypical
The “Atypical” category is used when the cytologic or extracellular features are beyond what is recognized as normal, but fall short of outright high-grade dysplasia or malignancy. These aspirates cannot be classified as “Negative” because mild cytologic atypia, be it neoplastic or reactive, is present. In addition, sometimes evaluation of these specimens is limited by artifact or by the lack of sufficient cellularity.

This category has historically included specimens with reactive atypia (change), low cellularity, dysplasia (prenecursory changes), and cases where the cytologist is exercising caution. According to one study, the risk of malignancy in the “Atypical” category for pancreatic and bile duct brushings is approximately 44%. For solid pancreatic masses, the risk of malignancy approaches 82%.

Aspirates diagnosed as “Atypical” connote the possibility of neoplasia, most likely low grade, when there is insufficient cytologic evidence for the specimen to be placed in the “Suspicious” or “Positive for Malignancy” categories. Traditionally, most dysplastic mucinous cysts have been placed in the “Atypical” (high grade) or “Negative” (low grade) categories. Often, the placement of mucinous cysts into more definitive diagnostic categories is hampered by the lack of a standardized classification system. It is important that aspirates of mucinous cysts, with or without high-grade dysplasia, be properly identified so that proper treatment algorithms can be followed.

Definition
The “Atypical” category should only be used when an aspirate is sufficiently cellular and possesses cytoplasmic, nuclear, and/or architectural features not considered normal or overtly reactive. Moreover, the morphologic features should be inadequate for definitive determination of a neoplastic or overtly malignant process. The cytologic findings may also not be sufficient to explain clinical or radiographic findings. For lesions placed in this category, follow-up evaluation is usually strongly suggested.

Example Diagnoses
1. Evaluation limited by scant cellularity
   Atypical
   Atypical bile duct epithelium with background acute inflammation, suggestive of repair.
2. Evaluation limited by preparation artifact
   Atypical
   Atypical cells obscured by crush artifact.
3. Evaluation limited by scant cellularity
   Atypical
   Atypical bile duct epithelium with mucinous metaplasia and mild nuclear atypia.

Category IV. Neoplastic
The neoplastic category is divided into two distinct subcategories, “Neoplastic: benign” and Neoplastic: other". The former category includes neoplasms that are clearly benign, serous cystadenoma being the quintessential example. The “Neoplastic: other” category includes numerous neoplasms that are pre-invasive (e.g., mucinous cystadenoma with low-grade dysplasia) or with low-grade malignant behavior (e.g., pancreatic neuroendocrine tumor).

Category IVa. Neoplastic: benign
As mentioned, this category is best represented by pancreatic serous cystadenoma. Other benign neoplasia, such as cystic teratoma and Schwannoma, are also included in this category, but are extremely rare.

Serous cystadenomas are composed of fine fibrous septae lined by bland cuboidal cells with clear cytoplasm (glycogen rich). Other than for occasional degenerative or reactive cells, atypia is minimal or absent. Aspirations of this entity may be hemorrhagic due to numerous small capillaries traversing the fibrous septae. Because of the hemorrhagic nature of the lesion, aspirates may be populated by numerous hemosiderin-laden macrophages. In fact, as compared to mucinous cystic neoplasms, up to 63% of aspirates of serous cystadenomas contain hemosiderin-laden macrophages.
In addition to cytologic, radiologic, and clinical features indicating a diagnosis of serous cystadenomas, low fluid CEA levels (typically less than 5 ng/ml) and relatively low amylase levels are characteristic of the entity. As a caveat though, some mucinous cystic neoplasms also have low fluid CEA levels and occasional serous cystadenomas may have elevated CEA levels.14-16

Definition
The definition of the “Neoplastic: benign” category requires a sufficiently cellular and representative aspirate, with or without supporting radiographic, clinical, or ancillary information, diagnostic of a benign neoplasm, e.g., serous cystadenoma.

Example Diagnoses
1. Evaluation limited by scant cellularity
   Neoplasm: benign
   Scant specimen; nonmucinous cuboidal epithelial cells and numerous hemosiderin-laden macrophages compatible with serous cystadenoma (see comment).
   Comment: Low fluid CEA (0.5 ng/ml) and amylase levels (150 U/ml) support the diagnosis (if available).

Category IVb. Neoplastic: other
The purpose of this category is to provide a place for tumors with an uncertain or low-grade malignant potential. The addition of this category allows these neoplasms NOT to be classified as “Atypical” or “Suspicious for Malignancy,” possible avoiding inappropriate management. The use of this category also brings pancreatic cytologic diagnoses more in line with the 2010 WHO classification and terminology of pancreatic lesions. This category is the most important contribution of the Papanicoloau Society guidelines.

The “Neoplastic: other” category is populated by several neoplastic entities with preinvasive features and/or low-malignant potential. This group of neoplasms includes 1) Intraductal papillary mucinous neoplasia (IPMN; with low-, intermediate-, or high-grade dysplasia), 2) mucinous cystic neoplasia (MCN; with low-, intermediate-, or high-grade dysplasia), 3) pancreatic neuroendocrine tumor (PanNET), 4) solid-pseudopapillary neoplasia, 5) intraductal papillary neoplasm of the bile ducts, and 5) gastrointestinal stromal tumor (GIST).

Definition
This category connotes a premalignant (e.g., IPMN with low-, intermediate-, or high-grade dysplasia) or low-grade malignant potential (e.g., PanNET). Mucinous epithelia with low-grade changes in brushing specimens should still be classified as “Atypical” because of the unclear management of these lesions.

Pancreatic Neuroendocrine Tumor
When used, the diagnosis of PanNET describes a well-differentiated neoplasm. This term should be used regardless of whether the tumor is in a primary site or represents a metastasis. In contrast to PanNET, neuroendocrine carcinoma is the terminology that should be used for high-grade large cell neuroendocrine carcinoma or small cell carcinoma. These overtly malignant tumors should be placed in the “Positive (for malignancy)” category if there are enough cytologic features to do so.

PanNET infers a well-differentiated proliferation of pancreatic neuroendocrine cells forming a mass greater than 0.5 cm. The tumor cells may or may not be functional and may or may not exhibit aggressive features in histologic specimens. These tumors do have malignant potential, but the tumors are usually slow growing and early tumors may be curable. PanNET is placed in the “Neoplastic: other” category to distinguish them from more highly aggressive malignant tumors and to offer management flexibility in patients, e.g., the elderly, where the benefits of surgery are not certain.

Solid-Pseudopapillary Neoplasm (SPN)
SPN usually occurs in young females and exhibit solid and cystic features on imaging. These tumors are low-grade, but do demonstrate the ability to metastasize. When diagnosed, these tumors are almost always resected. However, because SPN is considered a low-grade malignancy, it should be categorized as “Neoplastic: other”.

Neoplastic Mucinous Cysts of the Pancreas, IPMN and MCN
IPMN and MCN are the two most common neoplastic mucinous cysts of the pancreas. Cytologic diagnosis of these tumors is supplemented by knowledge of the clinical
findings, radiographic features, and by biochemical and/or molecular cyst fluid analysis.

Management guidelines have become more conservative for mucinous cysts due to the prevalence of incidental pancreatic cysts in the general population, especially the elderly. MCNs, although almost always low grade, are usually found in the mid to distal pancreas and can be resected by distal pancreatectomy. Main duct and combined type IPMNs are always resected due to the high risk of malignancy; however, for most mucinous cystic neoplasms of the pancreas without high-grade dysplasia or carcinoma, conservative management is reasonable.

For the pathologist, the task involves accurate grading of the cyst epithelium to determine if conservative management is possible or if more radical management is needed. This task is made more difficult by a specimen with few epithelial cells or cells that are poorly preserved. Moreover, many of the specimens contain mucin contamination from the stomach or duodenum. Regardless, it is contingent upon the pathologist to be able to distinguish low-grade from high-grade dysplasia as the latter lesions may benefit from more definitive surgical resection.

**Mucinous Cystic Neoplasia (MCN)**

These tumors are usually multiloculated, mucin-producing neoplasms with an adjacent ovarian-type stroma occurring almost exclusively in women. These tumors are usually not connected to the pancreatic ductal system.

Cytologically, these tumors are graded by the degree of nuclear and architectural atypia, i.e., low-grade, intermediate-grade, high-grade dysplasia (non-invasive) and invasive mucinous carcinoma. A similar neoplasm occurs in the biliary tract and shares the same cytologic features.

**Intraductal Papillary Mucinous Neoplasm (IPMN)**

IPMNs (including intraductal tubulopapillary neoplasms), as their name implies, are primarily a neoplastic proliferation of ductal epithelium. There are three types of IPMNs: 1) main-duct IPMN, 2) branch duct (BD)-IPMN, and 3) combined-type IPMN. The main-duct IPMN generally causes dilatation of the main pancreatic duct or the entire pancreas. These neoplasms usually have an intestinal-type epithelium (MUC 5AC, MUC 2, and CDX-2 positive) and, by definition, display at least intermediate grade dysplasia.

BD-IPMNs primarily are found in the uncinate process and manifest as cysts adjacent to the non-dilated main pancreatic duct. These cysts are most often lined by a gastric foveolar-type epithelium displaying intermediate- to high-grade dysplasia. One caveat is tumors lined by a low-grade gastric foveolar-type epithelium may be confused with contaminating gastric epithelium. Invasive carcinomas arising from BD-IPMNs are usually tubular with a prognosis similar to conventional pancreatic adenocarcinoma.

In addition to intestinal and gastric foveolar-type epithelia, IPMNs may be lined by a pancreatobiliary and oncocytic type epithelium. Pancreatobiliary-type epithelium is relatively rare and is considered high-grade by definition. Oncocytic-type epithelium is the least common and features cells with an eosinophilic granular cytoplasm, large nucleus, and a prominent nucleolus. It is not possible or necessary to distinguish between the epithelial types in intermediate to high-high grade dysplastic IPMNs.

**Intraductal Papillary Neoplasm of Bile Ducts (IPN-BD) and GIST**

IPN-BDs share many of the clinical and pathological features of IPMNs. Composed of a papillary proliferation of mucin-producing neoplastic cells, this entity can occur anywhere in the ductal system. The four types of epithelium associated with IPMNs (intestinal, gastric foveolar, pancreatobiliary, oncocytic) can also be found in IPN-BD, but show a different distribution pattern.17,18 These lesions are more likely to be sampled by brushing than by fine needle aspiration.

GISTs are very rare primary pancreatic tumors, but can be found in peripancreatic locations (omentum, mesentery, duodenum, and stomach). Typically, these tumors express c-kit protein (CD117 positive) and are also CD34 and DOG1 immunoreactive. A cell block may greatly facilitate definitive diagnosis.

**Ancillary Tests**

As mentioned previously, ancillary biochemical and/
or molecular tests may greatly aid in making a definitive diagnosis. For cyst fluids, the determination of the levels of CEA and amylase are invaluable to help determine the classification of the cyst, i.e., mucinous versus non-mucinous. A cyst fluid CEA level greater than 200 ng/ml is strongly supportive of a mucinous cyst. In contrast, low fluid CEA levels cannot be used by itself to diagnose non-mucinous cysts as a low CEA level does not necessarily exclude a mucinous cyst. In addition, CEA levels cannot distinguish between benign and malignant cysts. The level of fluid amylase is another parameter useful in analyzing pancreatic cysts. For example, fluid amylase levels are usually elevated (typically in the thousands) in pseudocysts. Amylase levels cannot be used to distinguish between IPMN and MCN. And finally, serous cystadenoma and PanNET usually have low CEA and amylase levels. KRAS testing may also prove useful for the diagnosis of mucinous cysts. Similarly, the detection of GNAS in pancreatic cyst supports the diagnosis of IPMN. Neither the detection of KRAS or GRAS can distinguish between pre-malignant lesions versus an invasive malignancy. Interpretation of pancreatic aspirates is sometimes hindered by several factors necessitating indeterminate categorization of the neoplasm, i.e., “Suspicious.” The first mitigating factor is the level of differentiation displayed by some pancreatic adenocarcinomas. Second is the possibility of few diagnostic cells in the aspirate. Finally, gastrointestinal (GI) contamination may be severe enough to obscure the presence of malignant cells. GI contaminates can also confound interpretation if the contaminating GI epithelium are themselves atypical, either through injury or a reactive process. If the listed factors confound the delivery of a definitive diagnosis, the “Suspicious” category may be used.

Another mimicker of malignancy that must be considered is autoimmune pancreatitis. This entity is a well-known pitfall of adenocarcinoma of the pancreaticobiliary system. For all these confounding factors, when criteria are stringently used and there is high clinical and radiographic suspicion for malignancy, the diagnosis of “Suspicious (for malignancy)” most likely represents cancer.

Definition
“Suspicious (for malignancy)” may be used when there are insufficient features to make a definitive diagnosis of a malignant neoplasm (usually pancreatic ductal adenocarcinoma). The cytologic findings are highly

Category V. Suspicious (for malignancy)
This category has traditionally been used for pancreatic adenocarcinoma, but may be used for any malignant neoplasm. The use of this category is recommended for any high-grade, aggressive neoplasm where there is inadequate cytologic features to make a definitive malignant diagnosis. It is important to remember that “suspicious for” does not mean “diagnostic of,” so surgical intervention is inappropriate unless there is supporting clinical and radiographic data in addition to the cytologic findings.
suspicious for malignancy, but the quantitative and qualitative characteristics of the aspirate are inadequate to render a conclusive diagnosis. The cytologic features should be atypical enough where a malignant process is considered more probable than not.

Example Diagnoses
1. Satisfactory for evaluation
   Suspicious (for malignancy)
   Rare markedly atypical cells suspicious for adenocarcinoma.
2. Satisfactory for evaluation
   Suspicious (for malignancy)
   Mucinous cyst with high-grade dysplasia and abundant background necrosis, suspicious for invasive carcinoma.

Category VI. Positive for Malignancy
Most malignancies diagnosed in the pancreas (~90%) are conventional pancreatic ductal adenocarcinomas. The specificity of a malignant diagnosis from pancreatic fine needle aspiration or biliary brush is very high, ~90-95%.24-31
In order to obtain this high level of diagnostic specificity, strict interpretation and implementation of features associated with malignancy must be used. However, strict adherence to criteria defining malignancy will mitigate sensitivity. One-way to increase diagnostic yield, and potentially sensitivity, is rapid onsite evaluation.32-34 This is especially true for solid masses.

Definition
This category includes malignancies exhibiting unequivocal cytologic evidence of malignancy. Included in this category are pancreatic ductal adenocarcinoma and its variants, cholangiocarcinoma, acinar cell carcinoma, high-grade neuroendocrine carcinoma (i.e., large cell and small cell), pancreatoblastoma, adenosquamous carcinoma, lymphoma, sarcomas, and metastases to the pancreas.

Example Diagnoses
1. Satisfactory for evaluation
   Positive (for malignancy)
   Adenocarcinoma.
2. Satisfactory for evaluation
   Positive (for malignancy)
   Malignant glandular and squamous epithelial cells, compatible with adenosquamous carcinoma.

Recommended Approach to the Cytologic Analysis of Pancreatic and Biliary Tract Cysts
In addition to outlining the guidelines for the standardization of terminology and nomenclature for pancreaticobiliary cytology, the Papanicolaou Society also provided guidance on how to evaluate cystic neoplasms of the pancreas and biliary tract. When encountering a cystic neoplasm of the pancreas or biliary tract, two fundamental questions should be addressed: 1) is the cyst mucinous or non-mucinous? and 2) is high-grade dysplasia present or not?
For overtly malignant appearing aspirates, the "Positive (for malignancy)” category should be used. For those cysts with less than definitive cytologic evidence of malignancy, the 'Neoplastic: other’ category should be used. Determining whether aspirated cyst fluid is mucinous or not can be initially assessed during the time of collection, if the specimen is evaluated on site by the cytopathologist or cytotechnologist. Otherwise, information provided by the gastroenterologist may help determine the nature of the cyst, i.e., is the fluid thick and viscous or thin and watery. Thicker fluid can be directly applied to a slide and a smear prepared. Less viscous cystic fluid is best processed as a cytospin preparation. Placing the fluid in a preservation or transport medium may dilute the fluid making the identification of mucin on the slide difficult or impossible to detect.

The aspirate may also be contaminated with mucin from the gastrointestinal tract. Thick, colloid-like mucin is most likely neoplastic whereas thin mucin with naked, grooved nuclei most likely represents gastrointestinal contamination.3 Mucin populated with cellular cyst debris is also most likely neoplastic.

Biochemical (elevated CEA) or molecular analysis (KRAS) of the fluid can also be used to help document a fluid is neoplastic. It is important to remember, however, that a low CEA level or the absence of KRAS does not necessarily exclude a mucinous cyst.

Determining whether high-grade dysplasia is present or not requires the microscopic examination of epithelial cells. If overt evidence of malignancy is not present, it is best to interpret the aspirate as either low-grade or high-grade dysplasia. A recent article describing the characteristics
distinguishing low-grade from high-grade atypia in pancreatic cyst fluid has been published. According to these authors, increased nuclear-to-cytoplasmic ratio, an abnormal chromatin pattern, and background necrosis are the most important cytologic features for determining a pancreatic cyst at high-risk for malignancy.

The approach to evaluate cysts arising from the biliary tract has not been as well characterized as those in the pancreas. It is assumed IPMNs and MCNs originating from the biliary tract share the same cytologic features as their counterparts in the pancreas. The role of CEA levels and KRAS is not as well established in biliary-derived cysts.

References
Missing Data Was Common In Pathology Reports Of Vulvar Carcinoma: A Population Based Ontario Cohort

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Abstract

Purpose: We conducted a population based patterns of care study of vulvar carcinoma. This paper describes the completeness of pathology reporting for this cohort.

Methods: This is a retrospective population-based cohort study. We obtained all pathology records available from the provincial cancer registry for primary invasive squamous cell carcinoma of the vulva diagnosed between 1998 and 2007. Original pathology reports of vulva specimens pertaining to initial management were included. Abstracted variables included tumor size, grade, depth of invasion, thickness, margin status, lympho-vascular space invasion (LVSI), date, institution and pathologist type.

Results: 1011 vulvar resection reports were identified. Overall, 16% of reports were complete for all variables. Frequency of reporting each individual variable improved over time as did overall completeness. Peripheral margins were as reported most frequently (88%) and thickness was reported least frequently (43%). Gyne-pathologists reported each variable more frequently than general pathologists (48% complete for all variables vs. 22%). There was significant variation by institution. The largest improvement was observed in a single institution that implemented a checklist midway through the study period.

Preliminary versions of this work have been presented at the 2014 annual meeting of the Society of Gynecologic Oncology (SGO) in Tampa, FL and The Society of Gynecologic Oncology in Canada (GOC) in Niagara Falls, Canada.

This article has been peer reviewed.

Competing interests: None to declare

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Conclusions: Pathology reports for vulva carcinoma are frequently missing information important for clinical decision making. Checklists or synoptic reporting are likely to improve the amount of missing information.

(Keywords: vulvar carcinoma, quality of reporting, synoptic reporting, missing data)

Résumé
Objectif: Nous avons mené une étude sur les modèles de soins pour le cancer de la vulve. L'article porte sur l’exhaustivité des rapports de pathologie pour la cohorte étudiée.


Résultats: Nous avons étudié 1011 rapports de résection vulvaire. Dans l’ensemble, 16 % des rapports comportent toutes les variables. La consignation de chacune des variables s’améliore au fil du temps, de même que l’exhaustivité globale. L’état des marges est la variable consignée le plus fréquemment (88 %), alors que l’épaisseur est celle qui est rapportée le moins fréquemment (43 %). Les gynécopathologistes consignent chacune des variables plus fréquemment que les pathologistes généralistes (48 % des premiers consignent toutes les variables, contre 22 % pour les seconds). Il y a une différence importante d’un établissement à l’autre. L’amélioration la plus importante s’est produite dans un établissement qui s’est doté d’une liste de vérification au milieu de la période étudiée.

Conclusions: Dans les rapports de pathologie sur les cancers de la vulve, il manque souvent des données importantes pour la prise de décisions cliniques. L’utilisation de listes de vérification ou de fiches synoptiques pourrait vraisemblablement améliorer la situation.
Introduction
High quality pathology reporting is of vital importance to decision making in oncology. The foundation of oncologic practice is to choose therapy based on risk of recurrence. Usually, one or more pathologic features define the level of risk for a patient which guides subsequent choice for management. For vulvar carcinoma, ascertaining the level of risk for groin node involvement is pivotal for planning management. Several pathologic criteria inform this decision but the most critical feature is depth of tumor invasion below the basement membrane. The risk of nodal involvement increases with increasing depth of invasion\(^1\) and the decision to surgically assess the groins is based on depth >1mm. When the nodes are involved, adjuvant nodal radiotherapy is typically recommended to improve overall survival.\(^3\) Failure to manage the groins optimally may result in increased groin relapse which is uniformly fatal.\(^3\)

Prior research has demonstrated that pathologists frequently omit important elements required for optimal care in common cancers such as lung\(^4\) or colorectal.\(^5\) Synoptic reporting has been shown to improve the completeness of oncologic pathology reports.\(^6,10\) The province of Ontario has been moving to synoptic reporting over the past decade. Vulvar carcinoma has only been recently included in this initiative in spite of the availability of a checklist of important pathologic features since 1994.\(^11\)

This team of investigators has conducted a population-based patterns of care study for vulvar carcinoma in the province of Ontario for incident cases between 1998 and 2007. As part of this study, we collected all pathology reports for this cohort. The purpose of this paper is to describe the completeness of pathology reporting for vulva cancer in the province of Ontario using a contemporary, population-based cohort.

Methods
This is a retrospective population-based cohort study. The pathology reports, which are the focus of this study, were obtained as part of a larger study to evaluate patterns of care for vulvar carcinoma. The study was conducted with approval from the Sunnybrook Health Sciences Research Ethics Board.

We obtained all pathology records available from the provincial cancer registry for primary invasive squamous cell carcinoma of the vulva (ICD 9 184.1-184.4) diagnosed between 1998 and 2007. Original pathology reports of vulva specimens, pertaining to initial management, are included in this report. Reports issued as a second pathological opinion or pathology review, are not included in this report.

Two investigators (LB, LG) abstracted all pathology reports collecting data on tumor size, grade, depth of invasion, thickness, margin status (deep and peripheral) and lympho-vascular space invasion (LVSI).\(^12\) These are factors known to have prognostic importance for recurrence and survival. A report was considered complete when all of these variables were described. Other abstracted variables included: procedure date, reporting institution, specimen size and pathologist type (general versus gyne-pathologist). A report was assigned to the year in which it was issued, not the patient’s year of diagnosis. The specimen was considered a resection when the specimen size was greater than 1.5cm. Pathologist type was assigned based on a list of individuals known to have either completed additional subspecialty training (in gyne-pathology) or are the recognized regional expert who would accept cases for consultation. The abstraction process was validated by re-abstracting 25 reports by both reviewers. In 60% of the reports there was 99-100% agreement. In all reports there was >95% agreement.

The analysis is descriptive. Proportions are compared with chi-square tests. Trends over time are compared with the Cochrane-Armitage test for trend. Data analysis was conducted using SAS 9.2.

Results
We identified 1830 original vulva specimen reports pertaining to 1109 patients. 819 were vulvar biopsies (defined as specimen size <1.5cm). A total of 1011 were vulvar resections which are the focus of this study. Reports for these specimens were issued from 75 different institutions. Almost half of the reports were issued from 6 higher volume centres. The study did not quantify the total number of unique pathologists.
Figure 1. Proportion of vulva pathology reports with all variables recorded, by year. Number of reports contributing to analysis shown for each year.

Figure 2. Proportion of vulva pathology reports with all variables recorded by year and institution. Each institution contributed the following number of cases across all years: B: \( n=155 \), C \( n=178 \), D \( n=153 \), E \( n=169 \).
Figure 3. Proportion of vulva pathology reports with a specific variable recorded, by year.

Figure 4. Proportion of vulva pathology reports with a specific variable recorded, by institution. Each institution contributed the following number of cases across all years: A: 64, B: n=155, C n=178, D n=153, E n=169, F n=51.
Figure 1 demonstrates the proportion of reports with complete information for tumor size, grade, depth of invasion, thickness, LVSI and margin status by year. Overall, only 16% of reports were complete. The completeness of reporting increased with time ($p<0.0001$) with a peak value of 25%. There was a noticeable change in 2002; however, no provincial initiative was identified that could have influenced pathology reporting. An analysis of the 4 largest volume centres by year (>100 cases in total, other centres had too few cases to analyze by year) demonstrated that one centre (centre E) was the main driver of the provincial change over time (Figure 2, $p<0.0001$). On further inquiry we confirmed that this institution adopted a pathology checklist for vulvar carcinoma that year. We secondarily evaluated reports that were complete for depth, LVSI and margin only. When this more limited number of variables was included, 39% of the reports were considered to be complete.

Figure 3 demonstrates the proportion of reports which described each individual variable by year. Peripheral margin status was reported most often. Thickness was reported least often. The proportion of cases that reported depth of invasion increased over time from about 30% to about 70% ($p<0.0001$). Tumor size and LVSI also improved, to a lesser degree ($p<0.0001$ and $p=0.003$ respectively).

Figure 4 demonstrates the proportion of reports that described a particular variable, by centre. The top six centres reporting the largest volume of cases are shown (>50 cases). Many other centres contributed data, but typically had only a few cases in total. All centres consistently reported on peripheral margin status. Although there was significant variation by centre for the remaining variables, there was no pattern for which variables were reported or omitted by centre.

Gyne-pathologists were more likely to have complete reports than general pathologists, 21% versus 8% respectively ($p<0.0001$). The same observation was made when a complete report was defined with depth, LVSI and margin (48% versus 22%, $p<0.0001$). Missing data was common for...
both specialists and generalists. Figure 5 shows the frequency of reporting for each variable by pathologist type.

Discussion
We conducted a retrospective population based cohort study of the patterns of care of vulvar carcinoma in Ontario. As part of this study we reviewed the pathology reports for 1011 vulva resections and observed a high proportion of incomplete reports. This improved over time but the change was primarily driven by the adoption of a checklist within a single large volume centre. From a provincial perspective, the completeness rate did not exceed 25%. Depth of invasion was increasingly reported over time approaching 80% completeness by the end of the observation window.

This study contributes two important findings. The first important finding is that we observed the completeness for vulvar carcinoma reporting to be poor during the time of this cohort. While any individual variable was reported the majority of the time, it was very common for at least one variable to be missing rendering the report incomplete. We are not aware of any studies in the literature describing pathology reporting exclusively for vulvar carcinoma. Amongst gynecologic malignancies, pathology reporting for endometrial carcinoma has been typically viewed as problematic. However, even when narrative reporting was used for endometrial carcinoma in Ontario, the completeness rate was much higher than for vulvar carcinoma, 79% compared with 16% from our study. Since endometrial cancer is more common than vulvar cancer, perhaps pathologists are more familiar with which features are key in clinical decision making. In some circumstances, reports may be incomplete for legitimate technical reasons, for example, poor specimen orientation.

The second important finding is the impact of synoptic reporting for vulvar carcinoma. Prior research has clearly demonstrated that, in other malignancies, synoptic reporting is associated with more complete reports when compared with narrative reports. However, there is very little data in the gynecologic oncology literature in general and none that we could identify specifically related to vulvar carcinoma, in spite of the publication of a vulvar carcinoma pathology checklist in 1994. Cancer Care Ontario has initiated the provincial adoption of synoptic reporting across all cancer sites. More common cancers were addressed first. Synoptic reporting for vulvar carcinoma began in 2008, therefore, one would expect that this has improved completeness rates. Our data confirms that one centre increased completeness of reporting with the adoption of a checklist in 2002. This centre’s completeness rate did decline in subsequent years. From a management perspective this demonstrates the importance of efforts to maintain change, including on-going quality assurance.

The implications of incomplete reporting for vulvar carcinomas are significant. Incomplete data hinders optimal clinical decision making. One of the few randomized trials in vulvar cancer demonstrated improved survival for patients with groin node involvement who received adjuvant nodal radiotherapy. Incomplete pathology information about the primary may result in sub-optimal decision making regarding the need for surgical groin node evaluation and adjuvant groin irradiation. Close margins are associated with increased local relapse. The absence of complete information about margin status may result in sub-optimal decisions about the need for adjuvant radiation or a re-excision.

The strength of this study is that it is population-based which minimizes selection bias. Our observations are a potential concern for any other jurisdiction not using synoptic reporting. The pathology reports were abstracted by two physicians who are content experts. Re-abstraction showed a high level of agreement. The dataset is a high quality reflection of real world practice. One limitation was that we were unable to comment on the accuracy of the reporting. This would have required a centralized review of all cases. In addition, we are unable to comment on frequency of poorly oriented specimens; however, this is unlikely to be responsible for all of the missing data described. Since it is difficult to determine the intent of the surgical procedure in a retrospective fashion, we limited this analysis to specimens larger than 1.5cm in size. Missing data for the smaller specimens was as common, if not worse than reported here. For example, in our dataset, depth was missing in more than 80% of the reports for specimens less than 1.5cm. Arguably, the decision to do a lymph node...
dissection was actually based on the biopsy information and not the resection specimen, in which case our results may have under-estimated the clinical implications.

Synoptic reporting for vulvar carcinoma is being introduced province-wide. Our data strongly suggests that synoptic reporting results in more complete reporting of pathologic factors key to clinical management decision making. Our data also illustrate the need to include uncommon diagnoses in wide scale quality initiatives.

References

Erratum

The Crisis in Cytotechnology in Ontario: Disruptive Practice Patterns and Technology (p. 68)

The following reference is to be removed: “QMPLS. (2013). Committee Comments CYTO-1305-PP Patterns-of-Practice Survey. Toronto, Ontario: Quality Management Program - Laboratory Services”.

The cited document is not available in the public domain and it is IQMH policy that such internal documents are not referenced in the public domain.
Endoscopic Mucosal Resection (EMR) In Barrett’s Esophagus Associated Neoplasia: Recommendations For Pathological Evaluation And Reporting

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Abstract
Endoscopic mucosal resection (EMR) is a minimally-invasive technique increasingly adopted for resection of superficial neoplasia arising in Barrett’s esophagus (BE). High-grade dysplasia or adenocarcinoma confined to the mucosa (pT1a) should be treated by EMR rather than esophagectomy, as this has been shown to attain similar long-term survival with lower immediate morbidity and mortality rates. As the prevalence of BE continues to rise and gastroenterologists gain comfort with EMR, it is likely that pathologists in both academic and community settings will evaluate more EMR specimens in the future. Accurate assessment of EMR specimens depends upon appropriate macroscopic handling and microscopic diagnosis. Specimens should be pinned flat prior to fixation and the margins should be inked with a vivid colour both to help orient the fragments during embedding and for assessment of their relationship to invasive lesions. The specimen should then be serially sectioned at 2 mm intervals and submitted sequentially for histological evaluation. Microscopic assessment should include the histological type, grade, stage, tumour size, margin status, and distance of carcinoma from the margin, as well as the presence or absence of lymphovascular invasion and tumour budding. Depth of invasion should be reported according to the AJCC 7th edition or the Vieth and Stolte system with special attention paid to the frequent finding of a duplicated muscularis mucosae. Evaluation of EMR specimens according to these recommendations will allow consistency among pathologists and ensure that patient prognosis and treatment decisions are based on complete and accurate information.

Keywords: Endoscopic mucosal resection (EMR), Barrett’s esophagus, esophageal adenocarcinoma, dysplasia

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RÉSUMÉ
La résection muqueuse endoscopique (RME) est une technique peu invasive de plus en plus utilisée pour la résection de néoplasies superficielles dans l’œsophage de Barrett (OB). Une dysplasie de haut grade ou un adénocarcinome confiné à la muqueuse (pT1a) devrait être traité par RME plutôt que par une œsophagectomie, avec un taux de survie à long terme semblable et une réduction de la mortalité et de la morbidité immédiates. Au fur et à mesure que la prévalence de l’OB augmentera et que les gastroentérologues apprivoiseront la RME, les pathologistes auront davantage de prélèvements de RME à analyser. La précision de ces analyses dépend du traitement macroscopique et du diagnostic microscopique. Les échantillons doivent être épinglés à plat avant la fixation, et les marges doivent être encrées avec une couleur vive pour aider à orienter les fragments pendant l’enrobage et à évaluer leur relation avec des lésions invasives. Les échantillons doivent ensuite sectionnés en coupes séries de 2 mm et soumis séquentiellement à l’évaluation histologique. L’analyse microscopique doit comprendre le type histologique, le grade, le stade et la taille de la tumeur, l’état des marges, la distance entre le carcinome et la marge ainsi que la présence ou l’absence d’invasion lymphovasculaire et de bourgeonnement tumoral. La profondeur de l’invasion doit être consignée selon la 7e édition du manuel de l’AJCC ou le système de Vieth et Stolte, avec une attention particulière pour le dédoublement fréquent de la musculaire muqueuse. L’application de ces recommandations à l’analyse des échantillons de RME améliorera la cohérence des résultats et permettra d’obtenir des données complètes et précises pour établir le pronostic et choisir le traitement.

Introduction
Endoscopic mucosal resection (EMR) is a technique for minimally-invasive removal of superficial mucosal lesions in the gastrointestinal tract. It has been increasingly applied in recent years for staging and management of dysplasia and early neoplasia arising in Barrett’s esophagus (BE). Clinical guidelines now recommend EMR for the treatment of high-grade dysplasia (HGD) and early adenocarcinoma confined to the esophageal mucosa, scenarios that would have led to surgical management in the past.1-3

Other therapies such as radiofrequency ablation, argon plasma coagulation, photodynamic therapy, and cryotherapy may be used, but while these ablative modalities allow for treatment of larger areas of mucosa, they preclude histological evaluation and are not recommended for treatment of adenocarcinoma or HGD associated with endoscopically-visible lesions.2,4 Similarly, a technique called endoscopic mucosal dissection (ESD) provides another alternative to EMR. It is practised mainly in Japan and involves dissection within the submucosa to remove early lesions en bloc rather than piecemeal.4 In this review, we focus on EMR as it is widely used in Canada, and given the rising incidence of BE and associated neoplasia in North America and gastroenterologists’ growing comfort with EMR, pathologists are more likely to encounter EMR specimens in the future. At our centre we handle approximately 800-1000 EMR specimens per year. The purpose of this review is to provide some background information about EMR, as well as a practical set of recommendations for processing and reporting of EMR specimens by Canadian pathologists.
Who Benefits from EMR?

EMR is recommended for staging and treatment of patients with BE who present with HGD and optical abnormalities on endoscopy, as well as for patients with adenocarcinoma confined to the mucosa (American Joint Committee on Cancer [AJCC] pT1a lesions). In such patients, EMR has similar long-term survival but lower immediate morbidity and mortality when compared to esophagectomy. EMR is indicated in HGD associated with visible lesions both because of the high incidence of progression to adenocarcinoma (up to 6% per year) and to ensure that the patient has not been under-staged or over-staged by biopsies, which occurs in about 24-55% of cases. EMR may also be indicated in select patients with carcinoma invading beyond the mucosa when these patients would have a high risk of morbidity and mortality with esophagectomy. In such cases, EMR may be considered curative when tumors show limited invasion into the submucosa (pT1b) and favorable histological parameters associated with a low-risk of lymph node involvement (well-differentiated carcinoma, no lymphovascular invasion, and no tumour budding).

Endoscopic Assessment and Treatment

There are two main EMR techniques used. They have similar success rates, and selection usually depends on operator preference. First, in the cap-snare technique (Inoue cap), a transparent cap is attached to the tip of the endoscope. This cap has a rim on the distal edge that is able to fit and hold an expanded snare placed through the scope. Following submucosal lifting by solution injection, the mucosa is sucked into the cap forming a pseudopolyp, the snare is closed and electrocautery is applied for resection of the specimen. The multiband ligation system (Duette) consists of a cap, preloaded with six outer rubber bands, that is attached to the tip of the scope. A pseudopolyp is formed by suctioning mucosa into the cap, the rubber band is deployed using a triggering device, and the pseudopolyp is resected using a snare (Figure 1). These two suction modalities usually ensure that muscularis propria is not involved in the pseudopolyp.

Specimen Handling and Macroscopic Assessment

EMRs of esophageal lesions typically range in size from 1-2 cm in greatest dimension. Specimens should be gently stretched and pinned flat with cut surface down on stiff paper, cardboard, cork, wax or Styrofoam board (Figure 2A), ideally at the time of resection. Pinning helps to minimize retraction of the muscularis mucosae and rolling of the margins. Specimens should then be fixed by floating them tissue-down in 10% neutral buffered formalin for a period of at least 6 hours. Following fixation, the size of the specimen should be measured and pins carefully removed.

Figure 1. The technique of endoscopic mucosal resection (EMR). A) The endoscopic appearance of Barrett’s esophagus; note the darker, salmon-pink tongues of columnar mucosa extending upward from the gastroesophageal junction. B) In the multiband ligation (Duette) system, a pseudopolyp is formed by suctioning mucosa into the cap, and a band is placed around the pseudopolyp, which is then removed using a snare. C) The endoscopic appearance of the esophagus following EMR.
In most cases, multiple unoriented EMRs of a single area are received, therefore, only the deep resection margin is of interest to the endoscopist and a single ink colour may be used to mark the deep resection margins. Using a vivid colour helps to orient the specimen perpendicularly during embedding. In cases where only one EMR specimen is removed or when one area of interest is taken out separately from the other fragments and appropriately oriented, the lateral margins are of interest and should be marked with a different ink colour.

After inking, the specimen should be serially sectioned into slices approximately 2 mm in thickness and embedded on edge (Figure 2B). Specimens should always be submitted in toto, as any dysplastic or malignant lesions may be focal and because it is essential to document the maximum depth of invasion accurately. Slices should be submitted sequentially from one end of the specimen to the other, with no more than four slices per cassette.

Microscopic Assessment

In our institution, 4 levels are initially performed on each block: levels 1 and 3 are stained with H&E, level 2 with hematoxylin phloxine saffron (HPS) to facilitate evaluation of the muscularis mucosae, and level 4 with H&E with Alcian blue to highlight intestinal metaplasia. The main features which should be documented on microscopic assessment are listed in Table 1. The esophageal carcinoma synoptic report mandated by the College of American Pathologists is completed for each case with invasive carcinoma. In our institution, we most often receive multiple unoriented EMR specimens but only one synoptic report is completed. In these cases, some items listed in the synoptic report, particularly the proximal and distal resection margins, are not applicable and only the deep resection margin may be evaluated.

<table>
<thead>
<tr>
<th>Histological type</th>
<th>WHO classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour size</td>
<td>Estimated using greatest dimension on one slide or measured across EMR specimens</td>
</tr>
<tr>
<td>Histological grade</td>
<td>well/moderate/poor/undifferentiated</td>
</tr>
<tr>
<td>Depth of invasion</td>
<td>AJCC and Vieth &amp; Stolte system</td>
</tr>
<tr>
<td>Margin status</td>
<td>positive/negative</td>
</tr>
<tr>
<td>Distance to deep margin</td>
<td>mm</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>present/absent</td>
</tr>
</tbody>
</table>

[WHO=World Health Organization; AJCC=American Joint Committee on Cancer]
Figure 3. Various patterns of adenocarcinoma are seen in Barrett’s neoplasia, and recognizing invasive carcinoma can sometimes be challenging. Indicators of malignancy include: A) Dilated glands filled with necrotic debris (inset); B) A never-ending/anastomosing gland pattern; C) Complex architecture, including papillary and micropapillary formations; D) Small and irregular or angulated glands; E) Cribriforming. In some cases, carcinoma may be very well-differentiated, with abnormal gland shape and location being the primary indicators of malignancy (F-H). Submucosal gland ducts must be distinguished from invasive carcinoma (arrow in H points to a duct with a double-layered lining; see also Figure 6D-F). Note that intramucosal carcinoma typically does not incite a desmoplastic reaction. [Hematoxylin & eosin]
Figure 4.  A) The duplicated muscularis mucosae (dMM) is seen on hematoxylin and eosin (H&E) staining superficial to the original muscularis mucosae (oMM). The presence of larger calibre vessels can help to identify the submucosa.  B) Both the dMM and the oMM are highlighted by immunohistochemistry for desmin. The fibres of the dMM tend to be more delicate and wispy.
Recognizing carcinoma

The distinction between HGD and intramucosal carcinoma (IMC) in BE can be challenging, and interobserver variability is high even among expert pathologists ($\kappa = 0.30$).\textsuperscript{14} Identifying invasive IMC is made more difficult by the fact that carcinoma confined to the esophageal mucosa does not typically incite a desmoplastic reaction.\textsuperscript{15} Features which suggest carcinoma include the presence of necrosis in dilated gland lumens, small angulated glands, complex architecture, single neoplastic cells in the lamina propria, cribriforming, or a never-ending/anastomosing gland pattern (Figure 3).\textsuperscript{14} In many institutions, IMC and HGD are treated identically, but in some centres, HGD may be treated endoscopically while IMC may trigger esophagectomy.\textsuperscript{14,16} Pathologists should be aware of the clinical implications of diagnoses at their institutions, and the threshold for expert consultation should be low. Given the high interobserver variability in the diagnosis of dysplasia and carcinoma in BE, it is recommended that at least two pathologists, including one with expertise in gastrointestinal pathology, come to a consensus diagnosis in all cases of dysplasia and carcinoma, as well as cases deemed indefinite for dysplasia.\textsuperscript{2,17}

Assessing depth of invasion: the duplicated muscularis mucosae

One of the challenges of assessing depth of invasion in the esophagus arises in the setting of duplication of the muscularis mucosae (MM) (Figure 4A), which occurs in about 79% of cases of BE.\textsuperscript{18} This duplication appears to occur only in BE, not in other esophageal processes such as squamous cell carcinoma.\textsuperscript{15,19} Histologically, the duplicated layer (dMM) is superficial to the original MM (oMM) and in 85% of cases is comprised of more delicate, wispy bundles of smooth muscle compared to the oMM.\textsuperscript{20} To distinguish the submucosa from the lamina propria between the dMM and oMM, it is helpful to note that the submucosa may contain submucosal glands and will frequently harbour thick-walled blood vessels. Of note, in about half of cases, normal or dysplastic benign glands may become entrapped between MM layers or within the dMM itself (but not within the oMM).\textsuperscript{15,20} These must be distinguished from invasive carcinoma.

Figure 5. There are two systems for reporting depth of invasion in esophageal EMR specimens, the AJCC system (A) and the Vieth & Stolte system (B). While they both classify submucosal invasion as sm1, sm2, or sm3, they differ in their classifications of mucosal invasion. In the AJCC system, m1 represents carcinoma in situ (i.e. HGD), m2 is lamina propria invasion, and m3 is invasion into the muscularis mucosae (dMM, oMM, or the space between them), while in the Vieth and Stolte system, m1 represents lamina propria invasion, m2 is invasion of the dMM, m3 is invasion of the space between the dMM and oMM, and m4 is invasion of the oMM. [Ep=epithelium, LP=lamina propria, dMM=duplicated muscularis mucosae, oMM=original muscularis mucosae, SM=submucosa, MP=muscularis propria.]
Figure 6. Pitfalls in the microscopic assessment of EMR specimens. A) Rolling under of the edges of the mucosa may mimic a positive deep margin. The mucosa in this region may also be cauterized and may be ‘inked’ which further adds to confusion. B) Mucosal trauma during suctioning of the mucosa to lift it during resection can cause loss of the superficial epithelium and accumulation of fibrin, mimicking ulceration. This may also complicate assessment of dysplasia, since surface maturation cannot be evaluated. C) Pinning of the specimen may push fragments of mucosa towards the deep margin, mimicking invasion in cases without invasive carcinoma or suggesting a deeper than actual level of invasion if the pin was introduced through an area of invasive carcinoma. D) Submucosal glands or ducts may mimic invasive carcinoma, but a lobular architecture is preserved. E) Invasive carcinoma is seen at the top left, high grade dysplasia at the top right, and a submucosal gland duct at the bottom right. The duct may initially be mistaken for carcinoma, giving the impression of a deeper level of invasion. However, the double-layered duct lining (F) is evidence that this is not carcinoma. [Hematoxylin & eosin]
Occasionally, duplication of the MM can lead to errors in staging. It is important that pathologists take care not to mistake the dMM for the oMM, or the oMM for the muscularis propria, which would lead to an over-assessment of the depth of invasion (i.e. pT1b or pT2 rather than pT1a). Furthermore, since the dMM is not universally present and when present it is frequently patchy,\(^{18}\) pathologists must not mistake invasion through a superficial smooth muscle layer as invasion through the dMM only, when in fact the dMM is absent and the carcinoma is invading through the oMM into the submucosa.

While the dMM is usually not difficult to identify in well-oriented EMR specimens, cases with extensive tumour involvement, cautery artefact, poor orientation, or extensive fibrosis can pose a challenge. In such cases, we have found immunohistochemical staining with desmin to be particularly helpful in highlighting both the oMM and dMM in cases where they appear indistinct on H&E or HPS (Figure 4B). While desmin does not differentiate between the oMM and dMM, it accentuates the wispy fibres of the duplicated layer, making it easier to identify when present.

**Reporting depth of invasion**

There are two widely used methods to report depth of invasion in EMR specimens—the AJCC system\(^ {21}\) and the Vieth & Stolte system.\(^ {22}\) These systems differ in how they classify invasion within the mucosa but they are identical in their subdivisions of the submucosa, dividing it into superficial, middle, and deep thirds (sm1, sm2, and sm3 respectively; Figure 5). Though this is useful and reproducible in esophagectomy specimens, it is difficult to apply in a standardized fashion to EMR specimens, where the amount of submucosa present depends on the depth of the resection performed. In most EMR specimens with submucosal invasion and a negative deep resection margin, the depth of invasion can be presumed to be sm1. In these cases, a numerical measurement of the depth of invasion and width of tumour within the submucosa is also reported as this gives clinicians an estimate of the amount of submucosal invasion, which guides clinical management in some cases. Depth of invasion is measured from the deepest point of the overlying oMM or an imaginary line in continuity with most of the oMM. While this approach has not been validated in esophageal EMR specimens, a measurement of submucosal invasion width and depth has been shown to be predictive of lymph node involvement in EMRs of early gastric cancer.\(^ {23}\)

Regarding mucosal subdivisions, the AJCC system was designed to be applied to both squamous cell carcinoma and adenocarcinoma of the esophagus, so duplication of the muscularis mucosae (which does not occur in squamous cell carcinoma) is not taken into account. As such, there are three levels of mucosal invasion in the AJCC system, and four in the Vieth & Stolte system (Figure 5). We recommend using the Vieth & Stolte system because it offers a more precise description of the depth of invasion in the setting of a dMM.

**Depth of invasion and prognosis**

The depth of invasion of carcinoma arising in BE is an important prognostic factor and can direct future treatment. Carcinomas confined to the mucosa have only a 1-2% risk of lymph node metastases—lower than the mortality risk with esophagectomy—whereas carcinomas invading the submucosa have a risk of lymph node metastases of approximately 20% and may trigger surgical intervention.\(^ {24-27}\) Overall survival is also dependent on depth of invasion, with 5-year survival reported at 74-100% for IMC compared to 53-58% for submucosal carcinoma.\(^ {28,29}\)

It is unclear whether the risk of lymph node metastases increases with depth of invasion within the mucosa itself (i.e. m1 vs. m2 vs. m3 vs. m4). Some studies have found no difference in metastases or survival based on mucosal depth of invasion,\(^ {15,30,31}\) a finding which is supported by evidence that the distribution of lymphatics between the dMM and the oMM is similar to that of the superficial lamina propria.\(^ {32}\) However, because lymph node metastases are so rare in early esophageal carcinoma, these studies included only 1-3 patients with IMC and lymph node metastases; therefore, a significant difference may be obscured by type II error. Conversely, a recent meta-analysis reported that 8/9 patients with IMC metastatic to lymph nodes had AJCC m3 tumours, while 1/9 had an m2 tumour.\(^ {24}\) Since some evidence exists that depth of invasion within the mucosa may affect prognosis, we recommend reporting this
feature. Consistent reporting of mucosal depth of invasion is also necessary for future research to address prognostic significance.

Similarly, the data is mixed as to whether deeper submucosal invasion (sm2-3) confers a higher risk of lymph node metastases and poorer survival compared to superficial submucosal invasion (sm1). Some studies have found lower rates of lymph node metastases and better survival in sm1 patients, but others fail to confirm this. Nevertheless, some clinical guidelines suggest EMR for patients with low risk sm1 invasion (well-differentiated carcinoma, no lymphovascular invasion) who are high-risk surgical candidates. The risk of lymph node metastases in sm1 invasion is reported to be 1-22%, with most estimates near the lower end of that range, which is why EMR may represent a lower risk than that of esophagectomy in some patients.

Margin status

The presence of carcinoma at the margins of an EMR specimen is one of the strongest indicators for further treatment because of the high risk of residual/recurrent carcinoma. In one study, patients with positive deep margins at EMR who were followed with subsequent endoscopic surveillance and biopsy had residual carcinoma in 7/8 (86%) cases, despite the use of photodynamic therapy in four. In addition, positive deep margins have been shown to be an independent predictor of poorer overall survival (hazard ratio 1.67; 95% confidence interval 1.09–2.55; p=0.02).

A margin should be considered positive only when there is carcinoma present directly at the margin. The presence of dysplasia at a margin should be noted, but does not constitute a positive margin. In most cases, EMR specimens are resected piecemeal and it is not possible to determine the status of peripheral margins. In such cases, the endoscopist must judge the completeness of resection at the time of the procedure. Microscopic status of the deep resection margin should still be reported in these cases.

The distance in millimetres to the deep margin should be reported to document completeness of resection. While close (<1mm) circumferential margins have been shown to portend worse prognosis in esophagectomy specimens and in EMR for gastric carcinoma (<2mm), we are not aware of any studies investigating the prognostic significance of the distance to margins in esophageal EMR. In our experience, the deep resection margin of EMR specimens containing adenocarcinoma with a depth of invasion m4 or greater may often be close (i.e. 0.1 mm or less) due to the size and nature of EMRs.

Tumour budding

Tumour budding, defined as single cells or detached clusters of <5 cells at the advancing front of a carcinoma, has been shown to be an independent risk factor for nodal metastases and poorer overall survival in superficial (pT1) esophageal adenocarcinoma. However, one important issue in the literature about tumour budding is the lack of consensus regarding what defines significant (or so-called “high-grade”) budding. The definition suggested by Ueno et al. is the most commonly used, and has proven prognostic significance in colorectal carcinoma. This definition states that high-grade budding constitutes 10 or more buds of <5 cells each per 250x field (0.385 mm²). While some have proposed the use of cytokeratins to improve visualization of buds, it should be noted that definitions like Ueno’s were developed on H&E-stained sections, and routine application of cytokeratin results in higher rates of high-grade budding.

We recommend reporting high-grade budding according to Ueno’s definition (≥10 buds per 250x field) if it is noted in esophageal EMR specimens. As literature accumulates about the role of budding in esophageal carcinoma, the presence of high-grade budding may increasingly influence treatment decisions.

Other features to report

Lymphovascular invasion and tumour grade affect survival and risk of lymph node metastases, and in some cases, particularly early (sm1) submucosal invasion, may...
influence further treatment (see Depth of invasion and prognosis above). D2-40 immunohistochemistry may be helpful, particularly in cases with submucosal invasion or poorly differentiated tumour where lymphovascular invasion is more likely and may be inconspicuous on H&E. Larger tumour size has also been shown to confer a worse prognosis,26 and tumour size should be reported. In cases of piecemeal resection, tumour size must be estimated; this may be given as the greatest dimension on one slide or estimated by adding the tumour size across multiple EMRs. The method used to obtain tumour size should be noted. Perineural invasion may also be reported, but does not appear to have strong prognostic significance.42-44

Pitfalls and artefacts
In addition to the pitfalls of the duplicated muscularis mucosae and entrapped glands discussed above, common pitfalls and histological artefacts encountered in EMR specimens are illustrated in Figure 6.

Conclusion
EMR specimens should be treated as surgical specimens with macroscopic and microscopic assessment performed according to the recommendations discussed above. A standardized approach to the processing and reporting of EMR specimens will ensure that accurate diagnoses are made and that subsequent treatment decisions are based on high-quality information.

REFERENCES:

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MUIR ET AL.
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1 complete response and 20 partial responses

Response duration in patients who responded to therapy (n=21) (secondary endpoint)1

24%

86%

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