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COMMENT

International Consensus Guidelines for Diagnostic Criteria and Checklist for Future Studies for Minimally Invasive Carcinoma ex Pleomorphic Adenoma: An HN CLEAR Initiative

Beth M. Beadle[1] · Nazim Benzerdjeb[2] · Junhun Cho[3] · Valérie Costes-Martineau[4] · William C. Faquin[5] · Ricardo Santiago Gomez[6] · Ruta Gupta[7,16] · Ivana Kholová[8,9] · Toshitaka Nagao[10] · Swapnil U. Rane[11] · Miguel Rito[12,13] · Lester D. R. Thompson[14] · Spinder Samra[15] · Peter P. Luk[16] · Simion I. Chiosea[17,18]

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Abstract

A variety of factors, including the extent of invasion, determine the clinical outcome in patients with carcinoma ex pleomorphic adenoma (Ca ex PA). A Head and Neck Consensus Language for Ease of Reproducibility (HN CLEAR) Steering Committee organized a working group (WG) to harmonize diagnostic and research approaches for assessing invasion in Ca ex PA.

WG of head and neck pathologists and a radiation oncologist conducted 6 iterative rounds of online voting (Modified Delphi), using Google Forms, over an 8-month period on invasion in the setting of Ca ex PA. Agreement was defined by the same opinion of at least 50% of the responders. The list of parameters with predetermined options was developed.

Minimally invasive Ca ex PA was defined as a pT1-2 pN0 carcinoma, resected *en bloc* with negative margins, with or without perineural invasion, without vascular invasion and without distant metastasis at presentation. Consensus was not reached on whether high grade histology is compatible with the concept of "minimal invasion". Diagnosis of minimal invasion is possible when tumor excision is complete (with negative margins), *en bloc* (without fragmentation), and requires sampling of the entire tumor capsule or tumor-normal interface. The consensus guidelines characterizing Ca ex PA and the list of challenging aspects are provided. The WG proposed a checklist for future research, aiming to refine the diagnosis of in situ and minimally invasive Ca ex PA.

Keywords Checklist · Consensus · Pathologists · Reproducibility of results · Neoplastic process · Carcinoma ex pleomorphic adenoma · Carcinoma arising in pleomorphic adenoma · Intracapsular · In situ · Minimally invasive · Salivary carcinoma

Introduction

About 3 to 15% of salivary gland carcinomas arise from pleomorphic adenomas, primary or recurrent [1, 2]. Conversely, 5–10% of pleomorphic adenomas may undergo malignant transformation when followed for more than 15 years [3]. The incidence of malignant transformation varies with patient age, size of pre-existing pleomorphic adenoma, and other factors [2]. The clinical course of patients with carcinoma ex pleomorphic adenoma (Ca ex PA) depends on TNM stage, primary anatomic site, histologic grade, histologic type of Ca ex PA, and extent of invasion [2]. Currently, there is no practical histological definition of the safe extent of invasion (with, if possible, exact cut-off, or threshold, in mm); this hinders the ability to tailor clinical decision-making based on these features. To this end, a Head and Neck Consensus Language for Ease of Reproducibility (HN CLEAR) Steering Committee organized a working group (WG) to comment on the current state of the pathologic approach to characterizing invasiveness of Ca ex PA.

Extended author information available on the last page of the article

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Materials and Methods

A WG of 14 head and neck pathologists and a radiation oncologist conducted six iterative rounds of online voting (Modified Delphi) comprised of six questionnaires, using Google Forms, over an 8-month period. The agreement was defined by the same opinion of at least 50% of the responders. Two types of databases (Excel file, template) and REDCap electronic data capture were tested by the members of the WG by reviewing and indexing one manuscript per WG member. The REDCap online tool proved more user-friendly for collecting inputs from numerous contributors. The final list of parameters relevant to the study of Ca ex PA is presented as an Excel spreadsheet (see supplemental material). The spreadsheet included options for each parameter as agreed upon by the WG.

Results

The WG on Ca ex PA agreed (13/14, 93%, Table 1) that classification of Ca ex PA by extent of invasion includes the following morphologic stages:

(1) Non-invasive: synonymous with intracapsular, confined or enclosed, to the contours of the pre-existing pleomorphic adenoma, or in situ. Non-invasive Ca ex PA also covers instances of intraductal carcinoma, where foci of early carcinoma may be confined to both the contour of the pre-existing pleomorphic adenoma and surrounded by myoepithelial cells [4].
(2) Minimally invasive: with invasion beyond the capsule and/or contour of the pre-existing pleomorphic adenoma. The clinical implications and histological parameters of minimal invasion are yet to be defined. In the experience of this WG, the potential management of patients diagnosed with minimally invasive Ca ex PA included observation (3/13 (27%), consideration for further treatment including radiotherapy (3/13, 27%), and either observation or further treatment depending on histologic grade and other histologic factors (6/13, 54%). For histologically low grade Ca ex PA, observation was the most common clinical management (10/15, 67%). In the experience of this WG, reporting of perineural invasion (PNI) in minimally invasive Ca ex PA typically prompts consideration of adjuvant radiation therapy (11/14, 79%). The WG agreed that, conceptually, vascular invasion is not compatible with the diagnosis of minimally invasive Ca ex PA (12/14, 86%). The WG agreed that perineural invasion is compatible with the diagnosis of minimal invasion (8/15, 53%).
(3) Widely invasive: these are typically higher-grade salivary carcinomas with extension beyond the parenchyma of the involved major salivary gland and with predominance of the carcinomatous component. For such cases, establishing the presence of invasion is rarely a diagnostic issue and ex PA origin is typically of academic interest only.

Table 1 Questionnaire and voting results among working group pathologists on definitional issues of carcinoma ex pleomorphic adenoma

Issue to be addressed	Answer options	Voting results (agree / all responders
Morphologic stages of Ca ex PA by extent of invasion	Agree with non-invasive, minimally invasive, and widely invasive stages	13/14, 93%
Is vascular invasion compatible with the diagnosis of minimally invasive Ca ex PA	No *vs* yes	No, 12/14, 86%
Is perineural invasion compatible with the diagnosis of minimally invasive Ca ex PA	Yes *vs* No	Yes, 8/15 (53%)
Should pN0 or cN0 define in situ or minimally invasive Ca ex PA?	Yes *vs* No	13/15, 87%
Are you using the term "atypical PA"?	No *vs* Yes	8/14, 57%

Eighty-six percent (12/14, 86%) of the WG indicated that the study of in situ and minimally invasive carcinoma ex PA is most clinically and practically helpful (as opposed to widely invasive carcinoma).

The extent of invasion by Ca ex PA may be defined by a combination of anatomic and clinical parameters (e.g., extraparenchymal extension beyond a major salivary gland, facial nerve symptoms, TNM stage), presence or absence of adverse histologic findings, or by histologic measurement in millimeters.

Based on clinical and anatomic parameters, the WG defined carcinoma in situ ex PA or minimally invasive Ca ex PA as a pT1-2 pN0 or cN0 tumor, without vascular invasion and without distant metastases at presentation. pN0 or cN0 as a criterion defining in situ or minimally invasive Ca ex PA was supported by 87% of the WG (13/15). When the pT1-2 criterion is employed, there must be an agreement on how to measure CA ex PA. The carcinomatous component is frequently distributed unevenly throughout the pre-existing PA. Using thyroid nodule evaluation as an example, the following approach is advised. In the presence of a single well-defined focus of carcinoma, still confined to the pre-existing PA (i.e., in situ) or minimally invasive (as currently defined by a pathology practice handling the case), pT should be assigned based on the size of the single focus of carcinomatous component. Such a measurement will most likely be done microscopically. When there is

more than one focus of carcinomatous component, the gross measurement of the entire pre-existing PA should be used to assign pT. The distinction between one and two foci of carcinomatous components (i.e., minimal distance between the two foci of carcinoma) is currently best left to the discretion of the pathologist evaluating the case. Proportion (rounded in 10% increments) and distribution / spatial relationship of carcinomatous and residual PA components (e.g., peripheral vs central location of the carcinomatous component) are additional variables not examined by the currently available studies. In cases of Ca ex PA with multinodular architecture, the largest aggregate measurement should be used to assign pT.

To measure the extent of invasion, one would first draw a typically arcuate line connecting retained normal capsule (or contour of pre-existing pleomorphic adenoma) on both sides of the invasion focus (Fig. 1, whole slide image link Digital Slide Viewer: Simon Chiosea/Salivary/79637840-e08f-c184-cf38-e3a9c5341106_103150.svs. For a more accurate assessment of the overall contour of the pre-existing pleomorphic adenoma, please refer to the whole slide image. The left periphery of the upper most tissue fragment shows hypocellular myxoid stroma consistent with residual pleomorphic adenoma, assisting with reconstruction of the overall contour of pre-existing pleomorphic adenoma). Next, a second line perpendicular to the first line and typically going through the middle of the invasive focus would be used to measure the extent of invasion (Fig. 1). A similar approach was recently recommended for measuring extranodal extension for squamous cell carcinoma metastatic to regional lymph nodes [5].

Fifty-seven percent of the WG (8/14) do not use the term of "atypical PA". One way to avoid the term "atypical" is to list concerning histologic findings and state in the pathology report that such findings are believed to be associated with a slightly increased risk of local recurrence. Worrisome histologic findings are:

a. increased cellularity, especially when the cellular component is predominant over the stromal component and represents > 80% of the adenoma.
b. Sclerotic / hyalinized fibrosis replacing chondromyxoid stroma.
c. Increased mitotic activity.
d. Nuclear pleomorphism.

The WG designed a checklist of items and offered a template for indexing parameters (see supplemental material) with the hope of facilitating future histological studies on CA ex PA.

Discussion and Guidelines

The clinical need to define "in situ" and "minimal invasion" in CA ex PA is likely driven by the desire to define a subset of CA ex PA patients with the most indolent behavior for whom observation may be a safe clinical management option. To this end, while determining the acceptable rate and time of local recurrence for Ca ex PA, it may be relevant to take into consideration a 2 to 8% recurrence rate characteristic of pleomorphic adenoma [6, 7].

The WG discussed the question of whether some adverse histologic factors are compatible with the expected indolent course of in situ or "minimally invasive" Ca ex PA. In the literature, the issue of vascular invasion in early carcinomas ex PA was not addressed directly. Most members of the WG feel that the adverse prognostic implication of vascular invasion is incompatible with the intended reassuring message of "minimal invasion".

There was no agreement on whether high grade of carcinoma ex PA (e.g., salivary duct carcinoma) can be reliably clinically managed as "in situ" or "minimally invasive". Since no agreement was reached on whether high histologic grade is compatible with the diagnosis of "minimal invasion", the WG did not attempt to discuss specific histologic subtypes of CA ex PA.

In the literature, a purely histologic approach to defining minimal invasion resulted in a variety of thresholds distinguishing minimal invasion from widely invasive Ca ex PA, from 1.5 to 10 mm [8]. Before a specific cut-off can be recommended, reporting of the several histological parameters should be standardized. WG agreed on the following list of conceptual questions and guidelines about non-invasive or minimally invasive Ca ex PA:

- An adequate study of Ca ex PA would comment on details of pathologic assessment, including such routine pathologic parameters as integrity of the specimen and margin status. Fragmentation of the specimen interferes with pathologists' ability to assess margin status independently and reliably. Positive or indeterminate margin is incompatible with the diagnosis of in situ carcinoma ex PA or minimally invasive carcinoma ex PA. Positive or indeterminate margin implies residual tumor or, at least, that the tumor-normal interface cannot be characterized / examined entirely. For instance, parotidectomy frequently (~40%) requires facial nerve dissection and even superficial parotidectomy frequently is not an *en bloc* resection. Studies of pleomorphic adenomas revealed a positive margin in about 25–33% of cases and/or breach of the tumor capsule in 14% of parotid resections [9, 10]. Pre-operative distinction between pleomorphic adenoma and Ca ex PA (especially an in situ

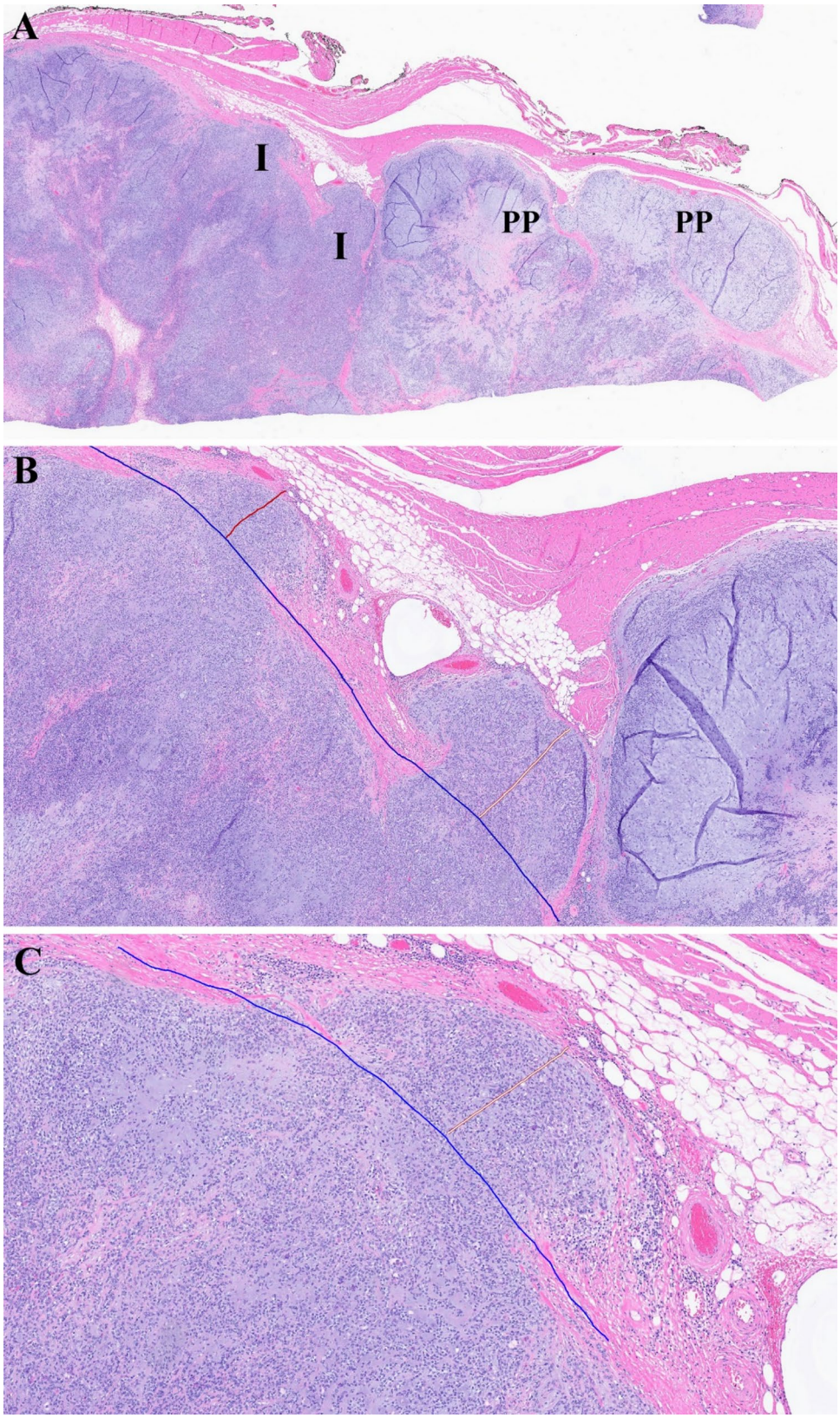

Fig. 1 Myoepithelial carcinoma arising in pleomorphic adenoma. **A**. Distinguishing pseudopodia (**PP**) from foci of minimal invasion (**I**) by myoepithelial carcinoma arising in pleomorphic adenoma, original magnification, H&E, 1.1x. Representative interface between normal tissue, myoepithelial carcinoma ex pleomorphic adenoma (left half of the image), and residual pleomorphic adenoma (right half of the image) are shown. In the right half of the image, there are more uniform in size, more rounded, less cellular (with myxoid stroma) pseudopodia, **PP**. In the left half of the image, there are smaller, more cellular, more angulated, foci of invasion. **B**. Details of invasion by myoepithelial carcinoma. Blue line highlights the contour of capsule. Red and white lines perpendicular to the blue line, through the middle of the invasive focus, are used to measure the extent of invasion, < 0.5 mm. H&E, original magnification, 3.5x. **C**. Details of invasion by myoepithelial carcinoma, one of the foci from **B**. Blue line highlights the contour of capsule. White lines perpendicular to the blue line, through the middle of the invasive focus, is used to measure the extent of invasion, < 0.5 mm. H&E, original magnification, 8x

or minimally invasive one) is challenging and surgical approach, prevalence of positive margins or breach of tumoral capsule are likely to be similar. However, the issues of margin and specimen fragmentation are not detailed by studies on in situ or minimally invasive CA ex PA.

- Similar to processing of encapsulated thyroid lesions, confident diagnosis of in situ or minimally invasive CA ex PA would require routine examination of the entire tumoral capsule.
- Histological measurement of the invasion relies on identifying a reference point / line from which the invasion is measured and raises the following issues:

    a. How to define the capsule of pre-existing PA when it is not represented by a well-developed fibrous band? The contour of pre-existing residual PA may be recognized by a variation in the tinctorial properties of the stroma of PA. For instance, hyalinized condensed stroma at the periphery of PA may represent a reference point to measure the extent of invasion in the absence of capsule. Alternatively, preserved and recognizable foci of chondromyxoid stroma of pre-existing PA flanking the area of invasive carcinomatous component may facilitate drawing an arcuate reference line to measure extent of invasion from.
    b. What is the significance of the contour of the interface between normal tissue and carcinoma ex PA? Well rounded, smooth and lobulated contours would typically be seen in the absence of invasion. Smaller and more angulated and flattened nodules, perhaps with desmoplasia, at the periphery of mass are most likely to be diagnostic of invasion (Fig. 1).
    c. Are criteria for invasion different in the setting of recurrent PA and/or multinodular growth?
    d. Does the number and size of foci of invasion matter?

- What defines pre-existing PA: morphology alone? Is the presence of *PLAG1* or *HMGA2* rearrangement sufficient for the diagnosis of Ca ex PA?

With the general considerations summarized above, the WG agreed on the checklist of criteria for an adequate study on carcinoma ex PA. Essential parameters that should be mentioned by future studies of carcinoma ex PA are listed below. Note, a list of standardized responses / options for each indexed parameter was agreed on by the WG and listed in the Excel spreadsheet file that may serve as a database template for future studies or literature reviews (see supplemental material).

1. Anatomical site
2. Tumor size and how tumor size was determined
3. Specimen integrity
4. Extent of sampling
5. Histologic carcinoma diagnosis and highest tumor grade
6. Description of tumor capsule / tumor-normal interface
7. Description of how invasion was measured
8. Margin status (positive, negative, distance to closest margin)
9. Quantification of carcinomatous component and its distribution throughout the tumor
10. Description of growth pattern (e.g., nodularity)
11. Recurrent vs primary pleomorphic adenoma
12. Perineural invasion
13. Vascular invasion
14. Lymphatic invasion
15. TNM classification with statement on cN0 or pN0
16. Any clinical follow-up (without minimal duration of follow-up, using local recurrence as a primary endpoint)
17. Treatment modality

In conclusion, the WG identified several conceptual and technical issues with current characterization of non-invasive and minimally invasive carcinomas arising in pleomorphic adenomas. The goal of defining "minimally invasive" subset of Ca ex PA and what local recurrence rate and which qualitative adverse histologic findings are compatible with the diagnosis of "minimal invasion" remain to be determined. Practically, a list of technical parameters is proposed for consideration while designing future studies. It is our hope that the proposed framework and suggested solutions will help with further characterization of Ca ex PA.

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Authors and Affiliations

Beth M. Beadle[1] · Nazim Benzerdjeb[2] · Junhun Cho[3] · Valérie Costes-Martineau[4] · William C. Faquin[5] · Ricardo Santiago Gomez[6] · Ruta Gupta[7,16] · Ivana Kholová[8,9] · Toshitaka Nagao[10] · Swapnil U. Rane[11] · Miguel Rito[12,13] · Lester D. R. Thompson[14] · Spinder Samra[15] · Peter P. Luk[16] · Simion I. Chiosea[17,18]

✉ Simion I. Chiosea
chioseasi@upmc.edu

Beth M. Beadle
bbeadle@stanford.edu

Nazim Benzerdjeb
nazim.benzerdjeb@chu-lyon.fr

Junhun Cho
jununius@naver.com

Valérie Costes-Martineau
v-costes_martineau@chu-montpellier.fr

William C. Faquin
wfaquin@mgh.harvard.edu

Ricardo Santiago Gomez
rsgomez.ufmg@gmail.com

Ruta Gupta
ruta.gupta@health.nsw.gov.au

Ivana Kholová
ivana.kholova@tuni.fi

Toshitaka Nagao
nagao-t@tokyo-med.ac.jp

Swapnil U. Rane
raneswapnil82@gmail.com

Miguel Rito
mrito@ipolisboa.min-saude.pt

Lester D. R. Thompson
consults@pathologyconsults.com

Spinder Samra
Samra@health.nsw.gov.au

Peter P. Luk
Peter.Luk@health.nsw.gov.au

[1] Department of Radiation Oncology, Stanford University, Stanford, CA, USA

[2] Department of Pathology, Institut de Pathologie Multisite, University Hospital of Lyon, Université Claude Bernard Lyon 1, Hospices Civils de Lyon, Lyon, France

[3] Department of Pathology, Samsung Medical Center, Seoul, Korea

[4] Department of Pathology, University Hospital Montpellier, Montpellier, France

[5] Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

[6] Department of Oral Surgery and Pathology, School of Dentistry, Universidade Federal de Minas Gerais and Faculty of Medical Sciences of Minas Gerais, Belo Horizonte, Brazil

[7] Faculty of Health and Medicine, The University of Sydney, Sydney, Australia

[8] Institute of Clinical Medicine, Pathology and Forensic Medicine, University of Eastern Finland and Department of Clinical Pathology, Diagnostic Imaging Center, Kuopio University Hospital, Kuopio, Finland

[9] Faculty of Medicine and Health Technology, Tampere University and Pathology, Fimlab Laboratories, Tampere, Finland

[10] Department of Anatomic Pathology, Tokyo Medical University, Tokyo, Japan

[11] Department of Pathology, Tata Memorial Centre-Advanced Centre for Training Research and Education in Cancer (TMC-ACTREC), Homi Bhaba National Institute (HBNI), Mumbai, India

[12] Department of Pathology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal

[13] Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

[14] Head and Neck Pathology Consultations, Woodland Hills, CA, USA

[15] Department of Tissue Pathology and Diagnostic Oncology, Westmead Hospital, Sydney, Australia

[16] Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, NSW Health Pathology, Sydney, Australia

[17] Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

[18] Department of Pathology, University of Pittsburgh Medical Center, Presbyterian University Hospital, PUH A610.3, 200 Lothrop Street, Pittsburgh, PA 15213, USA