Recent Advances in Pathology for Prognostication and Treatment of cancer

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The role of Pathologist in the era of precision medicine and precision pathology

- Accurate diagnosis and histologic classification

* Detection of sensitizing molecular alteration.

- Detection of resistance inducing molecular alteration.

Outline

- Current recommendations of reporting and biomarker testing in Lung, Breast and colon cancer.

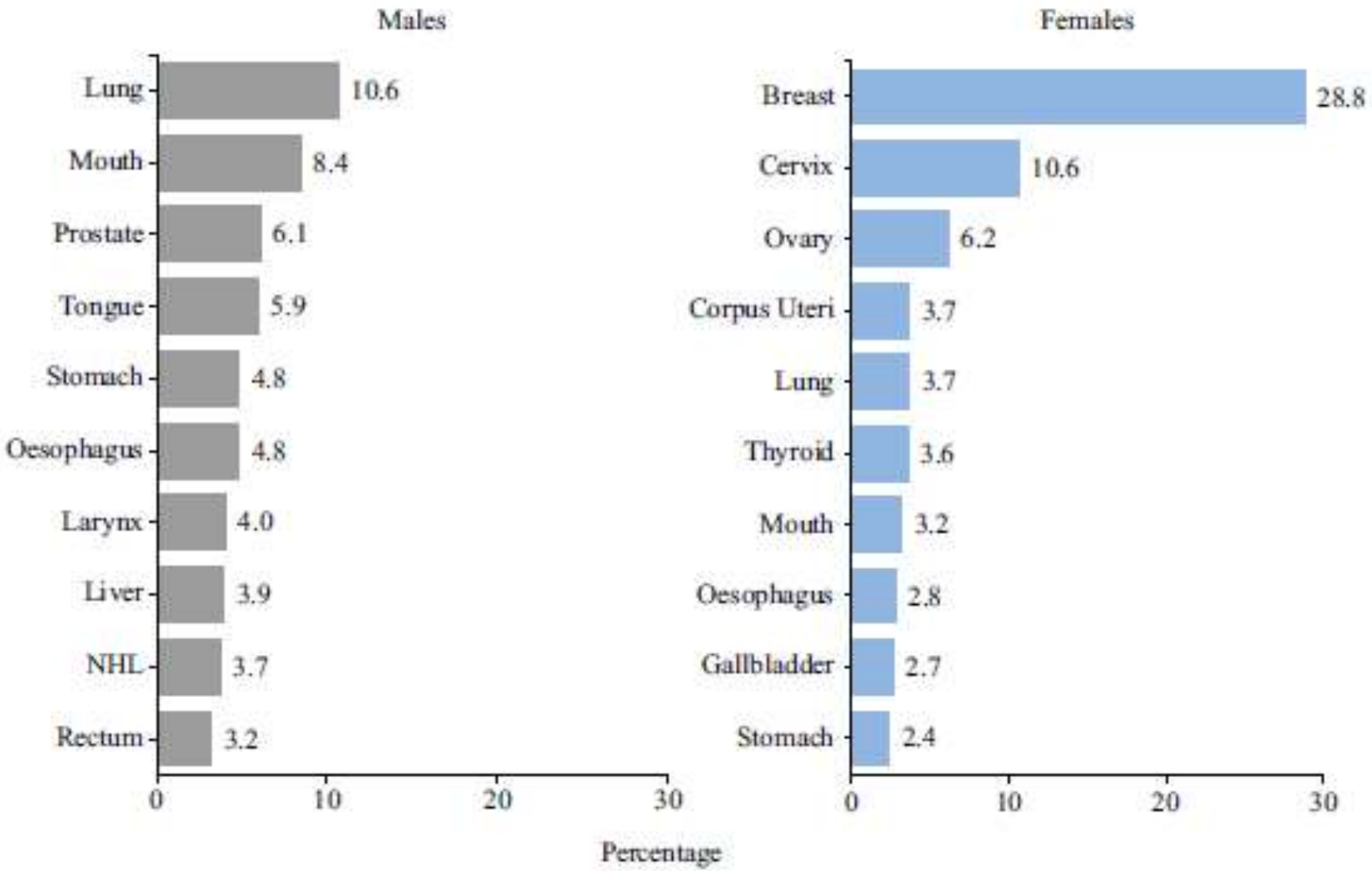


Fig. 1. Estimated proportion of top 10 leading sites of cancer in India by sex – 2022.

Sathishkumar et al. Indian J Med Res 156, October & November 2022,

The WHO 2021 Classification lung ca

Epithelial Tumors

- Squamous cell carcinoma
- Adenocarcinoma
- Adenosquamous carcinoma
- Large cell carcinoma
- Sarcomatoid carcinoma
- Other epithelial tumors:

  NUT carcinoma

  SMARCA 4-deficient undifferentiated carcinoma
- Salivary gland type tumors

Neuroendocrine tumors

- - Carcinoid Tumors

--Typical Carcinoid (NET grade 1)

-- Atypical Carcinoid (NET grade 2)

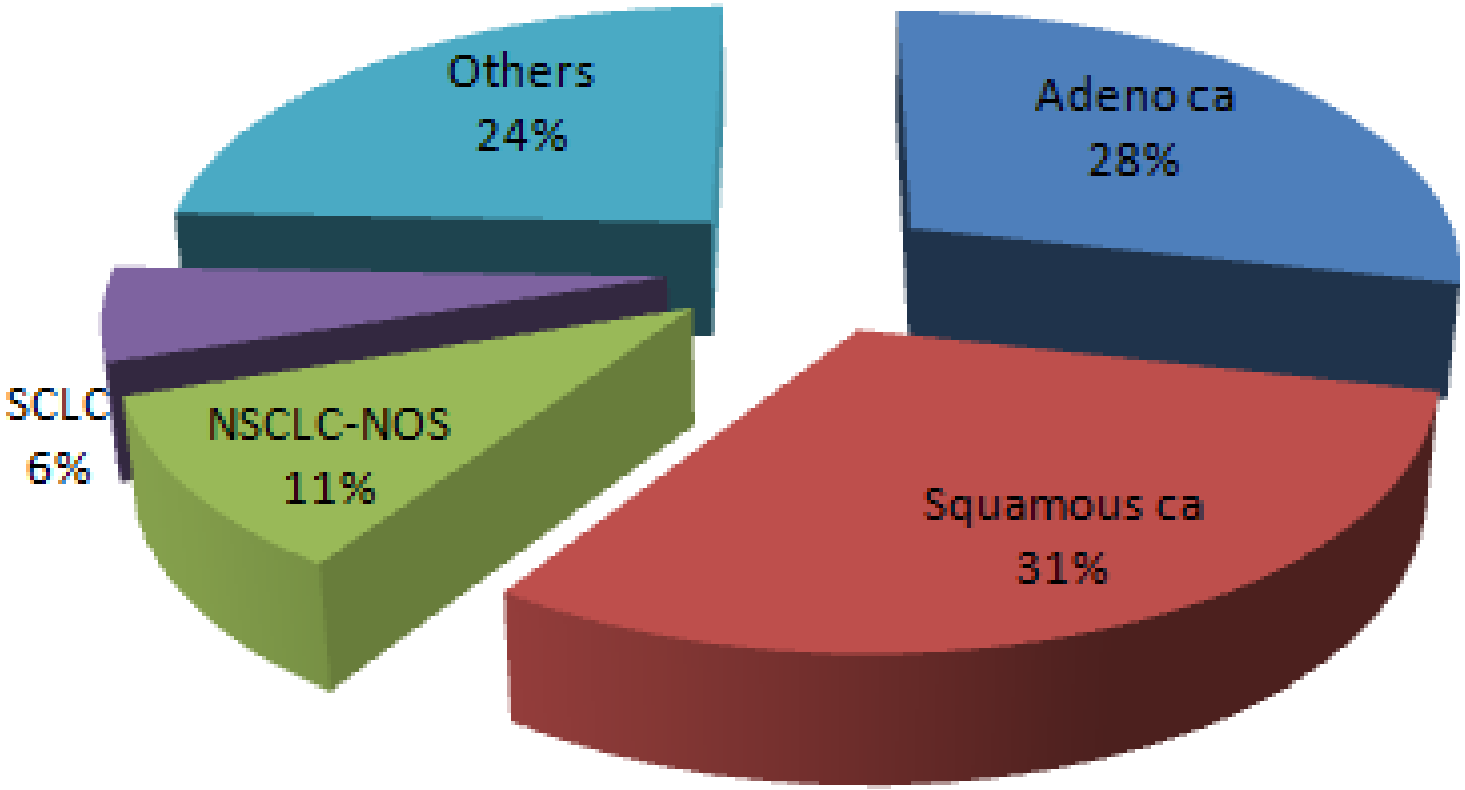
- Small cell carcinoma
- Large cell neuroendocrine carcinoma

- **Mesenchymal tumors**
- **PEComatous tumors**
- **Hematolymphoid tumors**
- **Metastatic tumors**.

Pathology reports for lung cancer diagnoses in small biopsy and cytology-

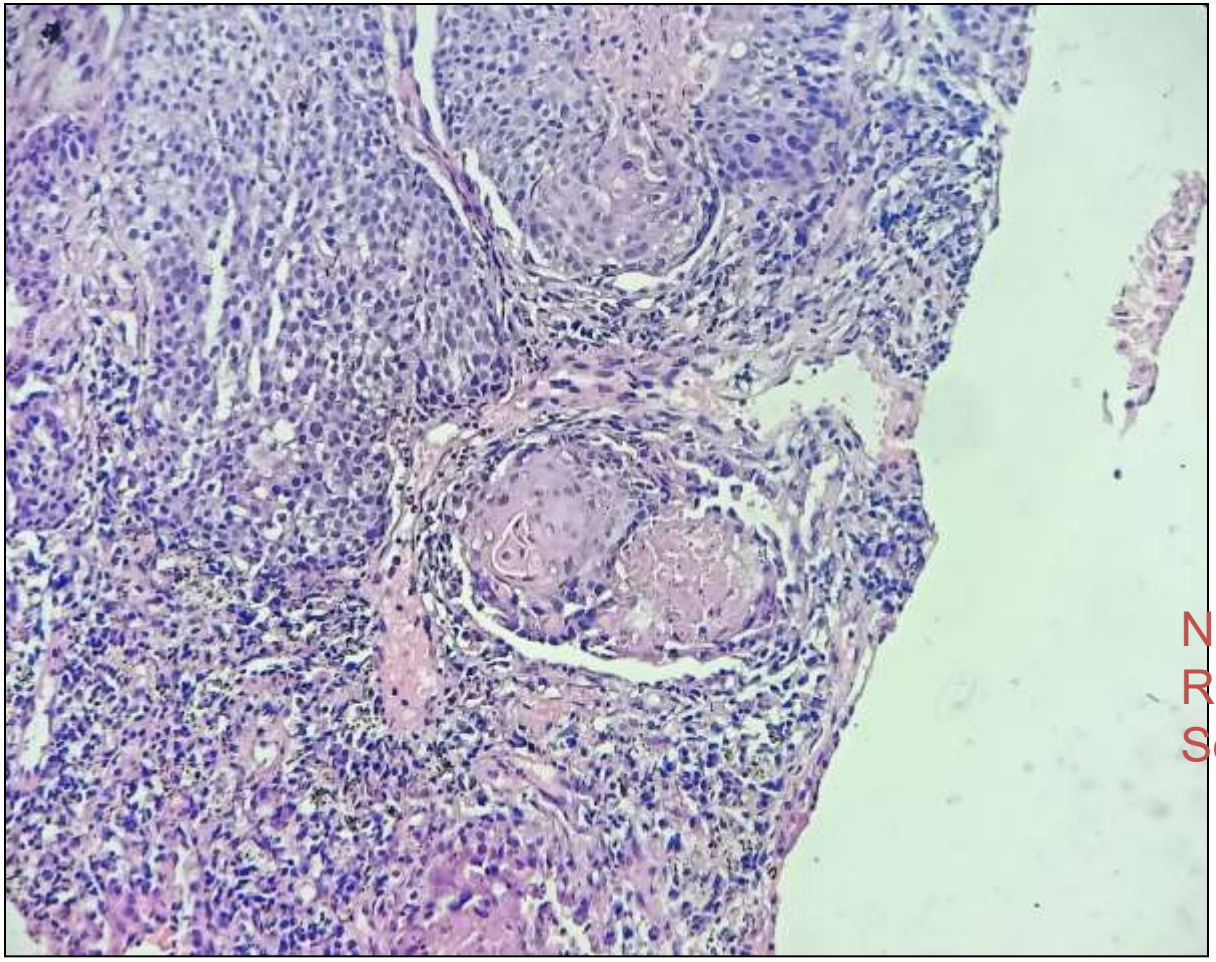
WHO 5th edition

- 1. Pathological or cytopathological diagnosis according to 2021 WHO classification
- 2. Results of IHC and/or mucin stains.
- 3. Comment about differential diagnosis (when appropriate)
- 4. Statement of whether any material has been submitted for molecular testing (and the results if available)
- Specify the block was used.
- Percentage of viable tumor cells in the specimen



NRSMCH : LUNG CANCER :2024,.

Squamous cell carcinoma

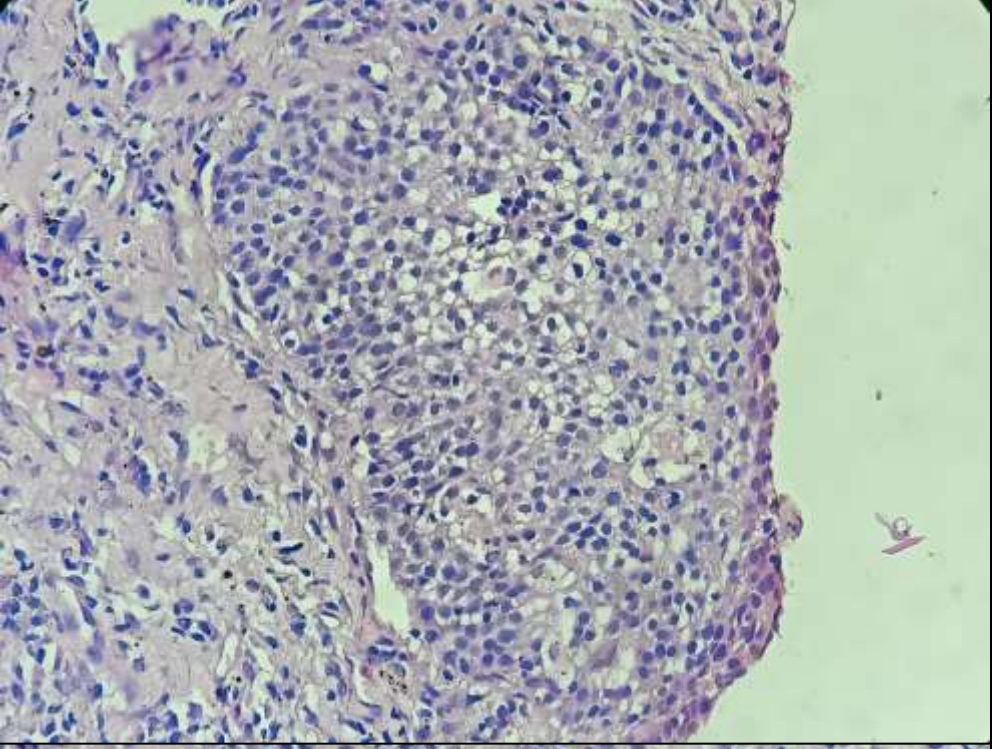


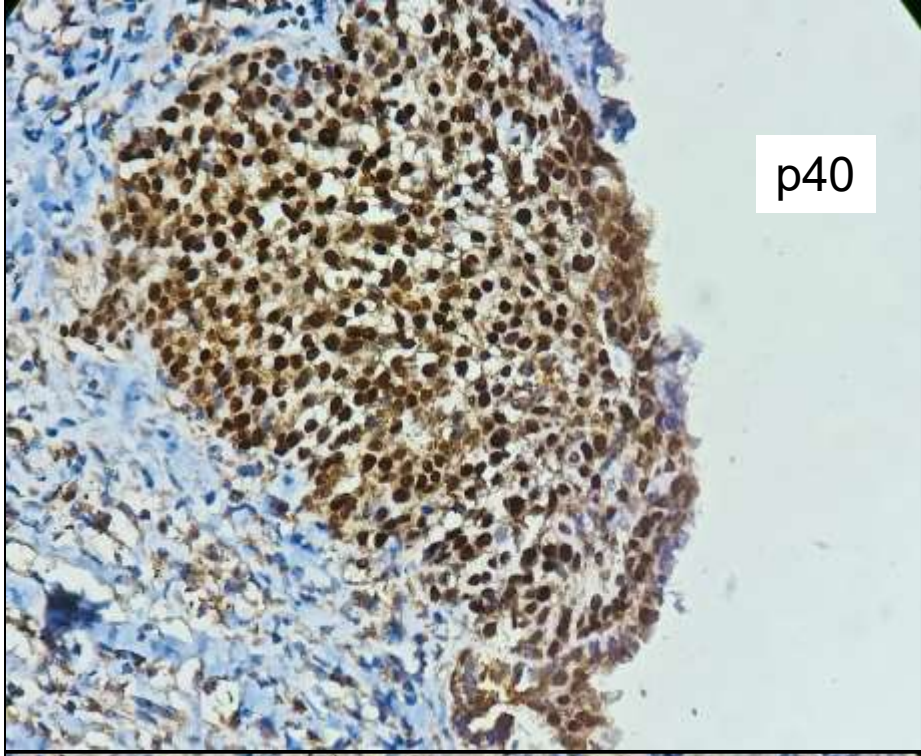
Sub types :

- Keratinizing
- Non Keratinizing
- Basaloid

- -No clinical implication

Non Keratinizing tumors
Require IHC to proof
Squamous differentiation

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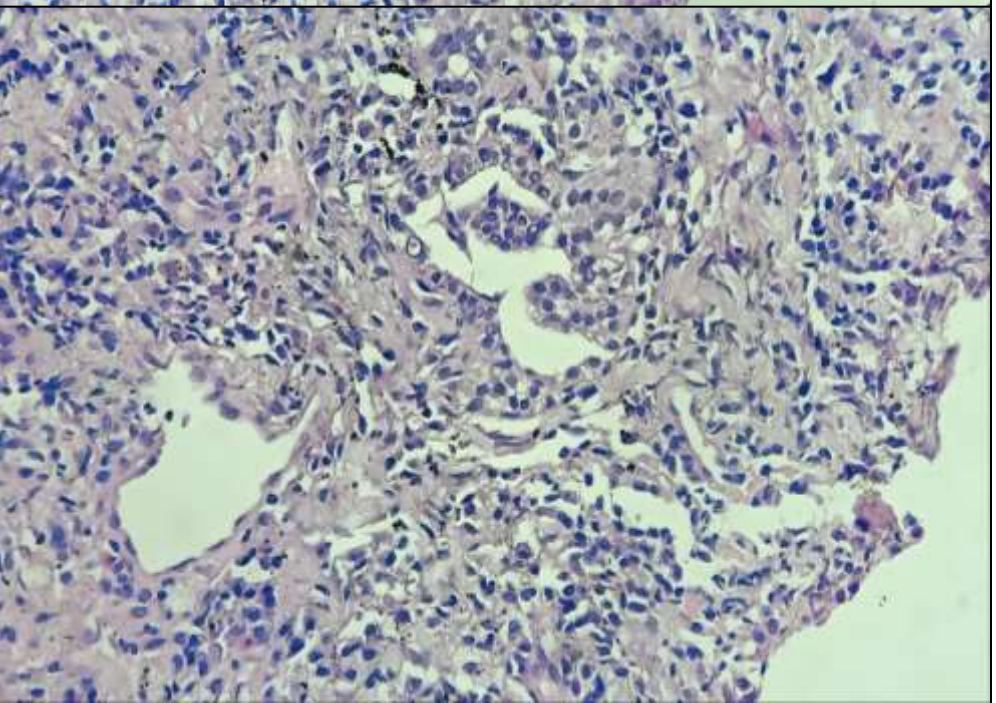
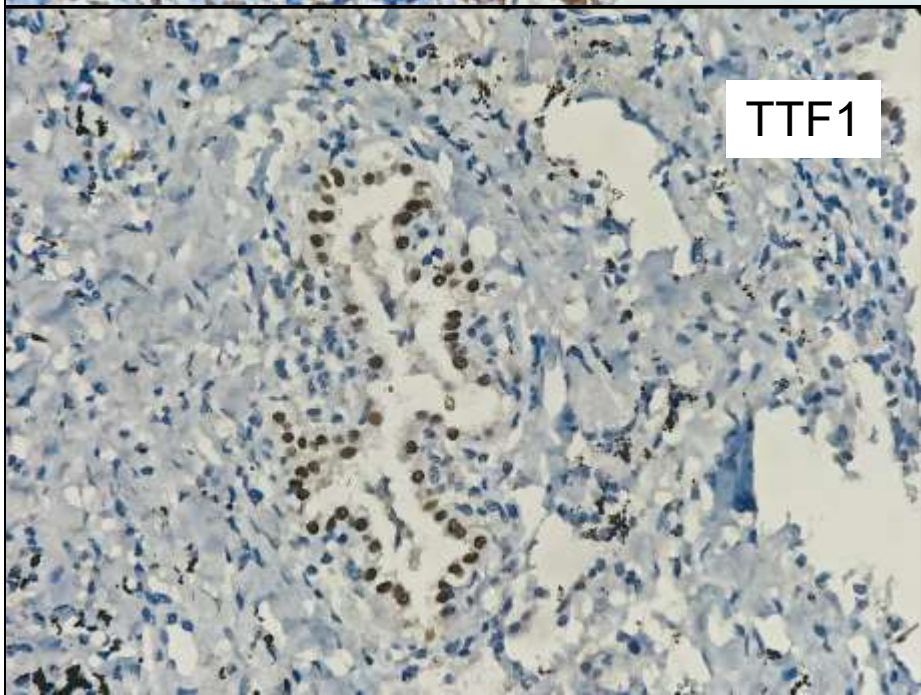



TTF1

Adenocarcinoma

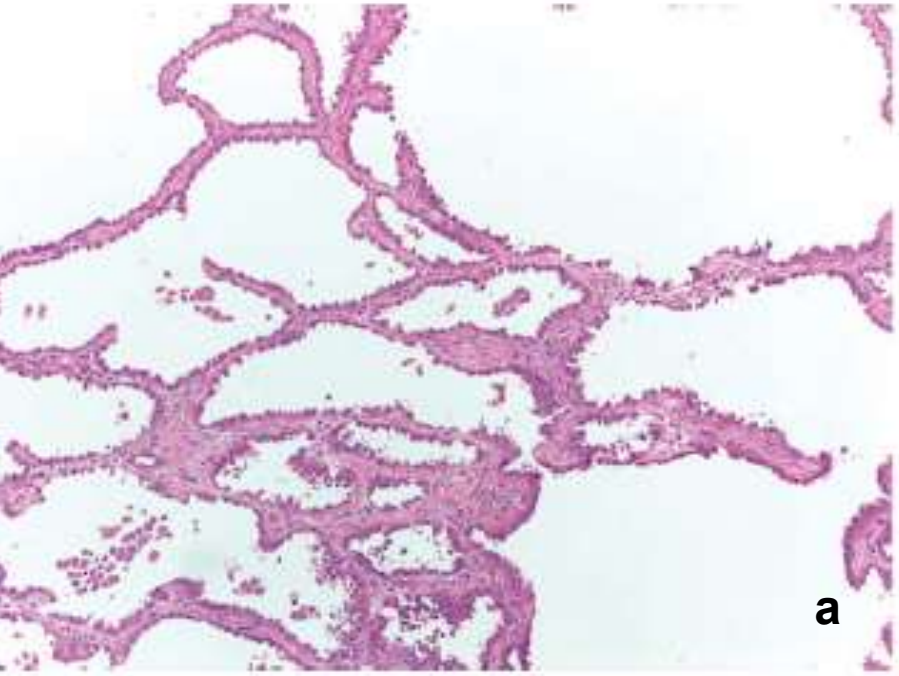
For resection specimen

Preinvasive lesions

- Atypical adenomatous hyperplasia (<5mm)
- Adenocarcinoma in situ, (<30mm, pure lepidic)
- Minimally invasive adenocarcinoma. (non-mucinous/mucinous) (<5 mm invasive component, other than lepidic)
- * **Adenocarcinoma with lepidic pattern (note: invasive component cannot be excluded)**

Record adenocarcinoma patterns in small biopsy

- Invasive non mucinous adenocarcinoma
- Lepidic, acinar, papillary, micropapillary, solid
- Invasive mucinous adenocarcinoma
- Variants : fetal, colloid, enteric type.
- **Solid and Micopapillary pattern with poor prognosis**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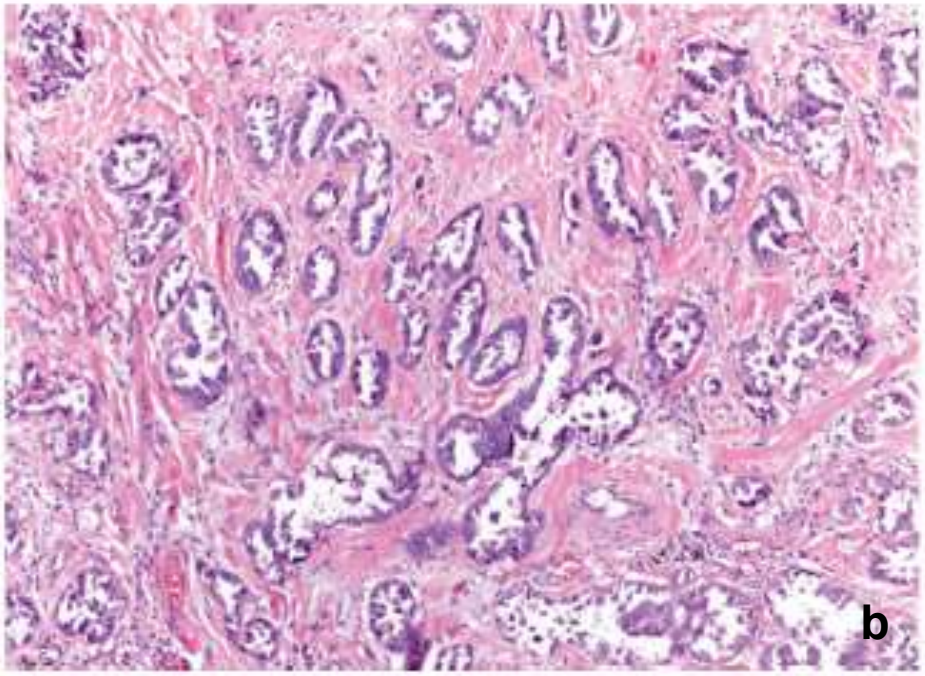
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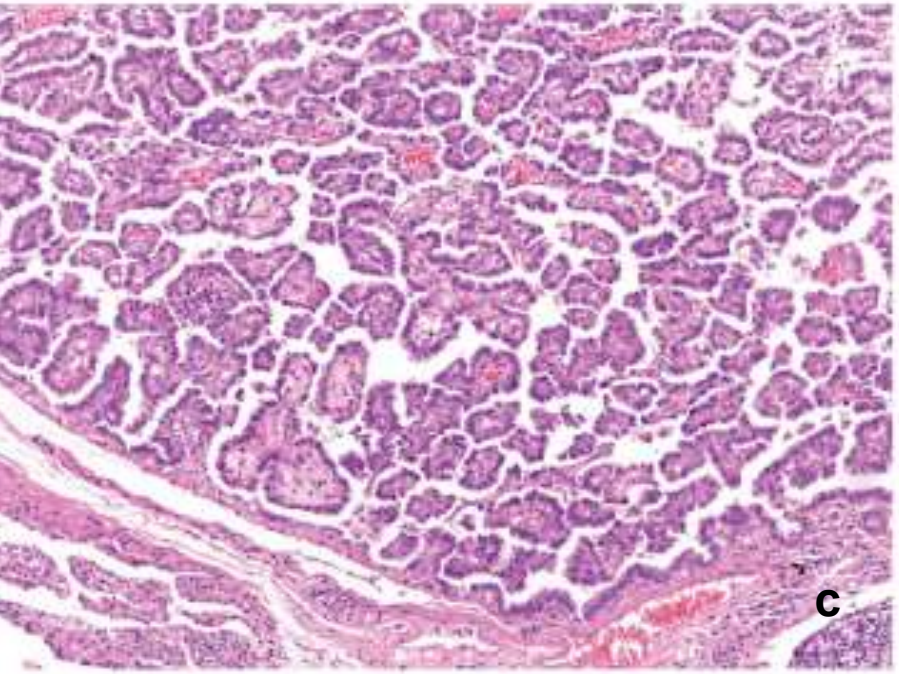
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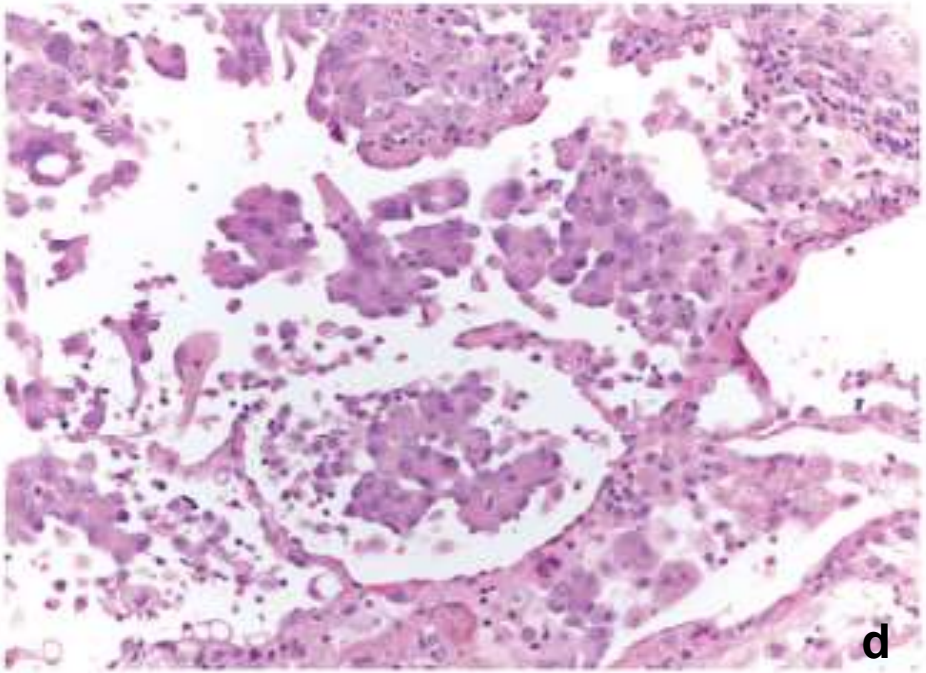
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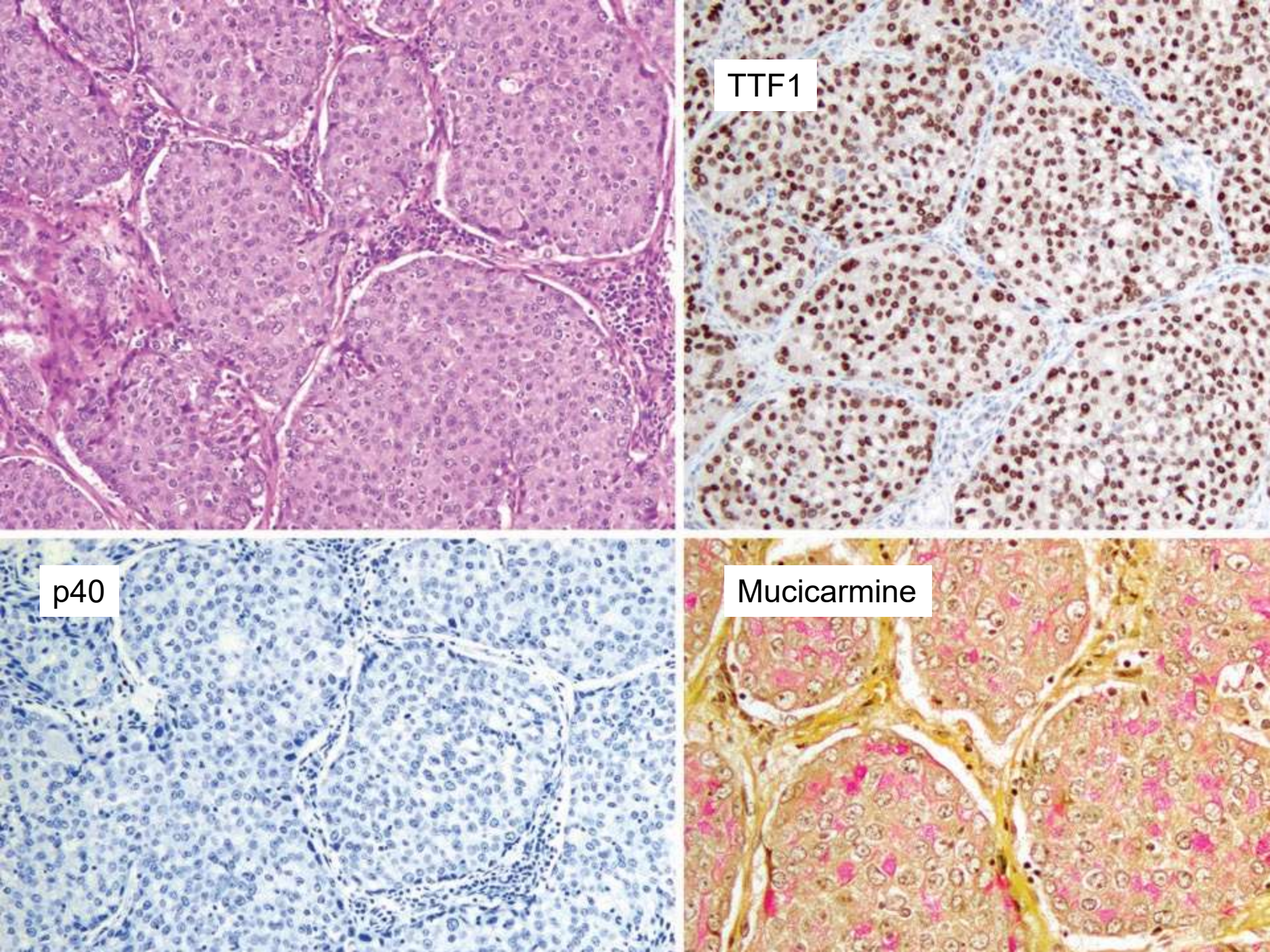

TTF1
p40
Mucicarmine

Avoiding over diagnosis of lung cancer

- Squamous metaplasia overdiagnosed as squamous cell carcinoma.
- Reactive Pneumocyte hyperplasia overdiagnosed as Adenocarcinoma (NO IHC)
- Primary mucinous ca vs Metastatic adenocarcinoma from extrapulmonary sites : Pancreaticobiliary, GIT, Ovary
- No useful markers, clinico-pathological tumor board is essential.

WHO 2021 diagnostic terminology of lung neuroendocrine neoplasm

- Precursor lesion:

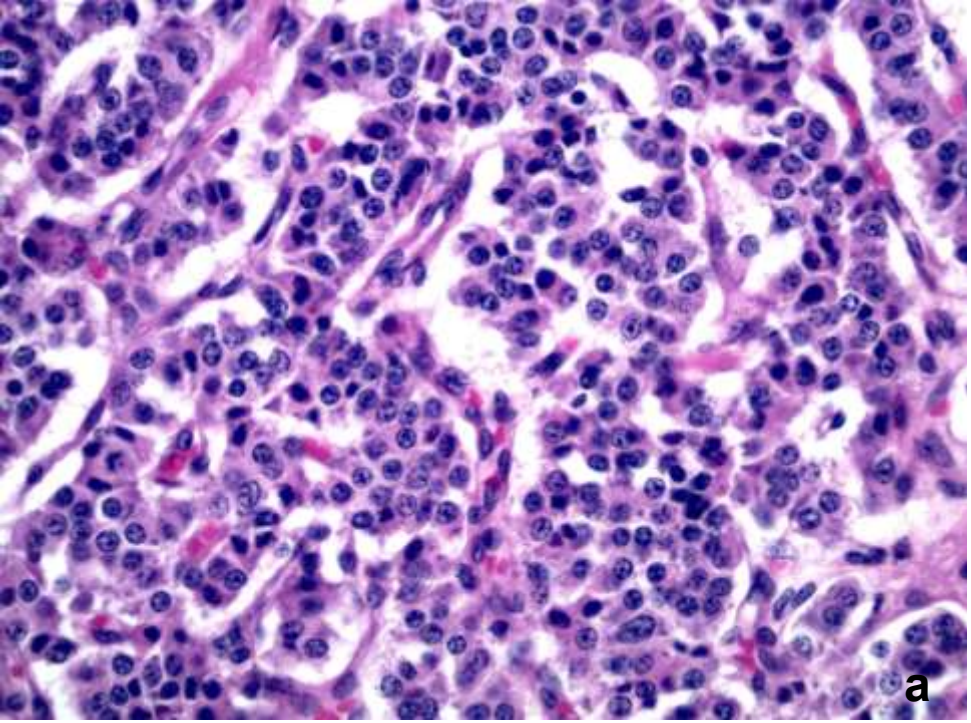
Diffuse idiopathic neuroendocrine cell hyperplasia

- Neuroendocrine tumors:

Carcinoid tumor NOS/Neuroendocrine tumor NOS

- Typical carcinoid/NET grade 1
- Atypical carcinoid /NET grade 2
- Neuroendocrine carcinoma
- Small cell carcinoma
- Combined small cell carcinoma
- Large cell neuroendocrine carcinoma
- Combined large cell neuroendocrine carcinoma

	Typical carcinoid	Atypical carcinoid	LCNEC	SCLC
Mitosis per 2 mm^2	<2	2-10	>10 (median 70)	>10 (median 80)
Necrosis	No	Focal, if any	Yes	Yes
Neuroendocrine morphology	yes	yes	yes	yes
Ki 67	Upto 5%	Upto 30%	30-100%	30-100%
TTF1	Mostly +ve in peripheral tumors	Mostly +ve in peripheral tumors	Positive (70%)	Positive (85%)
P40 expression	Negative	Negative	Negative	Negative
Combined NSCLC	No	No	Upto 25% resected specimen	Upto 25 % resected specimen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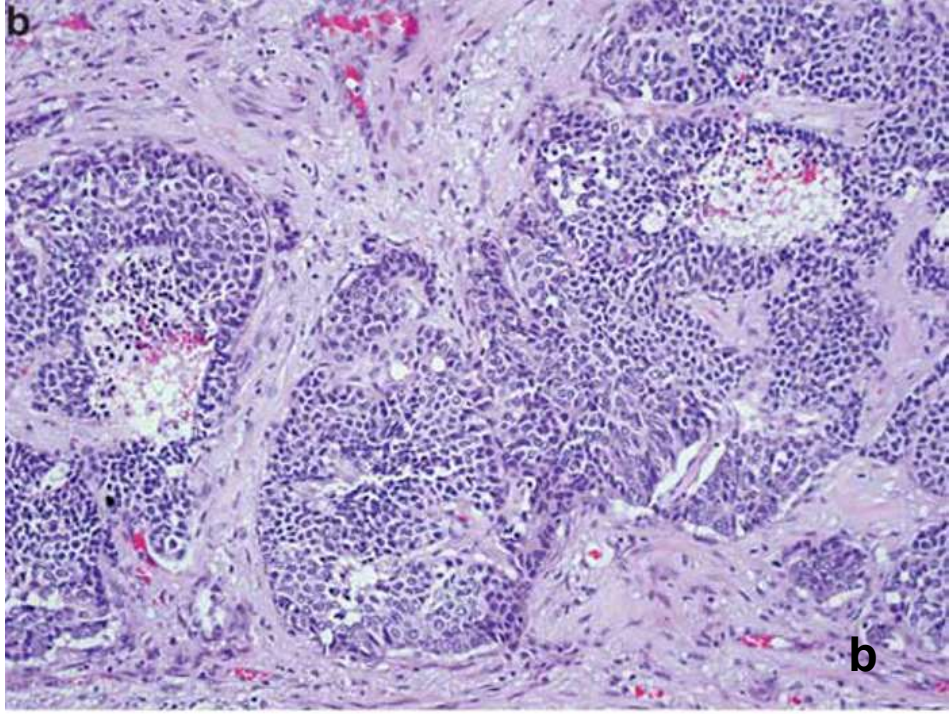
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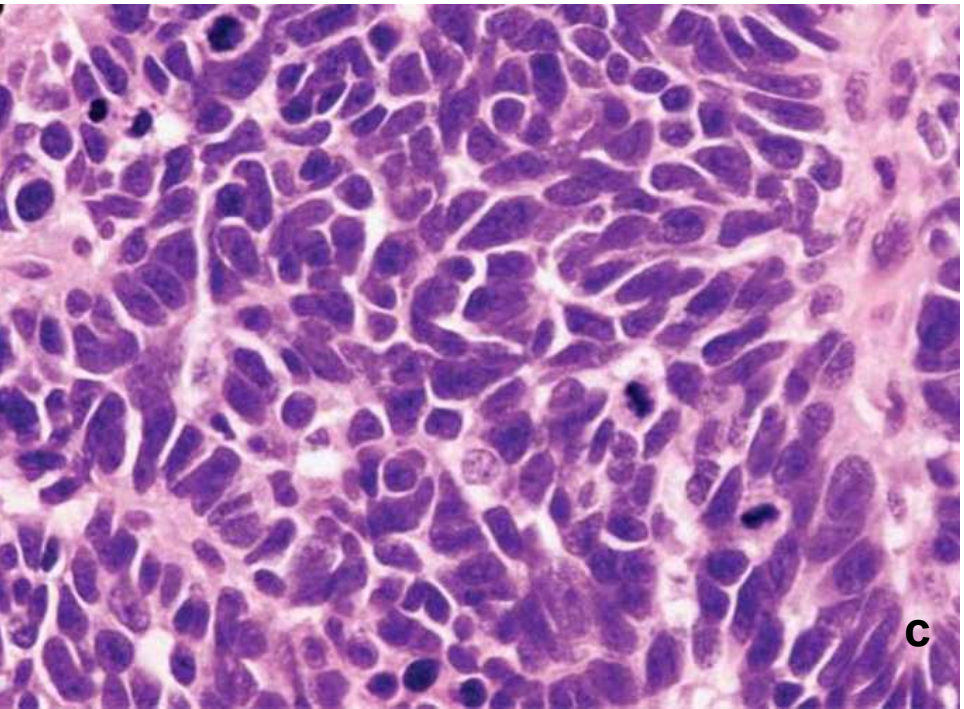
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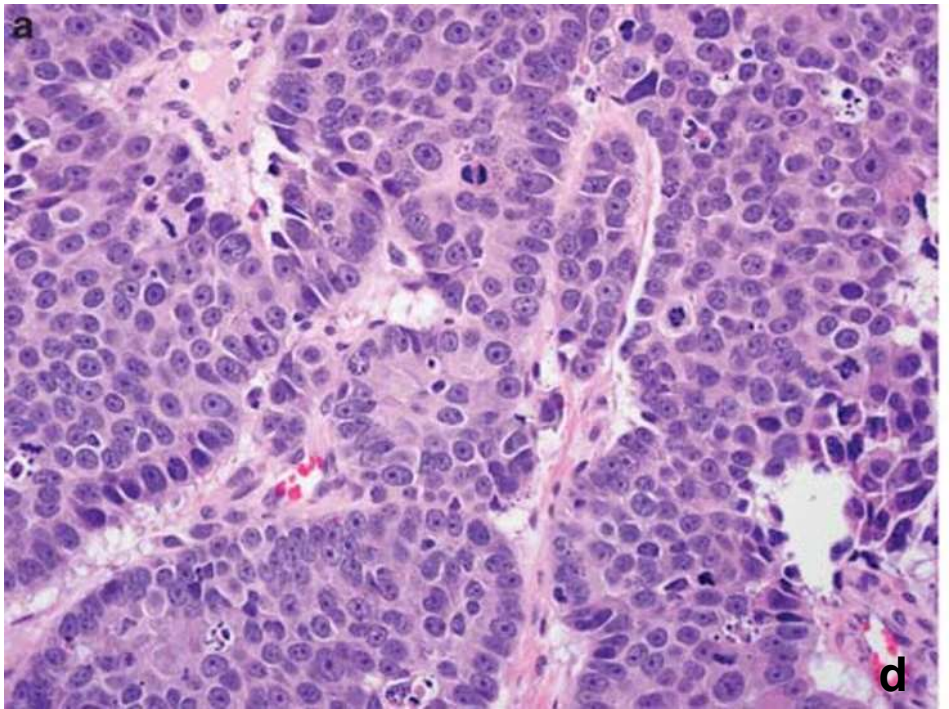
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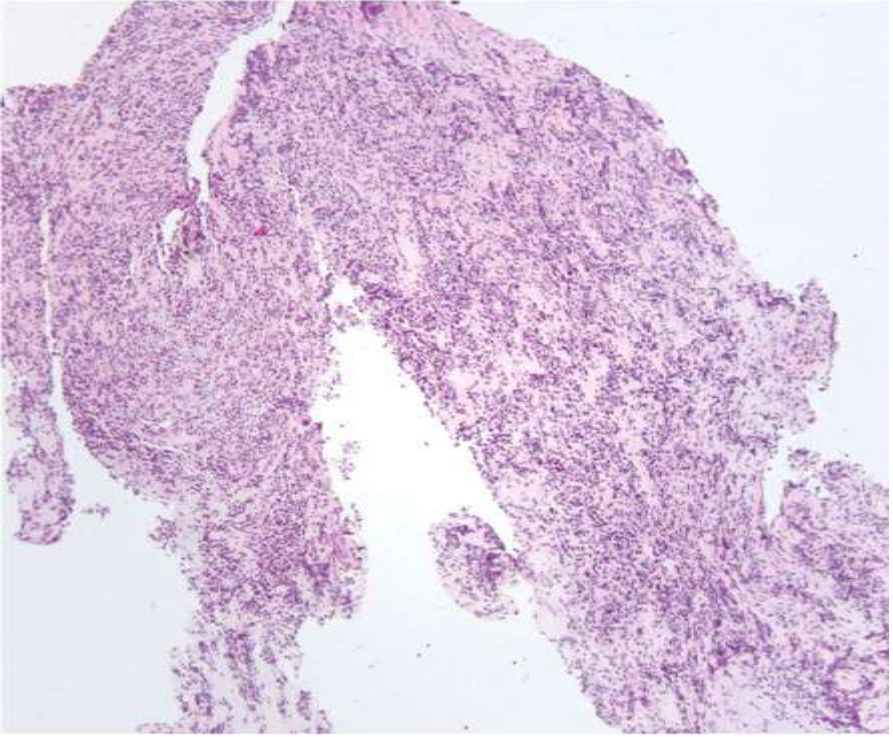
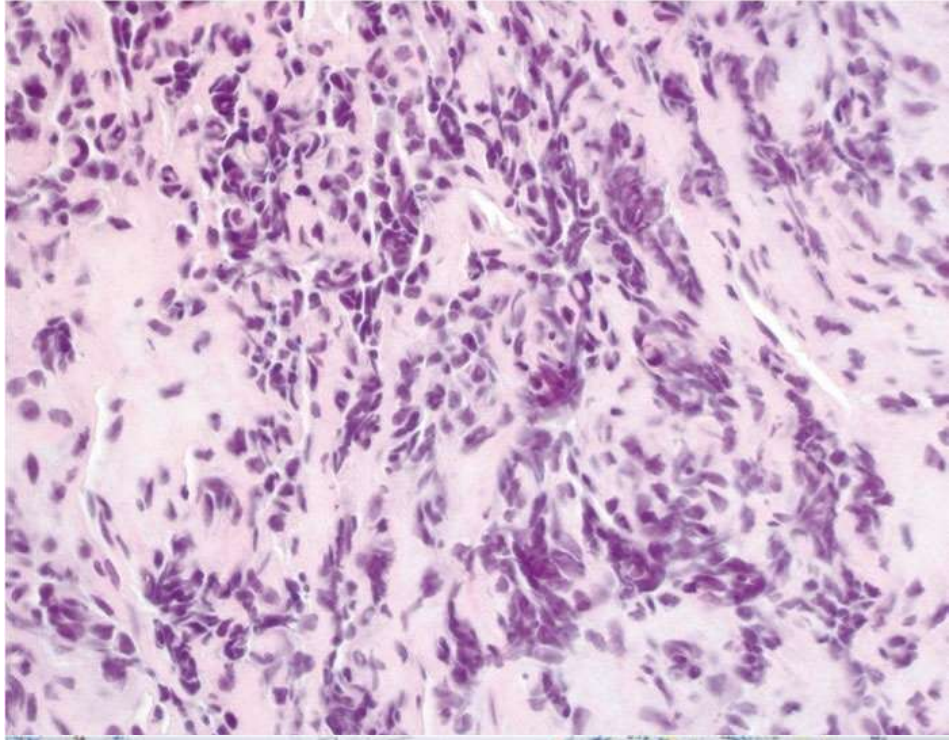
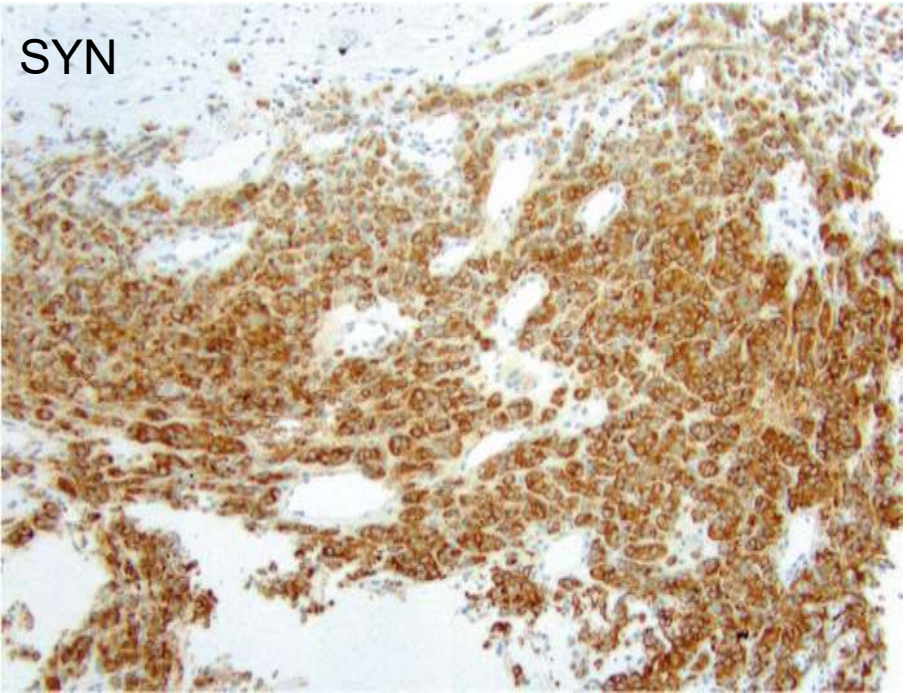
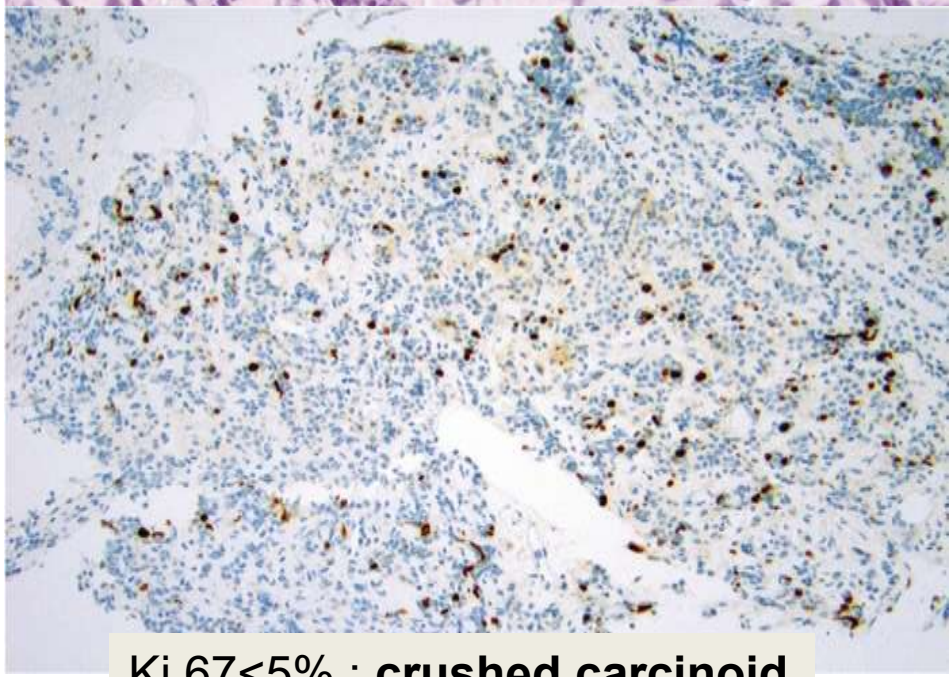








Ki 67<5% : **crushed carcinoid**

Recommendations of use of IHC in small biopsy of lung cancer

SPECIAL ARTICLE

Best Practices Recommendations for Diagnostic Immunohistochemistry in Lung Cancer

Yasushi Yatabe, MD, PhD,[a,*] Sanja Dacic, MD,[b] Alain C. Borczuk, MD,[c] Arne Warth, MD, PhD,[d] Prudence A. Russell, FRCPA,[e] Sylvie Lantuejoul, MD, PhD,[f] Mary Beth Beasley, MD,[g] Erik Thunnissen, MD, PhD,[h] Giuseppe Pelosi, MD,[i] Natasha Rekhtman, MD, PhD,[j] Lukas Bubendorf, MD,[k] Mari Mino-Kenudson, MD,[l] Akihiko Yoshida, MD, PhD,[m] Kim R. Geisinger, MD,[n] Masayuki Noguchi, MD, PhD,[o] Lucian R. Chirieac, MD,[p] Johan Bolting, MD,[q] Jin-Haeng Chung, MD, PhD,[r] Teh-Ying Chou, MD, PhD,[s] Gang Chen, MD,[t] Claudia Poleri, MD,[u] Fernando Lopez-Rios, MD, PhD,[v] Mauro Papotti, MD,[w] Lynette M. Sholl, MD,[p] Anja C. Roden, MD,[x] William D. Travis, MD,[j] Fred R. Hirsch, MD, PhD,[y] Keith M. Kerr, MD, PhD,[z] Ming-Sound Tsao, MD, FRCPC,[aa] Andrew G. Nicholson, DM,[bb] Ignacio Wistuba, MD,[cc] Andre L. Moreira, MD[dd]

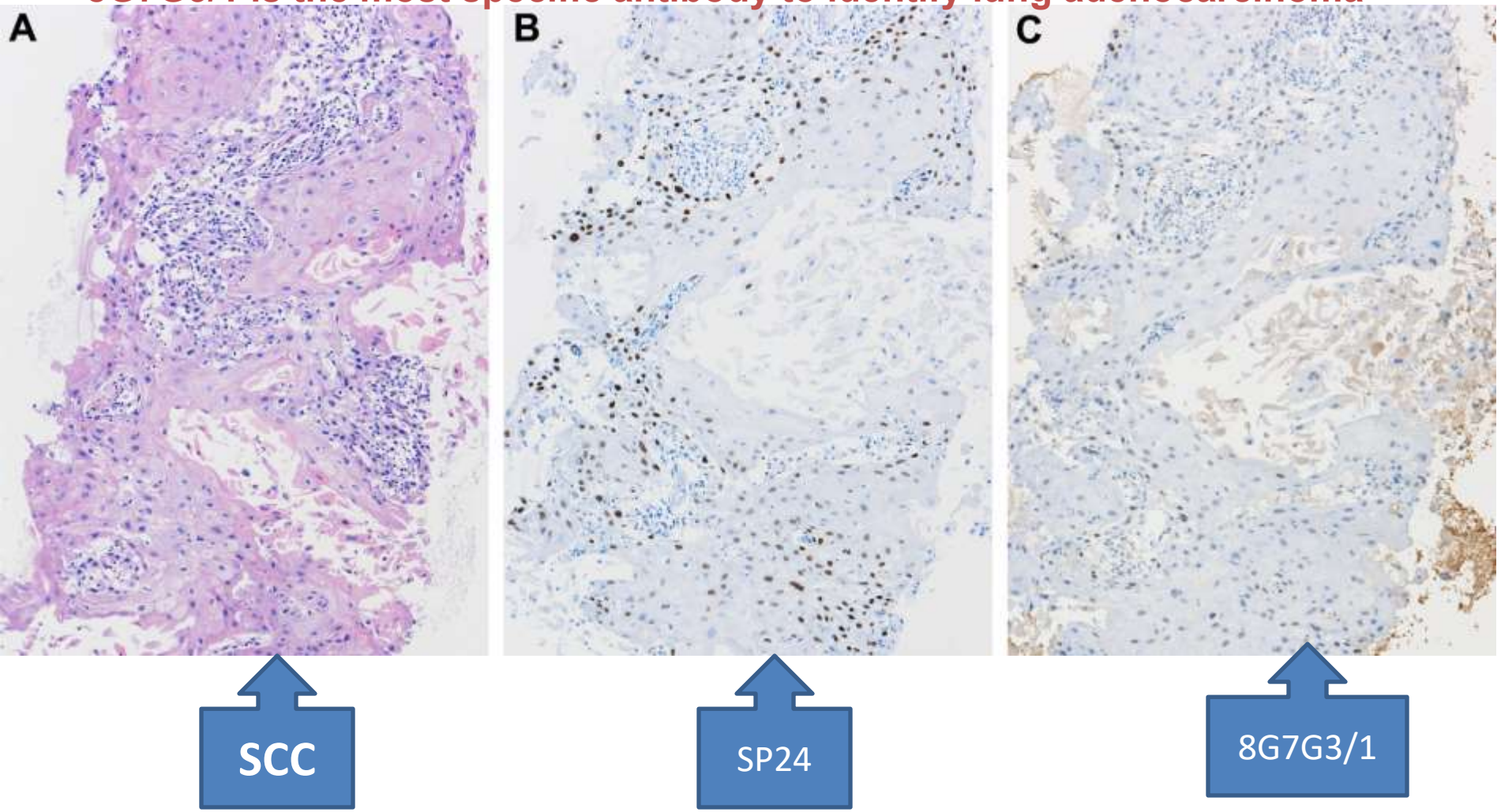
Journal of Thoracic Oncology 2018, vol. 14.

Best combination of markers in daily practice

- When IHC is needed to for sub typing of NSCLC : TTF1 and p40
- Better performance of Napsine A than TTF1 with greater sensitivity, TTF 1 is preferred as it is nuclear marker
- p63 and p40 : p40 IHC targets a splice variant of p63 , is more specific and sensitive.
- 20-30 % adenocarcinoma are positive for p63.
- Focal positivity of TTF1 is considered a positive reaction : pulmonary adenocarcinoma.
- The cut off for p40 > 50% of tumor nuclei
- Focal and weak positivity for p40 is not diagnostic for SCC

TTF 1 clones : which is the best SP24, SP141 and 8G7G3/1 ?

8G7G3/1 is the most specific antibody to identify lung adenocarcinoma

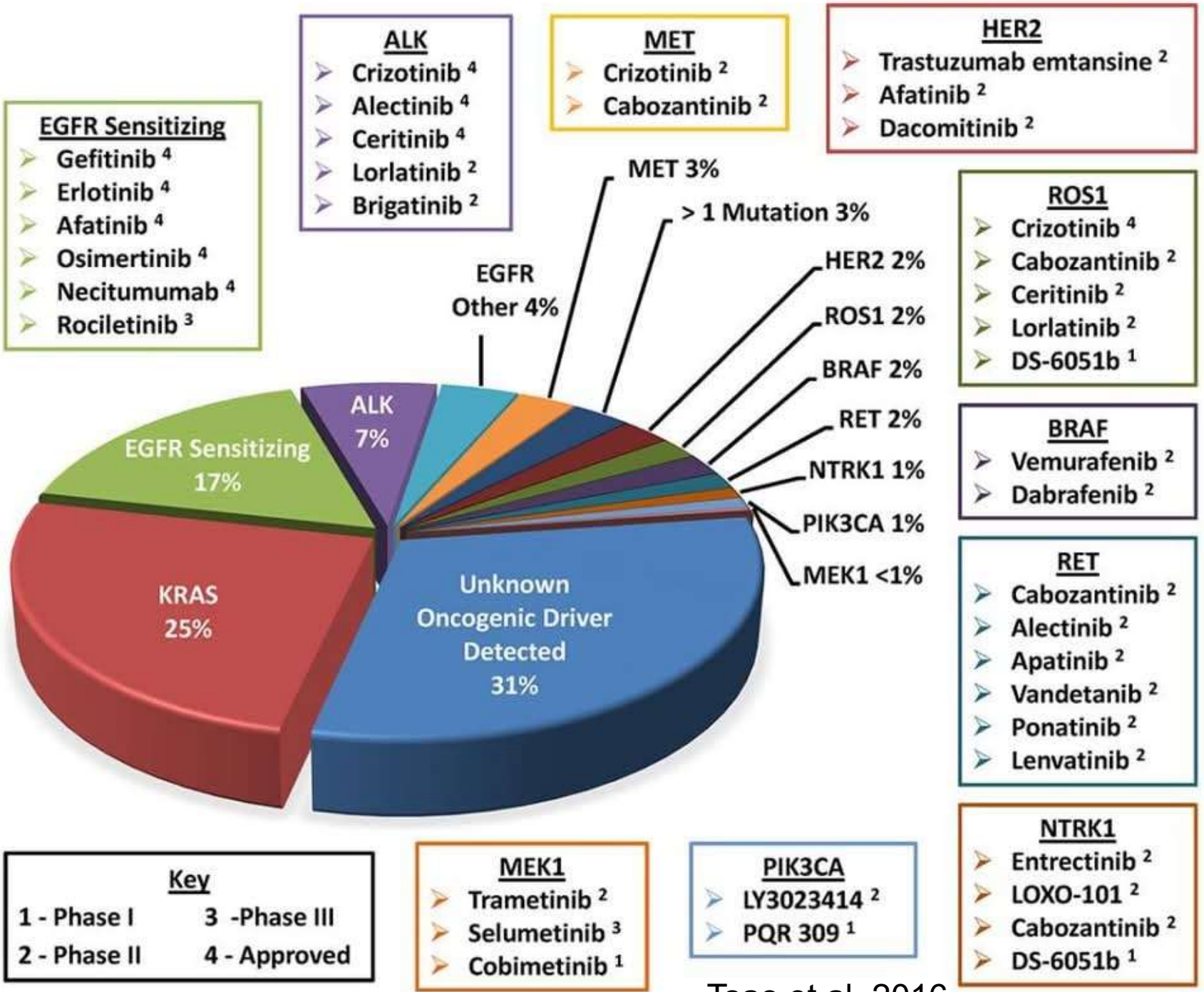


Best antibody panel to differentiate NE tumors from other types NSCLC

- A panel of chromogranin A, synaptophysin and CD56 is the best combination to identify NE tumors
- Upto 15-20% SCLC are negative for synaptophysin and chromogranin A, but most such tumors are +ve for CD56
- Currently no consensus as to whether one , two or three markers are used
- **Insulinoma associated protein 1 (INSM1)** : promicing : nuclear staining (95% + in SCLC and 92% in LCNEC)

Implication of accurate subtyping NSCLC on small biopsy

- Tyrosine kinase inhibitor(Gefitinib/Erlotinib/Afatinib) –adenocarcinoma with EGFR mutations
- Response to crizotinib/ newer drugs with ALK/ ROS 1 rearrangement
- Adenocarcinoma or NSCLC NOS –more responsive to pemetrexed
- Squamous cell carcinoma more responsive to Gemcitabine + Platinum
- Life threatening hemorrhage with Bevacizumab in SCC



Tsao et al. 2016

Biomarker testing in NSCLC : Guidelines

CAP Laboratory Improvement Programs

Arch Pathol Lab Med 2018 March ;142

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

Neal I. Lindeman, MD; Philip T. Cagle, MD; Dara L. Aisner, MD, PhD; Maria E. Arcila, MD; Mary Beth Beasley, MD; Eric H. Bernicker, MD; Carol Colasacco, MLIS, SCT(ASCP); Sanja Dacic, MD, PhD; Fred R. Hirsch, MD, PhD; Keith Kerr, MB, ChB; David J. Kwiatkowski, MD, PhD; Marc Ladanyi, MD; Jan A. Nowak, MD, PhD; Lynette Sholl, MD; Robyn Temple-Smolkin, PhD; Benjamin Solomon, MBBS, PhD; Lesley H. Souter, PhD; Erik Thunnissen, MD, PhD; Ming S. Tsao, MD; Christina B. Ventura, MPH, MT(ASCP); Murry W. Wynes, PhD; Yasushi Yatabe, MD, PhD

Adv Ther
https://doi.org/10.1007/s12325-019-00903-y

Check for updates

GUIDELINES

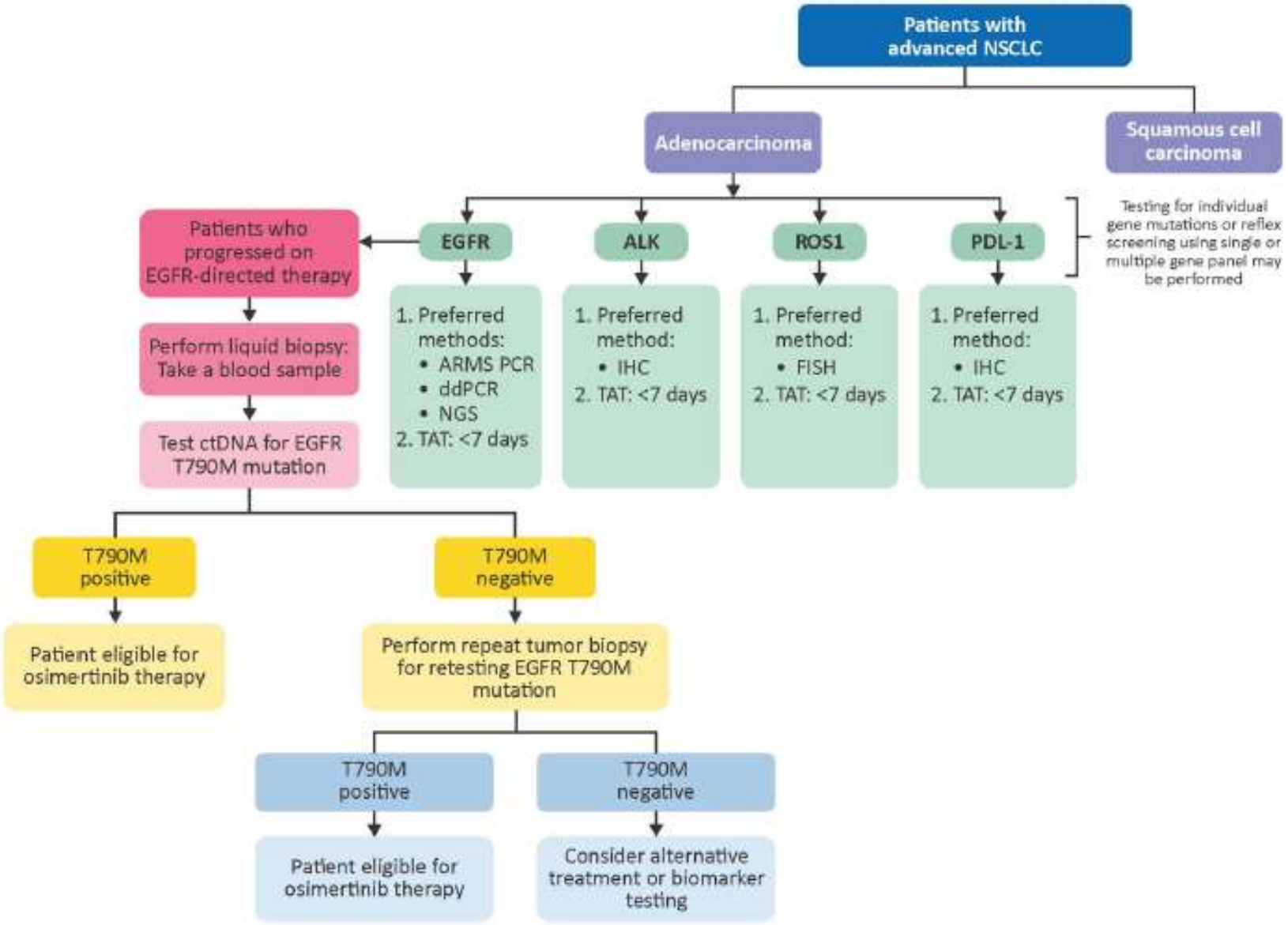
Biomarkers in Non-Small Cell Lung Cancers: Indian Consensus Guidelines for Molecular Testing

Kumar Prabhash · Suresh H. Advani · Ullas Batra · Bivas Biswas · Anuradha Chougule · Mithua Ghosh · Vamshi Krishna Mudda · T. P. Sahoo · Ashok K. Vaid

Received: January 3, 2019

Pre analytical variables

- Can use tissue biopsy or cytology specimen
- Fixation in 10 % neutral buffered formain
- Fixation time : 6- 24 hrs for biopsy and 24-72 hrs for resection specmen
- Decalcification : EDTA can be used
- In two block setting : one block for diagnosis, predictive IHC : ALK, ROS 1, PDL1; Second block : Molecular testing EGFR, NGS panel


Patients with advanced NSCLC
Adenocarcinoma
Squamous cell carcinoma
Testing for individual gene mutations or reflex screening using single or multiple gene panel may be performed
EGFR
ALK
ROS1
PDL-1
1. Preferred methods:
• ARMS PCR
• ddPCR
• NGS
2. TAT: <7 days
1. Preferred method:
• IHC
2. TAT: <7 days
1. Preferred method:
• FISH
2. TAT: <7 days
1. Preferred method:
• IHC
2. TAT: <7 days
Patients who progressed on EGFR-directed therapy
Perform liquid biopsy: Take a blood sample
Test ctDNA for EGFR T790M mutation
T790M positive
T790M negative
Patient eligible for osimertinib therapy
Perform repeat tumor biopsy for retesting EGFR T790M mutation
T790M positive
T790M negative
Patient eligible for osimertinib therapy
Consider alternative treatment or biomarker testing

Recommendation for EGFR testing

- EGFR mutation present in 22-65% of Indian NSCLC (adenocarcinoma)
- Deletion of exon 19 and exon 21 point mutation L858 R in 90% of EGFR mutation
- **Mutation specific antibodies need further evaluation**.(Clones :EP 344 & SP125)
- Preferred methods: ARMS PCR and NGS

EGFR Exon 18

- G719S (2155G>A)
- G719C (2155G>T)
- G719A (2156G>C)

EGFR Exon 20

- T790M (2369C>T)
- S768I (2303G>T)
- C797S (2389T>A)
- C797S (2390G>C)
- V769_D770insASV (2307_2308insGCCAGCGTG)
- D770_N771insG (2310_2311insGGT)
- H773_V774insH (2319_2320insCAC)

EGFR Exon 21

- L858R (2573T>G)
- L861Q (2582T>A)

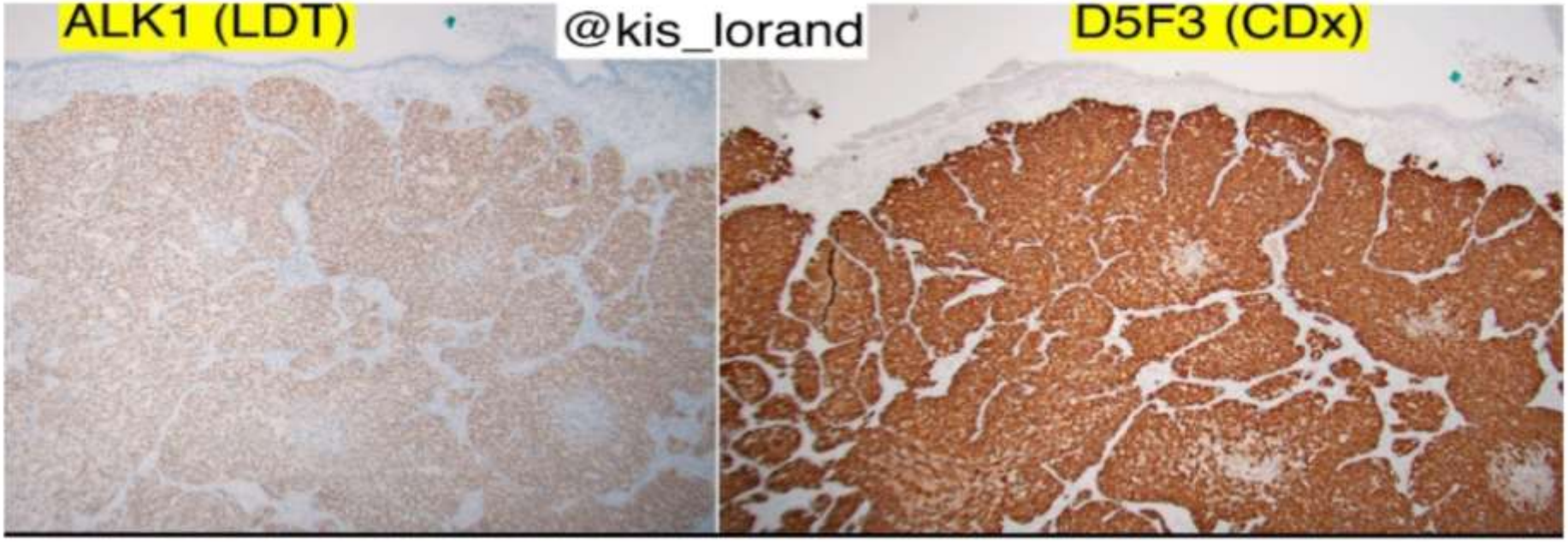
EGFR Exon 19

- E746_A750del(2235_2249del15)
- E746_A750del(2236_2250del15)
- L747_P753>S(2240_2257del18)
- L747_A750>P(2239_2248TTAAGAGAAG>C)
- E746_S752>V (2237_2255>T)
- L747_T751del (2240_2254del15)
- L747_S752del (2239_2256del18)
- E746_T751>A (2237_2251del15)
- L747_T751del (2239_2253del15)
- L747_T751>P (2239_2251>C)
- L747_E749del (2239_2247del9)
- E746_E749del (2235_2246del12)
- L747_P753>Q (2239_2258>CA)
- L747_T751>S (2240_2251del12)
- E746_S752>A (2237_2254del18)
- L747_A750>P (2238_2248>GC)
- E746_S752>D (2238_2255del18)
- E746_T751>I(2235_2252>AAT)
- L747_T751>Q(2238_2252>GCA)
- E746_T751del (2236_2253del18)

32 somatic Mutation at EGFR gene Short arm of Ch 7 By ARMS PCR

ALK and ROS rearrangements

- Indian patients : 3-7 % ALK and 1-2% ROS rearrangement
- Preferred methods : for ALK :IHC, for ROS :FISH
- FDA approved Ventana ALK IHC assay with D5F3 antibody clone : good concordance with FISH



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ScienceDirect

journal homepage: www.jascyto.org/

A brief review of the WHO reporting system for lung cytopathology

Sule Canberk, MD, MIAC[a,b,c], Andrew Field, MD, FIAC[d], Lukas Bubendorf, MD, PhD, MIAC[e], Ashish Chandra, MD, MIAC[f], Ian A. Cree, MD[g], Marianne Engels, MD, FIAC[h], Kenzo Hiroshima, MD[i], Deepali Jain, MD, FIAC[j], Ivana Kholová, MD, MIAC[k], Lester Layfield, MD[l], Ravi Mehrotra, MD[m], Claire Michael, MD[n], Robert Osamura, MD, FIAC[o], Martha B. Pitman, MD, MIAC[p], Sinchita Roy-Chowdhuri, MD, PhD, MIAC[q], Yukitoshi Satoh, MD, FIAC[r], Paul VanderLaan, MD, PhD, MIAC[s], Maureen Zakowski, MD[t], Fernando C. Schmitt, MD, PhD, FIAC[c,u,v,*]

Table 1 The WHO Reporting System for Lung Cytopathology on FNAB: implied ROM and clinical management options by diagnostic category.

Diagnostic category	Estimated ROM	Clinical management options
Insufficient/Inadequate/Nondiagnostic	43%-53%	Correlate with CLIN-IMG-MICRO, ideally discuss at an MDT meeting, and perform repeat FNAB with or without CNB
Benign	19%-64%	Correlate with CLIN-IMG-MICRO; if these confirm a benign diagnosis, then routine follow-up at 3-6 months; if no correlation, perform repeat FNAB with or without CNB
Atypical	46%-55%	Correlate with CLIN-IMG-MICRO, and ideally discuss at an MDT meeting; if all show a benign diagnosis, then routine follow-up at 3-6 months; if no correlation, perform repeat FNAB with ROSE with or without CNB
Suspicious for malignancy	75%-88%	Correlate with CLIN-IMG-MICRO, and ideally discuss at an MDT meeting; if all 4 support a diagnosis of malignancy, consider definitive treatment; if no correlation that lesion is malignant, perform repeat FNAB with ROSE with or without CNB
Malignant	87%-100%	Correlate with CLIN-IMG-MICRO, and ideally discuss at an MDT meeting; if all 4 support a diagnosis of malignancy, provide definitive treatment; if no correlation that lesion is malignant, consider repeat FNAB with ROSE with or without CNB

Abbreviations: CLIN-IMG-MICRO, clinical, imaging, and microbiologic findings; CNB, core needle biopsy, including endobronchial biopsy; FNAB, fine-needle aspiration biopsy, including endobronchial ultrasound–guided and transthoracic FNAB; MDT, multidisciplinary team; ROM, risk of malignancy; ROSE, rapid onsite evaluation.

International Academy of Cytology – International Agency for Research on Cancer – World Health Organization Joint Editorial Board. WHO Reporting System for Lung Cytopathology [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2022 [cited 2023 02 27]. (IAC-IARC-WHO cytopathology reporting systems series, 1st ed.; vol. 1). Available from: https://tumourclassification.iarc.who.int/chapters/48.

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Fernando C. Schmitt MD, PhD, FIAC [c u v]

among observers
Cytojournal, 15 (2018), p. 22
View article ↗ CrossRef ↗
Google Scholar ↗

15 A.K. Boler, N. Banu, K. Bose, S. Roy, A. Bandyopadhyay
Reproducibility of "the Papanicolaou Society of Cytopathology system for reporting respiratory cytology" - A retrospective analysis of 101 cases of CT-guided FNAC
Diagn Cytopathol, 48 (2020), pp. 701-705
View article ↗ CrossRef ↗
View in Scopus ↗ Google Scholar ↗

Cited by (0)

Invasive Breast Carcinoma

- IBC refers to large and heterogeneous group of malignant epithelial neoplasms of the glandular elements of the breast
- Most commonly diagnosed cancer in females

(accounting for 28% of all female cancer) and leading cause of cancer related death

Histopathologic Type - WHO Classification 5th Edition (2019)

In situ carcinomas

- Ductal carcinoma in situ (DCIS) (low nuclear grade, intermediate nuclear grade, and high nuclear grade)
- In situ papillary neoplasms (papillary DCIS, encapsulated papillary carcinoma, solid papillary carcinoma in situ)

Invasive Carcinomas

- Invasive breast carcinoma of no special type (ductal and other special patterns)
- Microinvasive carcinoma
- Invasive lobular carcinoma
- Tubular carcinoma
- Cribriform carcinoma
- Mucinous carcinoma
- Mucinous cystadenocarcinoma
- Invasive micropapillary carcinoma
- Invasive papillary carcinoma
- Invasive solid papillary carcinoma
- Carcinoma with apocrine differentiation
- Metaplastic carcinoma (spindle cell, squamous, with heterologous differentiation, low-grade adenosquamous carcinoma, low-grade fibromatosis-like and mixed metaplastic)
- Neuroendocrine tumor (NET)
- Neuroendocrine carcinoma (NEC)
- Salivary gland-type (acinic cell, adenoid cystic, secretory, mucoepidermoid, polymorphous adenocarcinoma)
- Tall cell carcinoma with reversed polarity

Favorable Histologic Types

- Tubular carcinoma
- Cribriform carcinoma
- Mucinous carcinoma
- Adenoid cystic
- Low-grade adenosquamous carcinoma metaplastic carcinoma
- Low-grade fibromatosis-like metaplastic carcinoma

*Tumor showing special histological pattern
In > 90% of tumor : special tumor type (eg. Lobular, mucinous, tubular etc)
*<10% special feature : IBC – NST : most common

Histopathology

Histopathology 2024, **85**, 418–436. DOI: 10.1111/his.15191

Dataset for reporting of the invasive carcinoma of the breast: recommendations from the International Collaboration on Cancer Reporting (ICCR)

Ian Ellis,[1] Fleur Webster,[2] Kimberly H Allison,[3] Chau Dang,[4] Helenice Gobbi,[5] Janina Kulka,[6] Sunil R Lakhani,[7] Takuya Moriya,[8] Cecily M Quinn,[9] Anna Sapino,[10,11] Stuart Schnitt,[12] D Mark Sibbering,[13] Elzbieta Slodkowska,[14] Wentao Yang[15] & Puay H Tan[16]

[1]*Department of Histopathology, Nottingham City Hospital, London, UK,* [2]*International Collaboration on Cancer Reporting, Surry Hills, NSW, Australia,* [3]*Department of Pathology, Stanford University School of Medicine, Stanford, CA,* [4]*Memorial Sloan Kettering Cancer Center, New York, USA,* [5]*Institute of Health Sciences, Federal University Triangulo Mineiro, Uberaba, Brazil,* [6]*Department of Pathology, Forensic and Insurance Medicine, Semmelweis University, Budapest, Hungary,* [7]*Centre for Clinical Research and Pathology Queensland, University of Queensland, Brisbane, Australia,* [8]*Department of Pathology, Kawasaki Medical School, Okayama, Japan,* [9]*Department of Histopathology, St. Vincent's University Hospital, Dublin 4, Ireland,* [10]*Department of Medical Sciences, University of Turin, Turin,* [11]*Candiolo Cancer Institute, FPO – IRCCS, Candiolo, Italy,* [12]*Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA,* [13]*Department of Breast Surgery, Royal Derby Hospital, Derby, UK,* [14]*Department of Anatomic Pathology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada,* [15]*Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China and* [16]*Luma Medical Centre, Royal Square, Singapore, Singapore*

Date of submission 16 November 2023
Accepted for publication 22 March 2024

Synoptic reporting of breast Cancer

- Procedure
- Laterality
- Histologic Type
- Histologic grade
- Tumor size
- Tumor focality
- DCIS
- Lympho –vascular invasion

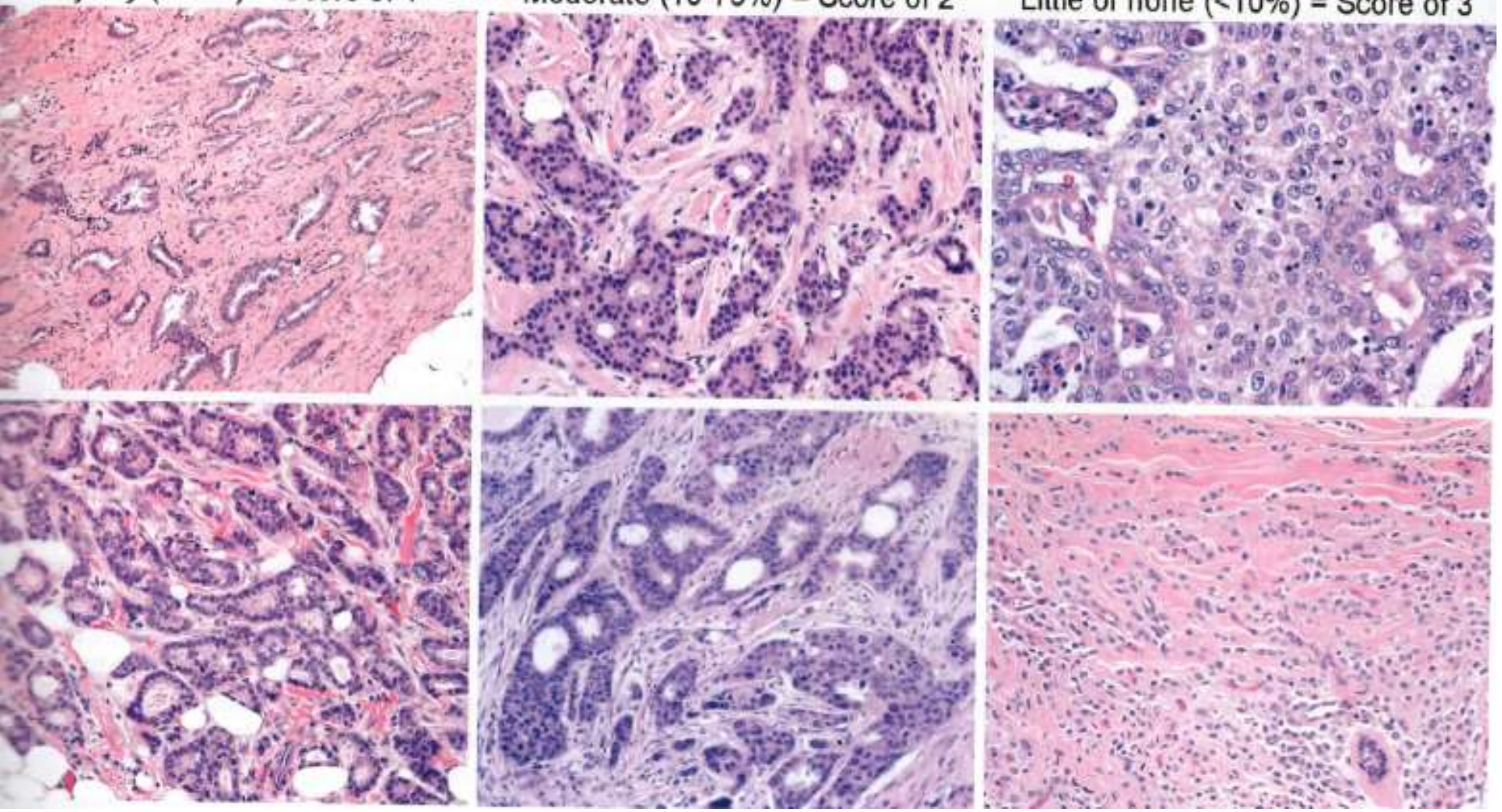
- Treatment effect
- Margins
- Regional Lymph node
- Distant Metastasis
- pTNM (AJCC 8th edition)
- Breast biomarkers
- ER, PR, HER2, Ki 67%

Nottingham Grading Examples: Tubule Formation

Majority (>75%) = Score of 1

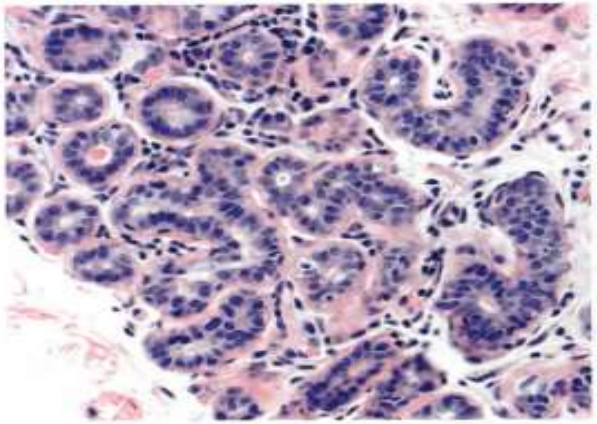
Moderate (10-75%) = Score of 2

Little or none (<10%) = Score of 3

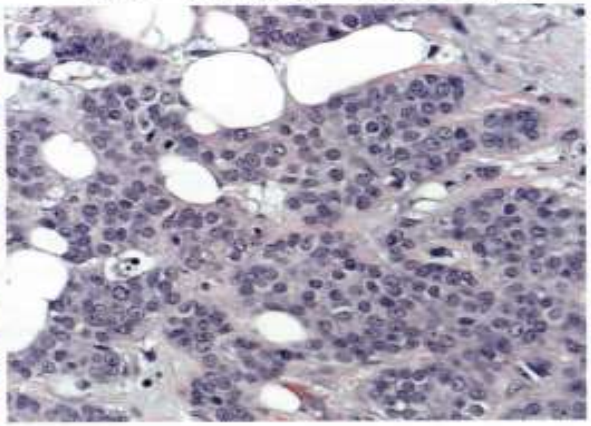


Nottingham Grading Examples: Nuclear Pleomorphism

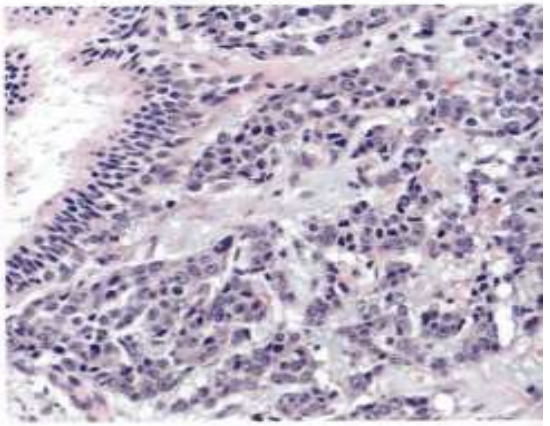
Normal



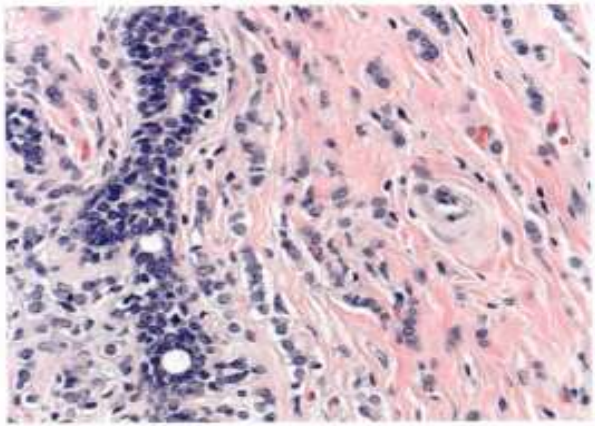
Moderate increase in size + variability = Score of 2



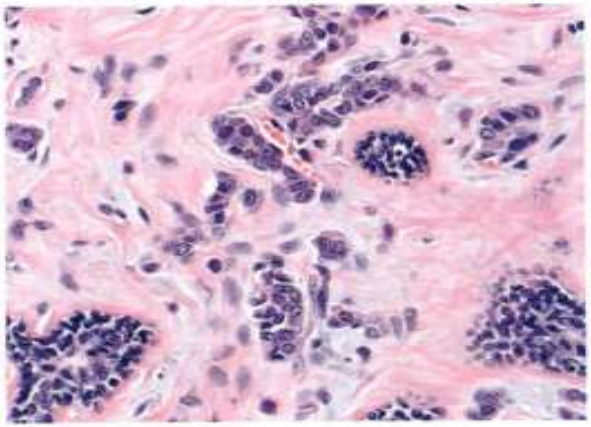
Marked variation = Score of 3



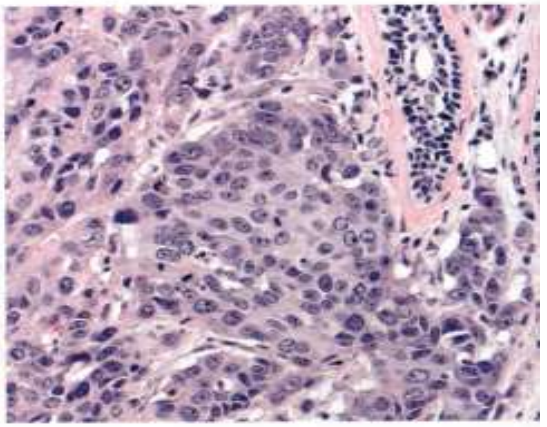
Small, regular uniform = Score of 1



Moderate increase in size + variability = Score of 2



Marked variation = Score of 3

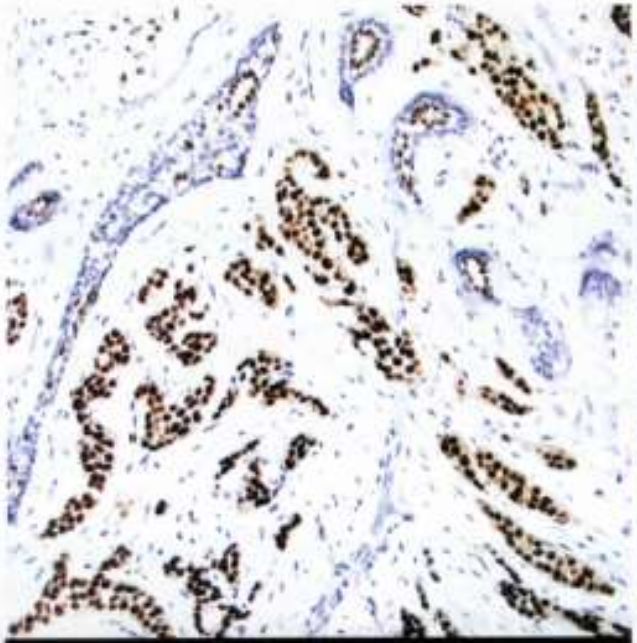


Total score	Grade
3-5	I
6-7	II
8-9	III

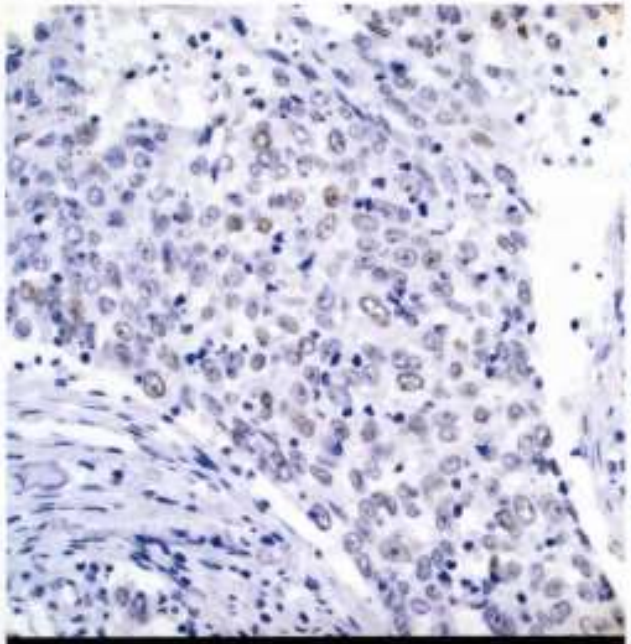
Immunohistochemistry

Hormone receptor staining interpretation (ER and PR)

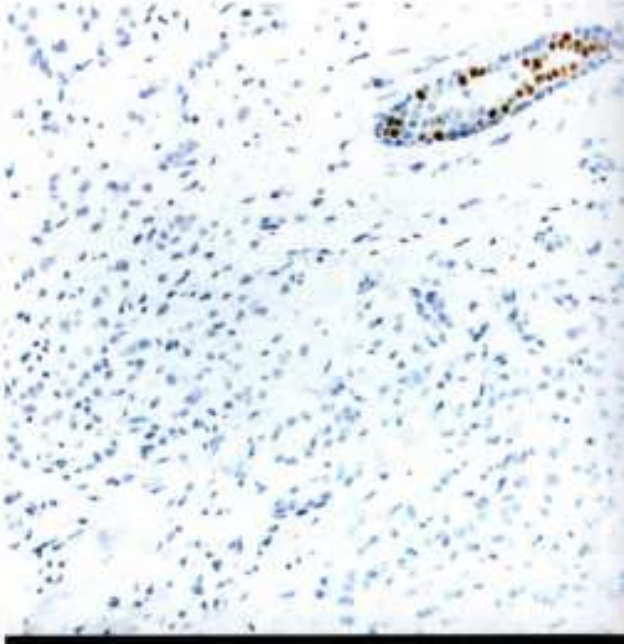
Evaluate overall percentage of cancer in sample with nuclear staining and intensity of stain



Example of a cancer with uniform strong staining



Example of a cancer with weak focal staining



Example of a cancer with no staining and a positive internal control

If ≥ 1% of cells stain

Interpretation: **Positive***

(include % and intensity in report)

*Report as low positive if 1–10% of cells stain

If < 1% or 0% of cells stain

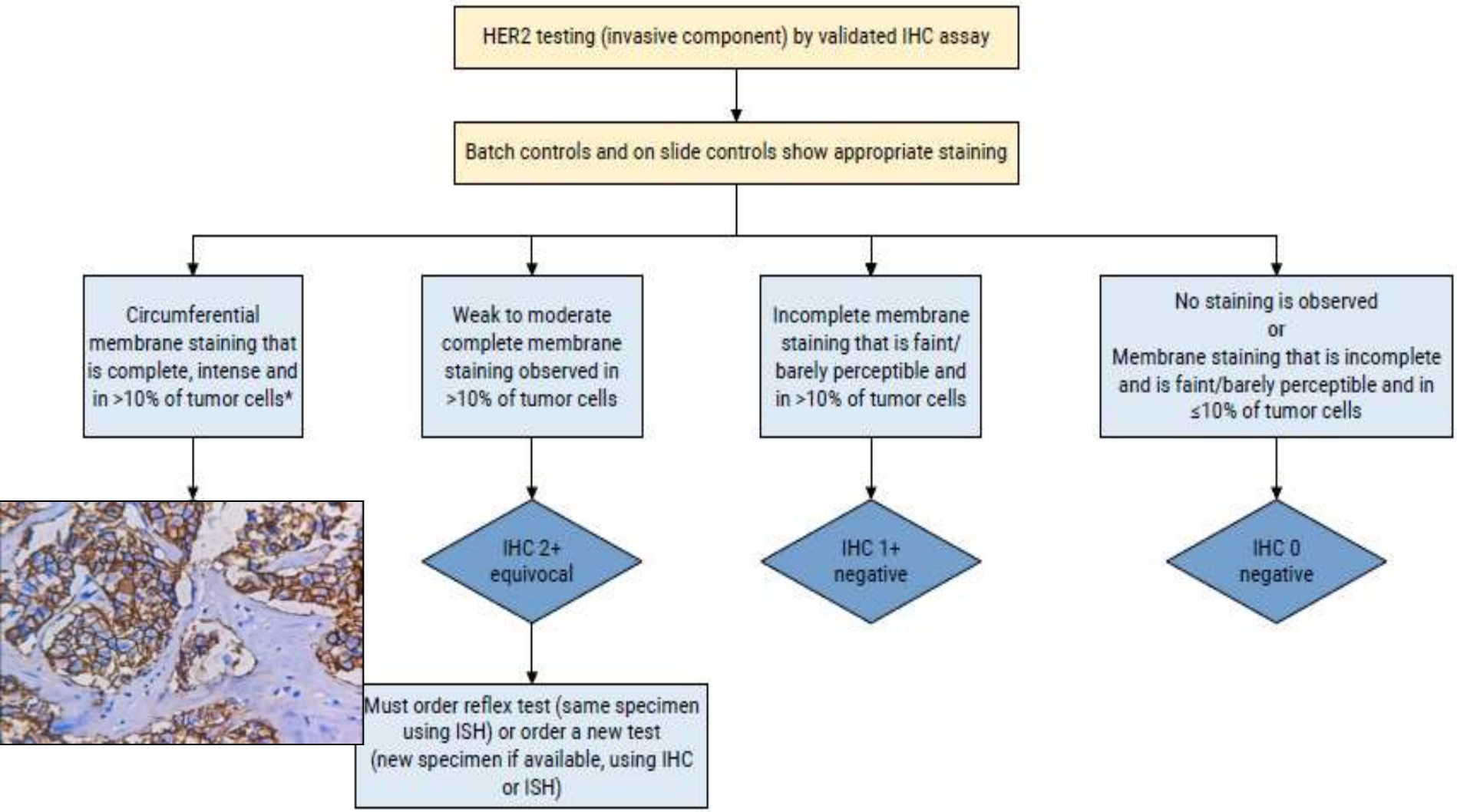
Interpretation: **Negative**

(note whether result was < 1% or 0%

ASCO Guidelines

COLLEGE of AMERICAN PATHOLOGISTS

Figure 1. Algorithm for evaluation of human epidermal growth factor receptor 2 (HER2) protein expression by immunohistochemistry (IHC) assay of the invasive component of a breast cancer specimen.



Histopathology

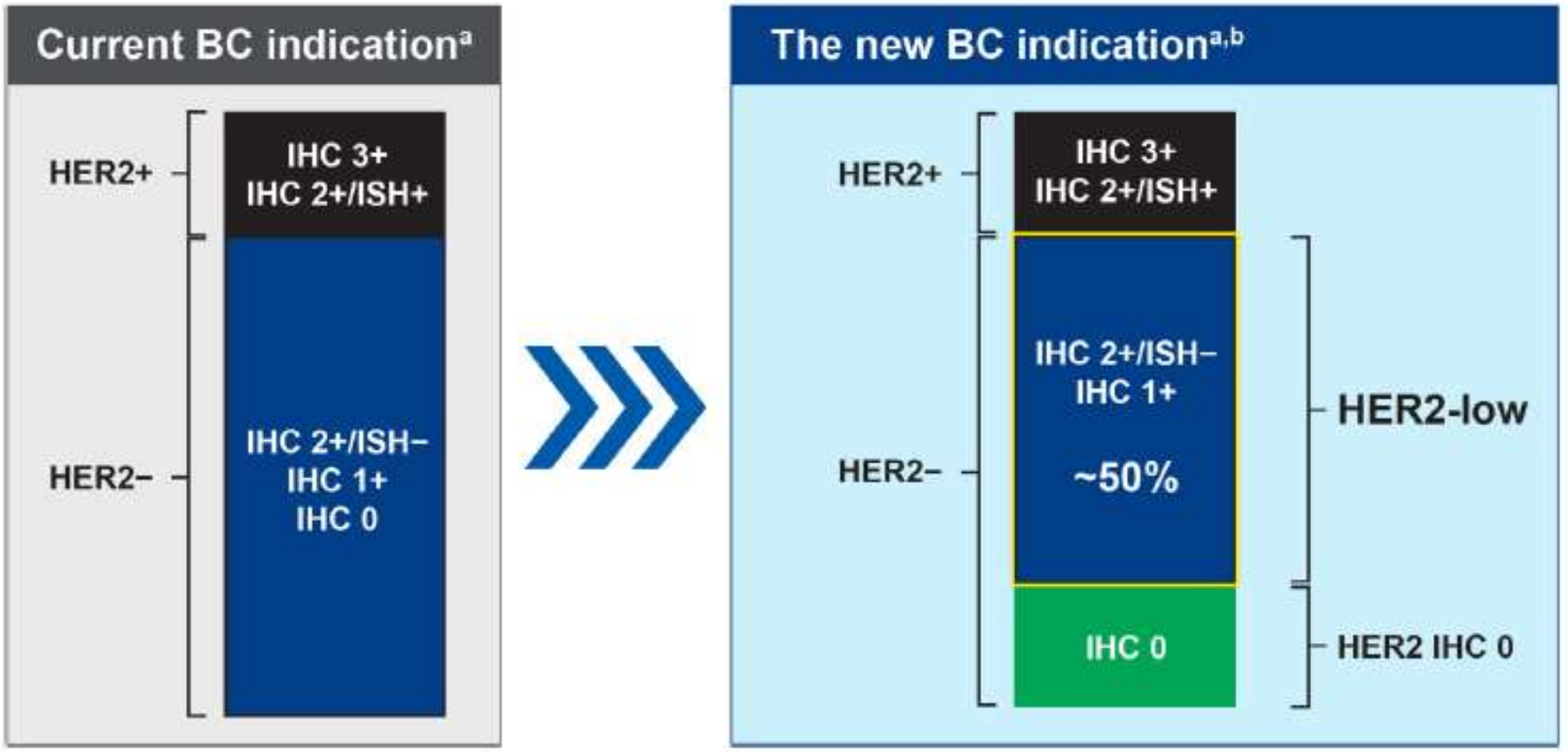
Histopathology 2024, **85**, 489–502. DOI: 10.1111/his.15275

Best practices for achieving consensus in HER2-low expression in breast cancer: current perspectives from practising pathologists

Gary Tozbikian,[1] Marilyn M. Bui,[2] David G Hicks,[3] Shabnam Jaffer,[4] Thaer Khoury,[5] Hannah Y Wen,[6] Savitri Krishnamurthy[7] & Shi Wei[8]

[1]Department of Pathology, The Ohio State University, Columbus, OH, [2]Department of Pathology, Moffitt Cancer Center and Research Institute, Tampa, FL, [3]Department of Pathology, University of Rochester Medical Center, Rochester, [4]Department of Pathology, Lenox Hill Hospital, New York, [5]Department of Pathology, Roswell Park Cancer Institute, Buffalo, [6]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, [7]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX and [8]Department of Pathology, The University of Alabama at Birmingham, Birmingham, AL, USA

The US Food and Drug Administration (FDA) approved trastuzumab Deruxtecan (T-DXd, also known as fam-trastuzumab deruxtecan-nxki in the US) for the treatment of HER2-low mBC.


Current BC indication[a]
HER2+
IHC 3+
IHC 2+/ISH+
HER2−
IHC 2+/ISH−
IHC 1+
IHC 0
The new BC indication[a,b]
HER2+
IHC 3+
IHC 2+/ISH+
HER2−
IHC 2+/ISH−
IHC 1+
~50%
IHC 0
HER2-low
HER2 IHC 0

Traditional molecular subtypes of invasive breast cancer: Diagnostic criteria

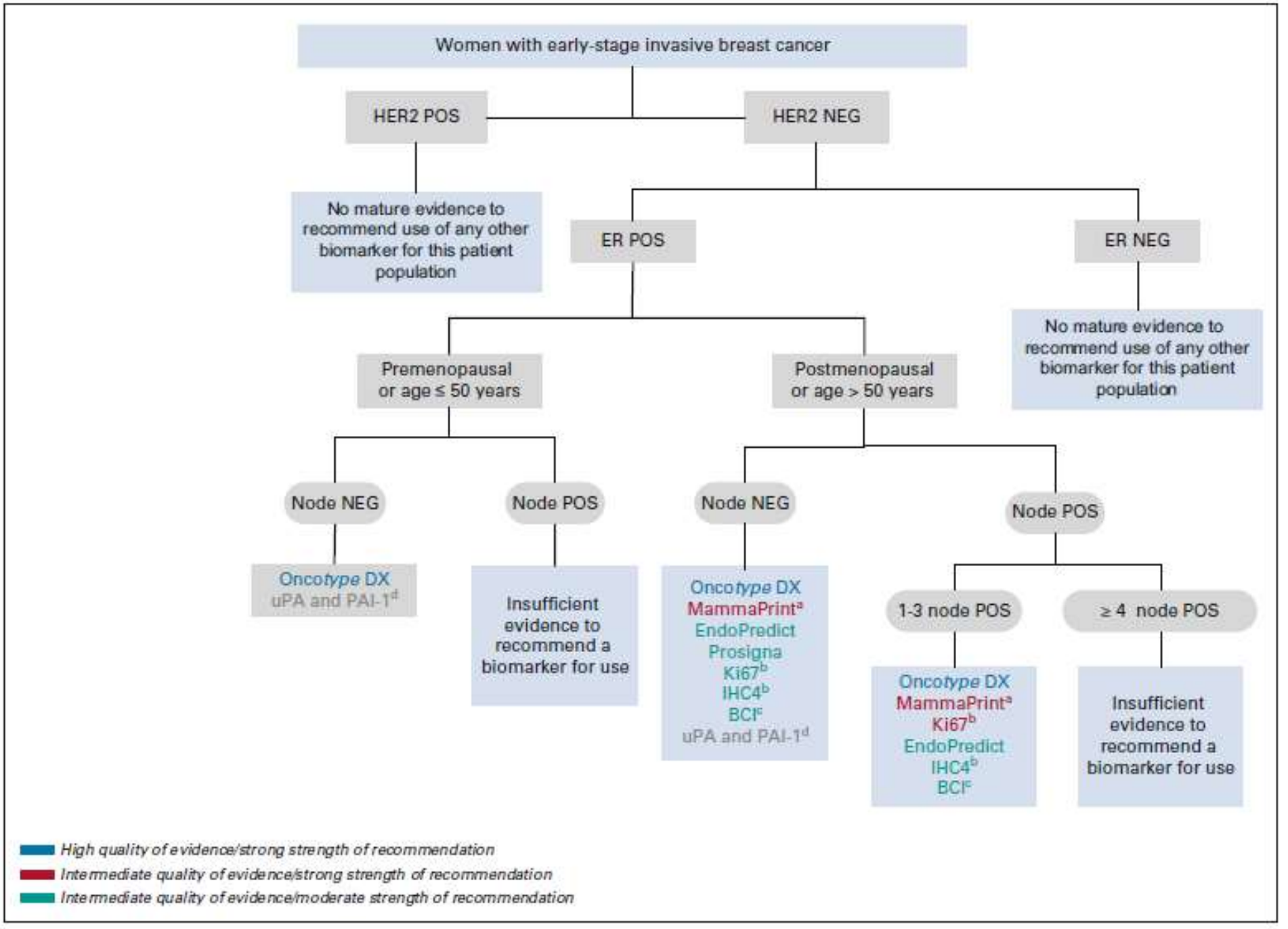
Subtypes	ER	PR	HER2	Ki-67
Luminal A	+	+/–	–	<14%
Luminal B	+	+/–	+/–	≥14%
HER2+	–	–	+	≥14%
TNBC	–	–	–	≥14%

ASCO special articles

Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update

Fabrice Andre, MD[1]; Nofisat Ismaila, MD, MSc[2]; Kimberly H. Allison, PhD[3]; William E. Barlow, PhD[4]; Deborah E. Collyar, BSc[5]; Senthil Damodaran, MD, PhD[6]; N. Lynn Henry, MD, PhD[7]; Komal Jhaveri, MD[8,9]; Kevin Kalinsky, MD, MS[10]; Nicole M. Kuderer, MD[11]; Anya Litvak, MD[12]; Erica L. Mayer, MD, MPH[13]; Lajos Pusztai, MD[14]; Rachel Raab, MD[15]; Antonio C. Wolff, MD[16]; and Vered Stearns, MD[16]

ascopubs.org /journal/ jco on April 19, 2022


Women with early-stage invasive breast cancer
HER2 POS
HER2 NEG
No mature evidence to recommend use of any other biomarker for this patient population
ER POS
ER NEG
No mature evidence to recommend use of any other biomarker for this patient population
Premenopausal or age ≤ 50 years
Postmenopausal or age > 50 years
Node NEG
Node POS
Node NEG
Node POS
Oncotype DX
uPA and PAI-1[d]
Insufficient evidence to recommend a biomarker for use
Oncotype DX
MammaPrint[a]
EndoPredict
Prosigna
Ki67[b]
IHC4[b]
BCI[c]
uPA and PAI-1[d]
1-3 node POS
≥ 4 node POS
Oncotype DX
MammaPrint[a]
Ki67[b]
EndoPredict
IHC4[b]
BCI[c]
Insufficient evidence to recommend a biomarker for use
High quality of evidence/strong strength of recommendation
Intermediate quality of evidence/strong strength of recommendation
Intermediate quality of evidence/moderate strength of recommendation

Emerging biomarkers

- Tumor infiltrating lymphocytes
- PD L1 testing
- uPA and PAI -1

Archives Of Breast Cancer

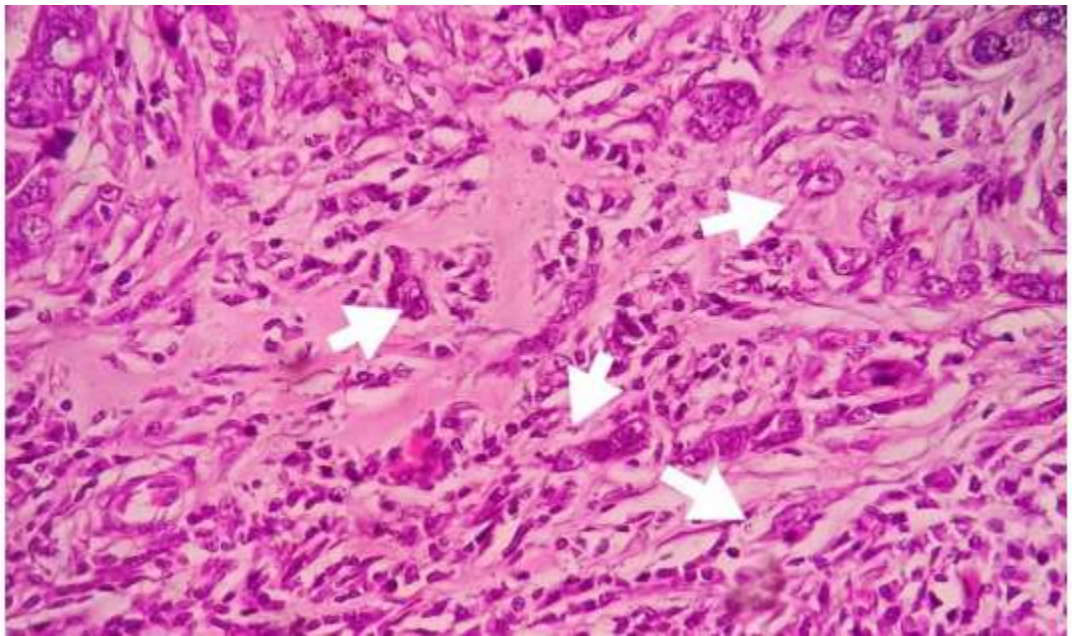
DOI: 10.32768/abc.2023103241-247

Tumor Infiltrating Lymphocytes (TILs) and Tumor Budding in Invasive Breast Carcinoma: Correlation with Known Prognostic Parameters

Arghya Bandyopadhyay*[a], M Pallavi Krishna[b]

[a]Department of Pathology, NRS Medical College, Kolkata, West Bengal University of Health Sciences, West Bengal, India

[b]Department of Pathology, Burdwan Medical College, Burdwan, West Bengal University of Health Sciences, West Bengal, India



<50% TILs associated with High grade TB and high lymph Node metastasis and poor prognosis

Bandyopadhyay et al. Arch Breast Cancer 2023; 10 (3)

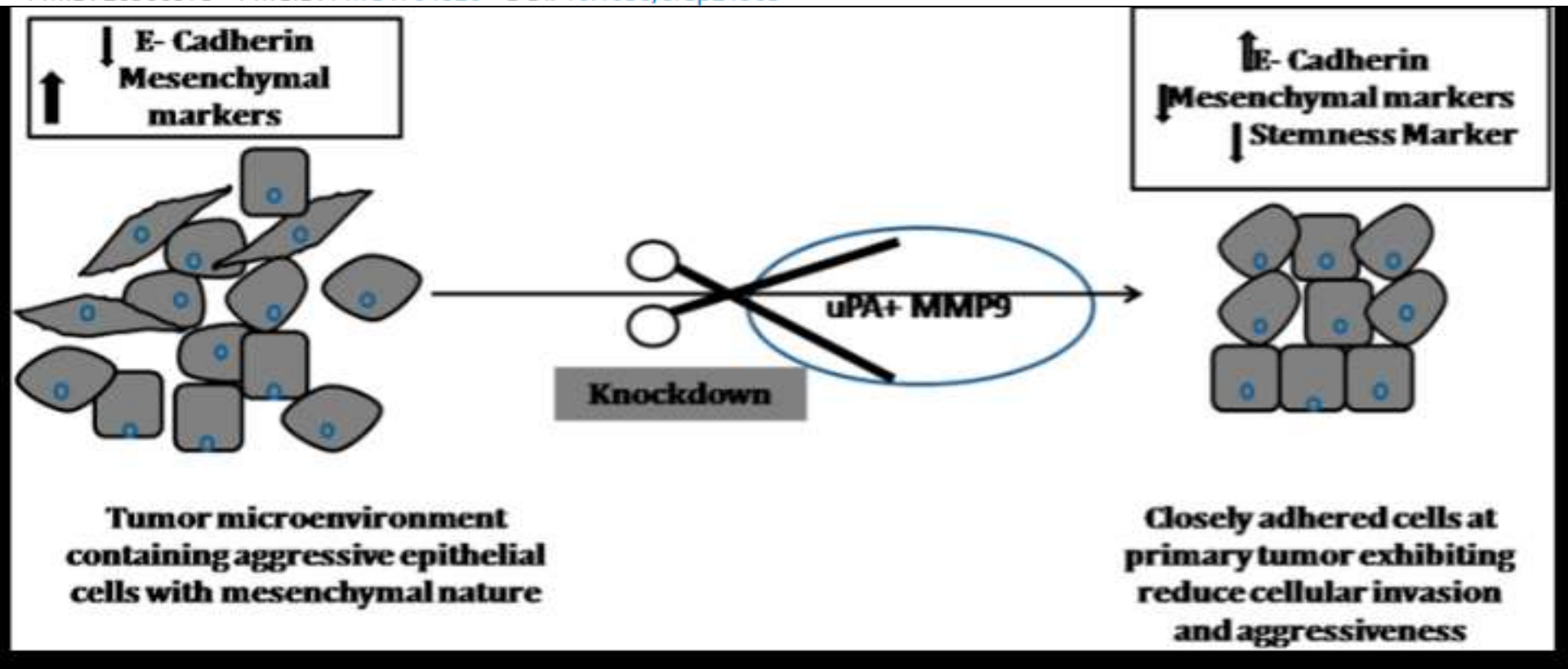
Sci Rep. 2016 Feb 24:6:21903. doi: 10.1038/srep21903.

Simultaneous knockdown of uPA and MMP9 can reduce breast cancer progression by increasing cell–cell adhesion and modulating EMT genes

Anuradha Moirangthem [1], Banashree Bondhopadhyay [1], Mala Mukherjee [2], Arghya Bandyopadhyay [2], Narendranath Mukherjee [3], Karabi Konar [2], Shubham Bhattacharya [2], Anupam Basu [1]

Affiliations + expand

PMID: 26906973 PMCID: PMC4764826 DOI: 10.1038/srep21903



Carcinoma of colon and rectum

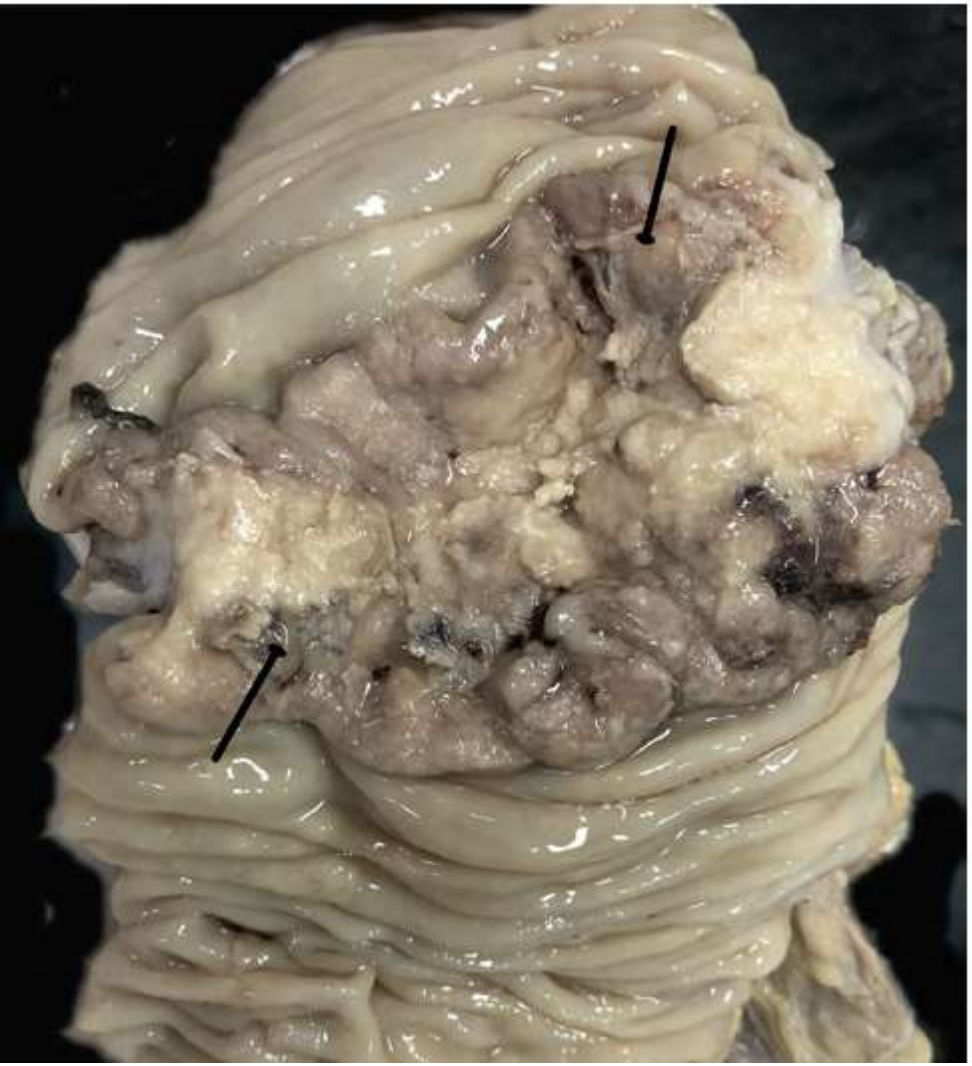
- CRC is a malignant epithelial tumor of colon or rectum showing glandular or mucinous differentiation.

- 4^{th} most common cancer worldwide

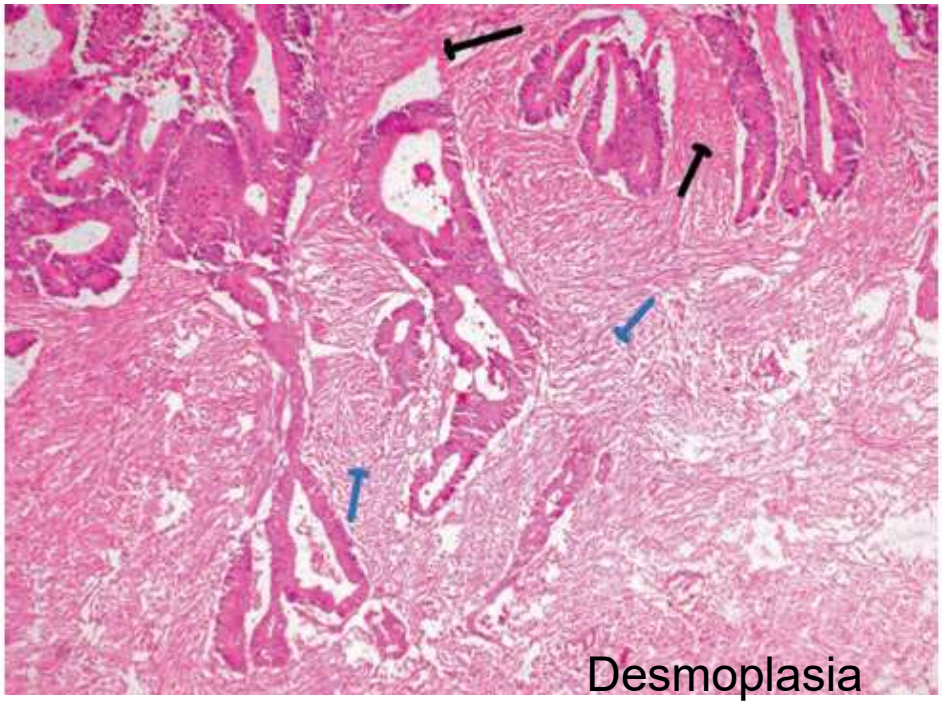
- It ranks ninth among all cancers in Indian men and women

WHO classification (5th edition)

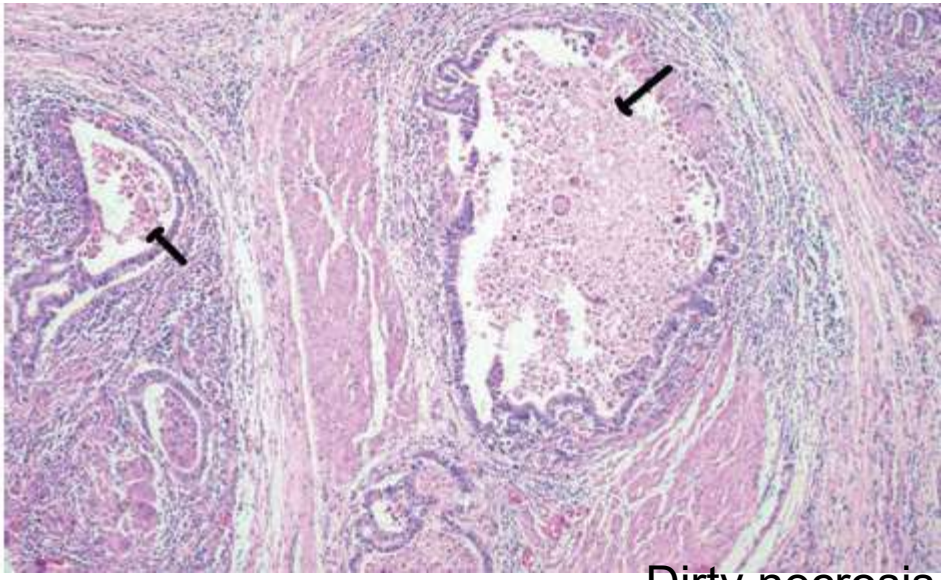
- Adenocarcinoma NOS
- Serrated adenocarcinoma
- Micropapillary adenocarcinoma
- Adenoma like adenocarcinoma
- Mucinous adenocarcinoma
- Signet ring cell carcinoma
- Medullary carcinoma NOS
- Poorly Cohesive Carcinoma
- Adenosquamous carcinoma
- Undifferentiated Carcinoma



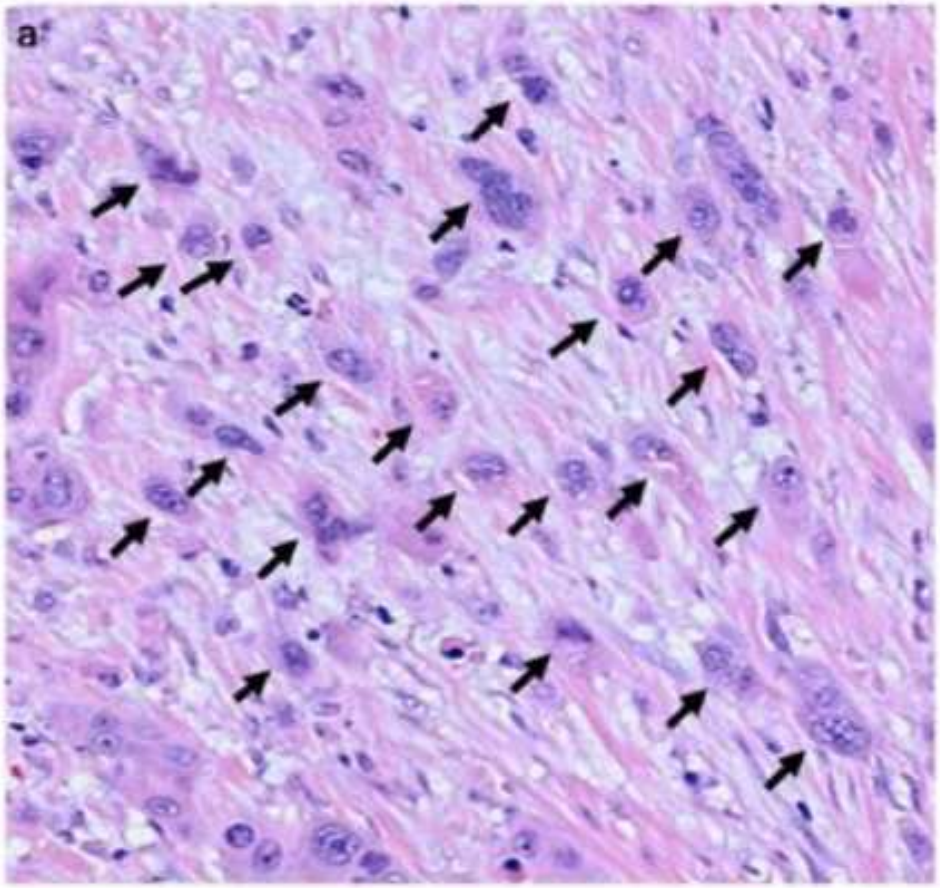
Circumferential exophytic tumor
Appearing like Napkin ring

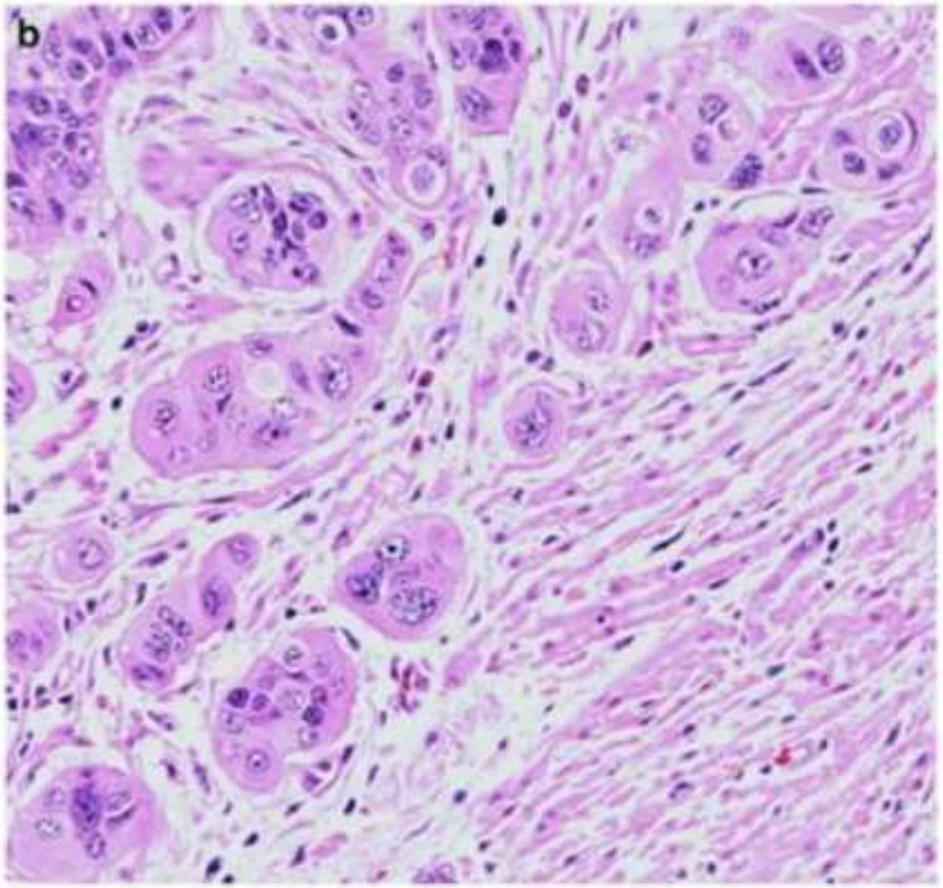


Desmoplasia



Dirty necrosis

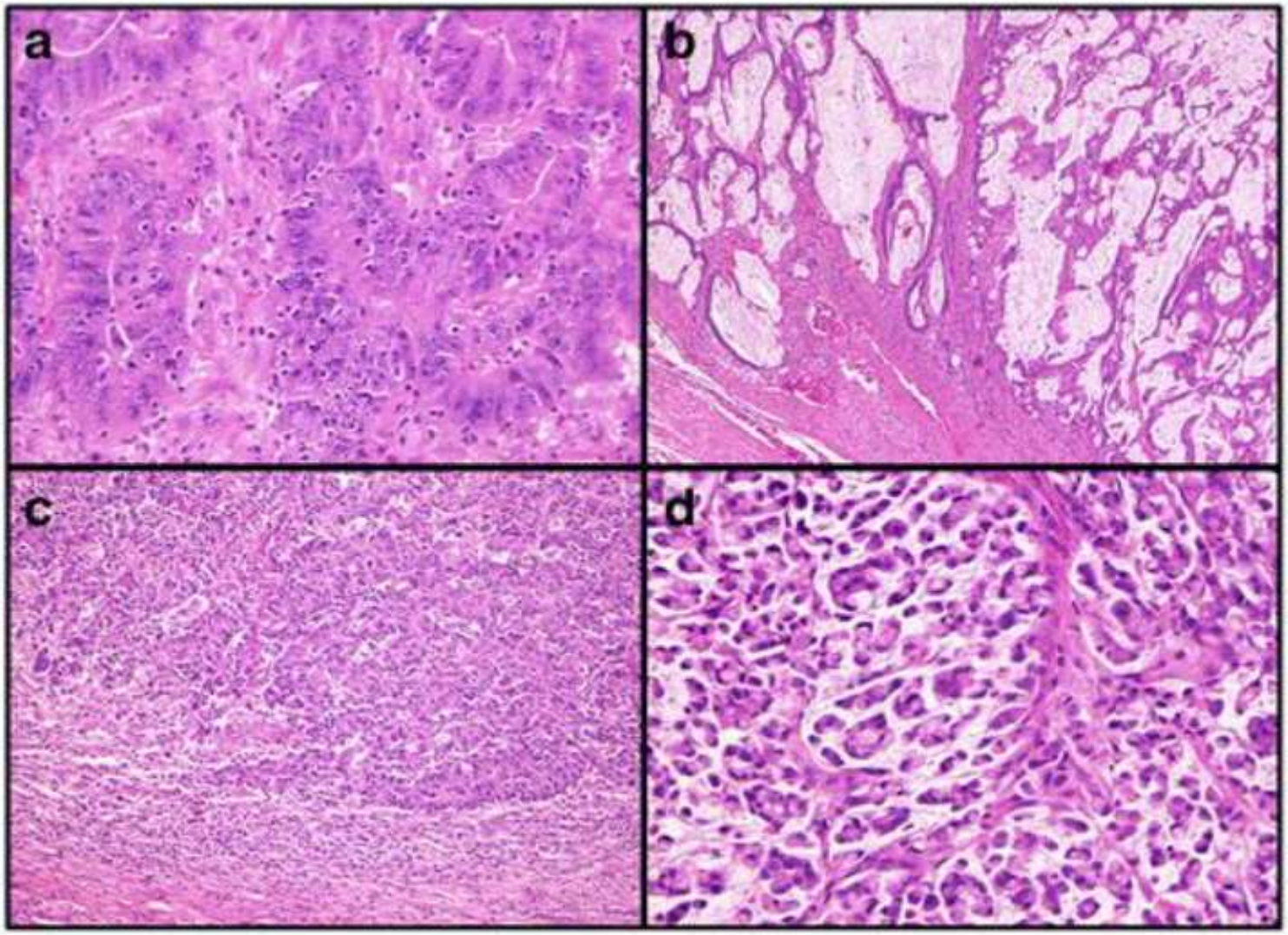




Tumor budding defined as single tumor cells or tumor cell clusters at up to 4 cells without gland formation at invasive edge of tumor

Poorly differentiated clusters defined as that are defined as 5 tumor cells or more without gland formation at invasive edge of tumor

Independent poor prognostic factor in colorectal cancer



MSI histology → a Moderate to Poorly differentiated adenocarcinoma with prominent tumor-infiltrating lymphocytes b. Mucinous adenocarcinoma c. Medullary carcinoma with a pushing border and prominent tumor-infiltrating lymphocytes d. Signet ring cell carcinoma

Tumor stage and high risk pathology features determine adjuvant therapy

- Poorly differentiated/ undifferentiated histology
- Lymphovascular invasion
- Bowel obstruction
- Perinural invasion
- Localised perforation
- Close/indeterminate positive margin
- High-tier tumor budding.

Ancillary workup

- Immunohistochemistry
- CK 20 +, CK 7 -, CDX2 +, SATB2 +
- Up to 20% of CRC may show CK 7 +/CK20-

Or CK 7-/CK 20 – pattern specially MSI H tumors

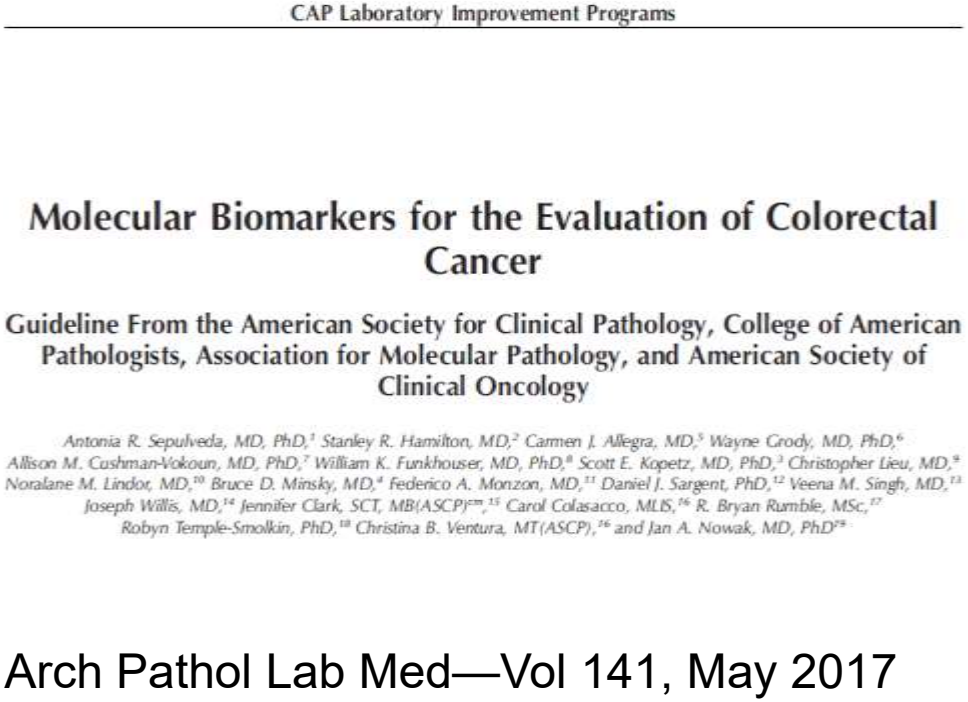
- Medullary carcinomas : may be negative for

CK 20 and CDX2.

- MMR IHC for MLH1, PMS2, MSH2, MSH 6
- HER2 testing
- PDL1 IHC

Recommended molecular test

- RAS mutation : Mutation of codons 12,13 and 61 of KRAS and NRAS : lack of response to monoclonal antibodies against EGFR (eg. cetuximab)
- MSI PCR/ MMR IHC
- BRAF V600E hot spot mutation



CAP Laboratory Improvement Programs

Molecular Biomarkers for the Evaluation of Colorectal Cancer

Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology

Antonia R. Sepulveda, MD, PhD,[1] Stanley R. Hamilton, MD,[2] Carmen J. Allegra, MD,[3] Wayne Grody, MD, PhD,[4] Allison M. Cushman-Vokoun, MD, PhD,[7] William K. Funkhouser, MD, PhD,[8] Scott E. Kopetz, MD, PhD,[3] Christopher Lieu, MD,[9] Noralane M. Lindor, MD,[10] Bruce D. Minsky, MD,[4] Federico A. Monzon, MD,[11] Daniel J. Sargent, PhD,[12] Veena M. Singh, MD,[13] Joseph Willis, MD,[14] Jennifer Clark, SCT, MB(ASCP)[CM],[15] Carol Colasacco, MLIS,[16] R. Bryan Rumble, MSc,[17] Robyn Temple-Smolkin, PhD,[18] Christina B. Ventura, MT(ASCP),[16] and Jan A. Nowak, MD, PhD[19]

Arch Pathol Lab Med—Vol 141, May 2017

What is microsatellite instability?

- Microsatellites are short, repetitive sequences of DNA present throughout the genome.
- Often difficult to replicate accurately → replication error like addition of extra or removal of nucleotide repeats is common (called 'slips')
- **Mismatch repair system (MMR)** identifies these 'slips' and prevent expansion or contraction of length of microsatellites i.e. **MMR maintains microsatellite stability (MSS)**
- **Defect in MMR system → replicative errors accumulate in microsatellites → microsatellite instability (MSI)**
- The length of the microsatellite should be same in both alleles in a normal somatic cell.
- In MSI, the length of the microsatellites in the two alleles differ.

#15% sporadic CRC and 95% of HNPCC Syn ;overall 5% of CRC

How to test for microsatellite instability in CRC?

- Two ways:-
- **MSI testing by real time PCR**
- **MMR protein IHC** → loss of expression is significant → MMR deficient (dMMR) tumor

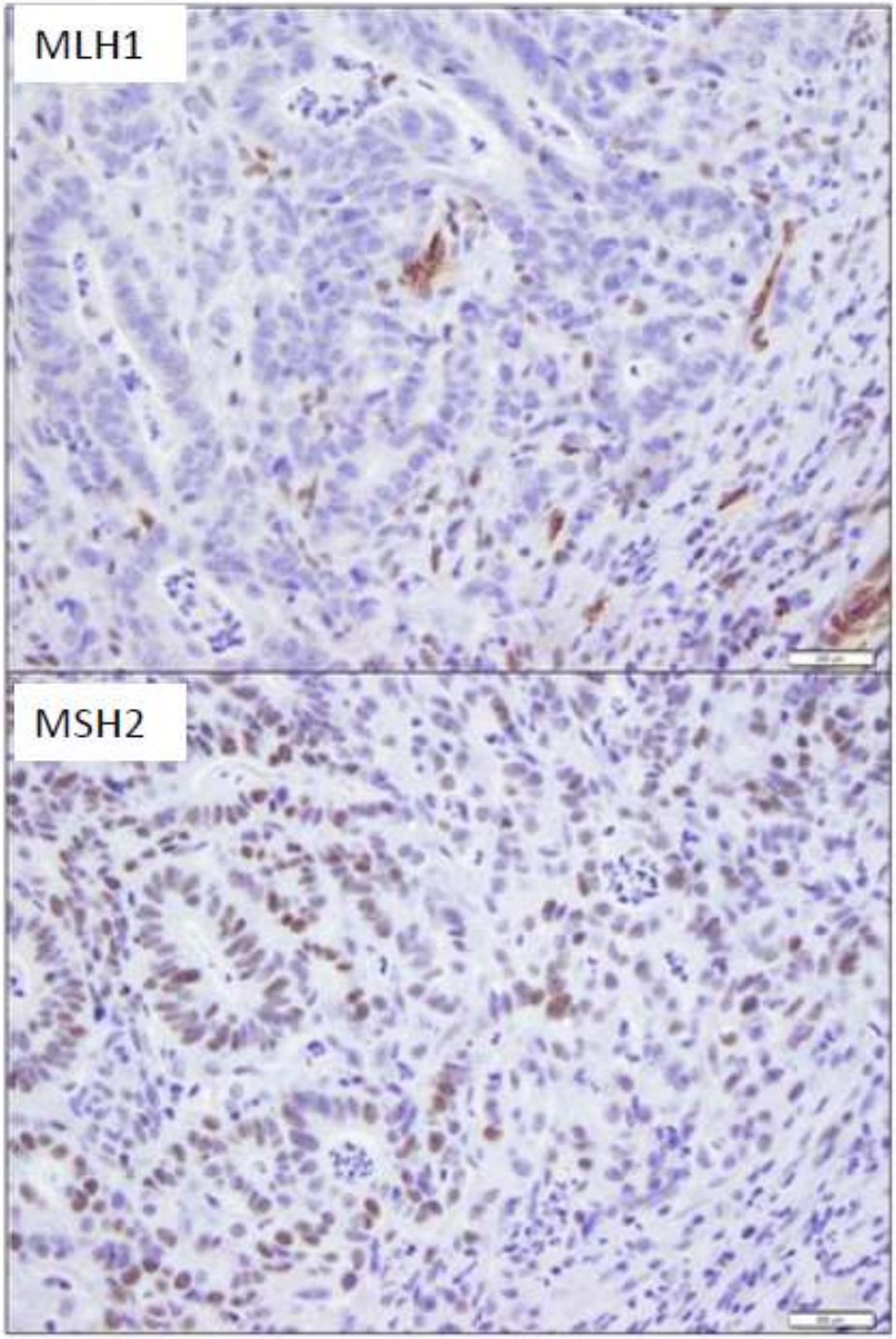
❖ MMR IHC and MSI are nearly 100% concordant and can be used interchangeably.

MMR IHC: An interpretation of loss of expression in tumor cells should be made only if a positive reaction is seen in internal control cells, such as the nuclei of stromal, inflammatory, or non-neoplastic epithelial cells.

Microsatellite instability in CRC

- **Microsatellite stable (MSS):** Instability in no microsatellites
- **Microsatellite instability-low (MSI-L):** Instability detected in only one microsatellite
- **Microsatellite instability-high (MSI-H):** Instability detected in 2 or more microsatellites

- **MSI-H tumors have indolent course and better prognosis than MSS tumors.**
- **The significance of MSI-L is uncertain.**



4 IHC markers : MLH1, PMS2, MSH2,MSH6

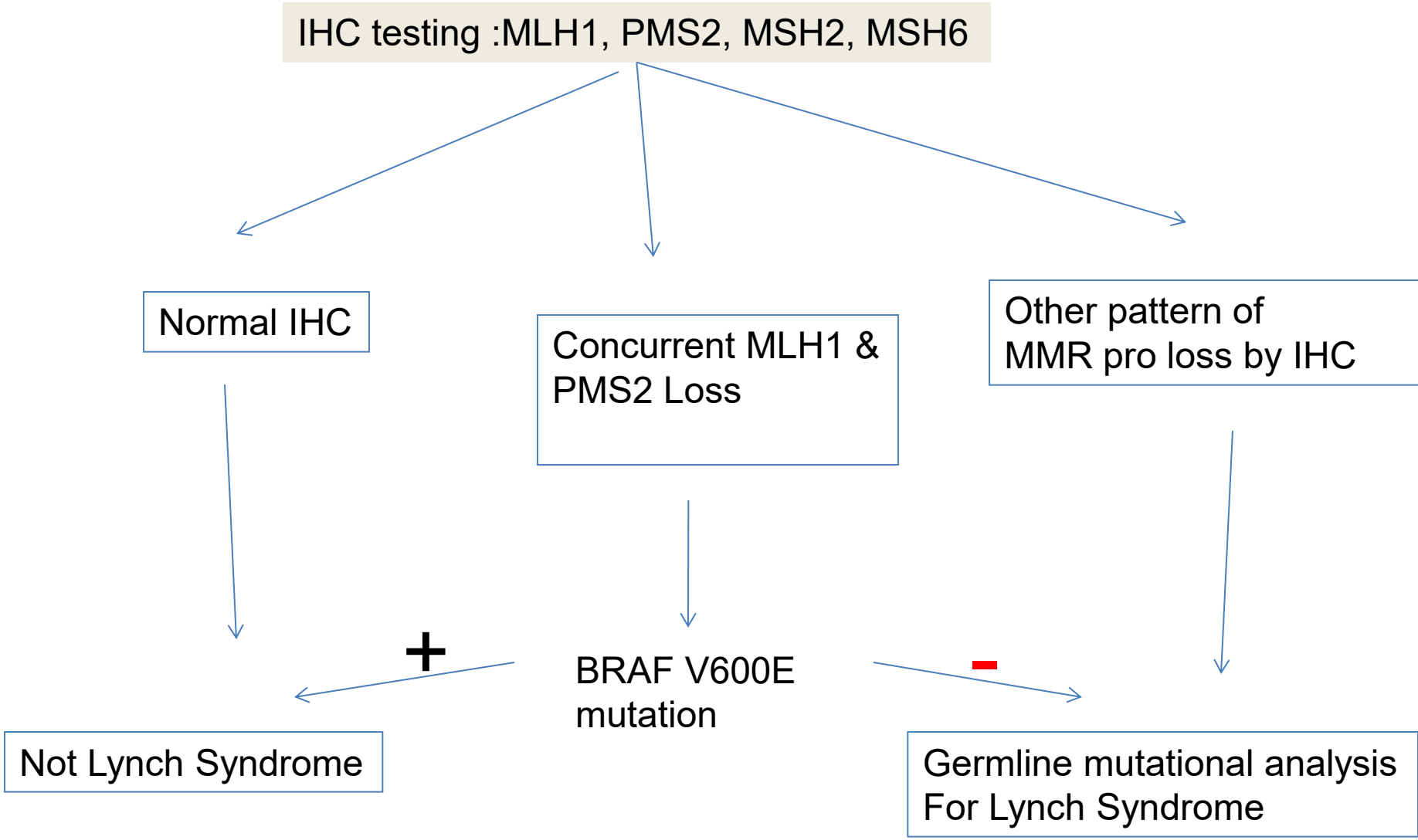
Loss of nuclear expression for MLH1 in the colorectal adenocarcinoma cells.

dMMR : MMR deficient =MSI H

Intact nuclear expression of MSH2in tumor cells

pMMR: MMR proficient=MSS

Algorithm for Lynch syndrome screening in tissue



IHC interpretation of MMR proteins (MLH1, MSH 2, MSH 6, PMS2)

- **No loss of nuclear expression of MMR proteins** → low probability of MSI-H tumors

- **Loss of nuclear expression of MLH1 and PMS2** → test for ***MLH1*** **promoter hypermethylation** and/or ***BRAF*** **V600E mutation**

❖ *BRAF* V600E mutation and/or *MLH1* gene promoter hypermethylation present → suggests tumor is sporadic → germline evaluation is not required

❖ *BRAF* V600E mutation and *MLH1* promotor hypermethylation absent → suggests possibility of Lynch syndrome → gene testing for germline mutation

- **Loss of nuclear expression of MSH2 and MSH6 or MSH 6 only or PMS2 only** → high probability of Lynch syndrome → gene testing for germline mutation

Therapeutic and prognostic implications of molecular testing in CRC

- Microsatellite stable (MSS) CRC with conventional/chromosomal instability (CIN) pathway of carcinogenesis: responds to 5-Fluorouracil based chemotherapy
- Microsatellite instability -high (MSI-H) CRC → do not benefit from 5-fluorouracil based treatment → responds to anti PD-1/ PD-L1 immunotherapy
- EGFR inhibitors (cetuximab) is also used as 1st or 2nd line treatment especially in stage IV inoperable CRC, but only if there is no mutation in downstream genes like RAS & BRAF
- KRAS mutation → resistance to anti-EGFR therapy
- BRAF mutation → poor survival and resistance to anti-EGFR therapy

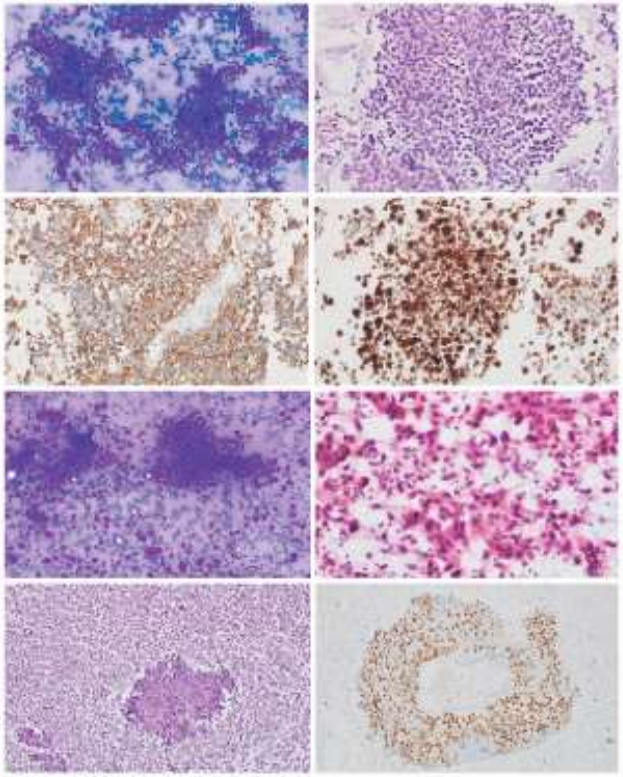
Overall survival in CIN vs. MSI pathway
MSI-H (best) > MSI-L > MSS/CIN CRC (worst)

Summary :

- Molecular pathology developed as a branch
- You should have clear idea about:
- Which test to order?
- Indication/ utility/ Interpretation/ treatment guidelines
- Turn around time and reliability of the test and Lab
- Cost of the test
- Whether your patient can afford ?

PATHOLOGY

Recent Advances in Pathology-1



Editor

Pranab Dey

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THANK YOU