

The International Academy of Pathology
Hong Kong Division

HKIAP Scientific Congress 2026

Intramucosal carcinoma: why now?

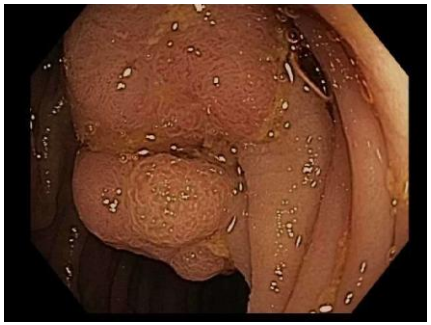
Gregory Y. Lauwers, MD

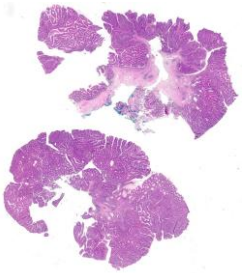
H. Lee Moffitt Cancer Center

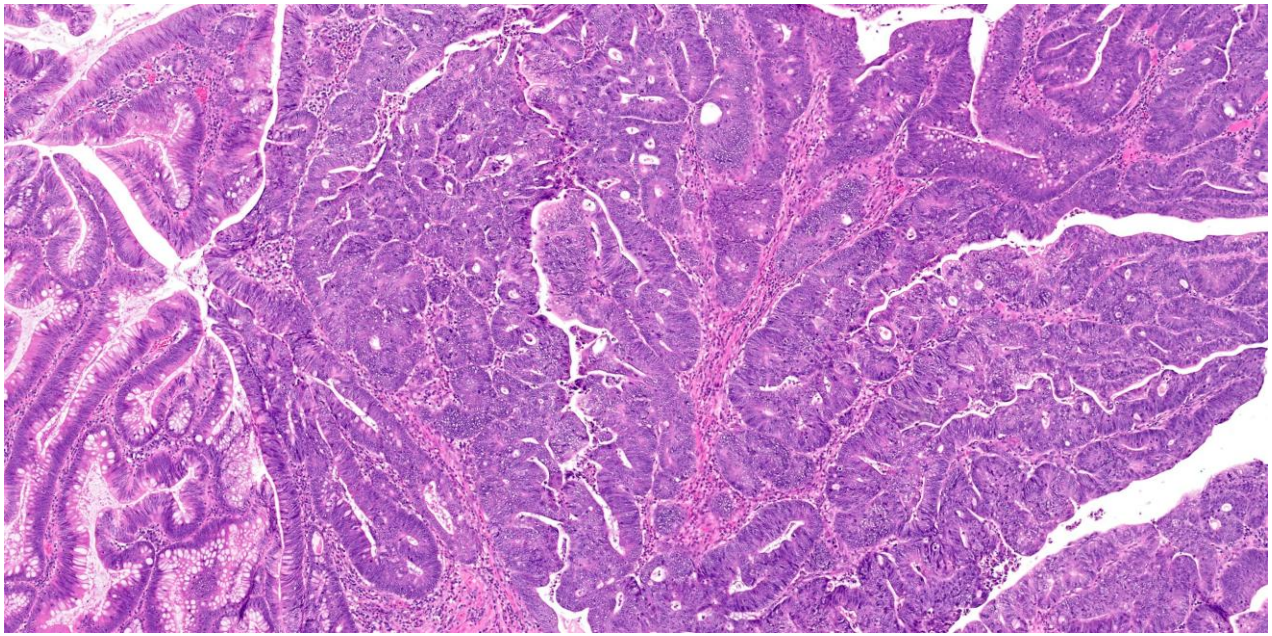
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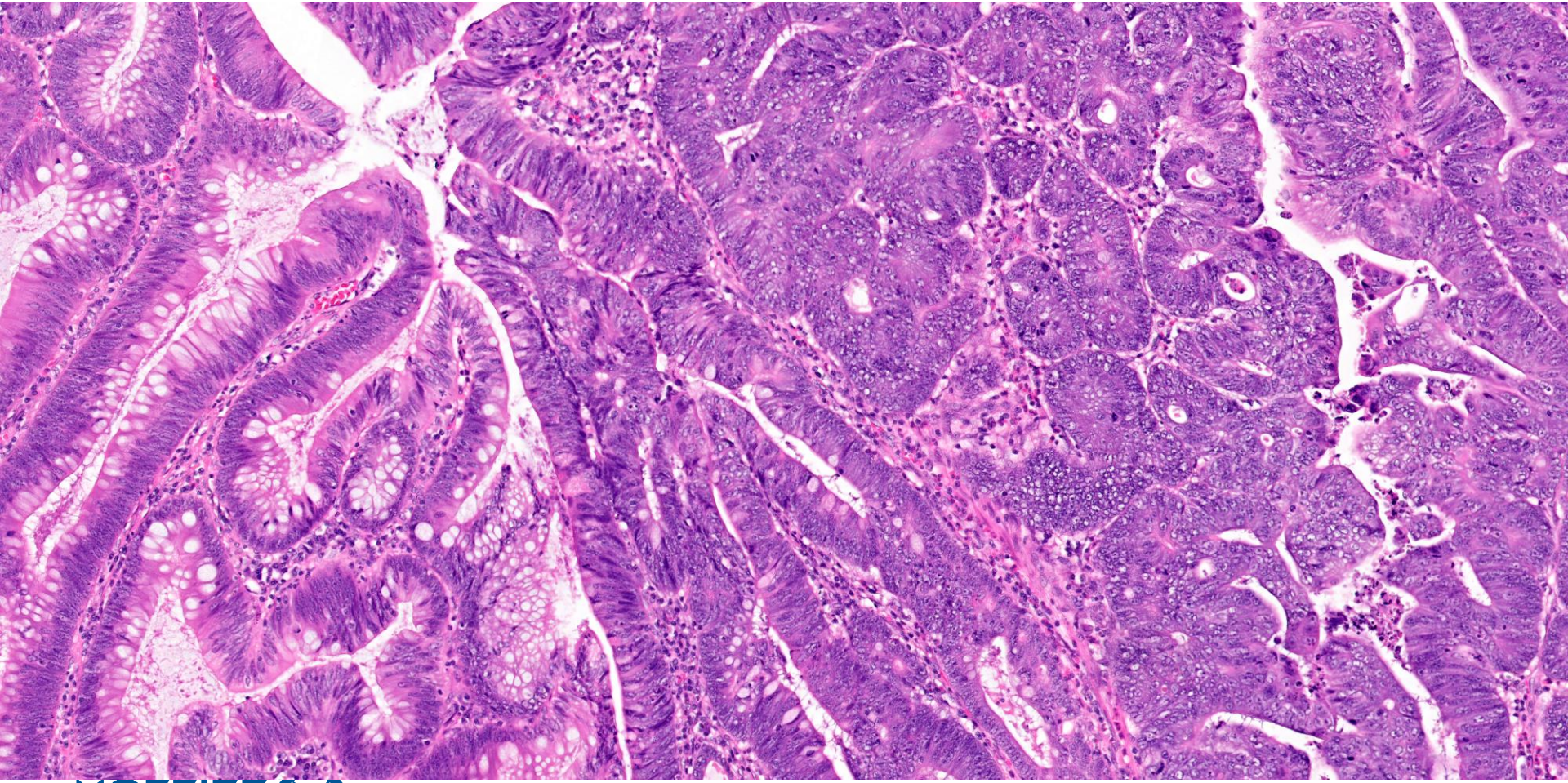
The case

65-year-old man with a 16 mm semi-sessile polyp in the ascending colon, removed by injection-lift and hot snare

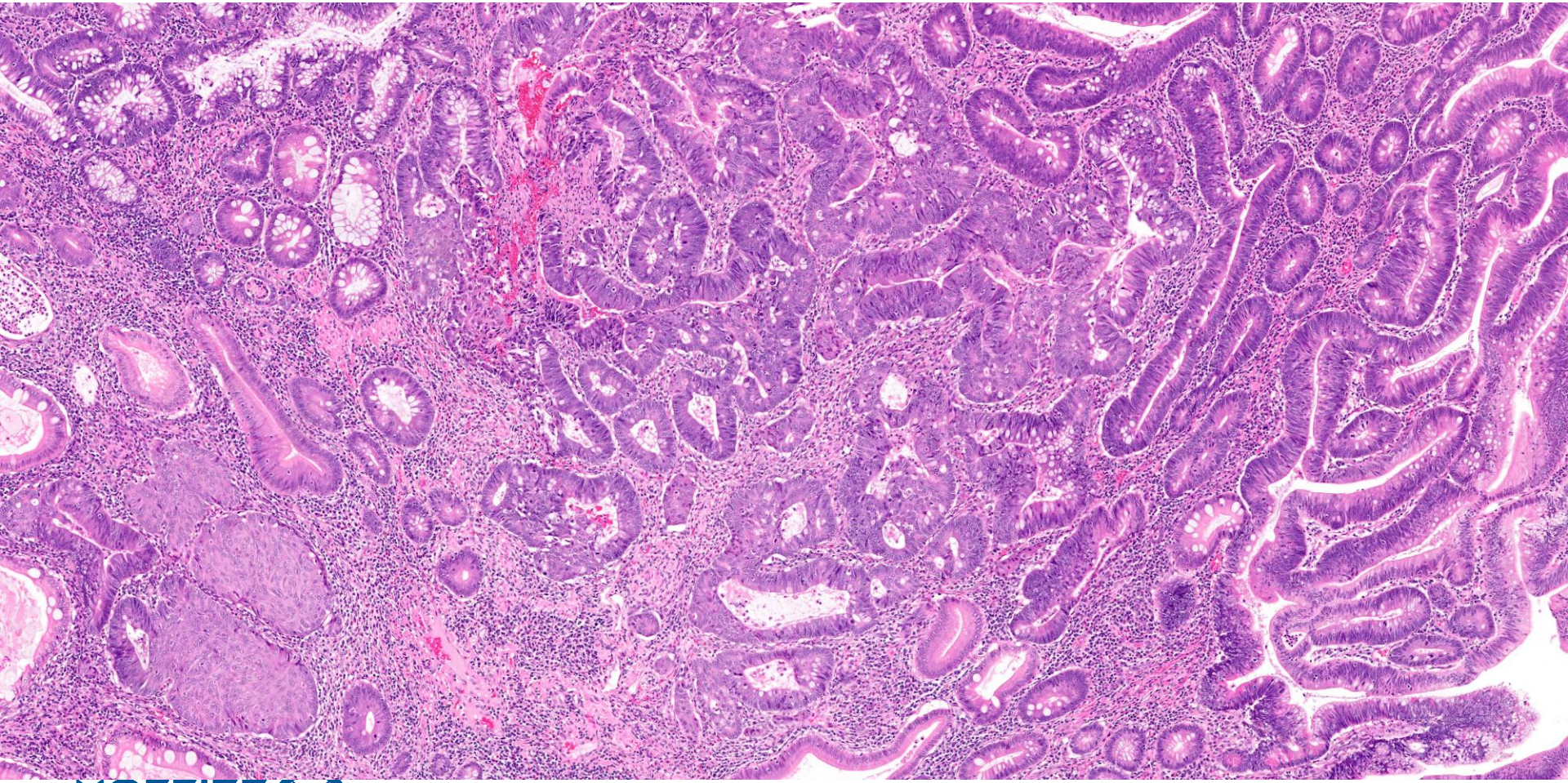




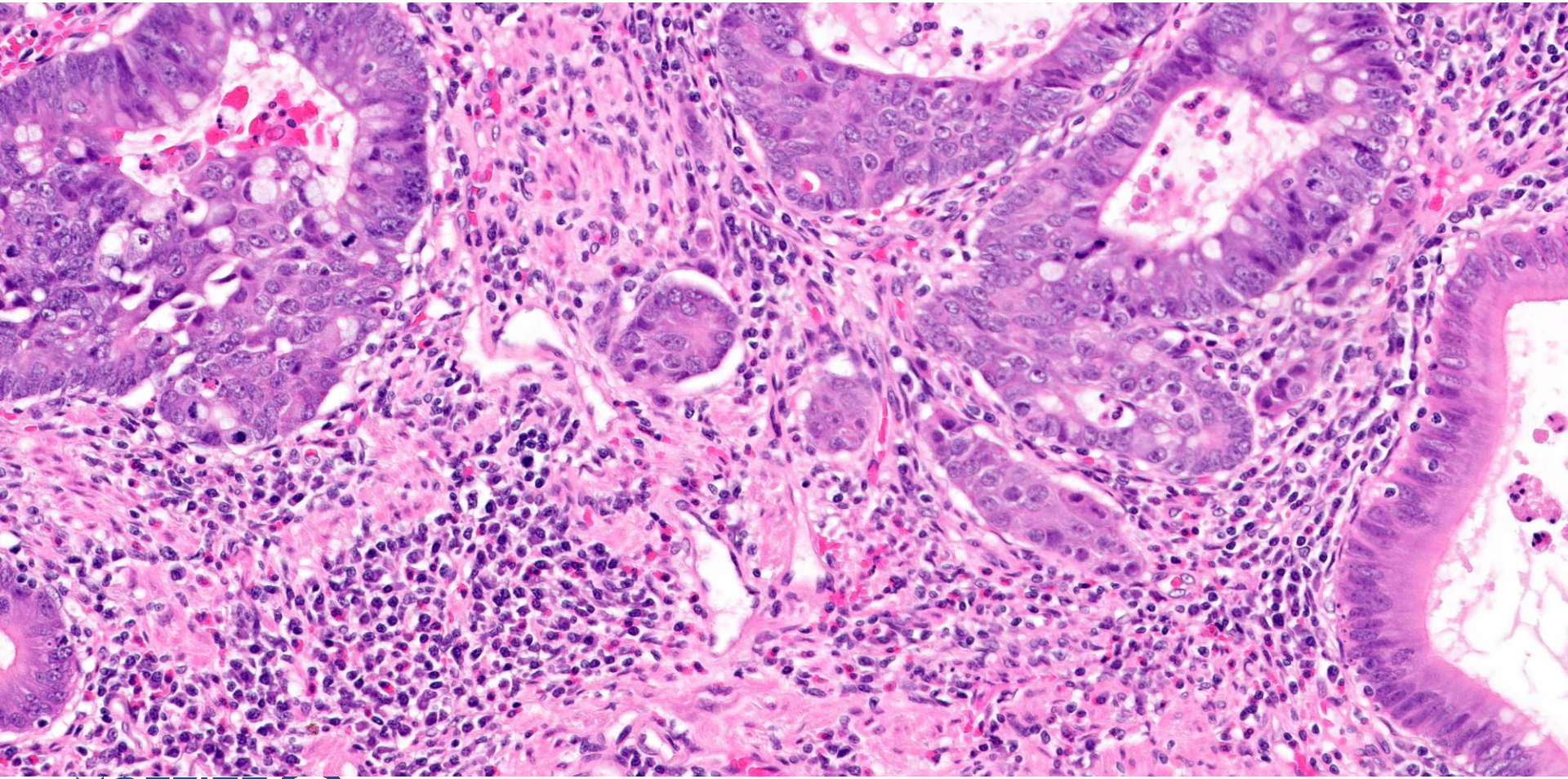




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What is your diagnosis?

a. Intramucosal adenocarcinoma arising in a tubular adenoma

b. Tubular adenoma

c. Tubular adenoma with high-grade dysplasia

d. Tubular adenoma with foci suspicious for intramucosal adenocarcinoma

e. Invasive adenocarcinoma arising in a tubular adenoma

Intramucosal carcinoma: a controversial concept

Not widely accepted in colorectal pathology — unlike elsewhere in the GI tract

Risk of overdiagnosis

IMC used as a synonym for high-grade dysplasia (HGD) causes "undue alarm" for patients and clinicians

Risk of underdiagnosis

Calling true lamina propria invasion "HGD" may lead to underdiagnosis and undertreatment

The dogma

The colonoscopist's guide to the vocabulary of colorectal neoplasia: histology, morphology, and management

Douglas K. Rex, MD,[1] Cesare Hassan, MD,[2] Michael J. Bourke, MD[3]

Indianapolis, Indiana, USA; Rome, Italy; Sydney, Australia

TABLE 1. Pathology terms we could do without

Confusing term	Better term
Carcinoma in situ, intramucosal adenocarcinoma	High-grade dysplasia

- In western countries, the term cancer is reserved (in the colorectum) exclusively for submucosal invasion
- Any neoplastic lesion confined to the mucosa, irrespective of its dysplastic or cytologic appearance, is best named low- or high-grade dysplasia

PMID: 28396276

Arguments in support of the dogma

1 No mucosal lymphatics

Colon has "no" mucosal lymphatics → endoscopy is adequate treatment for such lesions

2 Misleading terminology

"CA in situ" and "IMC" are often misinterpreted by patients and referring physicians because they include the word "carcinoma"

3 Overtreatment

The confusion can result in unnecessary surgery or excessive follow-up

4 NCCN definition

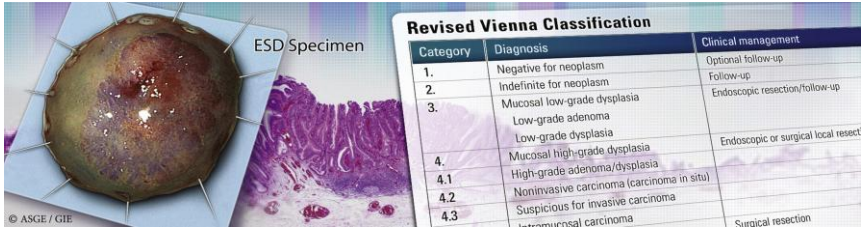
“A malignant polyp is defined as one with CA invading through the muscularis muc. and into the submucosa (T1)”

Tis is not considered a ‘malignant polyp’

Pathology definitions and resection strategies for early colorectal neoplasia: Eastern versus Western approaches in the post-Vienna era

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New York, New York; Tampa, Jacksonville, Florida, USA; Tokyo, Japan



PMID: 31874160

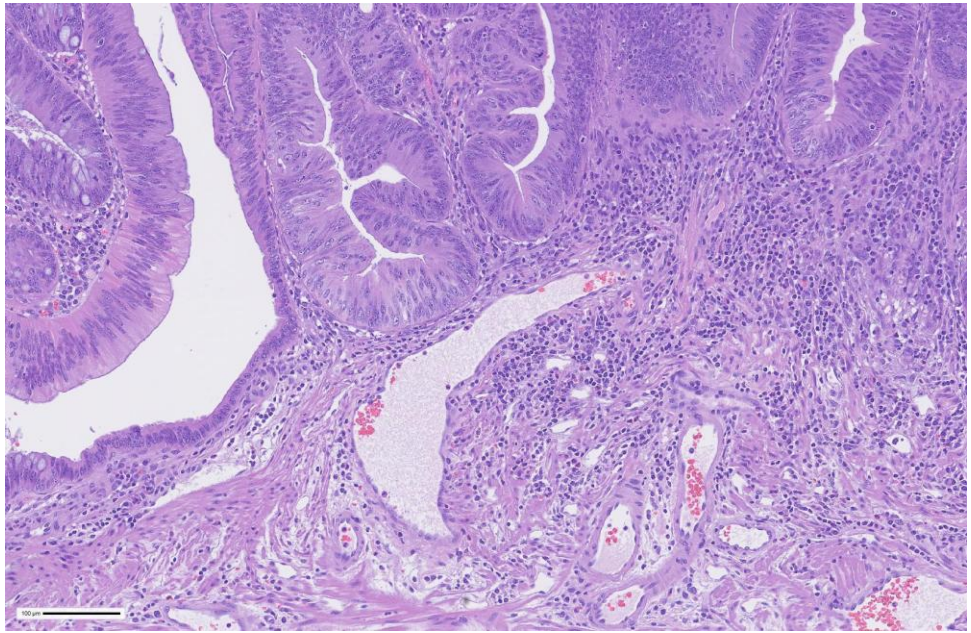
TABLE 1. Vienna classification

Category	Definition
Category 1	No neoplasia
Category 2	Indefinite for neoplasia
Category 3	Low-grade adenoma/dysplasia
Category 4	Noninvasive high-grade neoplasia
4.1.	High-grade adenoma/dysplasia
4.2.	Noninvasive carcinoma (carcinoma in situ)
4.3.	Suspicion for invasive carcinoma
Category 5	Invasive neoplasia
5.1.	Intramucosal carcinoma
5.2.	Submucosal carcinoma (or deeper infiltration)

TABLE 2. Revised Vienna classification

Category	Diagnosis	Clinical management
1.	Negative for neoplasia	Optional follow-up
2.	Indefinite for neoplasia	Follow-up
3.	Mucosal low-grade dysplasia	Endoscopic resection/ follow-up
	Low-grade adenoma	
	Low-grade dysplasia	
4.	Mucosal high-grade dysplasia	Endoscopic or surgical local resection
4.1	High-grade adenoma/dysplasia	
4.2	Noninvasive carcinoma (carcinoma in situ)	
4.3	Suspicious for invasive carcinoma	
4.4	Intramucosal carcinoma	
5.	Submucosal invasion by carcinoma	Surgical resection

The core of the debate: **lymph node risk**



- IMC grouped with high-grade adenomas due to perceived to *null or negligible nodal metastasis risk*
- The early dogma that colonic mucosa lacks lymphatics above the muscularis mucosae has been **disproven** (confirmed with specific antibodies)
- **Yet**, the Literature on actual lymph node risk is **scarce**

Tis / IMC Nodal Risk: Conflicting Information

REGISTRY "Tis"
n = 2,497 with known nodal status

4.6% **node-positive (n=114)**

N1: 95 (3.8%) **N2:** 19 (0.8%)

5-yr RS, N1 Tis **87.3%** ≈ N1 T1 **87.6%**

5-yr RS, N2 Tis **83.2%** (SE 14.5; n = 19)

Limitations
- No pathology review
- N2 survival too imprecise to interpret (95% CI ≈ 55% to >100%)

vs

SURGICALLY RESECTED IMC
n = 55

0% **node-positive (0 / 55)**

vs **9.5%** in surgically treated T1 (P = .041)

No LVI reported; budding in **1 case**

Limitations
- 48% had < 12 nodes (mean 14.1)
- No central pathology review

Reconciling: node-positive registry "Tis" behaves like T1 → likely misclassified invasive cancer. True IMC appears to carry little or no nodal risk — but neither dataset had central pathology review.

J Clin Oncol 28:264-271,2010

Gastrointest Endosc 2021;93:477-85

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Rationale for integrating IMC in the new WHO

1

Rising detection

Population screening + improved endoscopy → **increasing detection** of intramucosal CAs

Parallels the rise in pT1 CRC diagnoses

2

A chance to study it

Opportunity to prospectively study whether formal recognition of intramucosal CRC **improves patient care**

3

Outcomes

Small series suggest generally favorable outcomes, though rare poor outcomes are reported

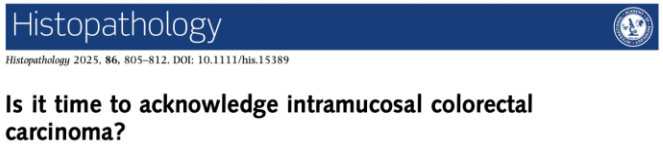
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A risk marker

Outcome differences alone should not drive the HGD vs IMC distinction

Intramucosal CRC may flag **high-risk patients** (e.g., Lynch syndrome, IBD)

A strict definition is needed: ***unequivocal* infiltration of the lamina propria**



High-grade dysplasia

- Atypical epithelial proliferation
- Basement membrane intact
- Includes complex/cribriform architecture

Intramucosal carcinoma

- Clear disruption of the basement membrane
- Unequivocal infiltrative growth in the lamina propria
- Easiest to recognise with poor differentiation, signet ring cells or tumour budding
- Invasion into muscularis mucosa qualifies

Invasive carcinoma (pT1+)

- Tumor beyond the lamina propria/muscularis mucosa
- Includes submucosal lymphovascular or intramural vascular invasion, nodal deposits

Study design: two complementary cohorts

A Institutional cohort

Radboud umc archives, 1990–2024

- Searched "intramucosal carcinoma", "carcinoma in situ", "intramucosal signet ring cells"
- Independently reviewed by 3 pathologists
- MMR IHC (MLH1, PMS2, MSH2, MSH6)
- Clinical data: risk factors (Lynch, IBD, polyposis), screening vs non-screening, follow-up

B National cohort

All Dutch CRC, 2014–2018

- Single CRC, age 55–70 (screening age band)
- Resected cases with known MMR status: n = 13,689
- Nodal positivity per pT category, by dMMR vs pMMR, inside vs outside screening
- Purpose: proxy estimate of nodal risk
- Local excisions excluded (no LN status)

Histopathology 2025;86:805–812.9

Only 14 of 134 “intramucosal” CRCs retained

134 archived cases retrieved by search



97 (72.4%) High-grade dysplasia

23 (17.2%) Invasive at surgery

14 (10.4%) True IMC

17%

of the series had invasive carcinoma at resection — IMC should not be diagnosed on biopsy; label these “suspicious for malignancy”

100%

observer agreement on the diagnosis of all 14 cases

0.09%

of screening cases

Local screening 2014–2024 (6 of 7031 patients)

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Histopathology 2025;86:805–812.9

Clinicopathologic characteristics

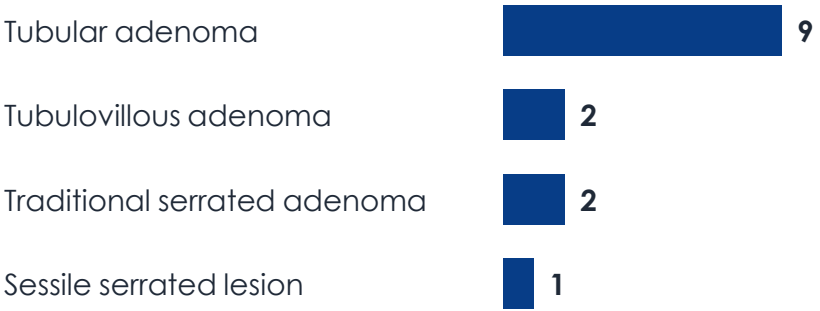
14
patients (6 F / 8 M)

58.3
mean age, years (range 43–72)

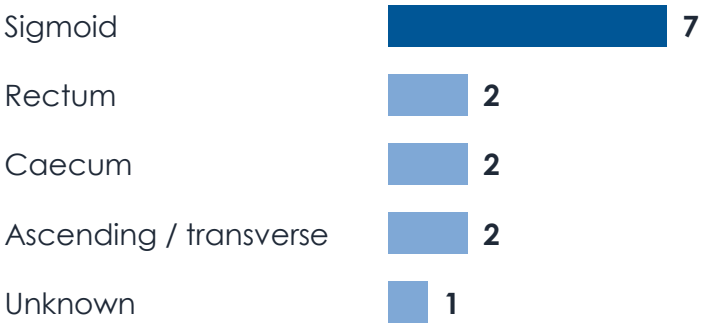
50%
dMMR (7/14) — about 5× the 11% in unselected CRC

6/7
dMMR cases had Lynch syndrome; the 7th (SSL) showed MLH1 hypermethylation

Precursor lesion · mean size 1.4 cm (0.2–2.5)



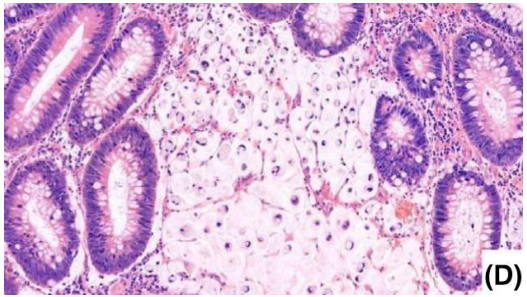
Location



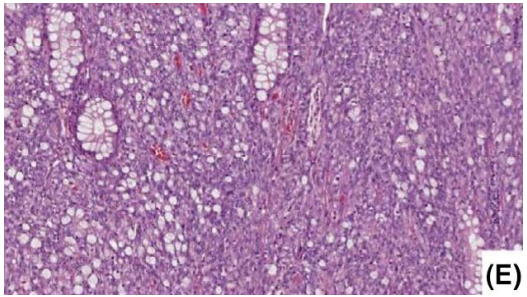
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Histopathology 2025;86:805–812.9

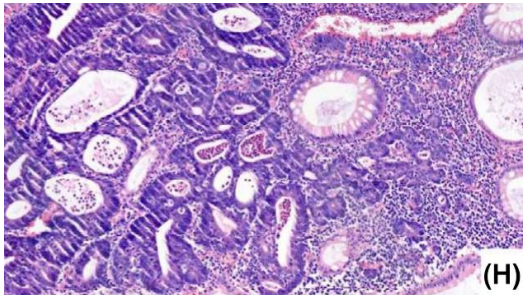
Morphologic spectrum of the 14 intramucosal CRCs



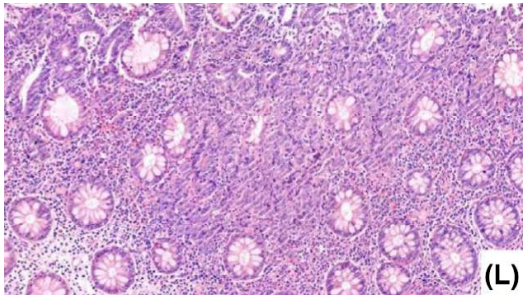
Signet ring cells in extracellular mucin



Goblet cell / signet ring cell proliferation in solid fields



Small glands, poorly differentiated clusters, budding



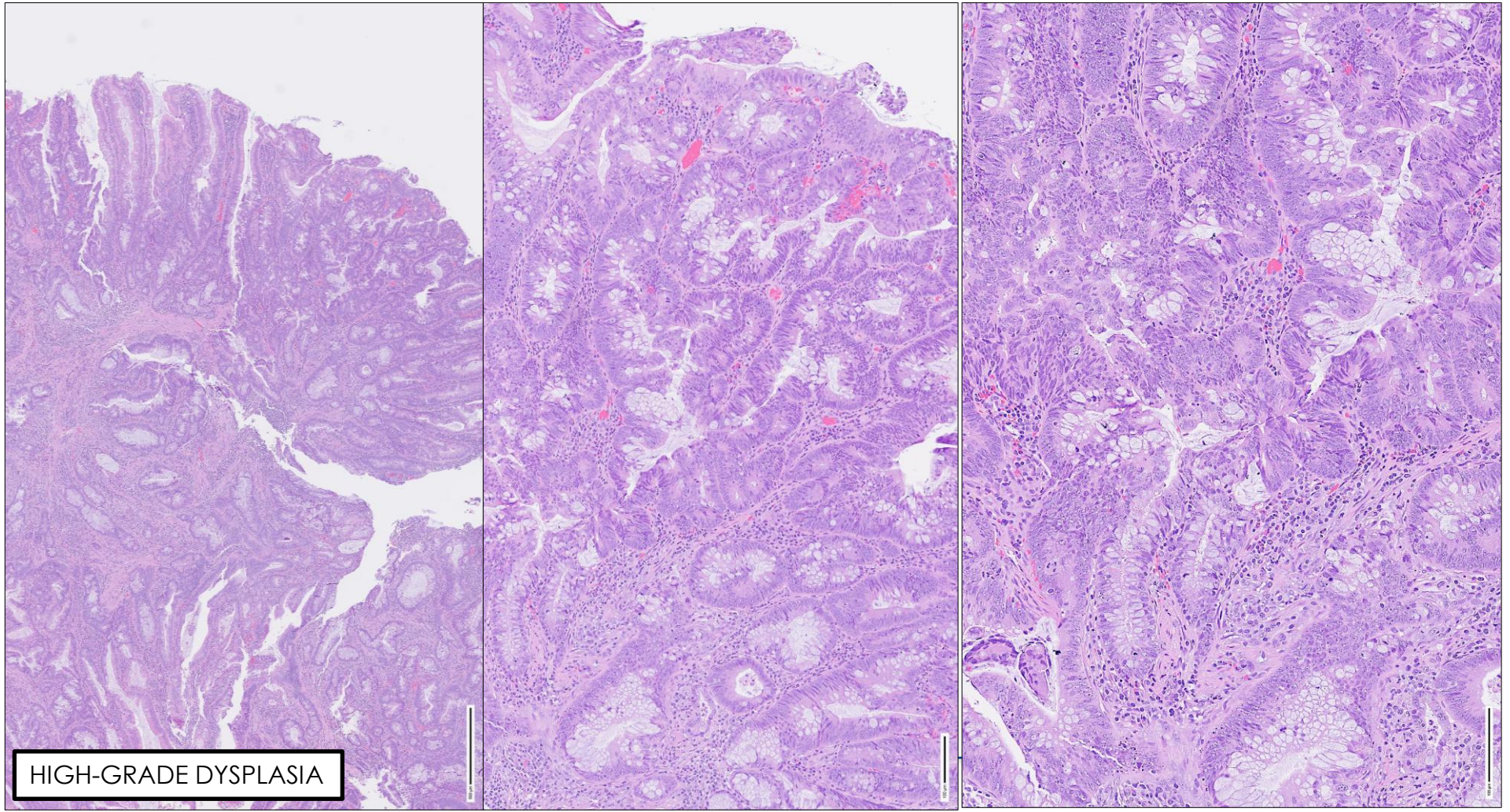
More solid growth pattern

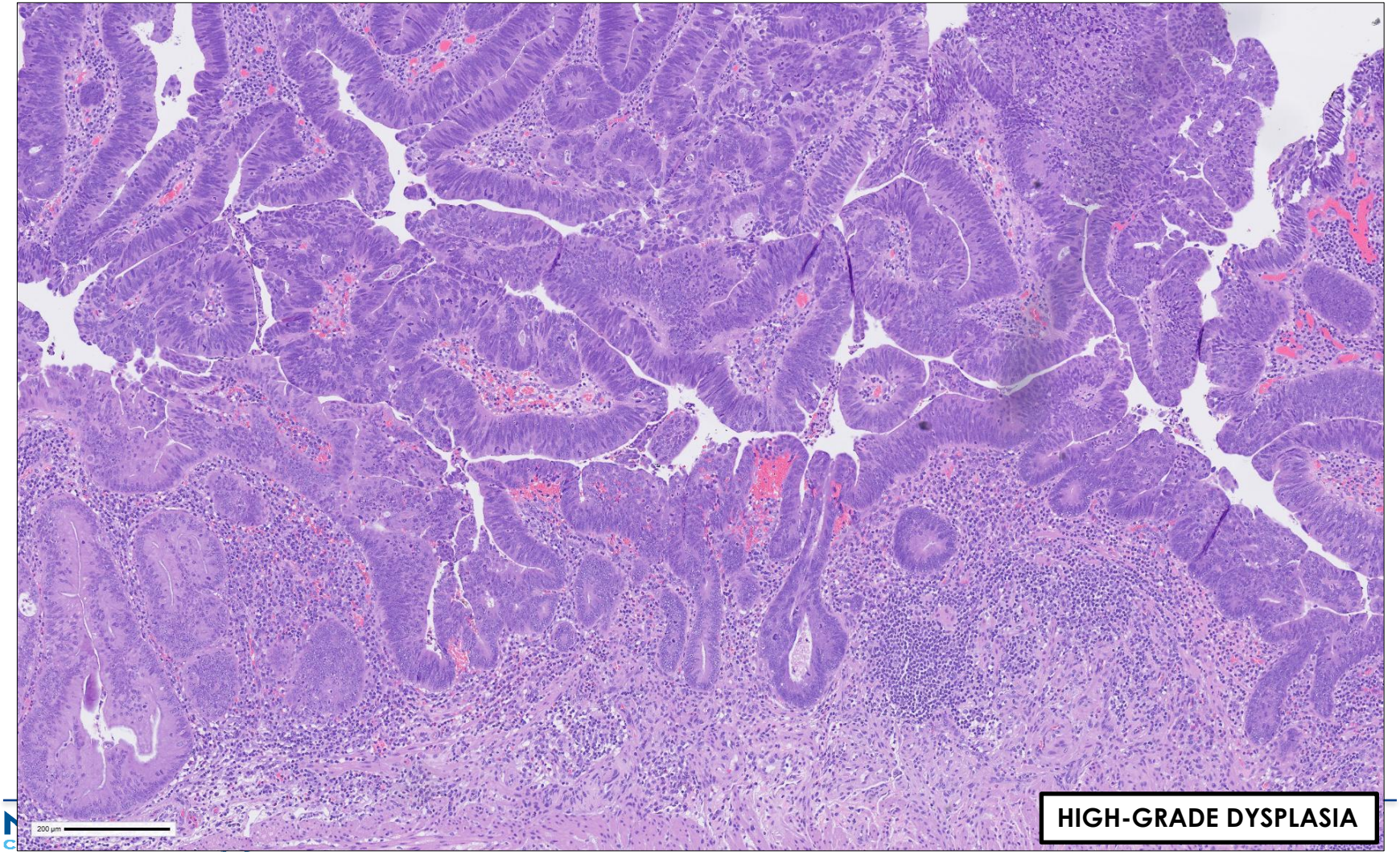
Histology

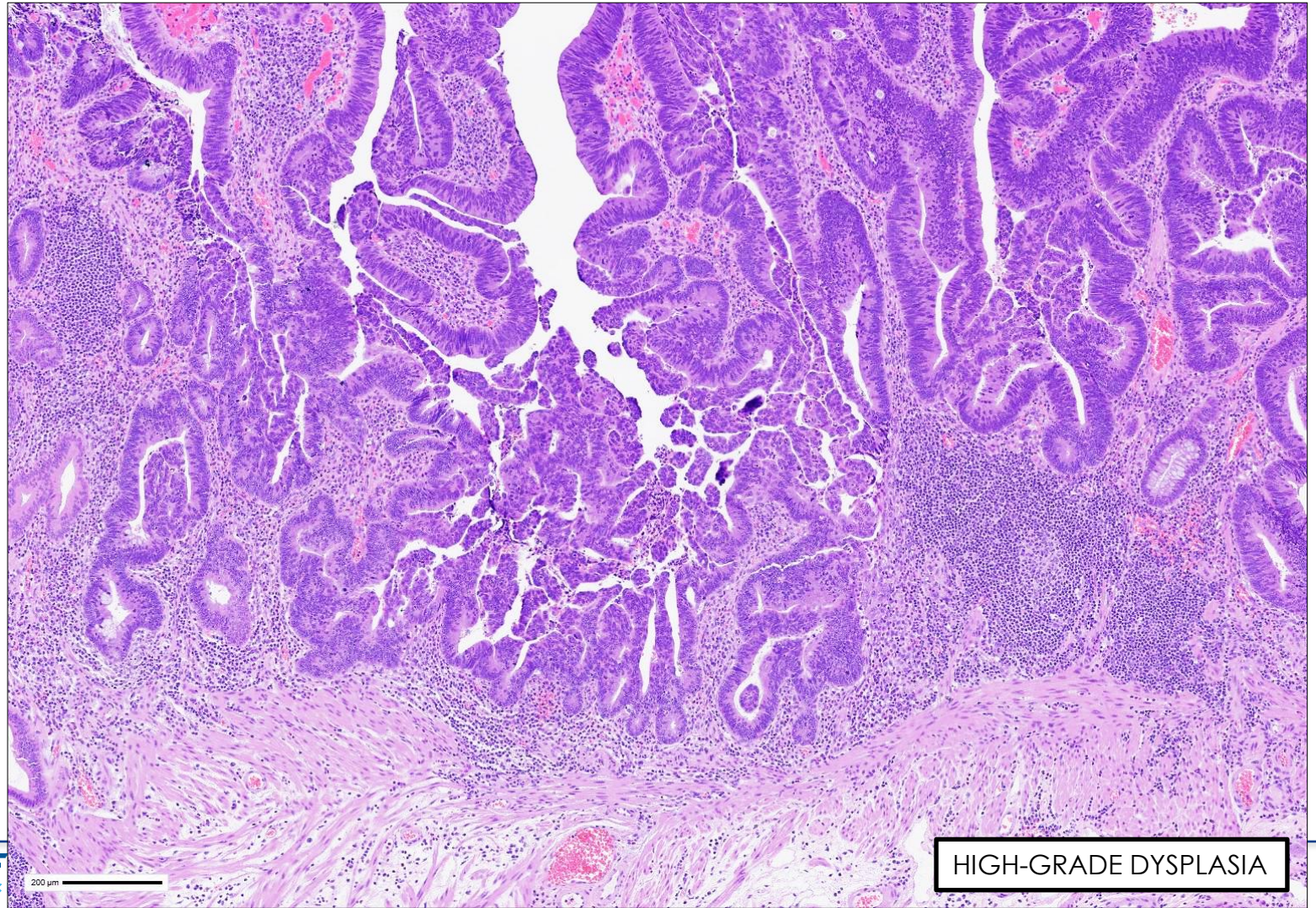
- Single cells or small clusters infiltrating between crypts
- Signet ring cells or poorly cohesive foci (50%)
- Tumor budding, or solid sheets replacing the lamina propria
- *Excluding complex but intact glandular architecture*

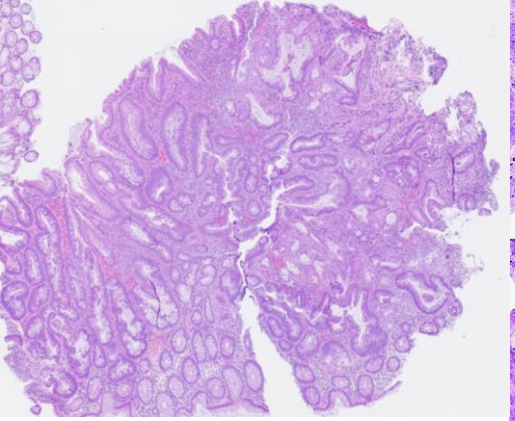
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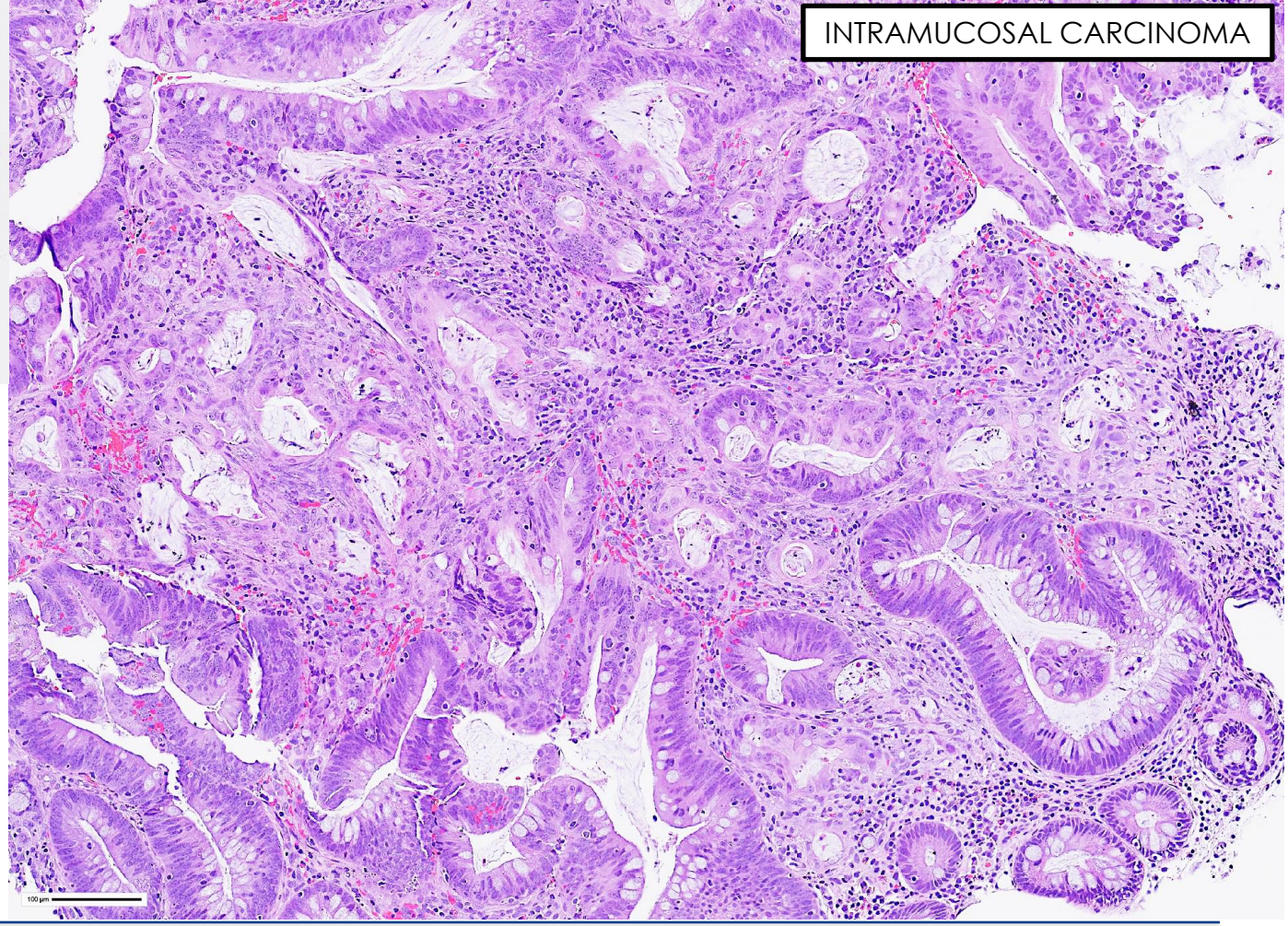
Histopathology 2025;86:805–812.


HIGH-GRADE DYSPLASIA


200 µm
HIGH-GRADE DYSPLASIA


200 µm
HIGH-GRADE DYSPLASIA





INTRAMUCOSAL CARCINOMA

Can we agree on IMC?:Interobserver variability in diagnosing IMC

Lamina propria invasion: clinicopathologic features, diagnostic accuracy & interobserver variability

32 cases identified (lamina propria invasion)

7 high-consensus cases (>75% agreement, 9 pathologists)

5.1% of 117 high-grade intramucosal lesions

Best objective criterion of invasion
Stromal infiltration by single cells or small clusters — the most reliable and reproducible indicator of lamina propria invasion

High-consensus tumor features
Atypical or complex glandular arrangements exceeding normal mucosal architecture were more frequent in the 7 high-consensus cases

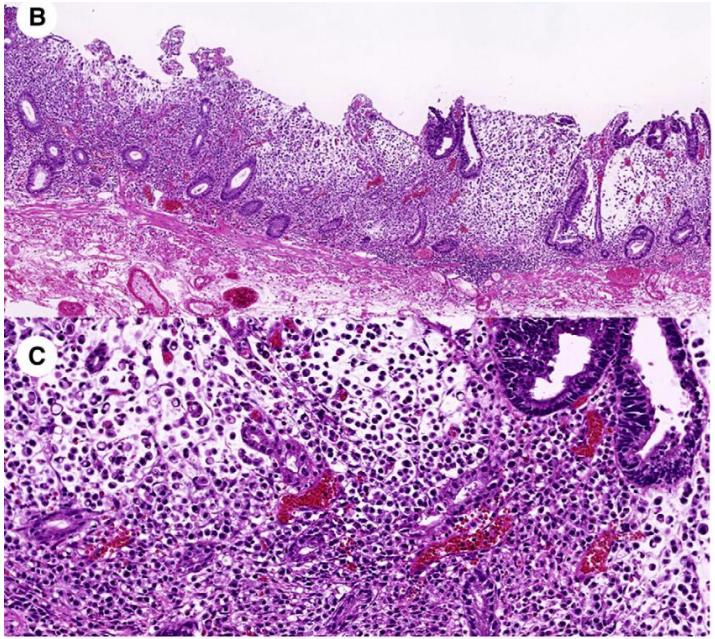
Ambiguous case features
3 cases remained equivocal (IMC vs pT1); desmoplasia and marked inflammation were more frequent in these cases.

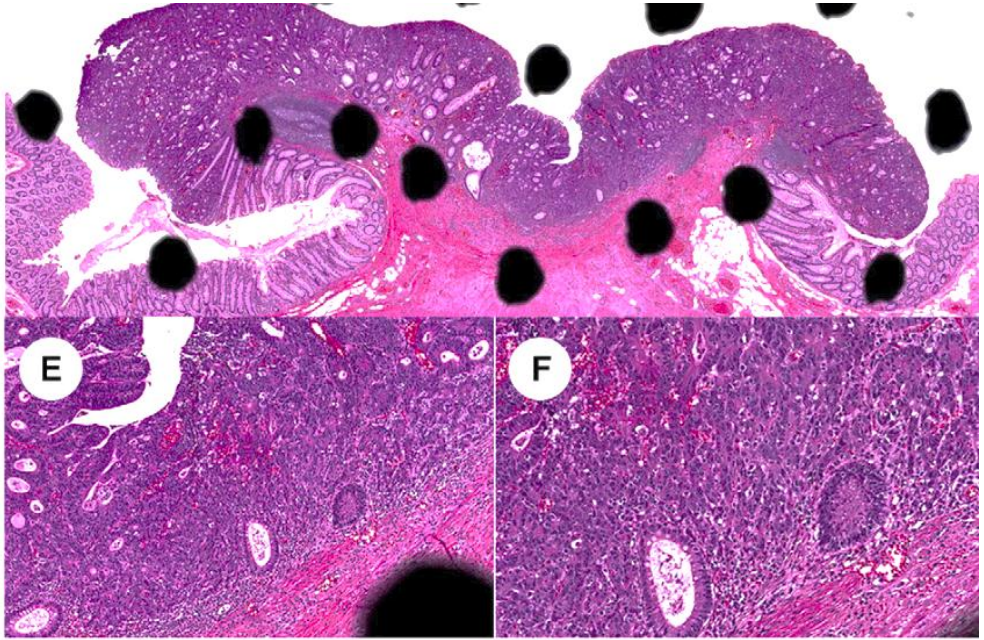
Diagnostic concordance
Agreement on diagnosis and on detection of invasion characteristics ranged only from poor to fair

Unanimous diagnoses
Clusters of infiltrative poorly differentiated adenocarcinoma and single infiltrative cells were agreed upon by all pathologists

Human Pathology (2017) 66, 230–237
Multi-institutional study, Japanese Society for Cancer of the Colon and Rectum

Representative intramucosal carcinomas





Favorable outcomes *but* metachronous neoplasia



Outcomes associated with intramucosal adenocarcinoma

0
nodal metastases in any of the 4 resected cases

8
cases with no evidence of disease on surveillance

10/14
developed further colorectal lesions (2–16 adenomas)

Metachronous and extracolonic cancers

- **2** developed metachronous CRC
- **1** died of metastatic CRC (polyposis, 3 metachronous CRCs)
- **Extracolonic cancers:** endometrial (Lynch), gastric (Lynch), 4 primaries in the CHEK2 patient.

Histopathology 2025;86:805–812.

Patients and outcome: **no metastasis** from any confirmed IMC

GOOD PROGNOSIS

15
Poorly differentiated IMCs
13 archival (1984–2006) + 2 prospective

62
median age, years (range 36–79)*

4:1
male : female

14/15
complete polypectomies, submitted entirely (1 fragmented)

Case definition & follow-up

- **Poorly Differentiated ACA w/ single cells infiltrating only the LP**
- No prior carcinoma; all seen endoscopically as "routine" polyps
- 14 patients followed; 1 lost. Colonoscopy surveillance or surgical resection

Follow-up of 15 patients · outcome counts per text†



- 7 Colonoscopy only, no residual
- 5 Resected: no carcinoma, N0
- 1 Separate T3 CRC, 8/10 N+
- 1 LAR: anal Paget disease
- 1 Lost to follow-up

0
metastases from IMC

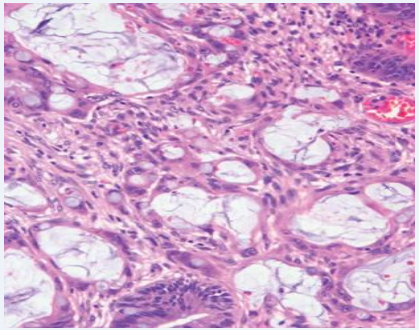
21.3 mo
mean follow-up (median 13; range 1–96)

1/15
"IMC" was a metastasis from a separate T3 colonic primary, with no in situ component

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Am J Surg Pathol 2007;31:1882–1886

BUT!! Intramucosal Carcinoma in Rectal Polyps: Two Cases



CASE 1

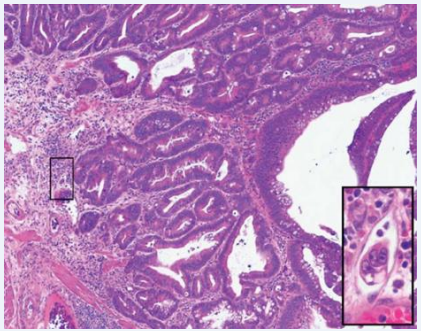
Apparent pTis That Recurred

74-year-old man · 4 cm upper rectal polyp

- Bx adenoma with HGD; EUS: confined to mucosa
- IMC in tubulovillous adenoma; single cells, signet ring cells
- Focal desmoplasia; no invasion beyond muscularis mucosae → pTis
- Entirely submitted; 1 H&E level per block

CLINICAL COURSE

1. **Low anterior resection (no RT)**
   LN: 0/8 lymph nodes positive
2. **Recurrence at 17 months**
   Omentum and liver; histology matched the IMC



CASE 2

Lymphatic Invasion on Deeper Levels

79-year-old man · 1.0 cm upper rectal polyp

- Polypectomy; fragmented, entirely embedded in one block
- IMC in tubulovillous adenoma: single cells, clusters, irregular glands; high-grade cytology; fibrotic stroma
- No carcinoma beyond muscularis mucosae on any level

CLINICAL COURSE

1. **Initial H&E levels (2 slides)**
   Only worrisome feature: poor differentiation
2. **5 deeper levels, 50 µm apart**
   Convincing LVI at the mucosal base
3. **Repeat endoscopy at 1 month**
   No residual or other GI disease
4. **2 months post-polypectomy**
   No additional treatment yet

Am J Surg Pathol 2008;32(10):1586–1588

Intramucosal CRC: conclusion for now (1 of 2)

True intramucosal carcinoma is rare

Source	IMC rate	Comment
Radboud umc (2025)	**0.7% of HGD, 0.1% of CRC**	**Strict criteria, full re-review**
Japanese Lynch cohort	**10.4% of colorectal lesions**	High-risk population; Eastern criteria
US registry (Gunderson 2010)	**5.4% of CRC (2.2% if N0)**	No pathology review; biopsy diagnoses not updated
French screening series	**26.6% of CRC vs 20% for T1**	Only 5% resected; no pathologist review

0.09%

of screening cases

Local screening 2014–2024
(6 of 7031 patients)

Intramucosal CRC: conclusion for now (2 of 2)

1. **_Rare_ but REAL (~0.1% of CRC) with standardization of strict definitions / do not downgrade to HGD**
   Unequivocal infiltration of the lamina propria; poor differentiation, Signet ring cell *or* budding

2. **Poorly differentiated pTis CRC can metastasize**
   Lymphatics exist in the muscularis mucosa and can give way to LVI. Thus, despite reports of likely indolent behavior: caution is required.

3. **Diagnose on the whole lesion**
   Excisions vs biopsies? (biopsy → "suspicious for malignancy"?). Multiple levels++; caution if desmoplasia

4. **MMR IHC on every case and consider the patient, not just the polyp**
   ~50% dMMR with strong Lynch association; trigger germline work-up as appropriate. IMC flags CRC risk (Lynch, polyposis, IBD, CHEK2); plan surveillance accordingly