Polyp sizing and pathology for diminutive polyps - Do we still need pathology?

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Accurate size measurement – Why important?

- Understand risk of advanced pathology and CRC based on size (5, 10, 20mm)
- Important when using resect-and-discard or diagnose-and-leave (5mm threshold)
- Choice of polypectomy technique (3, 10, 20mm thresholds) and referral for ESD/EMR
- Decision-making for surveillance intervals post polypectomy (10mm threshold)

Consequences of inaccurate size estimation

- Consequence of mis-sizing polyps at 10mm:

- USMSTF 2020: **10, 7, 5y** vs **3y** follow-up depending on pathology
  - Potential of surveillance 7 years too early/ too late
- ESGE 2020: **Return to screening (FIT)** vs **3y** follow-up

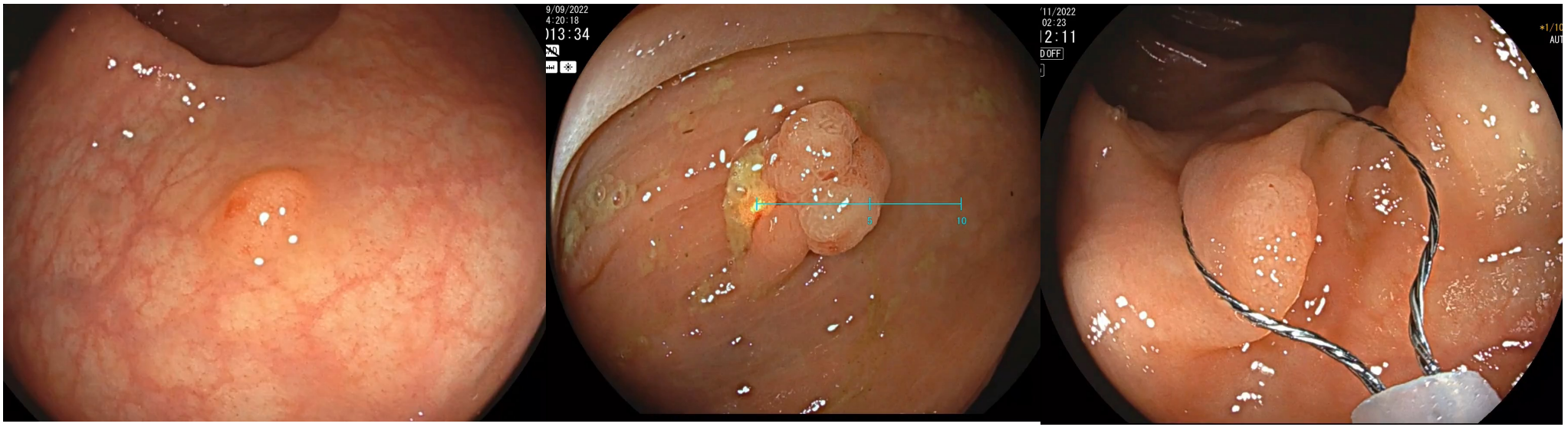
Gupta et al. GIE 2020

Hassan et al. Endoscopy 2020

What sizing methods are available?

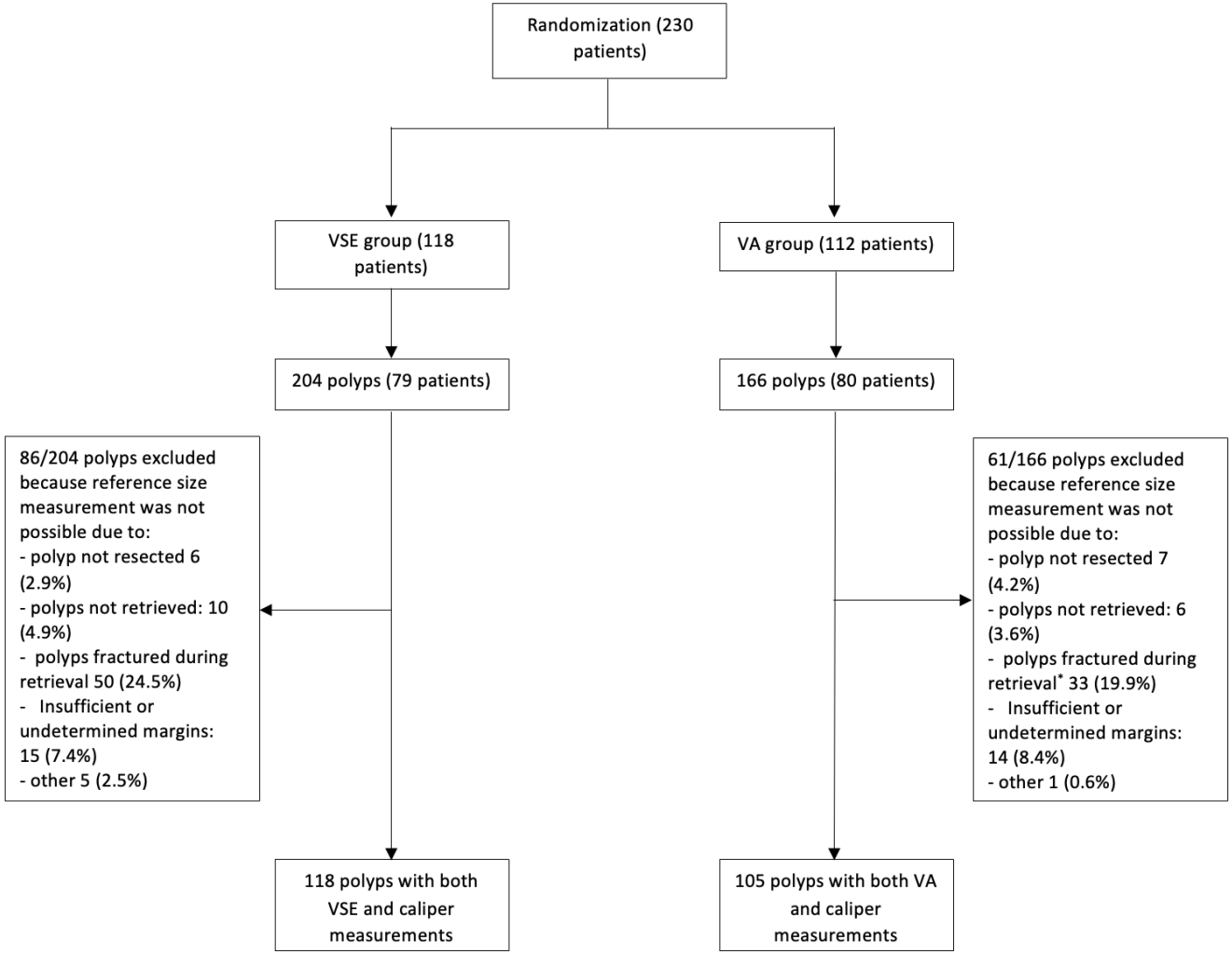
Your eyes (visual, most common practice; „carpenter‘s eye estimation“)	Forceps	Snare
Endoscopic ruler	Virtual scale endoscope	Pathology

- What’s the increase in relative accuracy when using VSE among experts?
- Is a non-calibrated measurement tool (iE snare) useful?



Study (year)	Study design	Reference standard used	Relative accuracy (95% confidence interval)			Mean difference of measurements by each tool against the true measurements (mean; mm (SD))		
			VSE	VA	p-value	VSE	VA	p-value
Masato et al (2021)	Colon model exploratory	Graph paper	5.3 ± 5.5%	Biopsy forceps: 11.9 ± 9.4%,	<0.001	-	-	-
Shomida et al (2022)	Colon model	Colon model LM-107 Simulator Type II (Koken Co., Ltd., Tokyo, Japan)	84.0% (SD=11.9)	62.5% (SD=21.1)	<0.001	*Normalized difference: -12.5	*Normalized difference: -34.3	<0.001
Djinbachian et al. (2022)	Colon model	Simulated polyps measured by a vernier caliper for the largest size	82.7% (80.8-84.8)	Biopsy forceps: 78.9% (76.2-81.5)	<0.001	1.1 (2.1)	Biopsy forceps: 1.9 (2.9)	<0.001
				Napoleon ruler: 78.4% (76.0-80.8)	<0.001		Napoleon ruler: 2.2 (2.9)	<0.001
Haumesser et al (2022)	Colon model	Simulated polyps measured by a vernier caliper for the largest size	82.0% (80.1-83.9)	71.7% (68.9-74.5)	<0.001	1.3 (3.2)	2.7 (4.8)	<0.001
von Renteln et al (2022)	Clinical pilot	Measurements of fresh specimens retrieved post-polypectomy with a vernier caliper	85.4% (81.62-89.26)	66.8% (61.35-72.21)	<0.001	-0.1	-0.2	<0.001

Clinical RCT



von Renteln et al. submitted as late breaking DDW 2023

Clinical RCT

- The RA of VSE was 84%, which was significantly higher than that of VA (68.4%, $p<0.001$).

- The obtained size measurement when using VSE did not differ significantly from the true polyp size ($p=0.29$), whereas the visually obtained size measurements were significantly different from the true polyp size ($p<0.001$).

von Renteln et al. UEGW 2023

How good is pathology?

Correcting the Shrinkage Effects of Formalin Fixation and Tissue Processing for Renal Tumors: toward Standardization of Pathological Reporting of Tumor Size

Thu Tran[1], Chandru P. Sundaram[2], Clinton D. Bahler[2], John N. Eble[1], David J. Grignon[1], M. Francesca Monn[2], Novae B. Simper[1], Liang Cheng[1,2]

The Effect of Formalin Fixation on Resection Margins in Colorectal Cancer

International Journal of Surgical Pathology
2019, Vol. 27(7) 700–705

DOI: 10.1177/1066896919854159
journals.sagepub.com/home/ijs
SAGE

David Lam, MBBS, FRACS, MSurgEd[I], Yui Kaneko, MBBS, PhD[I], Adam Scarlett, MBBS[I], Basil D'Souza, MBBS, FRACS[I], Richard Norris, MBBS, PhD, FRCPA[I], and Rodney Woods, MBBS, FRACS[I]

A prospective study of the accuracy and concordance between in-situ and postfixation measurements of colorectal polyp size and their potential impact upon surveillance

Jeff K. Turner[a], Melissa Wright[c], Meleri Morgan[b], Geraint T. Williams[d] and Sunil Dolwani[a,d]

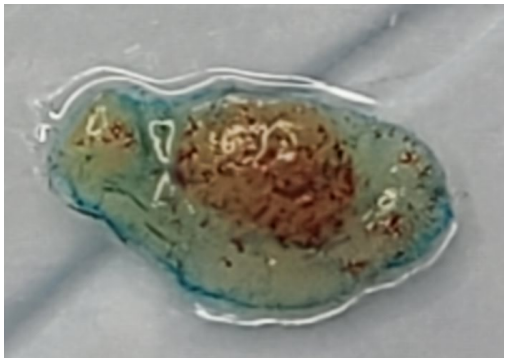
10-20% shrinkage after formalin fixation

Plus fragmentation after resection

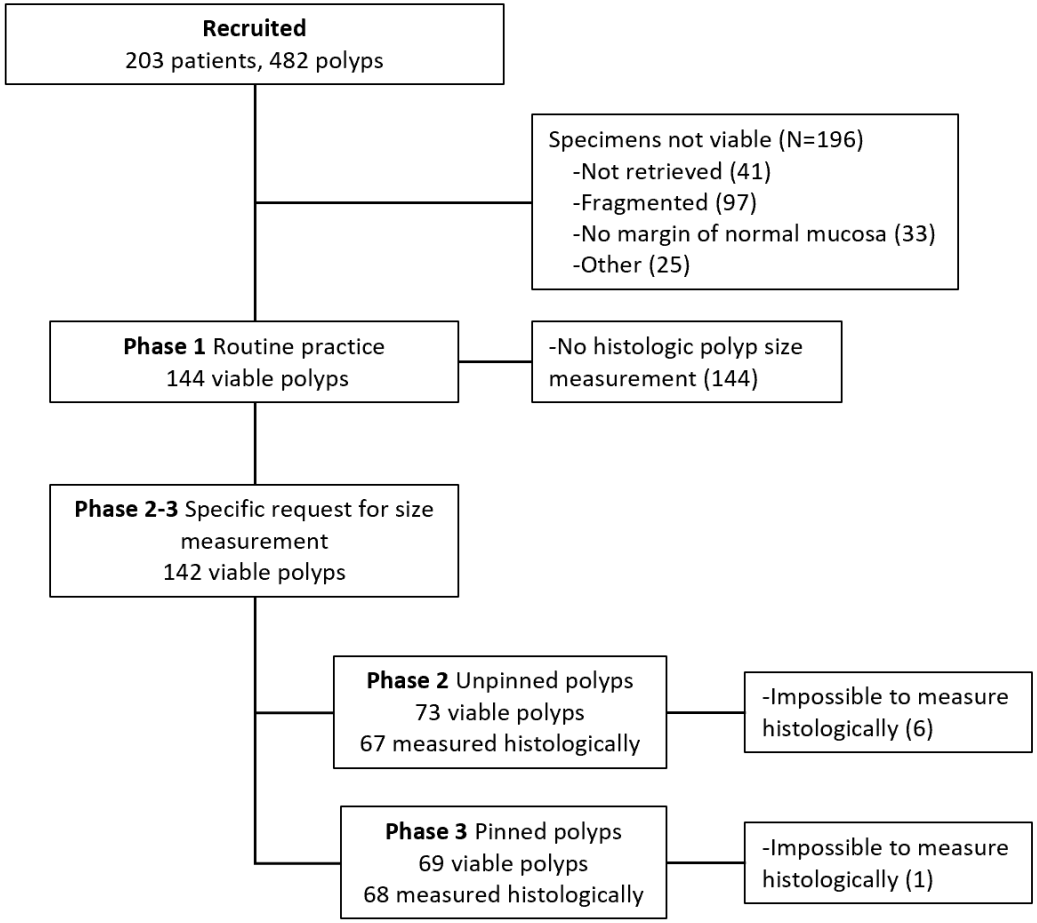
Tran et al. Journal of Cancer 2015
Lam et al. Int J. Surg Path 2019
Turner et al. Eur J. Gastro Hep 2013

Clinical study – evaluating size measurement in pathology

- Need for measuring size reference standard
- En-bloc resection, no fragmentation
- Methylene-blue staining to allow better delineation of polyp borders



von Renteln et al. Gut 2023



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DIAGNOSTIC :

A : Polype du côlon transverse :

- Lésion festonnée sessile sans dysplasie.
- Taille macroscopique : 5 mm.
- Taille microscopique : 3 mm.

B : Polype du côlon ascendant n° 1 :

- Lésion festonnée sessile sans dysplasie.
- Taille macroscopique : 3 mm.
- Taille microscopique : 5 mm.

C : Polype du côlon ascendant n° 2 :

- Lésion festonnée sessile sans dysplasie.
- Taille macroscopique : 8 mm.
- Taille microscopique : 5 mm.

D : Polype du côlon descendant :

- Polype hyperplasique.
- Taille macroscopique : 5 mm.
- Taille microscopique : 3 mm.

E : Polype du côlon descendant n° 2 :

- Polype hyperplasique.
- Taille macroscopique : 5 mm.
- Taille microscopique : 4 mm.

DIAGNOSTIC :

A : Polype du côlon transverse :

- Adénome tubuleux.
- Taille macroscopique : 5 mm.
- Taille microscopique : 3 mm.

B : Polype du côlon transverse n° 2 :

- Adénome tubuleux.
- Taille macroscopique : non évaluable (spécimen fragmenté).
- Taille microscopique : non évaluable (spécimen fragmenté).

C : Polype du côlon transverse n° 3 :

- Adénome tubuleux.
- Taille macroscopique : 8 mm.
- Taille microscopique : 7 mm.

D : Polype du côlon descendant :

- Adénome tubuleux.
- Taille macroscopique : 10 mm.
- Taille microscopique : 3 mm.

E : Lésion du descendant, biopsie :

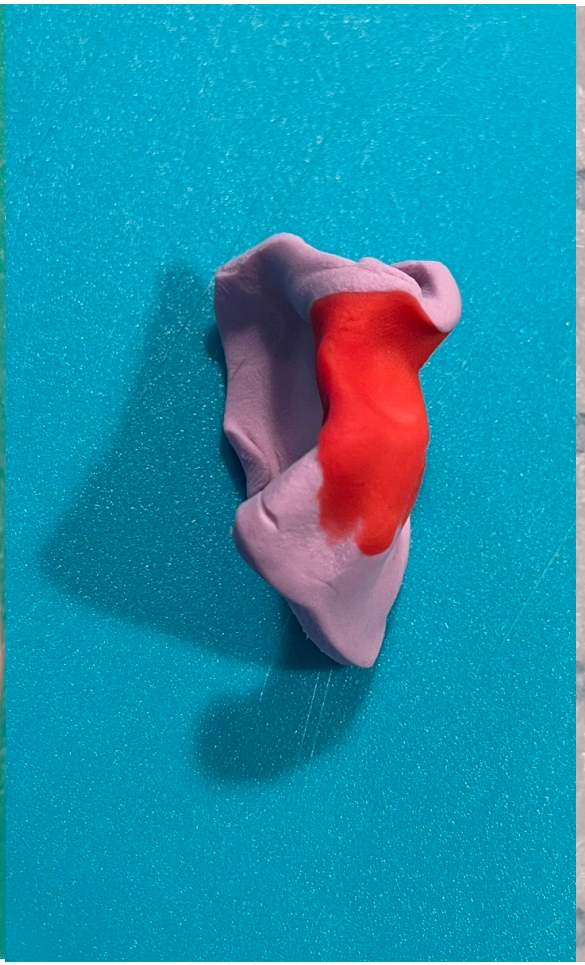
- Polype hyperplasique.
- Taille macroscopique : non évaluable (spécimen fragmenté).
- Taille microscopique : non évaluable (spécimen fragmenté).

Preparing a polyp from 3D for 2D evaluation

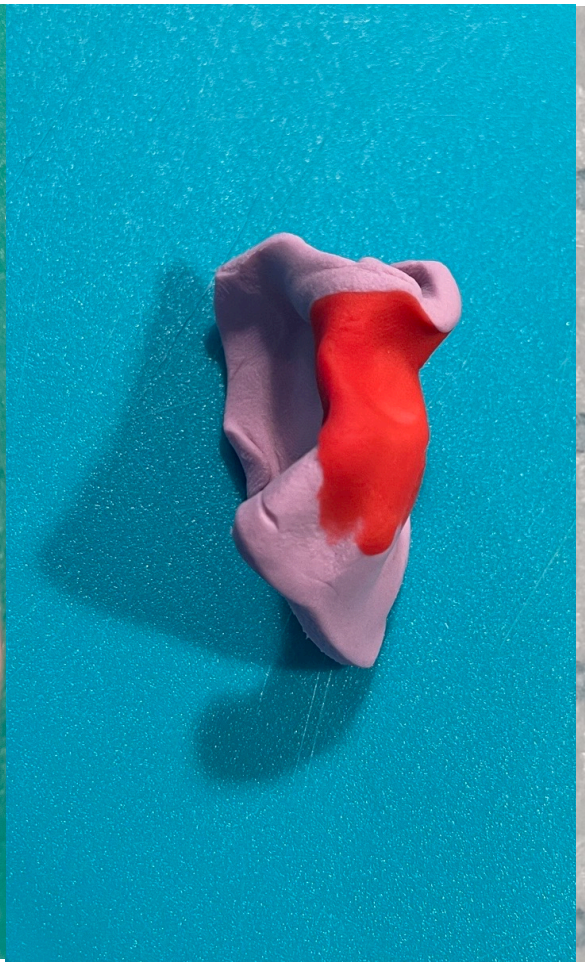
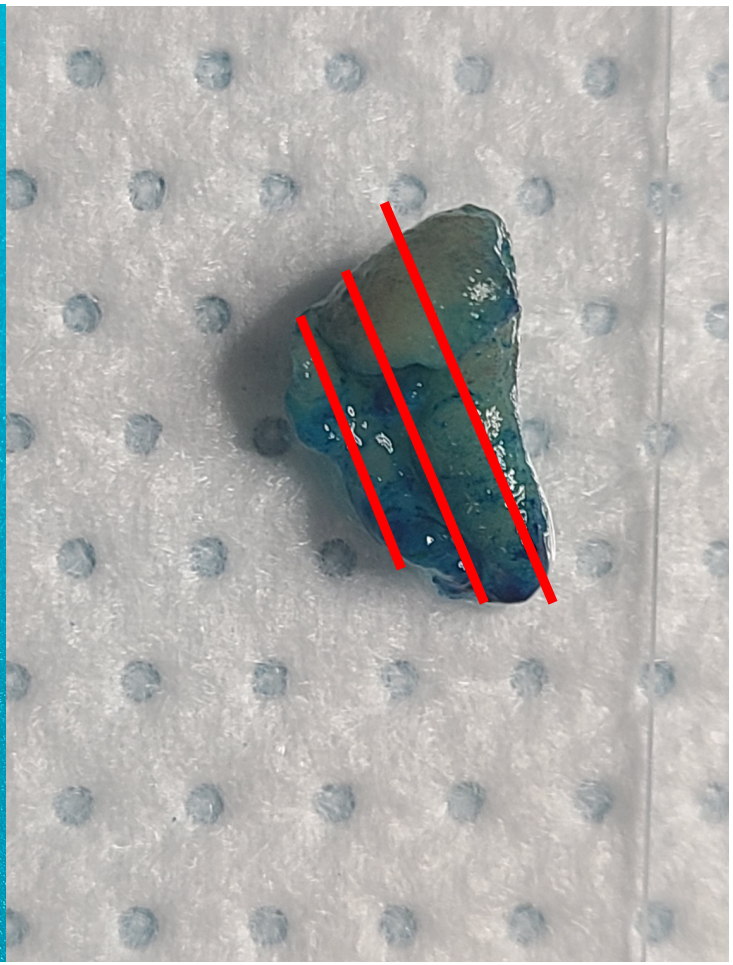
- “2-dimensional sections can never truly represent the 3-dimensional framework of the intestinal tissue under investigation.”
- Preparing polyp to avoid 2-dimensional interpretative errors.

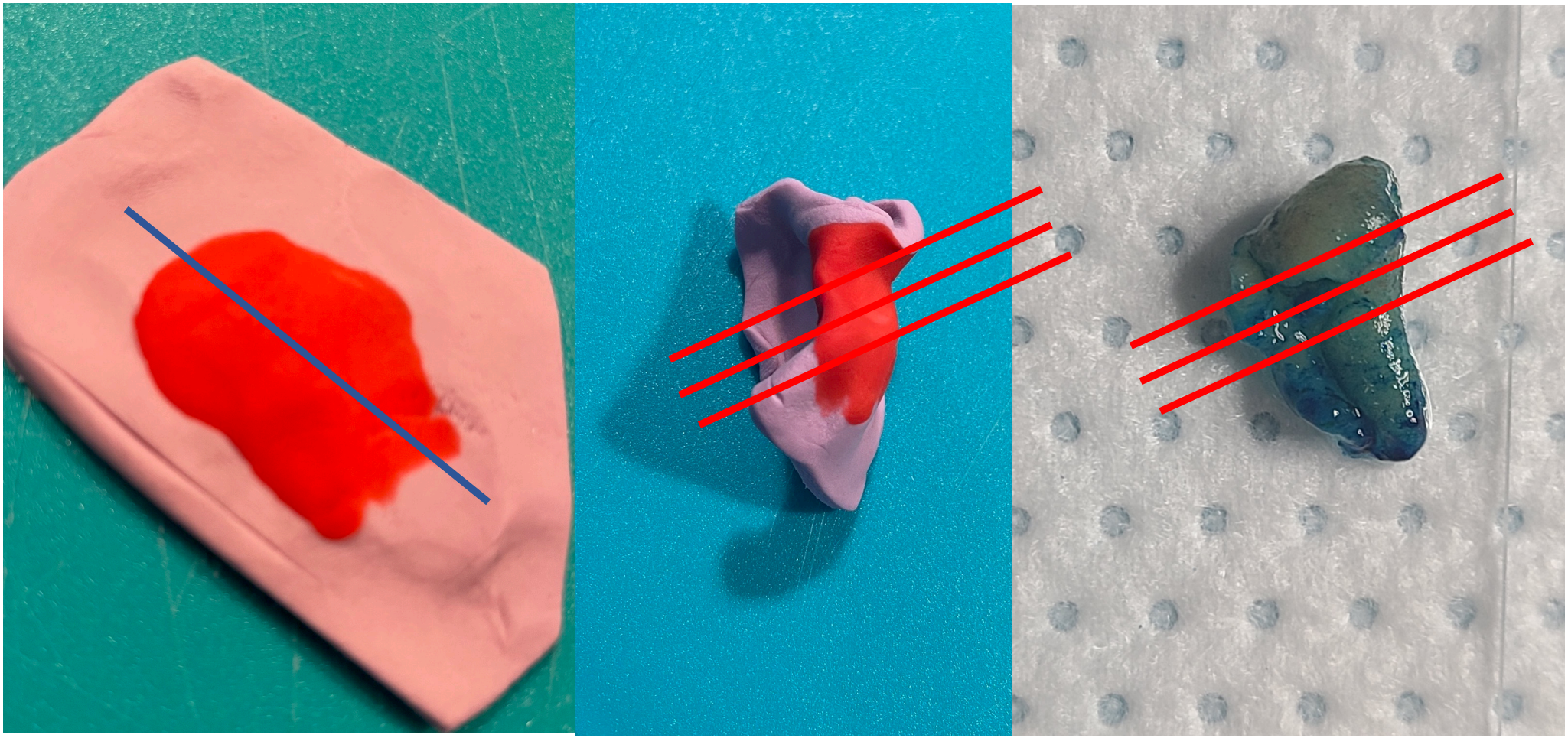
From 2-dimensional to 3-dimensional: Overcoming dilemmas in intestinal mucosal interpretation

Richard Pg Charlesworth [1], Michael N Marsh [2]





- For pathology-based polyp measurement, 78% of measurements were smaller than the original polyp size
- indicating that formalin fixation induces significant shrinkage of colorectal polyps.
- The estimated mean shrinkage effect of formalin fixation was 25.7%.
- This shrinkage effect resulted in 33.3% (5/14) of lesions ≥10mm being miscategorized as <10mm, and 33.3% (14/42) of lesions ≥5mm being miscategorized as <5mm.
- VSE size measurements was 84.2% and significantly higher compared to pathology sizing ($p<0.0001$).
- No difference in relative accuracy was observed between pinned and unpinned polyps (74.8 vs 73.4%; $p=0.67$) indicating that pinning polyps on cardboard does not reduce polyp shrinkage nor improve pathology size measurement accuracy.

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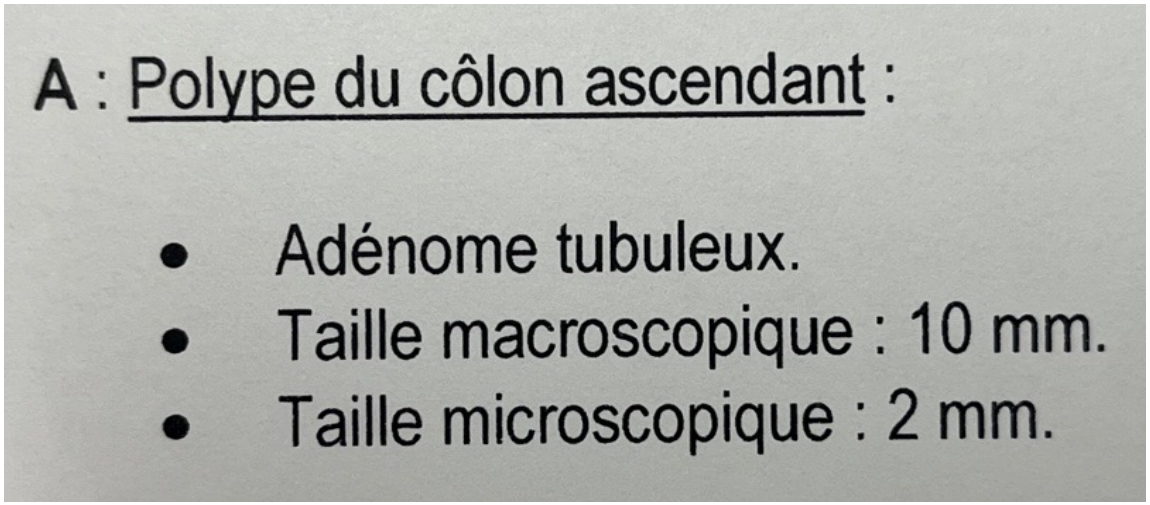
Conclusion

- Pathology is does not provide reliable polyp sizing information
- Polyps should be measured during colonocopy with validated tools



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CADx
or do we need pathology for “pathology”?

Mucosal folds, normal mucosa diagnosis

- Is common
- Usually 10% in published studies
- Previous manuscript by Neal Shahidi has indicated that high confidence adenoma Dx (CADx and expert)can be returned as "normal mucosa"

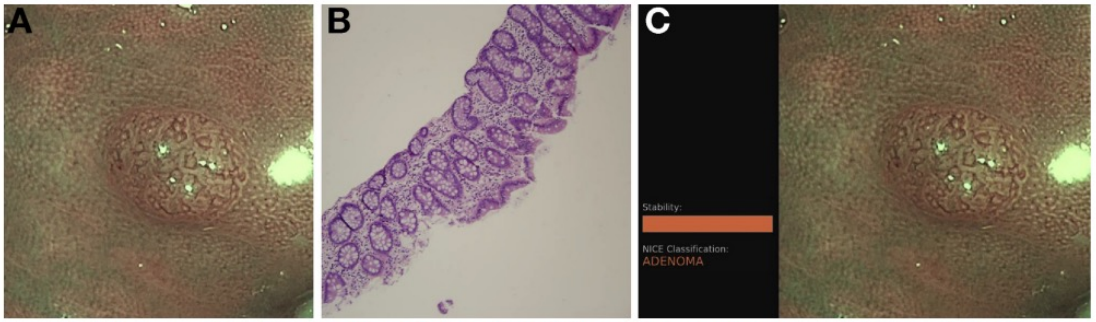


Figure 1. (*A*) A 3-mm colorectal lesion optically diagnosed with high confidence as adenomatous. (*B*) Histopathology identifies only normal mucosa. (*C*) CDSS supports the optical diagnosis.

Discordance between endoscopic & pathologic diagnoses is not infrequent

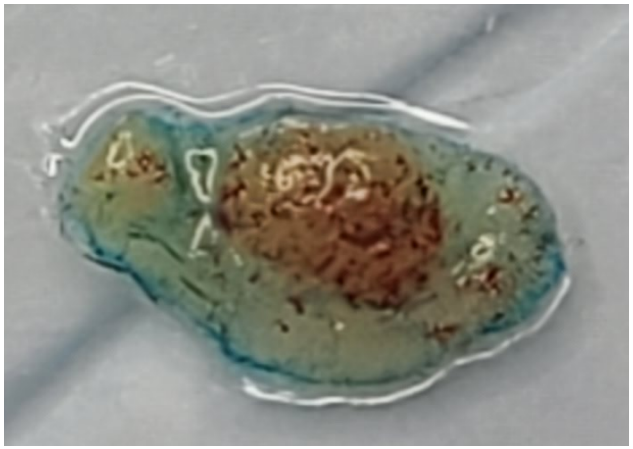
- 644 polyps ≤3mm with the diagnosis of high confidence adenomas by expert endoscopist (DKR) & with high quality images.
- **15.4%** reported as normal mucosa by pathologist.
- Images reviewed by two blinded outside experts, **nearly all lesions** were interpreted as high confidence adenomas (96.9% & 93.9%).
- Issues related to specimen retrieval & processing of tiny polyps.
- -Tissue specimen of tiny adenomas consists of substantially more normal tissue than adenoma, suboptimal sectioning causing the pathologist to believe that only normal tissue is present in the specimen.

Pathology may not always provide a superior ground truth!

Shahidi N et al. *Gastroenterology* 2019 Dec 18

“Mucosal fold, mucosal prolapse, normal mucosa” Re-evaluation study

- Because in scale eye study we evaluated post resection specimens
- 10% of pathology Dx was “normal mucosa”
- Seemed highly unlikely because of post resection evaluation



Mucosal folds

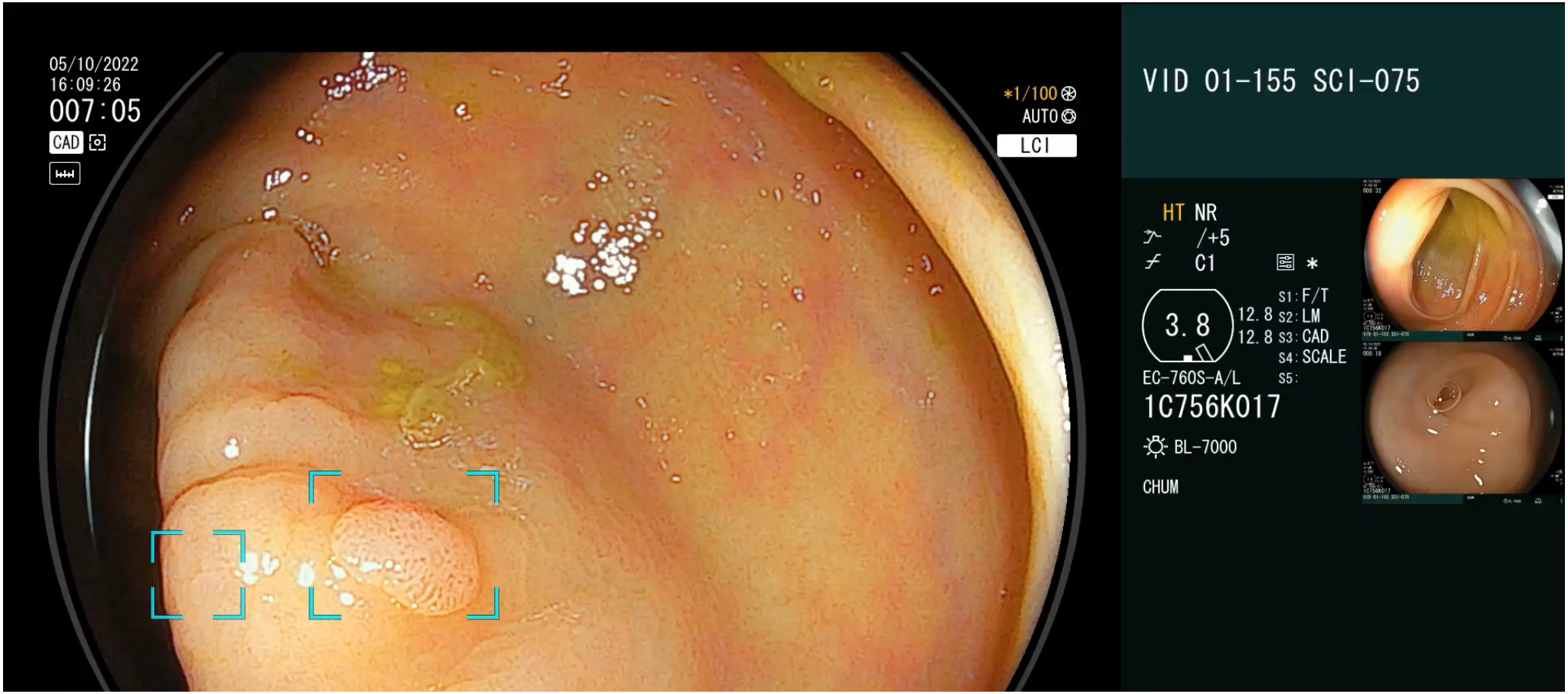
- 44 polyps diagnosed as mucosal folds by pathology
- 271 patients, 449 polyps in cohort

- 44 video recordings and CADx Dx during index colonsocopy

- CADx diagnosed 50% as adenomas, 50% as hyperplastic polyps.

“Mucosal folds”

- Invited 2 endoscopists with high expertise in optical diagnosis
  - Heiko Pohl, Douglas Rex for optical Dx review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S2:LM
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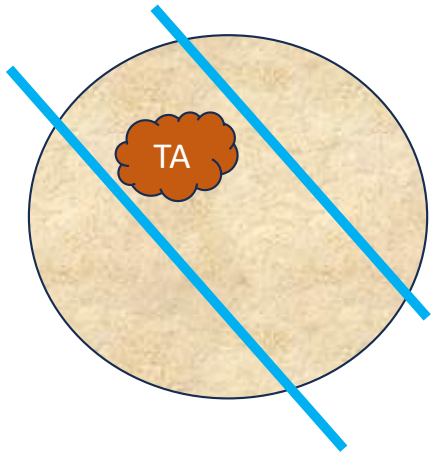
Wide margins: great for IRR, bad for histology

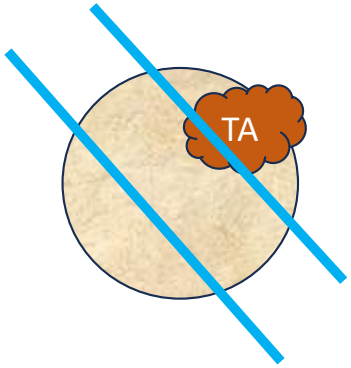


‘Normal colonic mucosa’

‘Mucosal prolapse’

‘Mucosal fold’

?



‘Tubular adenoma’

Results

- Both experts diagnosed ~55% as adenoma and ~45% as hyperplastic

- 15 cases were both reviewers and CADx diagnosed adenoma
- Surveillance intervals were assigned incorrectly in 25% of patients with a ‘mucosal fold’ due to the missed diagnosis.

- This also means that 10% of polyp histologies are missed when exclusively using pathology

Results

- Should we therefore use combination of optical diagnosis, CADx, and pathology?

Concluison

- ‘mucosal folds’ are most likely unrecognized HPs and adenomas
- Pathology misdiagnosis affects surveillance interval decisions

CADx
or do we need a “human in the loop”?

CADx – Human in the loop

- RCT with two arms
- Arm 1: Diagnosis based exclusively on CADx
- Arm 2: Endoscopist is aware of CADx diagnosis (Human is in the loop) and decides on fnla CADx informed diagnosis (whether they agree or not with CADx, SL Dx)

Results

- 467 patients randomized
- 229 CADx
- 238 Human in the loop (HiL)

Results

- CADx alone: Adenoma
  - Sensitivity: 89.7%
  - Specificity: 58.4%
  - PPV: 82.2%
  - NPV: 72.5%
- CADx+HiL: Adenoma
  - Sensitivity: 85.3%
  - Specificity: 69.6%
  - PPV: 81.8%
  - NPV: 74.8%
- CADx overall accuracy about 5% higher compared to HiL (mainly from incorrect SSL diagnoses by endoscopists)

Results – SSLs: Many false positives

- CADx cannot diagnose SSLs

- 20 SSLs in CADx arm, diagnoses:
  - 11 ‘neoplastic’
  - 10 ‘hyperplastic’

- HiL: 21 SSLs
  - Sensitivity: 66.6%
  - Specificity: 86.7%
  - PPV: 27.4%
  - NPV: 97.2%

Results

- “Flip flopping” = unclear CADx diagnosis in 12.4% of polyps in CADx arm
- Low confidence for endoscopists in 12.4% of polyps in HiL arm
- Equal percentage of ‘low confidence’ between CADx and Human in the loop

Conlcusion

- Promising results because CADx can function fairly well autonomously and human input is not required

- Once CADx systems with good SL characterisation accuracy come out CADx will likley outperform humans