Interobserver reliability of methods to determine complete resection of adenomas in colonoscopy

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ABSTRACT

Background Forceps margin biopsy and polypectomy specimen margins have both been used to assess for polypectomy resection adequacy. The interobserver reliability of the two methods has not been well described.

Methods The interpretability of polypectomy specimens for presence of residual neoplasia at the margin was assessed by two blinded pathologists. Next, the concordance of forceps margin biopsy interpretations between three blinded pathologists was evaluated by calculation of interobserver κ.

Results Rates of polypectomy specimen margin interpretability were low: 24/92 (26 %) for pathologist A, 28/92 (30.4 %) for pathologist B. Concordance of forceps margin biopsy interpretations (n = 129) between pathologists was high. Two internal pathologists showed substantial agreement in margin biopsy interpretations (κ 0.779; 95 %CL 0.543, 0.912). The concordance remained strong after biopsies were reviewed by a third, external pathologist (κ 0.829; 95 %CL 0.658, 0.924). There was complete agreement on 123/129 (95.3 %) between all three pathologists for presence of neoplasia.

Conclusion The majority of polypectomy specimen margins were uninterpretable by pathologists for presence of residual neoplasia. Forceps margin biopsy shows strong interobserver reliability in adenomatous lesions.

Introduction

Prior studies have shown that incomplete resection rates of adenomatous polyps are variable, but can be as high as 23 % for lesions measuring up to 2 cm found at colonoscopy when the post-polypectomy margin is biopsied [1]. Interval colorectal cancers (CRC) have been reported to occur more frequently at the sites of prior polypectomy, indicating that incomplete resection contributes to some interval CRC [2]. Evaluating the polypectomy specimen margin (PSM) and post-polypectomy forceps margin biopsy (FMB) are two different methods by which polypectomy resection completeness can be assessed. The interpretability and interreliability between pathologists' interpretations of these methods are not well described.

Methods

Study design

This was a prospective study that included 234 patients age 40 or above undergoing screening or surveillance of adenomatous polyps by colonoscopy from November 2013 to January 2020. Patients gave their informed consent to participate in the study prior to colonoscopy for marginal assessment of resected lesions. Institutional review board approval was obtained (IRB Identifier 16072702). Exclusion criteria included use of anticoagulants or clopidogrel, or a platelet count below $50 \times 10^3/\mu L$. Patients with polyposis syndromes such as familial adenomatous polyposis (FAP) were also excluded.

Snare polypectomy specimens (n = 92) taken during the screening or surveillance colonoscopy were evaluated for interpretability of the polypectomy margins. Polyps were reported as positive for neoplasia, negative, or uninterpretable. Marginal biopsies of adenomas (n = 129) from patients were performed following snare polypectomy removal of the polyp. Patients were reached by telephone 3 days after their procedure and asked about complications. Patients' charts were reviewed for 14-day rate of gastrointestinal bleeding and perforation after the procedure.

Endoscopic resection of lesions

Adenomatous polyps measuring 20 mm or less that were removed en bloc by snare polypectomy were included in this study. Eight endoscopists using high-definition colonoscopes (Olympus, Center Valley, Pennsylvania, USA) were instructed to obtain margin biopsies once complete resection was determined by the endoscopist. Polyps were described by Paris classification of morphology, by location, and by method of removal. Pedunculated polyps, polyps measuring more than 20 mm, those removed piecemeal, and those that gave concern for deep submucosal invasion were excluded. Polyps smaller than 6 mm were removed by cold snare polypectomy (Captivator Cold, Boston Scientific, Marlborough, Massachusetts, USA; or Exacto snare, US Endoscopy, Mentor, Ohio, USA) or with an RJ4 Jumbo forceps (Boston Scientific). Polyps 6–9 mm in size were variably removed with either cold snare or snare cautery. Polyps 10–20 mm in size were removed by snare cautery (Captivator 13 mm and 27 mm, Boston Scientific; or Lariat, US Endoscopy). Saline solution lift was performed at the discretion of the endoscopist.

FMB sampling at the post-polypectomy site

Following polyp removal, FMB were taken from the post-polypectomy sites. FMB were only taken after an assessment by the endoscopist that no residual polyp was evident. Margin biopsies (RJ4 Jumbo forceps, Boston Scientific) included four-quadrant forceps biopsies of polyps over 6 mm, and two marginal biopsies in lesions measuring under 5 mm. Polyps were retrieved into the Optimizer Polyp Trap (Conmed Endoscopic Technologies, Utica, New York, USA).

Polypectomy specimen protocol and interpretation

Polyps were placed in a formalin-filled specimen container and examined for size and number of tissue fragments within 4 hours of resection. Polyps were described as grossly fragmented if noted to be in multiple discrete fragments upon visual examination.

PSM were evaluated by two blinded board-certified pathologists from the same institution. A polypectomy specimen was deemed "intact" when it lacked gross or microscopic fragmentation. The PSM was deemed interpretable when it showed an identifiable resected base inferior to the mucosa and lateral edges on both sides of the polyp. The PSM was deemed uninterpretable when its resected base or lateral edges could not be interpreted (▶ **Fig.1**).

Polypectomy FMB protocol and interpretation

FMB were first evaluated by two blinded board-certified pathologists from the same institution. They were then evaluated by a third blinded board-certified pathologist from a separate institution. FMB results were reported as the presence or absence of residual neoplasia in any sample. All pathologists were blinded to the other pathologists' interpretations.

Statistical approach

The statistical significance of the interpretability of PSM when separated by categories including size, location of the polyp, histology, and method of removal was derived using Fisher's exact tests. The level of agreement of PSM interpretation between pathologists was derived by a Cohen's κ calculation: 0.81–1.00 indicating almost perfect agreement, 0.61–0.80 indicating substantial agreement, 0.41–0.60 indicating moderate agreement, and 0.21–0.40 indicating fair agreement. The magnitude of agreement noted reflects the guidelines established by Landis and Koch [3].

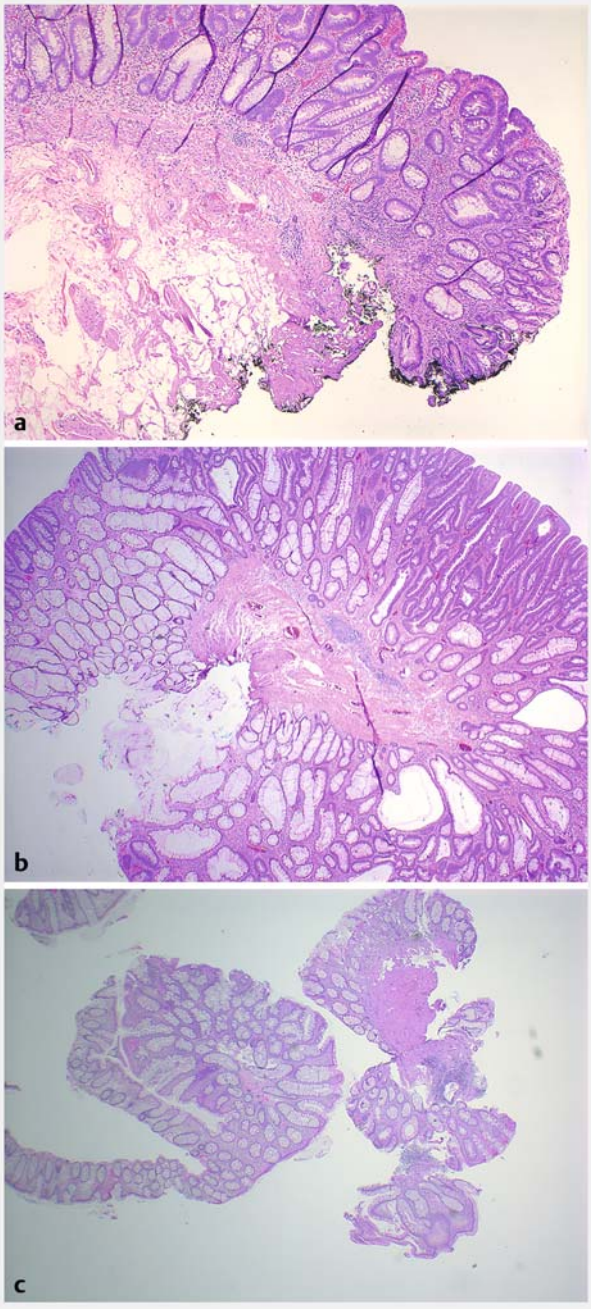
The pathology concordance of FMB interpretation was first assessed between the two internal pathologists and then between all three pathologists. The level of agreement of FMB interpretation between three pathologists was derived by a Fleiss' κ calculation.

Results

Assessment of PSM interpretability

Interpretation rate of PSM

Ninety-two polyps were included for the PSM-based interpretation of resection completeness. Of these, 24/92 (26 %) were deemed interpretable by pathologist A, and 28/92 (30.4 %) were deemed interpretable by pathologist B (▶ **Table 1**). ▶ **Table 1** shows that location, size, method of removal, and polyp histology did not predict a subset of polyps that were reliably interpretable.



▶ **Fig. 1** Polypectomy specimen margin histopathology. **a** Interpretable specimen of an adenoma with a positive margin. **b** Interpretable specimen of an adenoma with a negative margin. **c** Uninterpretable margin due to macroscopic fragmentation.

Fragmentation associated with lack of interpretability of PSM

Gross specimen fragmentation was noted in 45/92 of polyps (48.9%) by both pathologists. Of the 45 grossly fragmented polyps, 4/45 (8.9%) were interpretable by pathologist A and 8/45 (17.8%) were interpretable by pathologist B. Gross fragmentation was significantly correlated with reduced inability to interpret resection completeness ($p \leq 0.01$).

▶ **Table 1** Polypectomy specimen margin characteristics.

Polyp characteristics	All PSM (n = 92)	Interpretable PSM, pathologist A (n = 24)	Interpretable PSM, pathologist B (n = 28)
Size			
▪ < 6 mm	15	4/15 (26.7%)	3/15 (20%)
▪ 6 to < 10 mm	43	13/43 (30.2%)	13/43 (30.2%)
▪ 10 to 20 mm	34	7/34 (20.6%)	13/34 (38.2%)
		$P = 0.22$[1]	$P = 0.81$
Location in the colon			
▪ Right[2]	69	17/69 (24.6%)	20/69 (29%)
▪ Left	23	7/23 (30.4%)	8/23 (34.8%)
		$P = 0.99$	$P = 0.79$
Polyp histology			
▪ Tubular or tubulovillous adenoma	80	18/80 (22.5%)	25/80 (31.3%)
▪ Sessile serrated adenoma	12	6/12 (50%)	3/12 (25%)
		$P = 0.07$	$P = 0.75$
Method of removal			
▪ Snare cautery	66	17/66 (25.8%)	22/66 (33.3%)
▪ Cold snare	26	7/26 (26.9%)	6/26 (23.1%)
		$P = 0.99$	$P = 0.45$

PSM, polypectomy specimen margin.
[1] *P* values calculated separately for each pathologist to define subgroup predictors of margin neoplasia status interpretability.
[2] I.e., proximal to the splenic flexure.

Concordance of FMB interpretation

Of the 129 FMB, there was minimal variation in interpretation between the three pathologists, with FMB positivity for neoplasia ranging from 12/129 (9.3%) to 14/129 (10.9%). There was complete agreement on 124/129 (96.1%) between pathologist A and pathologist B. The concordance between internal pathologists was calculated to be $\kappa = 0.779$ (95% confidence limits [CL] 0.543, 0.912), suggesting substantial agreement. There was complete agreement on 123/129 (95.3%) for the presence of neoplastic tissue (i. e., positive margin) between all three pathologists. The concordance between pathologists was calculated to be $\kappa = 0.829$ (95%CL 0.658, 0.924), indicating almost perfect agreement (▶ **Table 2**). Size, location, and method of removal did not have an impact on the concordance between pathologists. Discordance of FMB interpretation was infrequent, occurring in only 6/129 FMB samples (4.6%). Discordance occurred in cases where cold snare, snare cautery, or forceps were used; thus, particular resection techniques were not associated with a significantly higher rate of discordant samples.

▶ **Table 2** Forceps margin biopsy characteristics.

	All FMB taken from adenomatous polyps (n = 129)	Positive FMB, pathologist A (n = 13)	Positive FMB, pathologist B (n = 12)	Positive FMB, pathologist C (n = 14)
All adenomatous polyps (κ 0.829, 95 %CL [0.658, 0.924])				
		13/129 (10.1 %)	12/129 (9.3 %)	14/129 (10.9 %)
Size				
▪ < 6 mm	104	10/104 (9.6 %)	7/104 (6.7 %)	9/104 (8.7 %)
▪ 6 to < 10 mm	17	2/17 (11.8 %)	4/17 (23.5 %)	4/17 (23.5 %)
▪ 10 to 20 mm	8	1/8 (12.5 %)	1/8 (12.5 %)	1/8 (12.5 %)
Location in the colon				
▪ Right*	99	11/99 (11.1 %)	9/99 (9.1 %)	11/99 (11.1 %)
▪ Left	30	2/30 (6.7 %)	3/30 (10 %)	3/30 (10 %)
Polyp histology				
▪ Tubular adenoma	125	12/125 (9.6 %)	11/125 (8.8 %)	13/125 (10.4 %)
▪ Tubulovillous adenoma	4	1/4 (25 %)	1/4 (25 %)	1/4 (25 %)
Paris classification				
▪ 1 s	120	11/120 (9.2 %)	10/120 (8.3 %)	12/120 (10 %)
▪ 1sp	3	0/3 (0 %)	0/3 (0 %)	0/3 (0 %)
▪ IIa/IIb	6	2/6 (33.3 %)	2/6 (33.3 %)	2/6 (33.3 %)
Method of removal				
▪ Snare cautery	22	3/22 (13.6 %)	5/22 (22.7 %)	5/22 (22.7 %)
▪ Cold snare	46	2/46 (4.3 %)	0/46 (0 %)	2/46 (4.3 %)
▪ Forceps	61	8/61 (13.1 %)	7/61 (11.5 %)	7/61 (11.5 %)
Use of saline lift				
▪ Yes	6	2/6 (33.3 %)	2/6 (33.3 %)	2/6 (33.3 %)
▪ No	123	11/123 (8.9 %)	10/123 (8.1 %)	12/123 (9.8 %)

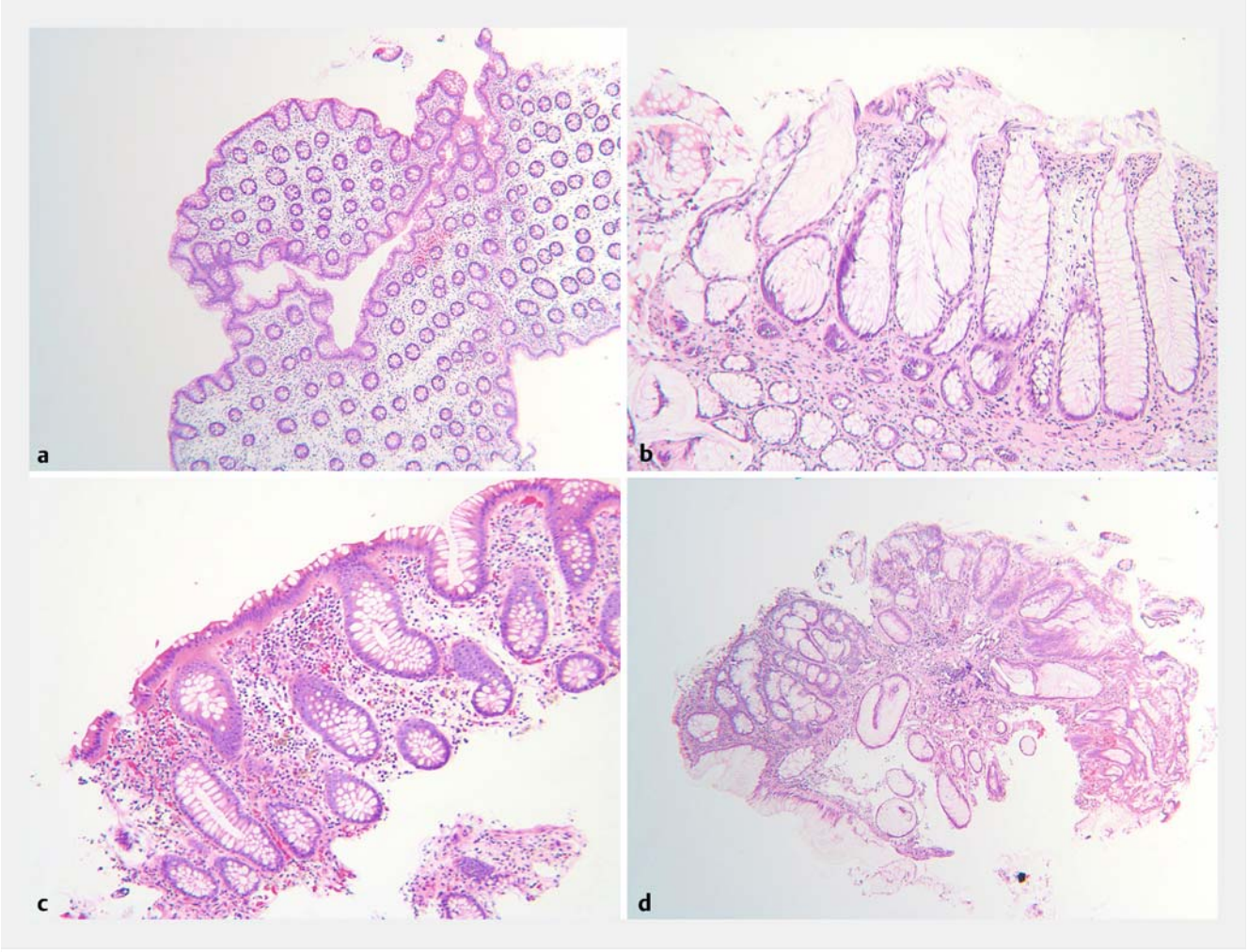
FMB, forceps margin biopsies.
* I.e., proximal to the splenic flexure.

Discussion

FMB interpretation was highly concordant amongst the three pathologists in defining whether neoplastic tissue remained at the margin of en bloc resected polyps, with minimal variation in rates of positivity between the three pathologists. In contrast, less than a third of PSM were interpretable by the pathologists. Gross fragmentation during polyp extraction occurred in nearly half of all polyps, and largely explains the low rates of interpretability. Our findings suggest that methods to improve extraction of the polyp, such as pressing the suction button firmly during removal [4, 5], and preservation of the polyp during processing with methods like polyp pinning [6, 7], should be explored to improve interpretability.

FMB as a method to define completeness of resection has now been used in multiple recent studies [1, 8–10]. Our rates of positive FMB in adenomatous polyps removed by snare polypectomy and forceps were calculated to be 9.3 % and 10.9 %, respectively. Snare polypectomy rates in our study, though not the endpoint of the study, were somewhat comparable to those in other reports [11]. Discordance amongst pathology interpretation of FMB samples was uncommon and may be due to sampling of cautery artifact and inflammation along the margins. Both can create tissue changes that can be difficult to interpret (▶ **Fig. 2**). This study also showed no appreciable risk of complications such as perforation or post-polypectomy bleeding due to FMB.

Strengths of the study include blinding of the pathologists to their colleagues' interpretations. In addition, we included only polyps removed en bloc when snared and with the endoscopic impression of complete eradication. There was a standardized uniform method for marginal sampling. Limitations of the study include that the sample size of polyps included was relatively modest. In the interpretation of PSM, no pinning or other techniques to preserve polyps were employed. A further limitation is that the clinical implications of having residual



▶ **Fig. 2** Forceps margin biopsy histopathology. **a** Margin biopsy with agreement between pathologists and negative for adenoma. **b** Margin biopsy with disagreement due to cautery artifact. **c** Margin biopsy with disagreement due to inflammation. **d** Margin biopsy with agreement between pathologists and positive for adenoma.

neoplasia on FMB were not defined in terms of metachronous neoplastic risk. Patient clinical safety outcomes were assessed, though it is possible the patients may have presented to another institution with an endoscopic complication.

The findings from our study are timely given the emerging role for machine learning in the detection and differentiation of colorectal lesions during colonoscopy. A real-time ability to determine true complete resection post-polypectomy is an aspirational goal that could allow the endoscopist to confirm during the procedure that complete eradication has been achieved. However, a true pathologic gold standard needs to be established if machine learning is to be used to determine resection completeness. While this study does not identify such a gold standard, it suggests that FMB is superior to PSM as a reproducible methodology with high interobserver reliability that may serve as a proxy for complete resection at this time. The clinical implications of a positive resection margin for future neoplasia progression deserve further study.

Competing interests

Dr. Joshua Melson serves on the medical advisory board for Virgo Imaging. He has received grant funding from Boston Scientific. The remaining authors have no conflict of interest to disclose.

Clinical trial

Trial Registration: ClinicalTrials.gov | Registration number (trial ID): NCT02217085 | Type of study: Prospective

Funding

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