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Incomplete Polyp Resection During Colonoscopy—Results of the Complete Adenoma Resection (CARE) Study

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BACKGROUND & AIMS: Although the adenoma detection rate is used as a measure of colonoscopy quality, there are limited data on the quality of endoscopic resection of detected adenomas. We determined the rate of incompletely resected neoplastic polyps in clinical practice. METHODS: We performed a prospective study on 1427 patients who underwent colonoscopy at 2 medical centers and had at least 1 nonpedunculated polyp (5–20 mm). After polyp removal was considered complete macroscopically, biopsies were obtained from the resection margin. The main outcome was the percentage of incompletely resected neoplastic polyps (incomplete resection rate [IRR]) determined by the presence of neoplastic tissue in post-polypectomy biopsies. Associations between IRR and polyp size, morphology, histology, and endoscopist were assessed by regression analysis. RESULTS: Of 346 neoplastic polyps (269 patients; 84.0% men; mean age, 63.4 years) removed by 11 gastroenterologists, 10.1% were incompletely resected. IRR increased with polyp size and was significantly higher for large (10–20 mm) than small (5–9 mm) neoplastic polyps (17.3% vs 6.8%; relative risk = 2.1), and for sessile serrated adenomas/polyps than for conventional adenomas (31.0% vs 7.2%; relative risk = 3.7). The IRR for endoscopists with at least 20 polypectomies ranged from 6.5% to 22.7%; there was a 3.4-fold difference between the highest and lowest IRR after adjusting for size and sessile serrated histology. CONCLUSIONS: Neoplastic polyps are often incompletely resected, and the rate of incomplete resection varies broadly among endoscopists. Incomplete resection might contribute to the development of colon cancers after colonoscopy (interval cancers). Efforts are needed to ensure complete resection, especially of larger lesions. ClinicalTrials.gov Number: NCT01224444.

Keywords: Colon Cancer Screening; Early Detection; CRC; CARE Study.

It is widely accepted that the benefit of screening colonoscopy largely derives from the detection and removal of the precancerous lesion—the adenomatous polyp—with subsequent reduction in colorectal cancer (CRC) incidence and mortality. In observational studies, previous exposure to colonoscopy is associated with a 77% reduction in CRC incidence and 29%–37% reduction in CRC death1–3 compared with those without previous colonoscopy. However, the risk reduction was primarily observed in the left colon and was either weaker or nil for right-sided cancers.

The observed lack of benefit from colonoscopy in the right colon combined with reports on the detection of post-polypectomy or so-called “interval” CRC4–7 have raised concerns about the effectiveness of colonoscopy and colonoscopic polypectomy. Three possible reasons have been suggested to explain the occurrence of interval CRC. First, interval cancers might be lesions that were missed during earlier colonoscopy; either missed cancers or missed adenomas that progressed to cancer during follow-up. Missed lesions can account for 70%–80% of interval cancers.8 Second, interval cancers can represent newly developed fast-growing cancers. This suggestion is based on the observation that some interval cancers have genetic features that can be associated with a more rapid progression to cancer.9 Third, interval cancers can result from an incompletely resected lesion—either a cancer or an adenoma that progressed to cancer. It has been estimated that incompletely resected lesions during earlier colonoscopy might explain 10%–27% of observed interval cancers.4,5,10

Although incomplete resection is recognized as an important contributor to interval CRC, there is surprisingly little direct information on the adequacy of polyp resection.11 It is generally assumed that resection is complete if no apparent polyp tissue is visible after resection. Using a snare with electrocautery should destroy any remaining polyp tissue. However, whether electrocautery resection completely removes all adenomatous is unknown. Residual adenoma tissue can grow and transition to cancer. We aimed to determine the proportion of incompletely re-
ected neoplastic polyps in clinical practice and to understand factors affecting incomplete resection.

Materials and Methods

Participants

Adults (aged 40 through 85 years) who presented for an outpatient colonoscopy at two academic medical centers (ie, Dartmouth-Hitchcock Medical Center, Lebanon, NH and VA Medical Center, White River Junction, VT) without a history of inflammatory bowel disease or a coagulopathy (international normalized ratio ≥1.8) were asked to participate. Those who agreed provided informed consent and were subsequently included into the study cohort if at least one polyp of eligible size (≥5 mm to ≤20 mm) was detected during colonoscopy. Pedunculated polyps were not included in the study.

Procedure

Colonoscopy, after preparation with polyethylene glycol solution was performed, by board-certified gastroenterologists using standard colonoscopes (CF/PCF 160, CF/PCF180, H-CF/H-PCF 180) and polypectomy snares (Snaremaster, Olympus, Center Valley, PA; Small oval; Boston Scientific, Natick, MA). Endoscopists were instructed to measure polyp size using the size of the snare catheter or the snare diameter. Polyp characteristics were documented at the time of detection. All polyps were removed using blended coagulation mode with available electrocautery equipment (Valleylab, Boulder, CO and ERBE, Marietta, GA) and an intention of en bloc resection. The ease of polyp resection (easy < 1 min, moderately difficult 1–3 min, difficult > 3 min) was noted. After resection and endoscopist’s attestation that polyp removal was complete by careful macroscopic inspection of the resection margins, forceps biopsies were obtained from the polyp resection margin. Use of narrow band imaging, chromoendoscopy, or application of argon plasma coagulation were not required as part of the resection protocol, but could be used at the discretion of the attending endoscopist. The study protocol directed that 2 biopsies from opposing sides of the margin for 5–9 mm polyps and 4 biopsies for 10–20 mm polyps from 4 quadrants be performed.

Histopathology Evaluation

A single-study expert gastrointestinal pathologist (AS) independently classified all polyps and interpreted all research biopsies for evaluation of residual adenomatous tissue at the polyp margins. The polyps were broadly grouped into “neoplastic polyps” and “other polyps.” Neoplastic polyps included all polyoid lesions currently accepted as direct precursors lesions of CRC and included conventional adenomas (categorized as tubular, tubulovillous, or villous using established criteria), traditional serrated adenomas (or tubulosserrated adenomas), sessile serrated adenomas/polyps (SSA/P), and lesions containing high-grade dysplasia or cancer. Although hyperplastic polyps share mutations similar to SSA/P lesions, they are not considered direct precursors of CRC at the present time and were, therefore, grouped with “other polyps.” Pathologic criteria used for diagnosis of SSA/P were based on those initially proposed by Torlakovic et al12 and that are now incorporated into the most recent World Health Organization classification of serrated polyps.13 For conventional adenomas and traditional serrated adenomas, polyp margins were considered to be positive if the research biopsies showed any dysplastic epithelium. SSA/P are not cytologically dysplastic and, as recognized in the new World Health Organization classification, “some areas of SSA/P may have straight crypts similar to microvesicular hyperplastic polyps.” Therefore, presence of any residual serrated epithelium in research biopsies, regardless of architectural features, was considered to be a positive margin for SSA/P. Hyperplastic polyps were considered incompletely resected if marginal biopsies showed the presence of any serrated epithelium.

Outcome Measures

The primary outcome of interest was the incomplete resection rate (IRR) of neoplastic polyps as determined by the histopathologic examination of polyp margin biopsies using the criteria described here. We further evaluated possible factors that could contribute to an incomplete resection. These included size, anatomic location (right side was defined as or proximal to the splenic flexure), location with respect to colonic folds (between/on the fold or partially/completely behind a fold), flat morphology (height < 2.5 mm as measured by the diameter of the 2.4-mm snare catheter), polyp histology, en bloc vs piecemeal resection, and ease of polyp resection (easy or < 1 min; moderately difficult or 1–3 min, difficult or > 3 min). Variation between endoscopists was not an a priori outcome measure and endoscopists contributed a varying number of study polyps. We calculated the IRR for those endoscopists with at least 20 study polyp resections.

Sample Size Calculation

The primary outcome was the incomplete resection rate of 5- to 20-mm neoplastic polyps. We hypothesized that size would affect incomplete resection and powered our analysis based on that factor—a comparison between incomplete resection of large (10–20 mm) and small polyps (5–9 mm). We considered a complete resection rate of at least 95% (95% confidence interval [CI] > 90%) as clinically sufficient and a rate of 85% (upper limit of the 95% CI of < 90%) as insufficient. Assuming a 10% absolute difference between these groups (95% vs 85%) 300 small and 100 large polyps needed to be included. Considering a 10% prevalence of large neoplastic polyps,14,15 we estimated that at least 1000 patients needed to be consented for the study.

Statistical Analysis

The main outcome (proportion of incompletely resected neoplastic polyps, IRR) is presented as a proportion with a 95% CI. For comparison of proportions, we applied the χ² test or the 2-tailed Fisher’s exact test when appropriate. We calculated relative risks (RR) for factors that affect completeness of resection using Poisson regression analysis using robust standard error calculation.16 Factors associated with the outcome in univariate analysis (P ≤ .20) were then examined in multivariable Poisson logistic regression analysis to identify factors independently associated with incomplete resection. Covariates that remained significant in the multivariate analysis were applied in the final regression model to compute adjusted odds ratios. The discriminatory ability of the model was reported using a C-index (area under the receiver operating characteristic curve) corrected for overfitting using bootstrap cross-validation. Interactions were tested for but none found. There were no issues related to collinearity. The frequency of missing data was zero except for morphology (12% missing) and no imputation was used. To examine the effect of endoscopists on incomplete resection, we used a fixed effect of endoscopist and a random effect of endoscopist. The variation between endoscopists was not an a priori outcome measure and endoscopists contributed a varying number of study polyps. We calculated the IRR for those endoscopists with at least 20 study polyp resections.
for each endoscopist with at least 20 study polyp resections compared with the endoscopist with the lowest IRR. All authors had access to the study data and had reviewed and approved the final manuscript.

## Results

### Patient Characteristics

An eligible polyp was found in 269 patients of the 1427 individuals who were consented for the study (Figure 1). The mean age in the study cohort was 63.4 years (±9.1 standard deviation) and 84.0% were men. Most colonoscopies were performed either for screening (36.8%) or surveillance (33.1%) (Table 1).

### Polyp Characteristics

A total of 418 study polyps were resected by 11 endoscopists; 346 polyps (82.8%) were neoplastic (Table 2), of which 286 (68.4%) were classified as tubular, tubulovillous, or villous adenomas. Forty-eight neoplastic polyps (11.5%) had a serrated histology, of which 6 (1.4%) were traditional serrated adenomas and 42 (10.1%) were SSA/P. High-grade dysplasia was found in 11 polyps (2.6%) and cancer in 1 polyp (0.2%). Mean size was 8.3 mm (±3.6 standard deviation) and 116 (27.8%) were large polyps. One hundred and ninety (50.4%) polyps were classified as flat. Two hundred and forty-one (57.7%) study polyps were resected by one endoscopist, and the remaining endoscopists removed between 1 and 29 study polyps. After the study biopsies, immediate bleeding requiring endoscopic treatment occurred in 8 patients (3.0%), with none requiring any additional therapy. There were no severe adverse events related to the study biopsies.

### Incomplete Resection Rate

The IRR for neoplastic polyps was 10.1% (95% CI: 6.9%–13.3%). Incomplete resection was significantly more common for large compared with small neoplastic polyps (17.3% vs 6.8%; \( P = .003 \)). SSA/P were more likely to be incompletely resected than other neoplastic polyps (31.0% vs 7.2%; \( P < .001 \)), and almost half (47.6%) of all large (10–20 mm) SSA/P were incompletely removed. None of the polyps containing high-grade dysplasia or cancer were incompletely resected. Only 2 of 64 (3.1%) hyperplastic polyps were incompletely removed.

### Factors Associated With IRR

Size and SSA/P diagnosis showed the strongest association with incomplete resection in multivariable
regression analysis (Table 3). The C-Index of the model was 0.71 and 0.69 when corrected for overfitting. The risk of incomplete resection increased significantly with size (test for trend $P < 0.001$). Large neoplastic polyps (10–20 mm) were more than 2 times more likely to be incompletely removed than small polyps (5–9 mm) ($RR = 2.1; 95\% CI: 1.13–3.86$). SSA/P were almost 4 times more likely to be incompletely resected than other neoplastic polyps.

Although the majority of SSA/P were flat (62.5%), incomplete resection of flat or nonflat SSA/P was similar (32.0% vs 26.7%; $RR = 1.2; 95\% CI: 0.43–3.36$).

In univariate analysis, more neoplastic polyps were incompletely resected if they were removed piecemeal (20.4% vs 8.4%) or when resection was perceived as difficult (15.0% vs 7.7%). However, piecemeal resection or difficult resection was not significantly associated with incomplete removal after adjustment for size and histology. Polyp location in the right or left colon or with respect to a fold or flat polyp morphology was also not significantly associated with incomplete resection.

### IRR Variability Between Endoscopists

For this analysis, IRR was determined only from the 5 endoscopists with at least 20 study polyp resections; it ranged from 6.5% to 22.7% (Figure 2). Using the endoscopist as a random effect in a mixed effects model with fixed effects of size and SSA/P diagnosis resulted in a $P$ value of .10 for the test of significant variation between endoscopists. When IRR was compared with the endoscopist with the lowest rate, other endoscopists were up to 3.4 times more likely to incompletely resect neoplastic polyps in the adjusted analysis (95% CI: 1.35–8.81).

![Figure 2. Rates of incompletely resected neoplastic polyps for endoscopists with at least 20 polyp resections and risks of incomplete resection for individual endoscopists compared with the endoscopist with the lowest incomplete resection rate (Endoscopist A). RRs are adjusted for size and diagnosis of sessile serrated adenoma/polyp.](image-url)
IRR for neoplastic polyps of all endoscopists with at least 20 polyp resections combined was not different from the IRR of the other 6 endoscopists with < 20 study polyp resections (9.7% vs 12.3%; P = .630).

Discussion

Our 2-center multi-endoscopist study showed that approximately 10% of all neoplastic polyps between 5 and 20 mm are incompletely resected, ie, neoplastic tissue was left behind, as proven by biopsies from resection margins. Incomplete resection was more frequent for large polyps (≥ 10 mm) and for SSA/P. We observed a broad variation in the resection rate between individual endoscopists.

The occurrence of post-colonoscopy CRC is well described and 3 main reasons have been implicated in such cases. The majority of interval cancers (70%–80%) are likely attributed to a missed lesion at the baseline colonoscopy. The occurrence of fast-growing de novo cancers. Lastly, incompletely resected lesions at baseline colonoscopy have been implicated in 10%–27% of interval cancers. These estimates are based on retrospective studies examining characteristics of interval cancers. The cancer was considered a result of incomplete resection if it occurred at a site of a previously resected adenoma, which could have been either any adenoma or limited to adenomas with high-risk features. Such estimates are inherently limited. It is also plausible that new cancers might have developed in the same segment or that additional adenomas were missed and transitioned to cancer. Because it is not feasible to study the natural progression of incompletely resected adenomas, the best evidence will remain circumstantial. Our findings that some neoplastic precursors of CRC are incompletely removed support the assertion that a subset of interval cancers might be the result of incomplete resection.

To our knowledge there has been only one other study evaluating completeness of polyp resection. This small study examined forceps biopsy removal of 54 diminutive (≤ 5 mm) polyps. Of 21 adenomas, 8 (38%) were incompletely removed. In contrast, our study included a much broader size range of polyps (5 and 20 mm) and likely has greater clinical relevance to the practice of colonoscopy.

Our study provides plausible data that incomplete polyp resection in daily clinical practice is relatively common and can contribute to future interval cancers. We found that larger polyps were more likely to be incompletely resected than smaller polyps. Because adenoma size is associated with both a higher prevalence of advanced histology and greater near-term risk of transition to cancer, incomplete resection of large neoplastic polyps is concerning. We also found a high IRR for SSA/P, which approached 50% for large lesions. SSA/P are considered precursors of microsatellite unstable CRC and express different patterns of genetic abnormalities, such as mutations in the BRAF gene, compared with tubular adenomas. These have been found more frequently in post-colonoscopy CRC, suggesting that SSA/P might more often be precursors of interval CRC as compared with noninterval CRC. In addition to our results, other studies have shown a broad variation in the detection of SSA/P, suggesting that SSA/P might also be often missed. These findings support the idea that SSA/P play a critical role in the phenomenon of post-colonoscopy CRC.

Although not a primary study aim, we found a wide range in the rate of incomplete resection among experienced endoscopists. The finding is consistent with earlier studies documenting variation in other aspects of technical competence (eg, cecal intubation rate, withdrawal time, and adenoma detection rate). Variability in the endoscopists’ technique and time spent to examine the polypectomy site for completeness of resection are likely critically important to assure effective polypectomy. Polyp resection technique is not standardized and approach depends primarily on individual experience and preference. A survey among gastroenterologists found broad variation in polypectomy practice, especially in the use of a forceps or snare, or the application of electrocautery. In our study, we used standardized snares and blended electrocautery for all resections. Each endoscopist was also instructed to assure visibly complete resection before obtaining marginal biopsies, which should have established a common starting point before obtaining study biopsies, even in the absence of a detailed resection protocol.

Several limitations to our study should be noted. First, all endoscopists were aware of their participation in the study and therefore might have been more careful to assure complete resection of polyps and affected the diligence with which marginal biopsies were obtained. Second, our main outcome measure is prone to sampling error, as marginal biopsies only represent part of the polyp margin. To minimize this error, we obtained additional biopsies for larger polyps to sample a similar proportion of the margin circumference; however, it is possible that remnant adenoma tissue was missed. Both factors bias the result toward a more favorable outcome. If anything, we are underestimating incomplete resection in clinical practice. The increased number of marginal biopsies that were obtained for larger polyps cannot explain the difference in incomplete resection, because we found an increase in incomplete resection independent of the number of biopsies obtained (Supplementary Figure 1). Third, variation across endoscopists was not an a priori outcome measure, and the study was not designed to examine differences between endoscopists. In addition, one endoscopist (who had a low IRR) performed a disproportionate number of the total cases. To limit the effect of this, analysis of variation was limited to endoscopists performing at least 20 study polypectomies. Still, the observed variation was based on a smaller number of cases and therefore only provides some initial data and should be confirmed by others with an even larger and more diverse set of endoscopists. Fourth, some might
argue that the resection technique was not adequate. For example, some endoscopists might perform additional maneuvers (ie, routine use of narrow band imaging to delineate polyp margins and to assess margins after resection) that were not routinely done as part of the study. Therefore, our results might not be generalizable to endoscopists who routinely practice in this fashion, although we suspect few do. Fifth, it is possible that remaining microscopic neoplastic tissue in the cauterized resection margin might not be of clinical importance. Interval cancers might rather be a result of a missed lesion in the same segment of incompletely resected polyps or represent de novo cancers. Because of the nature of our study, where remaining polyp tissue might have been completely removed by study biopsies, it is impossible to examine the true clinical importance of incompletely resected polyps. However, studies on post-colonoscopy CRC and their characteristics suggest that incomplete resection does occur and, to the extent it does, residual microscopic tissue is the first mechanistic step in those cases.

Our results raise questions about the quality of polyp resection and call for efforts to improve resection of neoplastic polyps, especially of large polyps and SSA/P. To establish an optimal resection technique, efforts should focus on preparation for resection, the resection technique, and assessment of complete polyp removal after resection. Especially an increased attention to the polyp margin supported by special imaging (ie, by using narrow band imaging, chromoendoscopy, or endomicroscopy) might improve outcomes. Outlining and marking the polyp margin before resection can enhance complete resection. In some cases, adjunctive ablation of the margins after resection of large polyps can be useful to assure complete removal, and marginal biopsies after resection may be useful to increase confidence in the completeness of removal and aid in post-polypectomy management. Identifying and addressing issues such as these will facilitate development of resection standards for polypectomy that can improve outcomes.

Conclusions

We found that 10% of neoplastic polyps between 5 and 20 mm were incompletely removed. Incomplete resection increased with polyp size, was significantly higher for SSA/P (both factors are associated with increased risk of malignant degeneration of adenomas), and varied broadly between endoscopists. To date, quality measures have predominantly focused on polyp detection (eg, adenoma detection rates). Our results suggest a need for quality metrics evaluating polyp resection. The performance of high-quality and effective colonoscopy not only requires expertise in finding neoplastic polyps, but also removing them.

Supplementary Materials

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2012.09.043.

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Supplementary Figure 1. Rates of incompletely resected neoplastic polyps by size group.