



Time to reduce the burden of removing diminutive polyps in colorectal cancer screening

In their very well conducted systematic review, Vleugels et al¹ identified and reviewed studies reporting on the natural history of diminutive (1-5 mm) and small (6-9 mm) colorectal polyps. Based on the limited evidence from the available studies, the estimated progression rates to advanced adenomas or colorectal cancer (CRC) were very low. The results seem to support suggestions that, overall, removal of diminutive and small polyps at screening colonoscopy may do more harm than good because the increased risk of adverse events and increased burden of histologic examinations and surveillance may be too high compared with the expected minimal gain in protection from CRC. The joint consideration with other existing epidemiologic evidence not only supports proposed and currently debated “diagnose and leave” or “resect and discard” strategies but gives further support to questioning any resection of nonneoplastic and adenomatous diminutive polyps.

Adherence to the so-called hierarchies of evidence might suggest that a definite answer about the benefits and harms of resection of diminutive and small polyps could come only from randomized controlled trials (RCTs) comparing offers of screening colonoscopy with or without the removal of diminutive and small polyps and including CRC mortality as a primary endpoint. However, this rather dogmatic choice of design would in this instance be of no use to inform clinical guidelines and public health policy, neither in the foreseeable future nor in the long run. The trials would be extremely inefficient and perhaps even impossible to conduct. Apart from their very long duration, requiring more than 10 years of follow-up, the expected very low 10-year CRC incidence and mortality among people with diminutive or small polyps only (but no large polyps) would necessitate prohibitively large sample sizes for disclosing any relevant differences in CRC mortality with reasonable power (or confirming equivalence with reasonable confidence). When the results of such RCTs were to become available, endoscopic technology or even other diagnostic approaches would be expected to have advanced to such an extent that results pertaining to diminutive and small polyps detected and characterized by technologies

available at recruitment would most likely be of some historical interest at best.

Potential changes in recommendations on how to deal with diminutive and small polyps might therefore have to be based on evidence from observational and simulation studies to be of any practical value. The request to exclusively or at least preferably rely on the results of RCTs for changing current recommendations on how to deal with diminutive and small polyps would be unjustified anyway because existing recommendations to remove these polyps have not been based on RCT results.

Much polypectomy and also surveillance could be avoided at essentially no risk by abandoning polypectomy of diminutive polyps (by far the most commonly detected type of polyps) altogether, at least in screening programs that foresee some type of repeated screening.

Vleugels et al¹ refer to simulation studies conducted by our group, which are based on estimates of transition rates between nonadvanced adenomas, advanced adenomas, preclinical CRC, and clinically manifest CRC.^{2,3} These estimates were derived at very high levels of precision by epidemiologic analyses from the very large national registry of screening colonoscopies and cancer registry data from Germany,⁵ and they indicate very low transition rates from nonadvanced adenomas to cancer within the commonly recommended 10-year interval of colonoscopy screening indeed.

The potential benefits and harms of removing diminutive and small polyps can be estimated on the basis of transition rates either derived from direct longitudinal observation, as provided by the studies reviewed by Vleugels et al,¹ or based on more complex epidemiologic analyses using repeated cross-sections from large databases, such as those derived from screening colonoscopy and cancer registry data.^{3,4} These data are crucial input parameters for microsimulation studies or other quantitative judgment of the potential benefits and harms of removing diminutive or small polyps. As clearly worked out by Vleugels et al,¹ evidence from direct longitudinal

observations is very limited, for several reasons. First, the number of such studies is very small, one of the main reasons being that such longitudinal observation without removing polyps would violate existing guidelines and might be considered unethical by many researchers and clinicians. Second, the results of these studies, most of which were very small and included very short follow-up periods, were quite heterogeneous and subject to substantial systematic variation in study populations assessed, modes of baseline and follow-up assessment procedures, length of follow-up, and random variation. For example, the estimates of transition of small polyps to advanced adenomas within a few years ranged from 0% to 38%. Confidence intervals for those estimates were not provided by Vleugels et al¹ but are likely wide, given the small number of advanced adenomas observed during follow-up, ranging from 0 to 23 (median, 2). Third, as pointed out by Vleugels et al,¹ most of the studies were prone to various biases, such as potential misclassification of size of adenomas at baseline or follow-up in CT colonography studies, which assessed transitions of polyps 6 to 9 mm to polyps 10 mm or larger^{6,7}; potential mismatch of polyps identified at baseline and follow-up; or potential modification of the natural history by biopsy specimens taken from polyps at baseline.

Although more and better studies with direct longitudinal observation of the natural history of small polyps would be desirable, overcoming all the aforementioned problems will be difficult even with the innovative designs suggested by Vleugels et al,¹ such as a design to select patients who will receive surveillance based on 1 or more polyps larger than 10 mm that were removed, along with polyps smaller than 10 mm that were left in situ. The majority of polyps smaller than 10 mm are detected without concomitant detection of polyps larger than 10 mm, and their natural history may be different from that of small polyps detected along with large polyps because the concomitant presence of large polyps may be indicative of a higher predisposition for polyp progression. The other alternative design suggested by Vleugels et al—that is, to use CT colonography as a surveillance method after initial endoscopic detection—would again suffer from the well-known limitations of CT colonography, as pointed out by the authors.¹

A potentially more promising approach might therefore be to identify the characteristics of diminutive and small polyps that are related to the risk of progression to advanced neoplasms and that can reliably be identified in vivo by colonoscopy without the need of biopsies. These could then be used for risk stratification and risk-specific management—that is, one of the following: “diagnose and leave,” “resect and discard,” or polypectomy with conventional ex vivo assessment of histologic features. One obvious such characteristic is polyp size, even within the limited range of 1 to 9 mm. For example, 3 of the studies reviewed by Vleugels et al¹ explicitly

addressed progression to advanced adenomas of diminutive polyps, that is, polyps 5 mm and under.⁸⁻¹⁰ In the by far largest such study, progression to advanced adenoma was observed for just 2 of 207 small polyps (1%) during a mean follow-up time of 7.8 years.¹⁰ In the 2 other studies, no such progression was observed during 2 years of follow-up of 35 and 98 small polyps, respectively.^{8,9}

Notwithstanding the limitations of these studies, it appears to be safe to state that from an epidemiologic perspective, much polypectomy and also surveillance could be avoided at essentially no risk by abandoning polypectomy of such diminutive polyps (by far the most commonly detected type of polyps)⁵ altogether, at least in screening programs that foresee some type of repeated screening, not just a once-only screening examination. This at present rather radical-seeming approach would entail immediate substantial cost savings and prevention of unnecessary (albeit rare) harms, even more so than a “resect and discard” strategy. At the same time, it would have the welcome side effect of putting even more pressure on the quality of colonoscopies, especially regarding the endoscopic diagnosis.

Further efforts to enhance imaging techniques should focus on ever better possibilities of optical characterization of small polyps with respect to histopathologic features related to risk of progression rather than on detecting ever-smaller polyps. Evolving polypectomy techniques with a lower incidence of adverse events may additionally help to positively affect the risk-benefit ratio of the management of small polyps. Finally, as pointed out by Vleugels et al¹ and illustrated by our previous work,^{2,3} simulation studies based on natural history parameters may help to quantify the risk for the development of CRC during defined time windows or during a lifetime associated with various types of polyps detected at various ages. The results of such studies may help to refine the guidelines on how to deal with specific colonoscopic findings (such as specific types of small polyps). They could also take additional participant and context parameters into account, such as age or other factors related to individual CRC risk and the specific screening examinations and their timing offered by the health care system.

Strategies that are currently still controversially discussed, such as “resect and discard” for certain diminutive polyps, might turn out to be only an intermediate step toward an even more differentiated, risk-specific, and prudent management of diminutive and small polyps in the years to come.

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Abbreviations: CRC, colorectal cancer; RCT, randomized clinical trial.

REFERENCES

1. Vleugels JLA, Hazewinkel Y, Fockens P, et al. Natural history of diminutive and small colorectal polyps: a systematic literature review. *Gastrointest Endosc* 2017;85:1169-76.
2. ASGE Technology Committee; Abu Dayyeh BK, Thosani N, Konda V, et al. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting real-time endoscopic assessment of the histology of diminutive colorectal polyps. *Gastrointest Endosc* 2015;81:502.e1-16.
3. Brenner H, Hoffmeister M, Stegmaier C, et al. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies. *Gut* 2007;56:1585-9.
4. Brenner H, Altenhofen L, Sock C, et al. Natural history of colorectal adenomas: birth cohort analysis among 3.6 million participants of screening colonoscopy. *Cancer Epidemiol Biomarkers Prev* 2013;108:1043-51.
5. Brenner H, Altenhofen L, Kretschmann J, et al. Trends in adenoma detection rates during the first 10 years of the German screening colonoscopy program. *Gastroenterology* 2015;149:356-66.
6. Nolthenius CJT, Boellaard TN, de Haan MC, et al. Evolution of screen-detected small (6-9 mm) polyps after a 3-year surveillance interval: assessment of growth with CT colonography compared with histopathology. *Am J Gastroenterol* 2015;110:1682-90.
7. Bersentes K, Fennerty MB, Sampliner RE, et al. Lack of spontaneous regression of tubular adenomas in two years of follow-up. *Am J Gastroenterol* 1997;92:1117-20.
8. Hoff G, Foerster A, Vatn MH. Epidemiology of polyps in the rectum and colon: recovery and evaluation of unresected polyps 2 years after detection. *Scand J Gastroenterol* 1986;21:853-62.
9. Ueyama T, Kawamoto K, Iwashita I, et al. Natural history of minute sessile colonic adenomas based on radiographic findings. Is endoscopic removal of every colonic adenoma necessary? *Dis Colon Rectum* 1995;38:268-72.
10. Mizuno KI, Suzuki Y, Takeuchi M, et al. Natural history of diminutive colorectal polyps: long-term prospective observation by colonoscopy. *Digest Endosc* 2014;26:84-9.

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