

**TITLE**

Diminutive polyps and future colorectal cancer risk perception: how low do we need to go?

**AUTHORS**

Elizabeth Bird-Lieberman<sup>1</sup>

James E. East<sup>1</sup>

**INSTITUTIONS**

1. Translational Gastroenterology Unit, John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom.

**ADDRESS FOR CORRESPONDENCE**

Dr. James E. East, Translational Gastroenterology Unit, Experimental Medicine Division, Nuffield Dept. of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU, United Kingdom

Telephone: +44 [0]1865 228753

Fax: +44 [0]1865 228763

E-mail: [james.east@ndm.ox.ac.uk](mailto:james.east@ndm.ox.ac.uk)

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## Main Manuscript

As cost efficiency pressures weigh increasingly on healthcare systems it is important to question current practice and the evidence upon which practice is based. Before instituting a randomised controlled trial (RCT) to categorically clarify whether diminutive polyps (less than or equal to 5mm) can be safely left *in situ* at colonoscopy we need evidence to reassure physicians, patients and regulatory agencies that such a study would be ethical and acceptable. In this month's issue of Endoscopy, von Renteln and colleagues present the argument that it is safe to defer resection of diminutive lesions and have examined the valuable question whether patients would find such practice acceptable [1]. This was a prospective multi-centre study undertaken in Canada and the US within patients at teaching hospitals awaiting colonoscopy. The majority of these patients were well educated and had had previous colonoscopy. Of the 557 eligible patients who completed the survey, half were found to be willing for their diminutive polyps to be left *in situ* and reassessed or removed at a subsequent surveillance procedure (95% confidence interval 46-55%) within an RCT. Higher levels of education were associated with increasing willingness to accept deferred removal. This provides invaluable data for setting up such an RCT.

Certainly the idea behind this study is clinically relevant. The histological assessment of polyps is both time consuming and costly, as are equipment costs. Undertaking polypectomy carries a finite risk, although it is extremely low in diminutive polyps, which can usually be removed by cold snare. There is also some data to suggest that these small polyps generally have a low rate of progression to advanced lesions (3.7-4.2% per annum) [2], although caution must be taken when interpreting data that is estimated and retrospective. A Japanese group did undertake a prospective study of 225 diminutive polyps (without morphological features of concern), which were marked and followed up with colonoscopy surveillance over a mean period of 7.8 years[3]. During this study period only one polyp grew to 10mm and only one polyp progressed to high-grade dysplasia and none to adenocarcinoma.

The European Society of Gastrointestinal Endoscopy(ESGE) recommends that diminutive lesions are removed by cold snare, a relatively inexpensive technique which provides high rates of complete resection, with low complication rates [4], but allows diminutive lesions in the rectum and sigmoid (that are felt with high confidence to be hyperplastic) to be left *in situ*. There are therefore already, in some countries, policies in place to leave some diminutive polyps behind. It must also be remembered that a 10-fold variability in the number of adenomas detected per patient exists between endoscopist, meaning we accept a proportion of endoscopist already leave adenomas *in situ*[5]. Given the good safety profile with removing polyps below 5mm, it raises the question of how appropriate it is to delay removal when the chances of complete removal decrease and the risks of removal increase as the polyp increases in size. In addition this relies on the patient being offered and returning for further surveillance.

Current surveillance guidelines depend on histology of the removed polyp since many are based on the histological classification (adenoma or not, presence of villous adenoma), the

degree of dysplasia seen by the histopathologist, as well as the total number of polyps removed. Surveillance strategies for adenomatous polyps as opposed to serrated polyps also differ[6]. The low risk nature of these diminutive polyps has already been taken into account in many surveillance protocols, where patients will often no longer require surveillance following resection of 1-2 diminutive polyps.

The study by von Renteln *et al.* was undertaken in Northern America where the current guidelines recommend that all identified polyps be removed and where financial reimbursement often relates to therapeutic procedures performed, and associated pathological analysis. The data from well-educated patients taking part in research in academic centres may not be translatable to the general population, who will not necessarily be offered further surveillance, or fail to attend if they are. Their proposed policy might also be hard to implement into a system where, not only the patient, but also the pathologist and physician may be opposed, especially if there is perceived or actual medicolegal risk.

If our understanding of the progression rates of adenomas is limited, our understanding of the progression of serrated polyps within the colon is even sparser. The ability of endoscopists to assess polyp risk is limited. Areas of depression (Paris 0-IIc) are considered a high-risk feature; however, Western experts only have moderate agreement for the Paris classification with a Kappa of 0.42, with worse figures for diminutive lesions[7]. Some polyps appear genetically “born to be bad” and develop rapidly to cancer, and although these are probably rare they may be hard to identify endoscopically[8]. Sessile serrated lesions with dysplasia might be misclassified as small adenomas and these are thought to be aggressive high-risk lesions that might well become cancer prior to the next surveillance.

The strongest concern about a potential policy to leave diminutive polyps *in situ* is that there is good evidence that each 1% *absolute* increase in adenoma detection rate is associated with 3% *relative* decreased risk of colorectal cancer for the patient[9]. This data comes from evaluation of 314,872 colonoscopies and looked at development of colorectal cancer 6 months to 10 years following colonoscopy and showed that the risk of interval cancer decreased in a linear manner with increasing adenoma detection rate (ADR), without evidence of any threshold. Since endoscopists with high ADRs are presumably those who identify and remove even the smallest of polyps. This suggests improved cancer protection with removal; however it remains to be seen whether it is the ADR with resection that is preventative, or whether this is simply a reflection of more comprehensive mucosal surveillance for significant lesions.

Perhaps a “resect and discard” strategy would be a more preferable middle ground strategy. This would save costs from decreased need for histopathological assessment, although the equipment and time for polypectomy would still be needed. This discard strategy is only recommended following optical biopsy by individuals who have >90% agreement between their optical diagnosis and subsequent histopathological assessment, which may be challenging to achieve for all endoscopists, though possible for some [10, 11]. A simplified DISCARD-lite protocol has also been suggested, where diminutive polyps in the rectum and

sigmoid (which are usually hyperplastic rather than serrated) only are characterised and selectively resected, while all others proximal to the recto-sigmoid are assumed to be neoplastic, and are removed and discarded without assessment[12].

When taking this study further, consideration will have to be made as to how best to quantify specific patient risk e.g. family history of colorectal cancer, age, the presence of familial or attenuated polyposis syndromes, or the different risk in screening FOBT positive populations (where the risk of advanced pathology or cancer in polyps is higher). ADR would be impacted, unless photographic evidence was to be permitted, although this might introduce the possibility of gaming this key performance indicator. Small polyps may not be found on a subsequent procedure, and if tattoo labelling is proposed it might theoretically impact on the biology of the marked polyp. Research and validation of how best to present risk to patients in this context would also be needed to ensure valid informed consent.

Von Renteln and colleagues are to be congratulated on this important step toward a formal trial to leave polyps *in situ*, but this is very much a first step with many issues outstanding. We might consider as an endoscopic community whether we want to go for no intervention in these lowest risk lesions, or whether the advantages and security of resection and pathology are balanced by the small risks and cost of cold resection.

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## References

1. von Renteln D, Barkun A, Weber A, et al. H. Patients' willingness to defer resection of diminutive polyps: Results of a multicenter survey. *Endoscopy*. 2017;[In press]
2. Brenner H, Altenhofen L, Stock C et al. Natural history of colorectal adenomas: birth cohort analysis among 3.6 million participants of screening colonoscopy. *Cancer Epidemiol Biomarkers Prev* 2013;22:1043-1051
3. Mizuno K, Suzuki Y, Takeuchi M et al. Natural history of diminutive colorectal polyps: long-term prospective observation by colonoscopy. *Dig Endosc* 2014;26 Suppl 2:84-89
4. Ferlitsch M, Moss A, Hassan C et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2017;49:270-297
5. Barclay RL, Vicari JJ, Doughty AS, et al. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. *New Engl J Med* 2006;355:2533-2541
6. East JE, Atkin WS, Bateman AC et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. *Gut*. 2017;66:1181-1196
7. van Doorn SC, Hazewinkel Y, East JE, et al. Polyp morphology: an interobserver evaluation for the Paris classification among international experts. *Am J Gastroenterol* 2015;110:180-187
8. Sottoriva A, Kang H, Ma Z, et al. A Big Bang model of human colorectal tumor growth. *Nat Gen* 2015;47:209-216
9. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. *New Engl J Med* 2014;370:1298-1306
10. Rex DK, Kahi C, O'Brien M et al. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on real-time endoscopic assessment of the histology of diminutive colorectal polyps. *Gastrointest Endosc* 2011;73:419-422
11. Vleugels JLA, Dijkgraaf MGW, Hazewinkel Y, et al. Discount Study Group. Implementation of an optical diagnosis strategy for diminutive polyps including sessile serrated lesions: training and long-term quality assurance. *United European Gastroenterol J* 2015;5 (Suppl 1):A105
12. Atkinson NS, East JE. Optical biopsy and sessile serrated polyps: Is DISCARD dead? Long live DISCARD-lite! *Gastrointest Endosc* 2015;82:118-121