Title

Serrated lesions and adenomas in colonoscopic surveillance: Additive or exponential?

Author

Prof James E. East MD(Res) FRCP[1,2]

1. Translational Gastroenterology Unit, Nuffield Department of Medicine, John Radcliffe Hospital, University of Oxford, Oxford, UK

2. Mayo Clinic Healthcare London, London, UK

Address for correspondence:

Prof. James E East, Translational Gastroenterology Unit and Oxford NIHR Biomedical Research Centre, Nuffield Department of Clinical Medicine, Experimental Medicine Division, University of Oxford, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, United Kingdom

Telephone: +44 [0]1865 228753

Fax: +44 [0]1865 228763

Email: james.east@ndm.ox.ac.uk

Keywords: Colorectal Neoplasms; Outcome Assessment, Health Care; Biomarkers; Artificial Intelligence

Word count: 1186

Abbreviations: Colorectal cancer (CRC); Sessile serrated lesion (SSL); Traditional Serrated Adenoma (TSA); Odds ratio (OR)

Commentary

Our view of serrated polyps has come a long way in the last two decades, moving from seeing them as benign lesions that do not develop into cancer, to recognising them as lesions that may account for up to one third of all colorectal cancers[1]. The “serrated pathway” to colorectal cancer (CRC) is now widely accepted, and serrated lesions are now a target for identification and removal at screening colonoscopy. They represent a special challenge for colonoscopists as they are difficult to detect and are up to 3.7 times more likely than adenomas to be incompletely resected[2]. It is assumed that removal of precursor serrated lesions prevents development of colorectal cancer in the future; however direct evidence for this is much more limited than for adenomas. Work on intensive surveillance of patients with serrated polyposis syndrome suggests that effective detection and resection can reduce cancer risk in a polyposis scenario [3].

The role of adenomas in colonoscopic screening is not just limited to being a removable precursor lesion that halts the “adenoma-carcinoma sequence” to reduce future risk. Adenoma size and multiplicity also predicts future risk of developing further advanced adenomas or colorectal cancer. On this basis international guidelines have recommended surveillance examinations after large or multiple adenomas have been resected [4,5]. Data to support such an approach for serrated polyps has been much more limited, in part because we do not have large longitudinal datasets at times where serrated polyps were being effectively detected by colonoscopists, and correctly classified by pathologists. The study by Li et al. in this issue of Gut is therefore, a very welcome addition to the limited data available [6]. By looking at a large retrospective database in Northern California, combined

with expert pathological review, they were able to develop a case-control cohort to estimate CRC risk subtyped by serrated polyp class (Hyperplastic polyp, sessile serrated lesion (SSL) with or without dysplasia, and traditional serrated adenoma (TSA)), demonstrating an increased future CRC risk with SSL alone, or with a synchronous adenoma.

These observations have implications for those developing guidelines on colonoscopic surveillance which are driven by future colorectal cancer risk. The first point, that SSLs (and TSAs) increase future CRC risk, and that they are broadly risk equivalent to adenomas is consistent with data from Erichsen et al. who also used a retrospective cohort-based approach in Denmark, again with expert pathological review [7]. While a strength of both studies, the wider gastroenterology community cannot afford expert pathological review of each serrated polyp to determine risk. Pathological diagnosis and concordance is slowly improving for SSLs; however a step change in pathology may be about to occur as deep learning based algorithms are likely to become available in GI pathology providing an "AI expert" for pathologist support in the community [8]. Similarly, computer aided detection (CADe) of serrated polyps at colonoscopy is likely to push detection toward expert levels [9], meaning that SSLs will be an increasing driver of our surveillance recommendations. Therefore, the approaches taken by Li and Erichsen, and the risks estimated from them, may be approximated in the community in the near future.

The second point that Li et al. demonstrate is that risk is additively increased with an adenoma plus an SSL, with the 10-year incidence of CRC per 1000 persons increasing from 10.3 to 20.7. Whether to treat adenomas and serrated lesions, and their associated molecular pathways, separately or together for future risk prediction has recently divided

guidelines developers on either side of the Atlantic. The US Multi-Society Task Force in 2020, while accepting that serrated lesions predict future colorectal cancer risks, keeps recommendations for each lesion class separate [4]. On the other hand the British Society of Gastroenterology, while separating the lesions classes in their 2017 position statement[1], consider adenomas and serrated lesions together in their 2020 guidelines[5]. This decision was taken based on several strands of emerging evidence that risk was at least additive for future advanced colonic neoplasia, in particular when one of the index polyp pairs was an advanced lesion. Australian data demonstrated a hazard ratio for future advanced neoplasia of 2.2 for a low-risk adenoma plus an SSL [10]. South Korean data report that a synchronous serrated polyp with an advanced adenoma was associated with a hazard ratio of 2.2 for metachronous advanced colorectal neoplasia, compared to advanced adenoma alone [11]. Most strikingly data from The US New Hampshire Colonoscopy Registry show the odds ratio (OR) of finding an advanced adenoma at surveillance was four-fold higher (OR 16.0 versus 3.9) when an advanced adenoma was found in conjunction with a serrated lesion at index examination compared to an advanced adenoma alone [12]. The Li data supports this additive concept, and critically advances the combination to include CRC risk, a much more important outcome measure for patients and guideline developers.

The New Hampshire data suggest risk might be even more than additive and Li et al. report the OR for advanced adenoma alone was 3.1 versus 11.6 for advanced adenoma plus SSL, a more than threefold increase. Li et al. also supply data on risk as the total number of polyps (serrated and adenomas) detected increases. In line with thinking on the low future risk of 1-2 small adenomas, risk is only slightly elevated with 1 or 2 total polyps (OR 2.8. and 1.8 respectively); however, at 3 total polyps this jumps to 6.6 and at four or more to 9.9. British

2020 guidelines used total polyps to define surveillance intervals and set a minimum of 5 small pre-malignant polyps (serrated lesions or adenomas) to trigger a 3-year surveillance examination; however, this was in part driven by risk estimates based on numbers of adenomas from the English Bowel Cancer Screening Programme, as data for combined serrated and adenoma numbers were not available [13]. It is possible therefore that when multiple serrated lesions and adenomas are found together risk may be more than additive compared to the equivalent numbers of adenomas alone, both for small and advanced lesions.

Perhaps we should adjust our thinking away from adenomas and serrated lesions as individual risk markers for a specific pathway and instead consider them as a more global marker of future CRC risk, with “polyp numbers” representing a snapshot combination biomarker of polygenic risk, environmental exposures, microbiome, inflammatory and metabolic risks. Mixtures of polyps may indicate multiple pathways being activated representing a final common pathway mucosal response. From this flows the concept that determining the pathology of each polyp becomes less important, or even irrelevant if small, and simply counting the polyps would determine the risk and hence surveillance interval. Such anatomically and numerically based approaches to surveillance intervals could significantly reduce pathology examination by 70%, despite achieving similar surveillance intervals in prospective studies[14].

Appealing as such approaches seem, it is notable that even with the 317,000 patient Kaiser Permenante cohort, the risk of some combination of polyps could not be determined. Even larger, international datasets will be needed if we are to model the risks of polyp

combinations, additive or exponential, for CRC in the future to guide our patients, and allocate surveillance resources simply and effectively.

Funding

James East is funded by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health.

Declarations of Interest

JEE has served on clinical advisory boards for Lumendi, Boston Scientific, and Paion; has served on the clinical advisory board and has share options in Satisfai Health; and reports speaker fees from Falk. He is an associate Editor for the Journal of Gastroenterology and Hepatology.

Contributorship

James East wrote the paper and is the guarantor.

References

1. 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.

2. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology 2013;144:74-80

3. IJspeert JE, Rana SA, Atkinson NS, et al. Clinical risk factors of colorectal cancer in patients with serrated polyposis syndrome: a multicentre cohort analysis. Gut 2017;66:278-284

4. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2020;158:1131-1153

5. Rutter MD, East J, Rees CJ, et al. British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. Gut 2020;69:201-223.

6. Li D, Doherty AR, Raju M, et al. Risk Stratification for Colorectal Cancer in Individuals with Subtypes of Serrated Polyps. Gut 2021; XXXXXX

7. Erichsen R, Baron JA, Hamilton-Dutoit SJ, et al. Increased Risk of Colorectal Cancer Development Among Patients With Serrated Polyps. Gastroenterology 2016;150:895-902

8. Wei JW, Suriawinata AA, Vaickus LJ, et al. Evaluation of a Deep Neural Network for Automated Classification of Colorectal Polyps on Histopathologic Slides. JAMA Netw Open 2020;3:e203398. doi: 10.1001/jamanetworkopen.2020.3398.

9. Hassan C, Spadaccini M, Iannone A, et al. Performance of artificial intelligence in colonoscopy for adenoma and polyp detection: a systematic review and meta-analysis. Gastrointest Endosc 2021;93:77-85

10. Symonds E, Anwar S, Young G, et al. Sessile Serrated Polyps with Synchronous Conventional Adenomas Increase Risk of Future Advanced Neoplasia. Dig Dis Sci 2019;64:1680-1685

11. Park SK, Kim HS, Yang HJ, et al. Coexistent adenoma and serrated polyps on index colonoscopy and the risk of metachronous advanced colorectal neoplasia. Endosc Int Open 2019;7:E1748-E1754

12 Anderson JC, Butterly LF, Robinson CM, et al. Risk of Metachronous High-Risk Adenomas and Large Serrated Polyps in Individuals With Serrated Polyps on Index Colonoscopy: Data From the New Hampshire Colonoscopy Registry. Gastroenterology. 2018;154:117-127

13. Bonnington SN, Sharp L, Rutter MD. Post-polypectomy surveillance in the English bowel cancer screening programme: multivariate logistic regression of factors influencing advanced adenoma detection at first surveillance (Abstract). Endoscopy 2019;51:S153.

14. Taghiakbari M, Pohl H, Djinbachian R, et al. The location-based resect and discard strategy for diminutive colorectal polyps: a prospective clinical study. Endoscopy 2021 Aug 26. doi: 10.1055/a-1546-9169. Online ahead of print.