Thinking Big About Small Adenomas: Moving Toward "Precision Surveillance"

Thomas F. Imperiale, MD[1,2,3]

Abstract: Quality metrics and technological advances for colonoscopy are contributing to detection of more diminutive and small adenomas, increasing the proportion of persons undergoing surveillance for non-advanced neoplasia. In this issue, Kim and colleagues report surveillance colonoscopy findings in average-risk Koreans who had one or more adenomas on a first screening colonoscopy and found a similar risk of metachronous advanced neoplasia between those with 1–2 non-advanced adenoma (the "low-risk adenoma" group) and those with 3 or more small adenomas. The validity, generalizability, and clinical implications of the findings are considered along with recent similar studies. In sum, these studies support expanding the low-risk subgroup to include up to four diminutive tubular adenomas and perhaps persons with up to four small tubular adenomas. They also prompt consideration of "precision surveillance" that considers features of not just the polyps, but of the patient and endoscopist.

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Surveillance colonoscopy—i.e., colonoscopy in persons with previous colorectal neoplasia—comprises an increasing part of the practice of gastrointestinal endoscopy, accounting for 20% of all colonoscopies performed in the US [1]. Guidelines for surveillance have evolved over the past 30 years despite the limited evidence for its effectiveness. The current US surveillance intervals are based on the highest degree of detected neoplasia: 3 years for advanced adenomas (a tubular adenoma 1 cm or larger, an adenoma with villous histology or high-grade dysplasia) or for 3 to 10 non-advanced adenomas; 5–10 years for low-risk adenomas (1 or 2 tubular adenomas < 1 cm); and less than 3 years for more than 10 non-advanced adenomas [2]. The goal of surveillance it do reduce colorectal cancer (CRC) incidence and mortality. Since studies of surveillance with these hard outcomes are challenging logistically, we use the surrogate outcome of metachronous advanced neoplasia (AN), which included advanced adenomas and CRC. Established risk factors for metachronous AN include older age, male sex, baseline findings (the number, size, and histology of adenomas), and location in the proximal colon [3]. In practice, only the polyp findings determine the surveillance interval, which may be a reason for their relatively poor discrimination for estimating risk of metachronous AN [4], particularly in this era of "personalized medicine".

Patients with low-risk adenomas dominate surveillance, yet it is this subgroup for which the effectiveness of surveillance is especially uncertain. High definition colonoscopes and quality metrics such as the adenoma detection rate (ADR) have likely contributed to the increased detection of adenomas, expanding the pool of patients for surveillance. And with detection of more diminutive (≤5 mm) and small (6–9 mm) adenomas, the subgroup with 3 or more non-advanced adenomas is expanding, increasing the proportion of patients for which a 3-year surveillance interval is recommended. While we await results of European trials of different surveillance intervals [5], information on the metachronous risk of AN in this subgroup could be useful for informing surveillance practice.

In this issue, Kim et al. [6] report the surveillance colonoscopy findings of a cohort of 5482 average-risk Korean patients who had one or more adenomas on a first screening colonoscopy. Baseline findings were categorized into one of four groups: 1–2 non-advanced adenomas (Group 1); 3 or more non-advanced diminutive adenomas (Group 2); 3 or more small adenomas (Group 3), and; advanced adenomas (Group 4). After a median follow-up of 38 months, metachronous AN was found in 3.9%, 5.9%, 10.6%, and 22.1%, respectively. For Groups 1 and 2, the 95% confidence intervals (CIs) overlap (3.3–4.5% and 3.9–8.0%, respectively), suggesting "no difference" statistically, although the 2.0% absolute difference might be considered clinically important by some providers and patients. Incident CRC was diagnosed in 2 (0.05%) and 1 (0.21%) members of Groups 1 and 2, respectively. The investigators adjusted their risk estimates for metachronous AN for confounding factors—something we don't do in clinical practice, but perhaps should. After adjusting for age, sex, body mass index (BMI), smoking status, alcohol consumption, regular exercise, regular aspirin use, bowel preparation quality, and ADR of both the screening and surveillance endoscopists, they found hazard ratios (HR) of 1.71 (CI, 0.99–2.94) for Group 2, 2.76 (CI, 1.72–4.44) for Group 3, and 5.23 (CI, 3.57–7.68) for group 4 relative to Group 1, which served as the reference group. Factors independently

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA. [2]Center for Innovation, Health Services Research and Development, The Richard L. Roudebush VA Medical Center, Indianapolis, IN, USA. [3]Regenstrief Institute, Inc, Indianapolis, IN, USA. **Correspondence:** T.F.I. (email: timperia@iu.edu)
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associated with metachronous AN were age, male sex, ADR of both endoscopists, and the baseline findings of Groups 3 (multiple small adenomas) and 4 (advanced adenoma). For group 2 (multiple diminutive adenomas), the multivariable *P*-value was 0.059—just missing the 0.05 threshold for model retention. The investigators interpreted these findings as showing "borderline increased risk of metachronous AN" in patients with 3 or more non-advanced diminutive adenomas compared with patients with low-risk adenomas, and offered that the "optimal surveillance interval" for Group 2 patients may be lengthened. This study raises several questions: How valid and generalizable are the study findings? How do the findings fit with recently published studies? How, if at all, do the findings affect our thinking about surveillance in general and our management of patients with multiple diminutive non-advanced adenomas more specifically? In what direction should it move surveillance research?

The study investigators are commended for identifying a large, homogeneous group (5482 average-risk persons 50 and older who had one or more adenomas on index screening colonoscopy) and for their thoughtful analysis, which attests to the importance of considering both patient factors and procedure factors (and not just the polyps). A limitation potentially affecting study validity is the interval between screening and surveillance colonoscopy. The median interval was 38 months overall, but for Groups 1 to 4, it was 38, 33, 33, and 36 months. These median intervals suggest that surveillance was performed sooner than usual in many cases and for Group 1 in particular, where a 5–10 year interval is recommended [2]. The effect of this sooner-than-recommended surveillance for Group 1 is underestimation of the (5 to 10 year) risk of metachronous AN, increasing the chances of finding a difference between Groups 1 and 2. Had the median surveillance interval for Group 1 been closer to even 4 years, the "borderline" difference in metachronous AN risk would likely have been smaller or even nil clinically and not close to significance statistically, strengthening the suggestion that an interval longer than 3 years is reasonable for Group 2. A second potential limitation is that the study cohort, while homogeneous clinically, is comprised of persons with baseline adenomas who showed up for surveillance. Due to the retrospective study design, we don't know how well they represent all persons with adenomas on index screening colonoscopy from that timeframe; it is possible that the risk for metachronous AN differs between those who had versus did not have surveillance. Whether the study cohort's risk for subsequent neoplasia is higher, lower, or no different from the non-adherent group is unknown. Further, the generalizability of the study findings to populations from other countries is uncertain; in general, the prevalence of colorectal neoplasia and risk factor profiles of Western populations are higher.

Despite the concerns about validity and generalizability, the study's findings are consistent with recent studies that have examined the yield of surveillance in subgroups of persons with non-advanced adenomas. In a retrospective cohort study of 1414 patients with adenomas, Vermulapalli and Rex found no difference in metachronous AN risk between persons with 1–2 versus 3–4 tubular adenomas < 10 mm [7]. Among persons whose largest adenoma was 6–9 mm, Arbib et al. found a 9.8% risk of metachronous AN in both 1–2 and 3–9 polyp groups [8]. AN risk was greater in those with small versus diminutive polyps, however, regardless of polyp number. In a multisite, retrospective cohort study, Moon et al. found no difference in metachronous AN risk between a low-risk adenoma group of 1–2 adenomas < 10 mm ($n = 1384$) and groups with 3–10 diminutive tubular adenomas with ($n = 145$) and without ($n = 117$) 1–2 small adenomas (respective hazard ratios of 1.30 [CI, 0.59–2.87] and 1.56 [CI, 0.83–2.92]) [9]. The hazard ratios were adjusted for several (risk factor) covariates, including age, sex, BMI, smoking, and regular use of aspirin/NSAIDs, among others. Finally, in 2570 patients with 1 or more adenomas at index colonoscopy, Park et al. found no difference in risk of metachronous AN between a group of 999 patients with 1–2 non-advanced adenomas and a group of 351 patients with 3–4 non-advanced adenomas (2.8% and 2.6%, respectively) [10]. In sum, these studies suggest that the low-risk adenoma group could include up to four diminutive tubular adenomas; and perhaps include persons with up to 4 small (i.e., 6–9 mm) tubular adenomas.

Revised guidelines for surveillance are expected soon; it will be interesting to see whether the surveillance interval of 5–10 years is extended to 10 years for the current low-risk adenoma group, given recent evidence that supports doing so [11, 12]. And will the low-risk adenoma group be extended to include persons with more than two non-advanced adenomas or will an "intermediate" group be recognized that includes persons with more than two diminutive and/or small non-advanced adenomas? As colonoscopic screening and surveillance continue to mature and as electronic databases with large numbers of subjects undergoing surveillance proliferate, we will see more studies on the yield of surveillance in adenoma subgroups. Some of these studies, like that of Moon et al. [9], will include risk estimates that consider and adjust for phenotypic and procedural factors. In contained health care systems, some studies will link baseline findings and surveillance to harder clinical endpoints of CRC incidence and mortality. Both individual studies of these kinds and meta-analyses of them that consider well-defined polyp subgroups may eventually move surveillance toward more tailored, personalized intervals. And since ADR of both baseline endoscopist and surveillance endoscopist have been shown to affect findings [13], these factors will be important to consider as well when deciding whether and when further colonoscopy is required. Surveillance in the future may be determined by a combination of patient phenotypic factors and exposures, baseline endoscopic findings, and quality metrics of endoscopists. To achieve this clinically sensible practice, software applications and systems that can identify and integrate these factors will be required. A prototype has been developed for CRC screening and surveillance [14], but requires additional development, integration with the electronic medical record and other databases, and further testing. The current study by Kim et al. may move the needle on extending the surveillance interval for a growing subgroup of persons with non-advanced adenomas. More importantly, it prompts us to consider future surveillance, where we understand its benefits and limitations more clearly, and tailor the interval based on more than just adenomas. We anticipate that such "precision surveillance"

will improve the balance between benefit and risk for individual patients, and increase the yield, precision, efficiency, and effectiveness of surveillance for the population as a whole.

CONFLICT OF INTEREST

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