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Can the Sum of Adenoma Diameters (Adenoma Bulk) on Index Exam Predict Risk of Metachronous Advanced Neoplasia?

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Abstract

Background—Recent data suggest that adenoma size and number are more important predictors of metachronous colorectal neoplasia than advanced histology. Furthermore, there is poor reproducibility in diagnosing advanced histology; high-grade dysplasia (HGD) and villous

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Statement of Interests

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histology. Therefore we developed a new metric, adenoma bulk, the sum of diameters of all baseline adenomas, regardless of advanced features.

Goal—Compare the predictive value for metachronous advanced neoplasia of adenoma bulk to conventional paradigm.

Study—Data were collected prospectively in a multi-center adenoma-chemoprevention trial (2004–13). For the conventional paradigm, high-risk baseline findings were defined as ≥ 3 adenomas, large adenomas (≥ 1 cm) or adenomas with villous components or HGD. Adenoma bulk was examined across quartiles and as a continuous variable. Predictive characteristics (sensitivities, specificities, c-statistics) for metachronous advanced neoplasia using conventional criteria and adenoma bulk were calculated. ROC curves were computed using logistic regression.

Results—1,948 adults had index and follow-up colonoscopies (mean follow-up 45.2 months). Those with an adenoma bulk ≥ 10 mm (4th quartile) had a higher metachronous advanced neoplasia risk (14.4% vs. 6.9%–8.2% in lower 3 quartiles; $p=0.0002$). The c-statistics and sensitivities (specificity fixed at 0.73) for the adenoma bulk and conventional models were 0.587 and 0.563 ($p=0.17$) and 0.396 and 0.390, respectively.

Conclusions—Categorizing sporadic adenoma patients as high vs. low-risk for metachronous advanced neoplasia by adenoma bulk of < 10 mm may be comparably predictive as conventional paradigm and simplifies risk stratification by obviating need for additional histology regarding extent of villous component or degree of dysplasia in resected polyps. The adenoma bulk metric and the 10 mm cutoff in particular would have to be validated in other populations before it can be used in clinical practice.

Introduction

In the current surveillance guidelines, individuals are considered low or high risk for adenoma recurrence based on the number, size, and histology of adenomas detected on an index exam¹. By convention, individuals with large (≥ 1 cm) tubular adenomas, multiple (> 2) small (< 1 cm) tubular adenomas, adenomas with villous component, high-grade dysplasia, or adenocarcinoma are considered to be at higher risk than those with 1 to 2 small (< 1 cm) tubular adenomas. However, metachronous advanced adenomas are only detected on surveillance exams in approximately 16% of individuals with high-risk findings on index colonoscopy². Furthermore, metachronous advanced adenomas are detected in about 6–8% of individuals with low risk or non-advanced findings on index colonoscopy^{1,3}. An analysis of pooled data from 8 prospective studies suggest that number and size of index adenomas may be more important in predicting metachronous advanced adenomas than advanced histology.² Advanced histology requires the pathologist to determine extent of a villous component and the degree of dysplasia in adenomas. These features have been shown to have poor reproducibility among pathologists^{4,5}. These observations suggest that an alternative strategy emphasizing size and number of adenomas rather than requiring additional data for advanced histology may aid in stratifying individuals with adenomas into high and low risk groups better than the current strategy.

Another important surveillance issue is the management of those with only small (< 1 cm) tubular adenomas. With advances in new technology and greater emphasis on improved

detection of colorectal adenomas during colonoscopy, a greater number of small (< 1 cm) tubular adenomas are being detected in current practice. Recent studies using high definition equipment have yielded adenoma detection rates of 40 to 60% in screening subjects,^{6,7} and a higher prevalence of individuals with multiple adenomas (14.5%)⁶ as compared to previous studies in average risk individuals (2.0%)⁸ or even in male veterans (4.3%).⁹ The recent United States Multi-Society Task Force (USMSTF) guidelines state that more data are needed to guide surveillance recommendations for those with multiple small tubular adenomas¹. They also state that there are few data to suggest that subjects with multiple (≥ 3) diminutive adenomas (< 6 mm) are at increased risk for advanced neoplasia¹. In addition, the ASGE/ACG Task Force on Quality for Colonoscopy suggested that not all individuals with multiple small adenomas require a 3-year surveillance interval¹⁰. Therefore, a revised surveillance strategy may aid in risk stratification of individuals with non-advanced neoplasia.

To improve surveillance recommendations, we developed a new measure, “adenoma bulk,” which is the sum of the estimated diameters of the resected adenomas. We used data prospectively collected as part of a large, multi-center chemoprevention trial in which all individuals underwent a baseline clearing colonoscopy and a subsequent surveillance colonoscopy, to compare the predictive value of this new metric for metachronous advanced neoplasia to conventional criteria.

Materials and Methods

Data Source

The data for this analysis were retrieved from colonoscopy information gathered for the Vitamin D/Calcium Polyp Prevention Study¹¹. The study was a randomized, double-blind, placebo-controlled trial of vitamin D and/or calcium supplementation for the prevention of metachronous large bowel adenomas over 3 to 5 years. As published elsewhere¹¹, there were no appreciable treatment effects in any active treatment arm relative to placebo (for trial primary outcome of recurrent adenomas as well as advanced adenomas), thus all subjects were included in the analysis. All data collection and study procedures were approved by the Committee for the Protection of Human Subjects at Dartmouth College, as well as by reviewing bodies at participating sites. Consenting subjects, ages 45–75 years, were recruited from 11 centers, from 5/2004–11/2008. Inclusion criteria required that individuals had at least one large bowel adenoma (≥ 2 mm) histologically confirmed and removed in the 4 months prior to study entry. In addition, eligible participants were required to have had a complete colonoscopy that was deemed free of any remaining polyps by the endoscopist and not to have had any diagnosis of invasive carcinoma of the large bowel (even if confined to a polyp). In all cases, the qualifying colonoscopy (i.e., one in which at least one adenoma ≥ 2 mm in diameter was detected) and the clearing colonoscopy (i.e., where the colon was deemed free of polyps) were the same examination and are simply referred to as the index exam. Trial eligibility also required that subjects receive either a 3-year or 5-year recommended interval for surveillance colonoscopy, as determined by the endoscopist at the index exam.

Study Population

For the secondary analyses reported in this paper, we included data from trial participants with complete size and histologic information for adenomas removed at the index and surveillance colonoscopies. We also performed a secondary analysis on a subsample of participants with *only* small tubular adenomas (< 1 cm in size) on the baseline exam, regardless of number.

Exposure and outcome variables

The main exposure variable was “adenoma bulk,” defined as the sum of the diameters of all of the adenomas detected on the index colonoscopy. We used the diameter estimated by the endoscopists at the time of the procedure that was abstracted from the endoscopy report. No special techniques to measure the size of removed polyps were required in the trial. For the “conventional paradigm”, high-risk findings on index colonoscopy were defined as multiple (≥ 3) or large (≥ 1 cm) adenomas, or adenomas with villous histology or high-grade dysplasia (HGD). For the subsample of subjects with small tubular adenomas, high-risk findings were defined as 3 or more small tubular adenomas. For both samples, adenoma bulk was examined as a continuous variable as well as divided into quartiles based on the numbers in the respective sample.

The main outcome of interest was the detection of advanced neoplasia at follow-up surveillance colonoscopy, defined as the presence of advanced features, including an adenoma with a villous component (>25%), HGD, adenocarcinoma, or size ≥ 1 cm. One study pathologist reviewed all excised colorectal lesions. The interpretations made by the study pathologist were compared with those of the pathologists at the centers. An adjudication algorithm was used to resolve any discrepancies.¹²

Statistical analysis

Logistic regression was used to calculate odds ratios and 95% confidence intervals for each quartile of adenoma bulk. A likelihood ratio test was performed to compare proportions between quartiles. For each set of risk prediction criteria we calculated the concordance statistic (c-statistic) as a measure of discrimination between subjects with and without advanced neoplasia detected on follow-up exam. These were computed using logistic regression output from univariate models that included either the continuous bulk variable or a marker variable for the conventional paradigm (i.e. advanced findings at index exam). In either case, the c-statistic can be interpreted as the probability that a random subject with metachronous advanced neoplasia has a higher predicted probability than a random subject without an advanced outcome.¹³

The point on the adenoma bulk receiver operator characteristic curve (ROC) with the same specificity as the rule using the conventional paradigm was identified. The sensitivity from the ROC curve at this point was compared to the sensitivity of the conventional paradigm rule. The calculations described above were performed for the entire study population as well as for the subsample who had only small (< 1 cm) tubular adenomas on the index exam. We utilized a chi-square test, using a non-parametric approach, to compare the ROC curves for the conventional and the adenoma bulk models¹⁴. All analyses were conducted with SAS

(SAS Institute Inc. 2015. SAS® 9.4 System Options: Reference, Fourth Edition. Cary, NC: SAS Institute Inc.) and $p < 0.05$ was taken to indicate statistical significance.

Results

There were 2,227 participants with a follow-up colonoscopy. 279 participants with incomplete or ambiguous baseline data for histology, degree of dysplasia and size were excluded, leaving 1,948 for analysis (Figure 1). Of the 1,948 in the analysis, 62.7% were men (37.3% women), average age was 58.0 (SD 6.7) years, 538 had high-risk findings according to conventional criteria on their index exam, and 187 had metachronous advanced neoplasia. The mean follow-up time was 45.2 months (range: 22.6–97.2 months). There were 1,574 individuals with small (<1 cm) tubular adenomas (of any number) only on index exam, 164 with 3 or more and 1,410 with 1 to 2 small adenomas. The adenoma size quartiles in the entire sample were: 1– < 4 mm, 4– < 6 mm, 6– < 10 mm and ≥ 10 mm. Based on the sub-sample of subjects who had only small (< 1cm) tubular adenomas, the quartiles were: 0– < 3 mm, 3 – < 5 mm, 5 – < 8 mm and ≥ 8 mm.

Associations of adenoma bulk with metachronous advanced neoplasia are shown in Table 1. Risk was statistically significantly higher among those in the 4th quartile (≥ 10 mm) of adenoma bulk relative to those in the first quartile (OR = 1.84, 95% CI, 1.22–2.77) (likelihood ratio test; $p=0.0002$), whereas risks for those in the second and third quartiles were close to the null (Table 1). In the subsample of subjects with only small tubular adenomas, we observed similar findings regarding the 4th quartile (≥ 8 mm), but the increased risk failed to achieve statistical significance (OR=1.41; 95% CI: 0.89–2.21) (likelihood ratio test; $p=0.075$).

Using the threshold pattern for the association of adenoma bulk with metachronous advanced neoplasia noted in Table 1, we assessed the predictive characteristics of a dichotomous adenoma bulk variable (< vs. ≥ 10 mm). Subjects with an adenoma bulk of ≥ 10 mm had a higher odds than those with < 10 mm (OR=2.02, 95% CI, 1.48–2.75) (Table 2). The corresponding sensitivity for metachronous advanced neoplasia was 42.8% (80/187) and the specificity was 73.0% (1285/1761). According to the conventional paradigm, participants with high-risk findings on their index exam had a 1.78-fold (95% CI, 1.31–2.44) higher odds for metachronous advanced neoplasia, with a sensitivity of 39.0% (73/187) and a specificity of 73.6% (1296/1761). Of note, a large proportion of participants with high-risk findings 82.3% (443/538) (conventional criteria) had an adenoma bulk ≥ 10 mm. In this subsample, the risk for metachronous advanced neoplasia was higher for an adenoma bulk of ≥ 10 mm (65/443; 14.7%) than that for < 10 mm (8/95; 8.4%) but the difference in risk was not statistically significant ($p=0.14$; Chi Square).

As noted above, a threshold at the 4th quartile (≥ 8 mm) was also seen in the subset of subjects with small tubular adenomas. Those with an adenoma bulk ≥ 8 mm had a higher odds than those with < 8 mm (OR=1.56, 95% CI, 1.08–2.25). The sensitivity for metachronous advanced neoplasia at this cutoff was 37.5% (51/136) and the specificity was 72.2% (1039/1438)]. In this subsample, the conventional paradigm would predict metachronous advanced neoplasia for those with ≥ 3 adenomas on index exam. The RR was

similar to that for high-risk findings in the total population: a 1.76-fold (95% CI, 1.08–2.87) higher odds (Table 2), with a sensitivity of 16.2% (22/136) and a specificity of 90.2% (1296/1438).

The ability of the current paradigm and adenoma bulk to discriminate subjects with, and without, advanced neoplasia on surveillance colonoscopies is shown in Table 3 for the total population and for the subsample. In the total population, the adenoma bulk model c-statistic was similar to that for the conventional model (0.587 vs. 0.563; Chi-Square: 1.19; $p=0.17$), and at a specificity of 73.6%, the sensitivity for the adenoma bulk model was similar to that for the conventional model (39.6% vs. 39.0%). On the other hand, among the sample restricted to small adenomas, the c-statistic for the adenoma bulk model was similar to that for the conventional model (0.549 vs. 0.532; Chi-Square: 0.51; $p=0.47$), and at a specificity of 90.9%, the sensitivity for adenoma bulk was similar to that for the conventional model (17.6% vs. 16.2%).

We also conducted the same analyses as above, using the size of the largest adenoma at the index colonoscopy as the predictor of interest. We observed that the c-statistic for this approach was 0.566, and at a specificity of 74.2%, the sensitivity was 34.2% (data not shown).

Discussion

Our findings from this analysis suggest that the sum of adenoma diameters on index colonoscopy, particularly at a value of < 10 mm, may have predictive characteristics for metachronous advanced neoplasia on future surveillance colonoscopies which are comparable to conventional categorizations. We developed this new metric based on previously published data that suggested that adenoma size and multiplicity are the most important factors for predicting metachronous advanced neoplasia on surveillance examination². Our findings suggest that these factors alone, without data regarding advanced histology, may predict metachronous advanced neoplasia as well as conventional criteria. Unfortunately, with c-statistics of 0.563 and 0.587 ($p=0.17$), neither the conventional nor the adenoma bulk schemas provide strong discriminative ability, indicating that more work on risk stratification is needed.

The current adenoma surveillance paradigm relies on three factors: histology, size, and number of index adenomas. However, there are conflicting data regarding the predictive value of each of the elements of this strategy. Risk for metachronous advanced neoplasia based on baseline exam findings was investigated in male veterans ($n = 1,171$ with index neoplasia and 501 with no neoplasia)³. Similar risk was observed for individuals with large (≥ 1 cm), multiple adenomas, or adenomas with villous components or HGD on the baseline exam. However, in an analysis based on pooled data from 8 prospective studies, it was found that risk for metachronous advanced neoplasia in participants with large (> 1 cm) or multiple adenomas (> 2) was greater than for those who had adenomas with advanced histology; i.e., villous/tubulovillous histology or high-grade dysplasia². Our new adenoma bulk measure, which accounts for index adenoma size and number but not advanced histology, had similar

predictive characteristics for predicting metachronous advanced neoplasia as did the conventional paradigm.

In addition to achieving c-statistics that were similar to the conventional paradigm, we also observed some interesting findings regarding adenoma bulk in our sample, especially at the 4th quartile cutoff of 10 mm. Specifically individuals with adenoma bulk ≥ 10 mm had a 2 fold increase risk of metachronous advanced neoplasia than that for those with < 10 mm. Of note, over 80% of all individuals with high-risk findings using the conventional paradigm had an adenoma bulk ≥ 10 mm. If validated in other populations, the use of an adenoma bulk value of ≥ 10 mm could be used as a criterion for endoscopists to recommend more intense surveillance.

There are some potential advantages to using adenoma bulk as opposed to the conventional model. Size and confirmation of adenomatous tissue alone are the only factors required in the calculation of adenoma bulk. By obviating the need to include advanced histologic information in the calculation, concerns regarding the variability and lack of reproducibility observed in the interpretation of villous tissue as well as high-grade dysplasia would be eliminated^{4,15}. Use of an adenoma bulk of 10 mm as a cutoff for high risk individuals may also mitigate an endoscopist's tendency to overestimate polyp size¹⁶, perhaps in an effort to be cautious, so that patients receive a more aggressive surveillance interval of 3 years as opposed to 5 to 10 years if an adenoma of size 10 mm or greater is reported.¹ On the other hand, for the same reason, the use of adenoma bulk may incentivize endoscopists to detect adenomas whose sizes will add up to 10 mm or more as opposed to focusing on the size of one adenoma. While the measurement of these polyps may still be subject to bias, detecting more adenomas may identify more high risk patients with multiple (> 2) polyps and also aid in lessening the "one and done" phenomena in which endoscopists detect only one adenoma in order to achieve an acceptable adenoma detection rate¹⁰.

Although not examined in this study, adenoma bulk could be useful with the application of the "resect and discard" method approach to adenoma surveillance^{17,18}. In this strategy, endoscopists would not submit diminutive polyps for pathologic review if they were confident of the histology based on endoscopic evaluation. One paper estimated that the strategy could save 33 million dollars per year in the United States¹⁸. Survey data suggest a potentially high acceptance rate among endoscopists and patients^{19–21}. A meta-analysis conducted as part of the American Society for the Gastrointestinal Endoscopy (ASGE) effort, "Preservation and Incorporation of Valuable Endoscopic Innovation" (PIVI), demonstrated a high negative predictive value (93%) for adenomatous polyp histology when the endoscopist used narrow band imaging technology (NBI) and had a high confidence level for the strategy^{22–24}. Thus, in cases where the endoscopist has a high confidence level that detected diminutive polyps are endoscopically consistent with adenomas, the endoscopist could measure the polyps' sizes and discard them after resection without accounting for advanced pathology. Thus, further interpretation of these polyps by a pathologist to determine if they have advanced features would not be necessary when using adenoma bulk. Although the rate for malignancy in diminutive (< 5mm) polyps has been shown to be minimal²⁵, we acknowledge that polyps with adenocarcinoma might not be correctly identified if they are discarded without review by a pathologist.

Since the detection of small adenomas in current practice is increasing⁶, likely due to better endoscopic technique, careful attention to bowel preparation, withdrawal time and technology, a secondary aim of our study was to examine the potential utility of adenoma bulk in managing persons with only small tubular adenomas. Although we observed higher risk for metachronous advanced neoplasia in this population for those with an adenoma bulk ≥ 8 mm, as in the main analysis, the c-statistic for its predictive strength was only slightly higher than that for the conventional approach of defining high risk as ≥ 3 adenomas (0.549 vs. 0.532; $p=0.47$). In this subsample, as compared to the total sample, there is no advantage for adenoma bulk obviating information about advanced pathology since all polyps are tubular adenomas. Thus, using adenoma bulk may not offer a superior alternative for managing small tubular adenomas.

Our study has several strengths, including its large size and the use of high quality prospectively collected data. Furthermore, inclusion criteria required clearing of all polyps from the colons of participants, minimizing the chance for missed adenomas.

We acknowledge that our findings, including the adenoma bulk value of 10 mm, need to be confirmed in separate populations since we did not internally or externally validate our results. A related concern includes the large percentage of index exams which were conducted for surveillance; thus, the characteristics of metachronous adenomas, such as location, may be different than that observed in screening exams of persons with no history of adenomas²⁶. Unfortunately we did not have data for adenomas that were resected on exams prior to the index colonoscopy. In addition, we did not account for presence of synchronous serrated polyps on index exam. Other limitations of our study are related to the colonoscopic practices in the time period in which these studies were performed. Specifically, we had no data on colonoscope withdrawal times or whether low or high definition colonoscopes were used in the study colonoscopies. We also relied on endoscopists' assessment of polyp size, which can vary greatly¹⁶. Some studies suggested that polyp size recorded by a pathologist may be more accurate than that recorded by the endoscopist^{12,16}. A final consideration that might limit generalizability is that we relied on one pathologist's interpretation of tubulovillous and villous adenomas for the interpretation of polyps detected on surveillance exam.

In conclusion, our findings suggest that categorizing sporadic adenoma patients following an index colonoscopy as high vs. low risk for metachronous advanced neoplasia on future surveillance colonoscopies according to an adenoma bulk of < 10 mm has comparable predictive characteristics to conventional categorizations schemes. While adenoma bulk provides little to no improvement in prediction, it is simpler to determine and less dependent on pathologist interpretation, especially for those adenomas with advanced features. Adenoma bulk may also be useful in settings in which histology might not routinely be available (resect and discard) but the endoscopist's optical diagnosis of adenoma was made with a high confidence level. Given that neither the conventional nor the adenoma bulk schemas provide strong predictive ability, more work on risk stratification of persons diagnosed with sporadic colorectal adenoma, especially those with multiple small adenomas, is needed. Future studies can determine whether adenoma bulk can be added to the current paradigm, perhaps to risk stratify individuals with multiple small tubular adenomas.

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References

1. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2012; 143:844–57. [PubMed: 22763141]
2. Martinez ME, Baron JA, Lieberman DA, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. *Gastroenterology*. 2009; 136:832–41. [PubMed: 19171141]
3. Lieberman DA, Weiss DG, Harford WV, et al. Five-year colon surveillance after screening colonoscopy. *Gastroenterology*. 2007; 133:1077–85. [PubMed: 17698067]
4. Appelman HD. Con: High-grade dysplasia and villous features should not be part of the routine diagnosis of colorectal adenomas. *The American journal of gastroenterology*. 2008; 103:1329–31. [PubMed: 18547220]
5. Mahajan D, Downs-Kelly E, Liu X, et al. Reproducibility of the villous component and high-grade dysplasia in colorectal adenomas <1 cm: implications for endoscopic surveillance. *The American journal of surgical pathology*. 2013; 37:427–33. [PubMed: 23348206]
6. Kahi CJ, Anderson JC, Waxman I, et al. High-definition chromocolonoscopy vs. high-definition white light colonoscopy for average-risk colorectal cancer screening. *Am J Gastroenterol*. 2010; 105:1301–7. [PubMed: 20179689]
7. Rex DK, Helbig CC. High yields of small and flat adenomas with high-definition colonoscopes using either white light or narrow band imaging. *Gastroenterology*. 2007; 133:42–7. [PubMed: 17631129]
8. Anderson JC, Attam R, Alpern Z, et al. Prevalence of colorectal neoplasia in smokers. *Am J Gastroenterol*. 2003; 98:2777–83. [PubMed: 14687832]
9. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med*. 2000; 343:162–8. [PubMed: 10900274]
10. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointestinal endoscopy*. 2015; 81:31–53. [PubMed: 25480100]
11. Baron JA, Barry EL, Mott LA, et al. A Trial of Calcium and Vitamin D for the Prevention of Colorectal Adenomas. *N Engl J Med*. 2015; 373:1519–30. [PubMed: 26465985]
12. Schoen RE, Gerber LD, Margulies C. The pathologic measurement of polyp size is preferable to the endoscopic estimate. *Gastrointestinal endoscopy*. 1997; 46:492–6. [PubMed: 9434214]
13. Pepe, MS. *The Statistical Evaluation of Medical Tests for Classification and Prediction* Oxford, U.K: Oxford University Press; 2003
14. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988; 44:837–45. [PubMed: 3203132]
15. Denis B, Peters C, Chapelain C, et al. Diagnostic accuracy of community pathologists in the interpretation of colorectal polyps. *Eur J Gastroenterol Hepatol*. 2009; 21:1153–60. [PubMed: 19696682]
16. Anderson BW, Smyrk TC, Anderson KS, et al. Endoscopic overestimation of colorectal polyp size. *Gastrointestinal endoscopy*. 2016; 83:201–8. [PubMed: 26318830]
17. Rex DK, Patel NJ, Vemulapalli KC. A survey of patient acceptance of resect and discard for diminutive polyps. *Gastrointest Endosc*. 2015; 82:376–80. e1. [PubMed: 26071067]
18. Hassan C, Pickhardt PJ, Rex DK. A resect and discard strategy would improve cost-effectiveness of colorectal cancer screening. *Clin Gastroenterol Hepatol*. 2010; 8:865–9. e1–3. [PubMed: 20621680]

19. Gellad ZF, Voils CI, Lin L, Provenzale D. Clinical practice variation in the management of diminutive colorectal polyps: results of a national survey of gastroenterologists. *The American journal of gastroenterology*. 2013; 108:873–8. [PubMed: 23735908]
20. Rex DK, Patel NJ, Vemulapalli KC. A survey of patient acceptance of resect and discard for diminutive polyps. *Gastrointestinal endoscopy*. 2015; 82:376–80. e1. [PubMed: 26071067]
21. Soudagar AS, Nguyen M, Bhatia A, Rastogi A, Gupta N. Are Gastroenterologists Willing to Implement the “Predict, Resect, and Discard” Management Strategy for Diminutive Colorectal Polyps?: Results From a National Survey. *Journal of clinical gastroenterology*. 2016; 50:e45–9. [PubMed: 26166144]
22. 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. *Gastrointestinal endoscopy*. 2011; 73:419–22. [PubMed: 21353837]
23. 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; 81:502e1–e16. [PubMed: 25597420]
24. Hewett DG, Kaltenbach T, Sano Y, et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. *Gastroenterology*. 2012; 143:599–607. e1. [PubMed: 22609383]
25. Ponugoti PL, Cummings OW, Rex DK. Risk of cancer in small and diminutive colorectal polyps. *Dig Liver Dis*. 2017; 49:34–7. [PubMed: 27443490]
26. Laiyemo AO, Doubeni C, Sanderson AK 2nd, et al. Likelihood of missed and recurrent adenomas in the proximal versus the distal colon. *Gastrointestinal endoscopy*. 2011; 74:253–61. [PubMed: 21549375]

Figure 1.

Flow diagram for study samples and index colonoscopy findings for total sample as well as subsample used in the small (< 1cm) tubular adenoma analysis.

Associations of quartiles adenoma bulk* on index colonoscopy with metachronous advanced neoplasia[†]; the Vitamin D/Calcium Polyp Prevention Study, 2004 – 2013

Table 1

Sample		Adenoma Bulk Quartile 1	Adenoma Bulk Quartile 2	Adenoma Bulk Quartile 3	Adenoma Bulk Quartile 4
Total sample (N = 1,948)	Adenoma bulk, mm (N)	1 – < 4 mm (N = 454)	4 – < 6 mm (N = 620)	6 – < 10 mm (N = 318)	10 mm (N = 556)
	Metachronous advanced neoplasia risk, % (N)	8.3% (N = 38)	6.9% (N = 43)	8.2% (N = 26)	14.4% [‡] (N = 80)
	OR (95% CI)	1.0 (ref)	0.82 (0.52 – 1.29)	0.98 (0.58 – 1.64)	1.84 (1.22 – 2.77)
Sub-sample** (N = 1,574)	Adenoma bulk, mm (N)	0 – < 3 mm (N = 420)	3 – < 5 mm (N = 214)	5 – < 8 mm (N = 490)	8 mm (N = 450)
	Metachronous advanced neoplasia risk, % (N)	8.3% (n = 35)	8.4% (n = 18)	6.5% (n = 32)	11.3% ^{‡‡} (n = 51)
	OR (95% CI)	1.0 (ref)	1.01 (0.56 – 1.83)	0.77 (0.47 – 1.27)	1.41 (0.89 – 2.21)

Abbreviations: OR, odds ratio; CI, confidence interval

* Adenoma bulk defined as sum of diameters of all resected adenomas

** Subsample: Participants with small (< 1 cm) tubular adenomas only

[‡] p = 0.0002 (Likelihood ratio test)

^{‡‡} p = 0.07 (Likelihood ratio test)

Table 2

Associations of baseline findings on index colonoscopy using conventional paradigm and dichotomous adenoma bulk ^{**} values with metachronous advanced neoplasia [†]; the Vitamin D/Calcium Polyp Prevention Study, 2004 – 2013

		Baseline findings (N)	Metachronous advanced neoplasia [†] % (N)	OR (95% CI) for metachronous advanced neoplasia [†]
All subjects (n=1948)	All subjects using conventional paradigm (N=1,948)	Conventional high risk findings [*] (N = 538)	13.6% (N = 73)	1.78 (1.31 – 2.44)
		Low risk findings (1–2 small tubular adenomas) (N=1,410)	8.1% (N = 114)	1.0 (ref)
	All subjects using adenoma bulk ^{**} 4th quartile (10 mm) (N=1,948)	Adenoma Bulk ^{**} ≥ 10 mm (N=556)	14.4% (N=80)	2.02 (1.48–2.75)
		Adenoma Bulk ^{**} < 10 mm (N=1,392)	7.7% (N=107)	1.0 (ref)
Subsample with only small tubular adenomas (n=1574)	Subsample ^{††} using 3 or more adenomas as high risk (N = 1,574)	3 small (< 1 cm) tubular adenomas (N = 164)	13.4% (N = 22)	1.76 (1.08 – 2.87)
		1 – 2 small (< 1 cm) tubular adenomas (N = 1,410)	8.1% (N = 114)	1.0 (ref)
	Subsample using adenoma bulk ^{**} 4th quartile (8 mm) (N = 1,574)	Adenoma Bulk ^{**} ≥ 8 mm (N=450)	11.3% (N=51)	1.56 (1.08–2.25)
		Adenoma Bulk ^{**} < 8 mm (N=1,124)	7.6% (N=85)	1.0 (ref)

Abbreviations: OR, odds ratio, CI, confidence interval

^{*} High-risk findings on index colonoscopy according to the conventional paradigm defined as multiple (≥ 3) or large (≥ 1 cm) adenomas, or adenomas with villous histology or high-grade dysplasia

^{**} Adenoma bulk defined as sum of diameters of all resected adenomas

[†] Advanced neoplasia defined as large (≥ 1 cm) adenomas, or adenomas with villous histology, high-grade dysplasia or adenocarcinoma

^{††} Subsample: Participants with small (< 1 cm) tubular adenomas only

Table 3

Predictive characteristics of conventional paradigm and adenoma bulk[†] on index colonoscopy in relation to advanced neoplasia on surveillance colonoscopies

Population	Model	C-statistic	Specificity	Sensitivity ^{††}
Total sample (N = 1,948)	Conventional high risk findings [*]	0.563 ^{**}	73.6%	39.0%
	Adenoma bulk [†]	0.587 ^{**}	73.2%	39.6%
Subsample [^] (N = 1,574)	3 small tubular adenomas	0.532 ^{***}	90.2%	16.2%
	Adenoma bulk [†]	0.549 ^{***}	90.9%	17.6%

^{*} High-risk findings on index colonoscopy according to the conventional paradigm defined as multiple (≥ 3) or large (≥ 1 cm) adenomas, or adenomas with villous histology or high-grade dysplasia

[^] Subsample: Participants with small (< 1 cm) tubular adenomas only

[†] Adenoma bulk defined as sum of diameters of all resected adenomas

^{††} The point on the adenoma bulk receiver operator characteristic curve (ROC) with the same specificity as the rule using the conventional paradigm was identified. The sensitivity from the ROC curve at this point was compared to the sensitivity of the conventional paradigm rule.

^{**}
p=0.17

^{***}
p=0.47