Title: Potential Impact of Extending Surveillance Intervals for Patients with 1-2 Low Risk Adenomas

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Conflicts of interest: All authors listed have nothing to disclose.

Funding: Research reported in this publication was supported by VA Health Services Research & Department awards I01HX001574 (Gupta, PI) and by the National Cancer Institute of the National Institutes of Health under award numbers R37CA222866 (Gupta, PI).

Data Transparency Statement: Data, analytic methods and study materials will not be made available to other researchers at this time, but may be made available upon request to the corresponding author.

Ethical Statement: The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

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The 2020 U.S Multi Society Task Force (USMSTF) guidelines on colonoscopy surveillance recommended the extension of surveillance intervals for patients with 1 to 2 low risk adenomas (LRA) to 7 to 10 years, longer than the 5 to 10 years recommended in 2012 by the same group\textsuperscript{1,2}. This recommendation was based on studies which showed the cumulative incidence of advanced neoplasia (AN) to be low, and similar to patients with a normal baseline colonoscopy\textsuperscript{3,4}. Subsequent studies have shown that while the incidence of colorectal cancer (CRC) is slightly increased in patients with 1-2 LRAs when compared to those with a normal baseline, there is no difference in CRC mortality\textsuperscript{5}. Extending intervals may decrease lifetime exposure to colonoscopies and reduce colonoscopy-associated risks. On a larger level, these extensions may serve as a safe, and impactful way of increasing colonoscopy screening capacity, something that is of particular importance in the wake of the COVID-19 pandemic.

While the 2020 guidelines recommend surveillance extensions for patients previously referred for shorter intervals, there has been limited data on clinical impacts, particularly whether this would lead to a delayed diagnosis of AN. Our aim was to compare prevalence of AN among patients who had appropriate follow up only per the prior 2012 USMSTF guidelines (4 to <7 years) and those with appropriate follow up per the new 2020 guidelines (7 to 10 years).

We performed a retrospective cross-sectional study of patients who received a colonoscopy at the Veterans Affairs Hospital San Diego 2/1/2019 – 2/1/2020. Patients were included if they had a colonoscopy 4 to 10 years prior that found 1 to 2 tubular adenomas <10 mm in size, and had a subsequent colonoscopy with fair or better bowel prep and advancement to the cecum. Patients were excluded if they were at increased CRC risk, such as due to history of CRC, family history of a first degree relative with CRC, a hereditary CRC syndrome, inflammatory bowel disease or an index colonoscopy with a surveillance indication for >2 adenomas, high grade dysplasia or villous adenoma.

Primary outcome was advanced neoplasia at surveillance, defined as an adenoma with size ≥10 mm, villous histology, or high grade dysplasia. Patients were categorized into either having colonoscopy at a short or extended surveillance interval, with the short interval defined as surveillance 4 to <7 years after index colonoscopy, and the extended interval defined as 7 to 10 years after index. Continuous variables were expressed as means ± standard deviation and the Shapiro-Wilk test was used to assess for normality. Comparisons between groups were done using the Mann-Whiney U, Chi-Squared or Fisher’s exact test where appropriate. A p-value cutoff of 0.05 was used to determine significance. Analysis was done using SPSS, version 27.0 (IBM).

3261 patients underwent colonoscopy between 2/1/2019 – 2/2/2020 of which 189 were included in our final cohort (Supplemental Figure 1). 44 (23.3%) patients received surveillance at a short interval while 145 (76.7%) patients received surveillance at an extended interval (Table 1). Both groups were similar in terms of age, sex, indication of index colonoscopy and number of tubular adenomas present.

Overall proportion with AN was 4.8% for both groups combined. No difference in proportion with AN between the short interval group and the extended interval group was observed (Figure 1, 5.52% vs 2.27%, \(p = 0.69\)). Regression analysis showed that extension of
surveillance interval was not associated with higher incidence of advanced neoplasia compared to the shorter interval (OR 0.40 [0.05 – 3.28], p = 0.39).

Our results suggest that an extended surveillance interval of 7 to 10 years did not result in a clinically meaningful difference in rate of advanced neoplasia detected on surveillance when compared to a short interval of 4 to <7 years.

Our findings are in line with prior studies that have demonstrated that patients with LRAs at baseline have low rates of AN at time of surveillance. The overall proportion of AN we found of 4.8% was within the 3.6-4.9% range described in Dube and Hassan’s meta-analyses of patients with low risk adenomas.3,4 In addition to there being no significant difference in proportion of AN between the short and extended interval groups, proportion with AN among the extended interval group is similar to rates seen among patients with a normal baseline colonoscopy 5-10 years prior 6. Heisser et al.’s meta-analysis demonstrated that patients with a normal index colonoscopy 5-10 years prior had a 3.2% incidence of AN. This similarity in prevalence supports the idea that patients with 1-2 LRAs can have a surveillance interval similar to individuals with prior normal colonoscopy, consistent with 2020 USMSTF guidelines.

The clinical implications of these findings are relevant because adherence to new guidelines over old can help mitigate post-COVID delays in colonoscopy access and unburden a system struggling to handle an increasing number of surveillance colonoscopies.7 As Xiao et al. demonstrated, adherence to old guidelines over new was the most common guideline-appropriate opportunity for delaying surveillance colonoscopy in their assessment of 769 referrals received at the outset of the COVID-19 pandemic, suggesting that the real world effects of this interval increase would be significant.8

Limitations include a population that skewed male, and only moderate sample size from a single study site, perhaps impacting generalizability and precision of AN estimates. Further, the ideal endpoint for evaluating tradeoffs of surveillance intervals would be CRC incidence, for which we were underpowered. Despite this, our study represents one of the first attempts to characterize the risks of re-triaging patients to a longer surveillance interval. Notably, the recently initiated Five or Ten Year Colonoscopy for 1-2 Non-Advanced Adenomatous Polyps (FORTE) trial will compare CRC incidence for shorter vs. longer-interval surveillance in the United States, and the European Polyp Surveillance trial will do the same, but results will not be available for many years9,10.

In the meantime, our results, taken together with existing literature suggest that delaying surveillance to 7 to 10 years for patients referred less than 7 years after prior LRA diagnosis, and routinely recommending 7 to 10 year follow up after new diagnosis of LRA are safe surveillance strategies.
Figure/Table Legends

Figure 1. The proportion with advanced neoplasia based on interval since last colonoscopy is shown. No statistically significant difference in the proportion with advanced neoplasia was seen between the short and extended surveillance colonoscopy groups.

Table 1

Continuous variables were compared using the Mann-Whitney U test, categorical were variables compared using Chi-Squared and Fisher’s exact test when appropriate.

References:

<table>
<thead>
<tr>
<th></th>
<th>Short Interval (4-7 Years)</th>
<th>Extended Interval (7-10 years)</th>
<th>p-value$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Patients (n=189)</strong></td>
<td>145 (76.7%)</td>
<td>44 (23.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (SD)</strong></td>
<td>69.9 ± 7.9</td>
<td>67.1 ± 6.7</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>134 (92.4%)</td>
<td>44 (100%)</td>
<td>0.07</td>
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<tr>
<td><strong>Indication for Prior Colonoscopy</strong></td>
<td></td>
<td></td>
<td>0.84</td>
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<tr>
<td>Screening</td>
<td>78 (53.8%)</td>
<td>25 (56.8%)</td>
<td></td>
</tr>
<tr>
<td>Previous Polyp</td>
<td>38 (26.2%)</td>
<td>13 (29.5%)</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>9 (6.2%)</td>
<td>1 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Heme Positive stool</td>
<td>7 (4.8%)</td>
<td>2 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>Iron Deficiency Anemia</td>
<td>4 (2.8%)</td>
<td>2 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>Adenoma on Flex Sig</td>
<td>3 (2.1%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (4.1%)</td>
<td>1 (2.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of adenomas at baseline colonoscopy</strong></td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>1</td>
<td>99 (68.3%)</td>
<td>29 (65.9%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>46 (31.7%)</td>
<td>15 (34.1%)</td>
<td></td>
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</tbody>
</table>
Proportion with Advanced Neoplasia by Interval Since Last Colonoscopy

- Short Interval (4 to <7 years): 5.52% (8/145)
- Extended Interval (7 to 10 years): 2.27% (1/44)

\( p \text{ comparison} = 0.69 \)