QUERI

Patients with Positive Screening Fecal Occult Blood Tests: Evidence Brief on the Relationship Between Time Delay to Colonoscopy and Colorectal Cancer Outcomes

April 2013

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Quality Enhancement Research Initiative
Health Services Research & Development Service
Washington, DC 20420

Prepared by:
Evidence-based Synthesis Program (ESP)
Coordinating Center
Portland VA Medical Center
Portland, OR
Mark Helfand, MD, MPH, MS, Director

Investigators:
Principal Investigator:
Kim Peterson, MS

Contributing Investigators:
Susan Carson, MPH
Linda Humphrey, MD, MPH
Mark Helfand, MD, MPH, MS

PREFACE

The Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout the VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, the Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence brief are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

Recommended Citation: Peterson K, Carson S, Humphrey L, Helfand M. Patients with Positive Screening Fecal Occult Blood Tests: Evidence Brief on the Relationship Between Time Delay to Colonoscopy and Colorectal Cancer Outcomes, VA-ESP Project #09-199; 2013.

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Coordinating Center located at the Portland VA Medical Center, Portland, OR and funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

INTRODUCTION

The American Cancer Society estimates that colorectal cancer (CRC) will be the third most common cause of cancer death for both men and women in the U.S. in 2013.[1] The natural history of the disease suggests that longer delays in CRC diagnosis will negatively influence stage at diagnosis and long-term survival. CRC may be diagnosed by screening asymptomatic patients or by evaluation of symptomatic patients. Previous studies investigating the influence of delays on survival or cancer stage at diagnosis have primarily focused on the evaluation of time from first symptom development in symptomatic patients and have demonstrated inconsistent results. For example, among 13 studies published between 1977 and 2006 included in a 2007 systematic review by Ramos and colleagues, 10 found no association between the symptom-to-diagnosis interval (SDI) and survival and the other three found that increased delays resulted in better chances of survival.[2] As for the relationship between SDI and tumor stage, among 18 studies, 11 found no association, four found that shorter delays were associated with an earlier stage at diagnosis and three paradoxically found that a greater delay was associated with an earlier stage at diagnosis.[3] As noted by Ramos et al., the SDI risk function is likely nonlinear and multifaceted, reflecting a complex interaction between tumor biology and location, the clinical course, patient behavior, and the functioning of the healthcare system, and the studies have varied in their methods for adjusting for these confounding factors. These findings highlight the importance of detecting colorectal cancer through screening, before symptoms appear.

Researchers have speculated that CRC detected by screening may be biologically different from symptomatic CRC.[4] The United States Preventive Services Task Force recommends routine screening, using either annual fecal occult blood test (FOBT), flexible sigmoidoscopy every five years, or colonoscopy every 10 years.[5] The practice of screening and removal of adenomatous polyps when detected evolved in part based on evidence from the National Polyp Study that provides support of the concept of the progressions of adenoma to adenocarcinoma.[6] Screening for colorectal cancer with FOBT has been shown to decrease mortality from colon cancer through detection and treatment of early-stage cancer and detection and removal of adenomatous polyps.[7] Screened patients have cancers detected at an earlier and more curable stage than unscreened patients.[8] For screening to be effective in preventing colon cancer, a positive FOBT should be followed by a complete colon evaluation with colonoscopy.[8] However, current guidelines are not specific on the recommended timing of colonoscopy following a positive screening test.

In 2003, FOBT was used for more than 90% of patients screened in the Veterans Health Administration (VHA).[9] Although current VHA policy states that colonoscopy must be done within 60 days of a positive FOBT, data show that frequently this objective is not met. In 2004, the average time from positive FOBT to colonoscopy for asymptomatic patients in the VHA was 199 days.[10] In studies inside and outside the VHA, time from positive screening to follow-up consistently averages over six months.[9] One study found that only 44% of VHA patients underwent a full colon evaluation within 12 months of positive FOBT.[11]

Recent qualitative data suggest that VHA providers attribute long delays in scheduling follow-up colonoscopies to ambiguity regarding referral guidelines, patient disengagement and nonadherence, and endoscopic resource limitations.[12] Analysis of quantitative data from a study of 104 patients from county hospitals in Texas found that the most common reason for colonoscopy delay was delayed future colonoscopy appointment date given by the gastroenterology service and found no statistically

significant differences in demographics or medical or mental health comorbidities in patients with and without delays.[12] Although not a specific measure of colonoscopy delay, another study of 468 patients from 15 Veterans Affairs Medical Center (VAMCs) found that being older, having comorbidities and residing in the Atlantic region were associated with a longer time to diagnosis.[13]

Numerous intervention programs have been developed to improve follow-up of positive FOBT screening. The VHA is a leader in the healthcare industry in their quality improvement efforts to improve the timeliness of colonoscopy after a positive screening FOBT. As a first step to improve timely follow-up of positive FOBTs, in 2005, the VHA enlisted the participation of 21 facilities in a quality improvement effort known as the Colorectal Cancer Care Collaborative (C4).[9] Each participating facility was paired with a quality improvement coach and received training on how to design, implement and evaluate tracking systems to follow-up positive FOBTs. Compared to before the study period, after one year, average days to colonoscopy decreased significantly (129 versus 103, P=0.004) and the proportion receiving 60-day follow-up increased significantly (27% versus 39%, P=0.008). Improvement rates varied across facilities and predictors of improvement included establishment of clear roles/goals, previous quality improvement training, more use of quality improvement tools, and incorporation of primary care education. Different types of VA electronic medical record interventions provide examples of specific quality improvement tools that have improved the follow-up of FOBT-positive results. Using a before-and-after study design, the VA Puget Sound HealthCare System found that an electronic provider reminder significantly increased the proportion of Veterans who received gastroenterology consultation within 14 days (+20.3%, P<0.001) and reduced the mean time to colonoscopy by 38 days (P<0.001).[14] In a randomized trial involving eight VAMCs, six-month rates of complete diagnostic evaluation improved by 9% to 31% (P<0.03) in sites using an automatic electronic consult directly sent to the gastroenterology providers following an FOBT-positive result, whereas follow-up rates did not change significantly in usual care sites.[15]

The VHA's current policy on CRC follow-up timelines states that for any positive screening test for which a diagnostic colonoscopy is indicated, the colonoscopy must be performed within 60 calendar days of the positive screening test. Based on this policy, in 2012, the VHA conducted a colorectal cancer lookback to assess and disclose if any colonoscopy completed more than 60 days after consultation or a positive FOBT was associated with evidence of harm to the Veteran. This policy is based on the assumption that a delay in diagnosis could lead to poorer health outcomes, but the evidence for this assumption has not been systematically evaluated. Additionally, modeling studies that use real-world data to simulate the progression of CRC through the adenocarcinoma sequence have consistently estimated mean sojourn times that range from 1.6 to 6 years.[16-18] The current state of knowledge about sojourn times suggest that it takes years for preclinical cancers to develop into clinical cancers and that much shorter delays, such as 60 days, may only plausibly affect outcomes in a very small proportion of Veterans with accelerated pathways of disease progression.

The Office of Patient Care Services engaged the Evidence-based Synthesis Program (ESP) to assist them with evaluating the evidence base for determining when a delay in diagnosis of colorectal cancer is significant enough to cause harm to a Veteran. The objective of this Evidence Brief is to evaluate the effects of time between referral for and completion of a colonoscopy on colorectal cancer-related outcomes. As the 60-day timeframe performance measure specified in the VA Directive is specific to follow-up of positive screening FOBTs, this Evidence Brief will focus on that relatively homogenous patient population.

SCOPE

KEY QUESTIONS

Key Question #1. How does variation in time to colonoscopy affect colorectal cancer-related outcomes in patients referred for diagnostic colonoscopy?

Key Question #2. What are the clinical factors (e.g., reason for referral, positive FOBT or symptoms; type and duration of symptoms; etc.) that moderate the relationship between time to colonoscopy and harm?

INCLUSION CRITERIA

Patients: Individuals referred for diagnostic colonoscopy with concern for colorectal cancer
Intervention: Time to colonoscopy
Comparators: Not applicable
Outcomes: Survival and colorectal cancer stage at diagnosis are the critical outcomes. Other included outcomes are type of treatment and complications of treatment. Prior to conducting the review, we did not list neoplasia as an included outcome because experts did not think it was sufficiently correlated with the critical outcomes.
Timing: Any
Setting: No restrictions
Study designs: Systematic reviews, randomized controlled trials and observational studies with multivariate analyses

METHODS

To identify articles relevant to the Key Questions, our librarian with expertise in the methods of systematic reviews, searched PubMed (1946 through December 28, 2012) by combining the MeSH term for colonoscopy with numerous MeSH terms and free text for time factors (for full search strategy, see Supplemental Materials). Additional citations were identified from reference lists, hand searching, and consultation with content experts.

Study selection was based on the eligibility criteria described above. Titles and abstracts and full-text articles were assessed by one reviewer. Full-text articles of all potentially relevant titles and abstracts were retrieved and were first assessed by one reviewer and then checked by a second reviewer. All disagreements were resolved using a consensus process.

We used predefined criteria to rate the internal validity of all individual studies. We rated the internal validity (quality) of controlled observational studies as good, fair or poor, using methods of the U.S. Preventive Services Task Force (USPSTF) and based on the adequacy of the patient selection process; completeness of follow-up; adequacy of outcome ascertainment; use of acceptable statistical techniques to minimize potential confounding factors; and whether the duration of follow-up was reasonable to capture investigated events.[19] We abstracted data from all included studies on population, intervention, comparator, and timing of colonoscopy and results for each included outcome. All data abstraction and internal validity ratings were first

completed by one reviewer and then checked by another. All disagreements were resolved using consensus.

We graded the strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ).[20] This approach incorporates four key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. Strength of evidence is graded for each key outcome measure and ratings range from high to insufficient, reflecting our confidence that the evidence reflects the true effect.

A draft version of this report was reviewed by technical experts as well as clinical leadership. Their comments and our responses are presented in Appendix A.

RESULTS

OVERVIEW

Figure 1 provides the results of the study selection process. A full listing of all studies excluded at the full-text level is provided in the supplemental materials. We identified 11 studies that addressed timeframes between referral for complete colon evaluation and follow-up testing.[4,10,13,21-28] Four studies were conducted in the United States,[4,10,13,23] three of which were from VAMC's.[4,10,13] Among the remainder, two were from Madrid,[21,27] two from the United Kingdom,[24,25] two from Northern European countries,[22,26] and one from Western Australia.[28]

Ten of 11 studies combined data from patients presenting with a variety of signs and symptoms prior to diagnosis.[4,13,21-28] For example, one study combined data from patients with various colorectal cancer signs and symptoms: abdominal pain (52%), altered stools (25%), anorexia (27%), constipation (27%), diarrhea (22%), fatigue (25%), mucus in stools (6%), nausea or vomiting (22%), obstruction (4%), any visible rectal bleeding (58%), rectal pain (5%), tenesmus (8%), change in bowel habit (51%), anemia (57%), weight loss (39%), and positive fecal occult blood test (77%).[23] Data specific to patients referred for colonoscopy to evaluate a positive FOBT are limited to one study that focused on such patients[10] and two subgroup analyses.[4,23]

As key patient characteristics were under-reported across all 11 studies, it is difficult to know their generalizability. Although age was consistently reported and was generally similar across studies (mean, 67 years; range, 59 to 70 years), gender was only reported in 64% of studies (proportion of males ranged from 51% to 99%) and race/ethnicity was only reported in 36% of studies (proportion of White patients ranged from 59% to 70%). Comorbidity index scores ranged from none to moderate, but were also only reported in 36% of studies. Evidence from studies of patients with a positive screening FOBT is likely highly applicable to the VAMC population as two of three studies involved data from VAMCs.[4,10] Supplemental Materials table 1 provides a complete description of study and patient characteristics and their results.

Referral timeframes were defined differently across the studies. The referral timeframe endpoint was limited to colonoscopy performance in four studies,[10,21,27,28] and more broadly defined as tissue diagnosis in five studies,[4,13,23,25,26] date of first hospital appointment in one study,[24] and initiation of treatment in one study.[22] Observed wait times were reported as means in four studies (range, 14 to 236 days),[10,21,26,27]medians in six studies (range, 8 to 108 days),[4,13,22-25] and not reported in one study.[28]

Internal validity (quality) of the studies was generally fair[4,10,13,22,23,25,26,28] to poor.[21,24,27] The main limitation of most studies is the potential for residual confounding due to inadequate control for comorbid risk factors (e.g., obesity). Studies that at least controlled for the confounding effects of patient demographics were generally rated fair quality and those that, in addition to other flaws, did not control for any potential confounding effects were rated poor quality. Supplemental Materials table 2 provides complete quality assessments for each study.

Key Question #1. How does variation in time to colonoscopy affect colorectal cancer-related outcomes in patients referred for diagnostic colonoscopy?

Patients with Positive Screening FOBT

Two studies specifically evaluated time delay from FOBT to colonoscopy and its relationship to CRC outcomes.[4,10] The strongest evidence comes from a retrospective medical chart review study from the VAMC in Durham, North Carolina that focused entirely on patients who underwent colonoscopy within 18 months of a positive FOBT and had no previous complete bowel evaluation within five years. Study authors reviewed records of 231 primary care patients who were 97% male, 59% Caucasian and had a mean age of 66 years. Mean days to colonoscopy was 236 (standard deviation, 112 days) and findings were no adenoma in 48%, adenoma in 36%, advanced adenoma in 11% and invasive cancer in 4%. The authors noted that their data are representative of the national Veteran CRC screening population in that the rate of neoplasia in their study (52%) is comparable to the rate of 54% in a 2001 multicenter VA study of one-time FOBT screening in asymptomatic patients.[29] Association between time to colonoscopy and survival and CRC stage was not reported. Instead, the study analyzed the surrogate and composite outcomes of neoplasia, defined as any adenoma, and advanced neoplasia, defined as advanced adenomas (i.e., diameter of 10 millimeters or more, > 25% villous architecture, high-grade dysplasia, or intramucosal carcinoma) or invasive cancer. For each additional 30-day delay to colonoscopy, their logistic regression analysis found a significant increase in risk of neoplasia, but not advanced neoplasia (Table 1).[10] As there were only 26 Veterans with advanced adenoma (advanced adenomas and invasive cancer), this study is likely inadequately powered to definitely determine whether any relationship exists between colonoscopy delays and CRC outcomes. Although their logistic regression results suggest a continuous pattern of increased risk of neoplasia with every 30-day increase in delay, their probability plot of raw data (reprinted here as Figure 2) suggests very similar distributions of patients with and without neoplasia for all delay periods up to 300 days. It is unclear how the results on the surrogate neoplasia endpoints may correlate with CRC outcomes.

A limitation of the study is that the reasons for delay were not examined. In Veterans with longer colonoscopy delays, it is conceivable that the development of symptoms prompted their ultimate follow-through with colon evaluation. But, in that case, the development of symptoms

or persistence of positive FOBTs may be responsible for the increased risk of neoplasia, rather than the colonoscopy delay itself. Another limitation is that no outcome data were obtained in patients who did not have a colonoscopy within 18 months or got one outside the VA.[11] These patients were excluded from the analysis, effectively making the lost to follow-up rate of the study at least 50% of the initial sample. If the excluded patients didn't have a colonoscopy within 18 months for reasons that were proxies for other factors that modify the risk of neoplasia, then the exclusions could have either over- or underestimated the relationship between colonoscopy delay and risk of neoplasia. For example, older age was associated with higher odds of neoplasia in this study (OR 1.10; 95% CI, 1.02 to 1.19) and also could have made it more difficult to obtain a colon evaluation. On the other hand, the risk of neoplasia could have been overestimated if the excluded patients actually did not have neoplasia and, likewise, didn't get a colonoscopy because they hadn't yet developed any symptoms or other risk factors that would raise concern about CRC. Finally, as the authors note, data about some potentially important confounders, such as obesity,[30,31] were not available for this study.[13]

The second study had poor internal validity and did not find an association between time delay from positive FOBT to colonoscopy and/or CRC survival or stage (Table 1).[4,23] This study was from the Michael E. DeBakey VAMC in Houston, Texas and evaluated a subgroup of 100 of 286 patients with an abnormal screening, defined as a positive FOBT or flexible sigmoidoscopy, not performed in the process of evaluating signs and symptoms.[4] Although in their main analysis of all patients with and without symptoms, they used linear regression analysis to adequately control for a variety of potential confounding variables, for their subgroup analysis of 100 patients referred following an abnormal CRC screening test, only chi-square analyses were performed, which do not control for any potentially confounding effects.[4]

These studies provide insufficient evidence to draw conclusions about the association between colonoscopy delay and survival in patients with a positive screening FOBT. Unfortunately, survival was not reported in the study from the Durham VAMC. Only the DeBakey VAMC study provides evidence about the association between colonoscopy delay and survival and it primarily applies to the overall study sample of 289 patients, two-thirds of whom were symptomatic.[4] In their unadjusted analysis of the overall sample of 289 patients, they found an inverse relationship between diagnostic delay and mortality, with a significantly lower hazards ratio for delays exceeding the median of 41 days compared with those below the median (0.61; 95% CI, 0.39 to 0.96). However, when the analysis adjusted for Dukes' stage, anatomic location, earliest initiator and earliest treatment, diagnostic delay was no longer associated with survival (HR 0.75; 95% CI, 0.47 to 1.21). Although the abstract states that no association was found between diagnostic delay and mortality in the subgroup of 100 patients referred for abnormal screening, the data supporting this finding were not described in the body of the article. Furthermore, by showing that their paradoxical finding of improved survival with longer duration of symptoms was mostly accounted for by the confounding effects of tumor stage and symptom type, the DeBakey VAMC study highlighted the inherent problem of confounding in studies with heterogeneous groups of patients with various signs and symptoms.

Table 1. Relationship between delay and CRC stage in patients with abnormal screening tests

Author Year Setting Sample Size Quality	Definition of delay period	Results	Strength of the Evidence
Gellad 2009[10] Durham VAMC N=231 Fair	Mean days between positive FOBT and colonoscopy: 236 (SD, 112)	Adjusted* odds ratio (95% CI) for the effect of additional 30-day wait: Advanced neoplasia: 1.07 (0.98 to 1.18) Neoplasia: 1.10 (1.02 to 1.19)	Insufficient: Medium risk of bias (fair-quality retrospective observational study), inconsistent, indirect, imprecise, dose-response relationship not present, plausible confounding present, weak strength of association.
Wattacheril 2008[4] Michael E. DeBakey VAMC Subgroup N=100 Poor	Median lagtime in days between diagnosis and referral for referral for colonoscopy due to abnormal screening: 41 days (range, 1-2063)	Median lagtime in days for Dukes' stage A=60.0, B=62.0, C=12.0, or D=80.0; *P*=0.39	Insufficient: High risk of bias (poor-quality retrospective observational study), inconsistent, indirect, imprecise

Abbreviations: CRC=colorectal cancer, VAMC=Veterans Affairs Medical Center, FOBT=fecal occult blood test, SD=standard deviation, CI=confidence interval, MD=medical doctor, NR=not reported
*Adjusted for age, race and gender

Patients with Various Signs and Symptoms

Among ten studies of patients with various signs and symptoms,[4,13,21-28] the effect of post-referral delays on survival and CRC stage were reported in four[4,22,24,25] and nine studies,[4,13,21,23-28] respectively. These studies provide low-strength evidence that longer post-referral delays do not significantly worsen survival or CRC stage in symptomatic patients (Table 2). However, these studies really cannot isolate the issue of delay of colonoscopy following a positive screening FOBT and the relationship between delay and stage or survival. Given the range of symptomatic presentations in these studies and the potential variation in their relationship to both time to colonoscopy and outcome, confounding is likely a bigger problem in these studies and could explain the nonsignificant results.

Table 2. Relationship between delay and survival and CRC stage in patients with various signs and symptoms

Author Year Sample Size Quality	CRC Stage	Survival
Fisher 2010[13] N=447 Fair	OR for late stage (reference=0-30 days): 31-90 days: 0.90 (95% CI, 0.53, 1.53) 91-180 days: 0.63 (0.34, 1.16) >180 days: 0.93 (0.54, 1.61)	NR

Author Year Sample Size Quality	CRC Stage	Survival
Gomez-Dominguez 2006[21] N=109 Poor	Dukes' stages by length of administrative delay Stage A: 15 days (SD 15) Stage B: 28 days (SD 26) Stage C: 36 days (SD 55) Stage D: 20 days (SD 20) NS (*P*-value NR)	NR
Iversen 2009[22] N=740 Fair	NR	HR (95% CI) Provider delay ≥ 60 days vs < 60 days: Colonic=0.85 (0.64 to 1.13) Rectal=1.16 (0.82 to 1.65) Hospital delay ≥ 60 days vs < 60 days: Colonic=0.82 (0.57, 1.18) Rectal=1.07 (0.69 to 1.67)
Majumdar 1999[23] N=194 Poor	Dukes' stages: *P*=0.92	NR
Neal 2007[24] N=239 Poor	Dukes' stage at diagnosis: A: 12% vs 18% B: 42% vs 37% C: 46% vs 43% D: 0% vs 2% (*P*=0.68) TNM stage at diagnosis: No difference (*P*=0.77)	Urgent referral routes compared with all other routes: Survival: 27.1% vs 32.7% (*P*=0.74) Mean survival days (SE): 609.5 (46.0) vs 720.3 (36.2); NS
Rupassara 2006[25] N=154 Fair	Dukes' A < 50 days=15.2% ≥ 50 days=38.6% *(P*=0.006)	5-year survival < 50 days=65.3% ≥ 50 days=93.7% *P*=0.007
Terhaar sive Droste 2010[26] N=272 Fair	Mean weeks for early stage CRC (Dukes' A and B)=6.1 weeks vs late stage CRC (Dukes' C and D)=5.2 weeks (*P*=0.09)	In early stage CRC, no difference in survival associated with longer delay. In late stage CRC, patients with a shorter delay had shorter survival.
Valentin-Lopez 2011[27] N=272 Poor	% patients with Astler-Coller stage in rapid vs standard pathway: A=26.0% vs 11.6% (*P*=0.007) B=36.0% vs 41.1% C=24.0% vs 32.4% D=14.0% vs 14.9%	NR

Author Year Sample Size Quality	CRC Stage	Survival
Viiala 2007[28] N=1632 Fair	Median days for early stage CRC (Dukes' A and B)=43 vs late stage CRC (Dukes' C and D)=51; *P*=NS	NR
Wattacheril 2008[4] N=289 Fair	Median lagtime in days for Dukes' stage A=60.0 B=62.0 C=12.0 D=80.0 (*P*=0.39)	≥ median (41 days) vs < median: HR 0.75; 95% CI, 0.47 to 1.21
Strength of the evidence	**Low: Fair-to-poor quality observational studies, consistent, indirect, imprecise**	

Abbreviations: CI=confidence interval; CRC=colorectal cancer; HR=hazards ratio; NR=not reported; SD=standard deviation; TNM=Tumor, node, metastasis staging system; vs=versus

Key Question #2. What are the clinical factors (e.g., reason for referral, positive FOBT or symptoms; type and duration of symptoms; etc.) that moderate the relationship between time to colonoscopy and harm?

None of the two studies that evaluated patients with positive screening FOBT evaluated the potential moderating effects of clinical factors (e.g., reason for referral, positive FOBT or symptoms; type and duration of symptoms; etc.) on the relationship between time to colonoscopy and harm.[4,10,23]

CONCLUSIONS

Patients with a Positive Screening FOBT

- No direct evidence supports the current VHA policy that requires follow-up colonoscopy to be done within 60 days of a positive screening FOBT.
    - There is insufficient evidence to draw conclusions about the effects of time between positive screening FOBT and colonoscopy on the critical outcomes of survival and CRC stage.
    - There is also insufficient evidence to draw conclusions about the effects of time to colonoscopy on the outcomes of type of treatment and complications of treatment or about the clinical factors (e.g., reason for referral, positive FOBT or symptoms; type and duration of symptoms; etc.) that moderate the relationship between time to colonoscopy and harm.
    - We also examined evidence concerning colonoscopy delay and neoplasia, but as discussed in the results, the evidence about it is sparse, has multiple methodological limitations, and it is not clear that it is relevant to the critical outcomes of survival and invasive cancer. For advanced neoplasia, a composite outcome made up of significant

polyps and invasive cancer, the positive association with longer time to colonoscopy over 18 months was not statistically significant (OR, 1.07; 95% CI, 0.98 to 1.18).

- The generalizability of the FOBT results to FIT-based testing (Fecal Immunochemical Test) is unclear. If the reasons for ordering a FIT instead of an FOBT are proxies for other factors that modify the risk of delay to colonoscopy and/or CRC outcomes, this may result in a different relationship between delay and CRC outcomes. Also, because the FIT characteristics differ from FOBT, this may impact the importance of delays in follow-up colonoscopy.

Patients with Various Signs and Symptoms

There is very low-strength evidence that longer post-referral delays do not worsen survival or CRC stage in patients with various signs and symptoms. One potential explanation for the nonsignificant results is the potential confounding effects of various symptomatic presentations; such that clinicians may prioritize colonoscopy in those with cancer-specific symptoms, thus obscuring a natural association between increased delays and more advanced cancers.

LIMITATIONS

Evidence evaluating the relationship of time to colonoscopy following a positive screening FOBT to patient outcomes is sparse. There are no prospective studies with a true inception cohort of patients that were all assembled as a direct result of a positive screening FOBT. The single VAMC study that specifically examined time delay from FOBT to colonoscopy was a retrospective chart review and the authors could not rule out that colonoscopy referral was due to development of symptoms long after the positive FOBT. There is no evidence regarding the potential mediating effects of clinical factors on the relationship between time to colonoscopy and harm in patients with a positive screening FOBT. Additionally, the studies were inconsistent in their findings regarding the association between delay and CRC stage in patients with abnormal screening tests. Design differences that likely contributed to the different results included variation in population characteristics (e.g., positive FOBT with or without polyps seen on flexible sigmoidoscopy), analytic approach (e.g., comparing median number of days for each of Dukes' stages, comparison of hazard ratios for risk above and below the median, comparison of odds of neoplasia or advanced neoplasia for 30-day incremental waits from positive FOBT, etc.), and extent of adjustment for confounders. We found no evidence regarding the relationship between post-referral delays and type of treatment and complications of treatment in patients with a positive screening FOBT. Overall applicability was limited by under-reporting of key patient characteristics, especially comorbid factors that may modify the risk of neoplasia or of undergoing colonoscopy in a timely manner (e.g., obesity).

Additionally, methodological limitations of this Evidence Brief include the exclusion of studies published in languages other than English and the lack of a specific search for unpublished studies. Another important limitation is that we did not attempt to evaluate the effect of delays on patient perceptions or satisfaction, which may be important considerations in developing policies about timing of follow-up for a positive FOBT. Delays may have important effects on perceptions of quality of care beyond the effect on survival or neoplasia.

FUTURE RESEARCH

A large, prospective observational study that focused on the time course of colonoscopies that were specifically ordered as a direct result of a positive screening FOBT, and measured potential confounders, could guide decisions about the appropriate timing of colonoscopy, but would take many years to complete. For example, there may be an opportunity to examine the effect of variation in time to colonoscopy on CRC mortality in those who are FIT-positive based on data from the ongoing 10-year randomized controlled trial of Colonoscopy Versus Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM) sponsored by the VHA (NCT01239082, CSP 577, Study Chairs Jason A. Dominitz, MD, MHS and Douglas Robertson, MD, MPH).[32]

A more immediate alternative is to use a Cancer Intervention and Surveillance Modeling Network (CISNET) CRC model to investigate the impact of delays in colonoscopy on cancer stage and survival. In addition, a CISNET model could be specifically used to assess the validity of the findings about neoplasia from the Durham VAMC study. Specifically, by adding a parameter representing the time between a positive screening FOBT and colonoscopy, a model could evaluate the relationship between specific delay intervals over the long-term, such as two years. Although systematic reviews have traditionally relied solely on empirical data, collaboration between systematic reviews and modeling studies is an emerging methodological concept that is being explored for its usages in confirming and/or expanding the findings from empiric studies. A demonstration of consistency between model-projected CRC stage and/or survival and empiric data reported in the literature would greatly increase the strength of the evidence about the impact of colonoscopy delay in patients with a positive screening FOBT and potentially better inform the need for refinement of the VHA's current wait time policy of 60 days between positive FOBT and follow-up colonoscopy.

Potentially, the dataset from the CRC arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial could be useful in evaluating the effects of delay in colonoscopy.[33] Although the PLCO focused on the effects of flexible sigmoidoscopy screening on CRC mortality, rather than FOBT, there may be data on the variability in timing between abnormal flexible sigmoidoscopy and subsequent colonoscopy that could be relevant to the overarching question of how much delay to colonoscopy after an abnormal screening is harmful.

SUPPLEMENTAL MATERIALS

The following supplement materials are available on the ESP website with this Evidence Brief:

1. Search Strategy
2. Excluded Studies
3. Table 1. Data Abstraction
4. Table 2. Quality Ratings – Cohort Studies

Figure 1. Literature Flow Chart

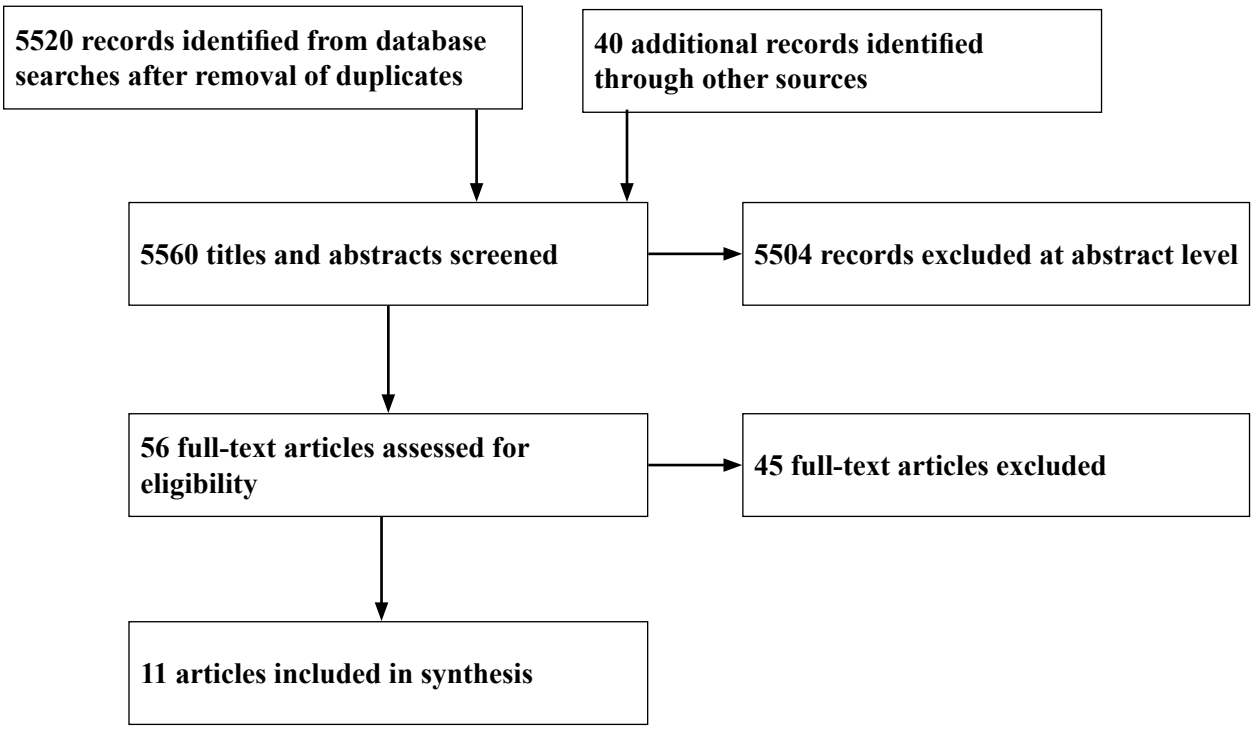
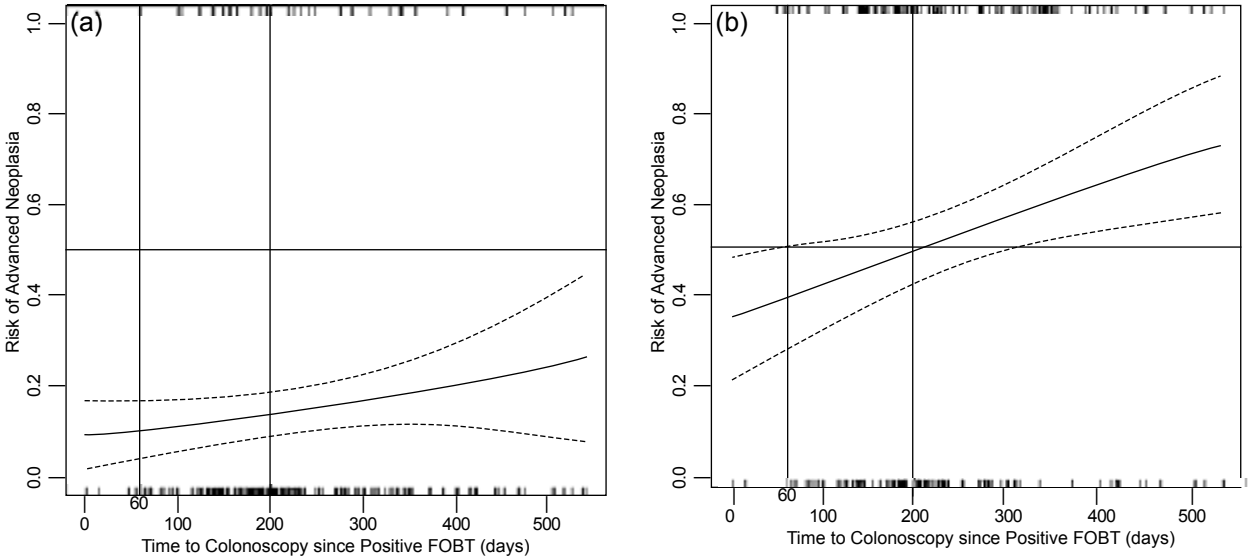


Figure 2. Predicted Probability of Advanced Neoplasia (a) and Neoplasia (b)



The predicted probability plots are derived from the fitted multivariate logistic regression models by averaging over age and race. The hatch marks on the top and bottom of the figures describe the distribution of time to colonoscopy for patients with and without (advanced) neoplasia, respectively. The dashed lines represent 95% point-wise confidence intervals.

*Source: Gellad ZF, Almirall D, Provenzale D, Fisher DA. Time from positive screening fecal occult blood test to colonoscopy and risk of neoplasia. Dig Dis Sci. Nov 2009;54(11):2497-2502.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin.* Jan 2013;63(1):11-30.
2. Ramos M, Esteva M, Cabeza E, Campillo C, Llobera J, Aguiló A. Relationship of diagnostic and therapeutic delay with survival in colorectal cancer: a review. *Eur J Cancer.* 2007;43(17):2467-2478.
3. Ramos M, Esteva M, Cabeza E, Llobera J, Ruiz A. Lack of association between diagnostic and therapeutic delay and stage of colorectal cancer. *Eur J Cancer.* 2008;44(4):510-521.
4. Wattacheril J, Kramer JR, Richardson P, et al. Lagtimes in diagnosis and treatment of colorectal cancer: determinants and association with cancer stage and survival. *Aliment Pharmacol Ther.* Nov 1 2008;28(9):1166-1174.
5. Force USPST. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* Nov 4 2008;149(9):627-637.
6. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med.* Dec 30 1993;329(27):1977-1981.
7. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database of Syst Rev.* 2007(1):CD001216.
8. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. *Gastroenterology.* 2003;124(2):544-560.
9. Powell AA, Nugent S, Ordin DL, Noorbaloochi S, Partin MR. Evaluation of a VHA collaborative to improve follow-up after a positive colorectal cancer screening test. *Med Care.* Oct 2011;49(10):897-903.
10. Gellad ZF, Almirall D, Provenzale D, Fisher DA. Time from positive screening fecal occult blood test to colonoscopy and risk of neoplasia. *Dig Dis Sci.* Nov 2009;54(11):2497-2502.
11. Fisher DA, Jeffreys A, Coffman CJ, Fasanella K. Barriers to full colon evaluation for a positive fecal occult blood test. *Cancer Epidemiol Biomarker Prev.* 2006;15(6):1232-1235.
12. Singh H, Khan R, Giardina TD, et al. Postreferral Colonoscopy Delays in Diagnosis of Colorectal Cancer: A Mixed-Methods Analysis. *Qual Manag Health Care.* 2012;21(4):252-261.
13. Fisher DA, Zullig LL, Grambow SC, et al. Determinants of medical system delay in the diagnosis of colorectal cancer within the Veteran Affairs Health System. *Dig Dis Sci.* 2010;55(5):1434-1441.
14. Larson MF, Ko CW, Dominitz JA. Effectiveness of a provider reminder on fecal occult blood test follow-up. *Dig Dis Sci.* Sep 2009;54(9):1991-1996.

15. Humphrey LL, Shannon J, Partin MR, O'Malley J, Chen Z, Helfand M. Improving the follow-up of positive hemoccult screening tests: an electronic intervention. *J Gen Intern Med.* 2011;26(7):691-697.

16. Brenner H, Altenhofen L, Katalinic A, Lansdorp-Vogelaar I, Hoffmeister M. Sojourn time of preclinical colorectal cancer by sex and age: estimates from the German national screening colonoscopy database. *Am J Epidemiol.* Nov 15 2011;174(10):1140-1146.

17. Kuntz KM, Lansdorp-Vogelaar I, Rutter CM, et al. A systematic comparison of microsimulation models of colorectal cancer: the role of assumptions about adenoma progression. *Med Decis Making.* Jul-Aug 2011;31(4):530-539.

18. Prevost TC, Launoy G, Duffy SW, Chen HH. Estimating sensitivity and sojourn time in screening for colorectal cancer: a comparison of statistical approaches. *Am J Epidemiol.* Sep 15 1998;148(6):609-619.

19. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force-A review of the process. *Am J Prev Med.* 2001;20(3):21-35.

20. Owens DK, Lohr KN, Atkins D, et al. Grading the Strength of a Body of Evidence When Comparing Medical Interventions Methods Guide for Effectiveness and Comparative Effectiveness Reviews. 2008.

21. Gómez-Domínguez E, Trapero-Marugán M, del Pozo A, Cantero J, Gisbert J, Maté J. The colorectal carcinoma prognosis factors. Significance of diagnosis delay. *Rev Esp Enferm Dig.* 2006;98(5):322.

22. Iversen LH, Antonsen S, Laurberg S, Lautrup M. Therapeutic delay reduces survival of rectal cancer but not of colonic cancer. *Br J Surg.* 2009;96(10):1183-1189.

23. Majumdar SR, Fletcher RH, Evans AT. How does colorectal cancer present? Symptoms, duration, and clues to location. *Am J Gastroenterol.* 1999;94(10):3039-3045.

24. Neal RD, Allgar VL, Ali N, et al. Stage, survival and delays in lung, colorectal, prostate and ovarian cancer: comparison between diagnostic routes. *Br J Gen Pract.* 2007;57(536):212.

25. Rupassara K, Ponnusamy S, Withanage N, Milewski P. A paradox explained? Patients with delayed diagnosis of symptomatic colorectal cancer have good prognosis. *Colorectal Dis.* 2006;8(5):423-429.

26. Terhaar sive Droste JS, Oort FA, van der Hulst RWM, et al. Does delay in diagnosing colorectal cancer in symptomatic patients affect tumor stage and survival? A population-based observational study. *BMC Cancer.* 2010;10(1):1-11.

27. Valentin-Lopez B, Ferrandiz-Santos J, Blasco-Amaro JA, Morillas-Sainz JD, Ruiz-Lopez P. Assessment of a rapid referral pathway for suspected colorectal cancer in Madrid. *Fam Pract.* Apr 2012;29(2):182-188.

28. Viiala CH, Tang KW, Lawrance IC, Murray K, Olynyk JK. Waiting times for colonoscopy and colorectal cancer diagnosis. *Med J Aust.* Mar 19 2007;186(6):282-285.

29. Lieberman DA, Weiss DG. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *N Engl J Med.* Aug 23 2001;345(8):555-560.

30. Almendingen K, Hofstad B, Vatn MH. Does high body fatness increase the risk of presence and growth of colorectal adenomas followed up in situ for 3 years? *Am J Gastroenterol.* Jul 2001;96(7):2238-2246.

31. Moghaddam AA, Woodward M, Huxley R. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. *Cancer Epidemiol Biomarkers Prev.* Dec 2007;16(12):2533-2547.

32. Department of Veterans Affairs. Colonoscopy Versus Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM) NCT01239082. *http://wwwclinicaltrials.gov.* 2010.

33. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal cancers not detected by screening flexible sigmoidoscopy in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Gastrointest Endosc.* Mar 2012;75(3):612-620.

APPENDIX A. PEER REVIEW COMMENTS/AUTHOR RESPONSES

REVIEWER COMMENT	RESPONSE
1. Are the objectives, scope, and methods for this review clearly described?	
Yes.	N/A
Yes.	N/A
Yes.	N/A
Yes.	N/A
Yes.	N/A
2. Is there any indication of bias in our synthesis of evidence?	
No.	N/A
No.	N/A
No.	N/A
No.	N/A
No.	N/A
3. Are there any published or unpublished studies that we may have overlooked?	
No. I reviewed some of my files that I keep on this topic and could not find references you didn't cite either in the included or excluded section of the document.	N/A
Yes. I am not sure if data can be requested from a recent study (PLCO project). Although not looking at FOBT, the delay between abnormal flexible sigmoidoscopy and subsequent colonoscopy may shed some light on the main aim of this evidence report. Most of the patients in this study underwent colonoscopy within one year. There may be more granular data on the timing of colonoscopy that can be useful (given the lack of good quality direct evidence).	Added as an option for future research: "Additionally, the dataset from the CRC arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial could be useful in evaluating the effects of delay in colonoscopy.[33] Although the PLCO focused on the effects of flexible sigmoidoscopy screening on CRC mortality, rather than FOBT, there may be data on the variability in timing between abnormal flexible sigmoidoscopy and subsequent colonoscopy that could be relevant to the overarching question of how much delay to colonoscopy after an abnormal screening is harmful."
No.	N/A
No.	N/A
No.	N/A
4. Please write additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.	
(Major) I find the conclusions (page 8) a bit tepid. I concur that the evidence base is relatively weak, but the VA has a policy that centers on a timeframe of 60 days (and that is the driving force behind this ESP). A cancer 'look back' exercise was built around this premise (including disclosure to Veterans with the implication of harm for longer delays than this). I think it can be fairly concluded that there is absolutely no evidence suggesting that a delay in this extremely short time frame is harmful when considering outcomes that matter. I suggest that the authors conclude (i.e. at least one of the bullets) that based on the evidence review that the 60 day timeframe appears arbitrary and is not supported by any direct evidence in the literature.	Agree. Added this conclusion: "No direct evidence supports the current VHA policy that requires follow-up colonoscopy to be done within 60 days of a positive screening FOBT."

REVIEWER COMMENT	RESPONSE
(Major) I find the section on page 9 (Future Research) a bit confusing. What kind of large prospective study is being proposed? It would be impossible to do a trial (randomizing individuals who are FOBT positive to a long period of delay). Perhaps the authors have something specific in mind (other designs would be heavily confounded like the studies that were identified With the current level of detail about a proposal for a prospective study, I was confused about what was being proposed and perhaps other readers would be too.	Added the following: "A large, prospective observational study that focused on the time course of colonoscopies that were specifically ordered as a direct result of a positive screening FOBT could guide decisions about the appropriate timing of colonoscopy, but would take many years to complete. For example, there may be an opportunity to examine the effect of variation in time to colonoscopy on CRC mortality in those who are FIT-positive (Fecal Immunochemical Test) based on data from the ongoing 10-year randomized controlled trial of Colonoscopy Versus Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM) sponsored by the VHA (NCT01239082, CSP 577, Study Chairs Jason A. Dominitz, MD, MHS and Douglas Robertson, MD, MPH)."
(Major) Interestingly, the authors go on to focus on modeling as a potential solution here (page 9). I think this section should be expanded. In fact, there are already many good studies that examine 'sojourn time'—the time for preclinical cancers to become clinical cancers. Some references would include: Med Decis Making 2011; 31:530; Am J Epid 2011; 174(10):1140 and Am J Epid 1998; 148:609-619). These types of models (that extrapolate from real world data) clearly suggest that an extremely short delay (i.e. a 60 day delay) could only plausibly affect outcome in the rarest of cases. For example estimates from the most reputable groups (including the CISNET group you mention) suggest mean sojourn times of 1.6-4.0 years. VA leadership should read that clearly in this document (current estimates of sojourn time). I think it would help inform decision making about the current '60 day rule'.	Agree. Added more detail about proposed modeling study approach: "A more immediate alternative is to use a Cancer Intervention and Surveillance Modeling Network (CISNET) CRC model to investigate the impact of delays in colonoscopy on cancer stage and survival. In addition, a CISNET model could be specifically used to assess the validity of the findings about neoplasia from the Durham VAMC study. Specifically, by adding a parameter representing the time between a positive screening FOBT and colonoscopy, a model could evaluate the relationship between specific delay intervals over the long-term, such as two years." Also added more detail about sojourn times to the Introduction: "Additionally, modeling studies that use real-world data to simulate the progression of CRC through the adenocarcinoma sequence have consistently estimated mean sojourn times that range from 1.6 to 6 years).[16] The current state of knowledge about sojourn times suggest that it takes years for preclinical cancers to develop into clinical cancers and that much shorter delays, such as 60 days, are unlikely to affect outcomes for most Veterans."
(Minor) The authors should carefully review the document examining the citation of reference 20. I think it is referenced on a number of occasions incorrectly. For example, pg 5 (line 1) cites 'two studies' (the VA studies are 4 &10), but reference 20 is also cited.	Corrected
(Minor) On pg 13, reference 20 is not formatted properly (the title is not correct).	Corrected
There is a typo on Page 5 –first paragraph. It should say three and not 2 (studies)	Two is correct. Reference #20 should not have been cited and has been deleted.
It may be a good idea to discuss the generalizability of the results from the three FOBT studies to FIT based testing	Agree. Added this bullet to the conclusions: "The generalizability of the results from the FOBT study to FIT-based testing (Fecal Immunochemical Test) is unclear. If the reasons for ordering a FIT instead of an FOBT are proxies for other factors that modify the risk of delay to colonoscopy and/or CRC outcomes, this may result in a different relationship between delay and CRC outcomes. Also, because the FIT characteristics differ from FOBT, this may impact the importance of delays in follow-up colonoscopy."

REVIEWER COMMENT	RESPONSE
1) Introduction: It may be worthwhile to provide a bit more information on the current state of knowledge about sojourn times. When you discuss the Gellad study in the results, it is hard to imagine that a 30 day delay is associated with a 10% increased odds of finding neoplasia. Some readers may not understand that polyps don't just appear out of nowhere. They typically take years to develop.	Agree. Added the following: "Additionally, modeling studies that use real-world data to simulate the progression of CRC through the adenocarcinoma sequence have consistently estimated mean sojourn times that range from 1.6 to 6 years).[16-18] The current state of knowledge about sojourn times suggest that it takes years for preclinical cancers to develop into clinical cancers and that much shorter delays, such as 60 days, are unlikely to affect outcomes for most Veterans."
2) Introduction, page 1, paragraph 1: The mention of the systematic reviews by Ramos includes "(2007 and 2008)" which may be a typo. The studies are referenced appropriately after that.	Agree. Changed to "…included in a 2007 systematic review by Ramos and colleagues…"
3) Introduction, page 2, paragraph 2: consider adding reference to another VA study that worked to improve follow-up of positive FOBT: Larson, Ko and Dominitz Dig Dis Sci. 2009 Sep;54(9):1991-6. doi: 10.1007/s10620-009-0751-2. Epub 2009 Mar 3. PMID:19255849	Agree. Added.
4) Introduction, page 2, paragraph 3: I don't think there is any policy to review all cases of positive FOBT with colonoscopy more than 60 days later. There was a one-time requirement to find all GI cancers over a 2 year period and then to see if any had a 60 day delay between FOBT and colonoscopy. But this is not a true policy as far as I know. You may be able to say something like: "In 2012, the VHA conducted a colorectal cancer lookback to assess if any colonoscopy completed more than 60 days after consultation or a positive FOBT was associated with evidence of harm to the Veteran due to delays in care. This assessment was based on the assumption that a delay in diagnosis of more than 60 days could lead to poorer health outcomes, but the evidence for this assumption has not been systematically evaluated. Also, the clinical relevance of the 60-day period is unclear given the recent estimates of mean sojourn times for preclinical CRC of between 4.5 to 5.8 years.15"	Agree. Changed to: "The VHA's current policy on CRC follow-up timelines states that for any positive screening test for which a diagnostic colonoscopy is indicated, the colonoscopy must be performed within 60 calendar days of the positive screening test. Based on this policy, in 2012 the VHA conducted a colorectal cancer lookback to assess and disclose if any colonoscopy completed more than 60 days after consultation or a positive FOBT was associated with evidence of harm to the Veteran."
5) Page 5, paragraph 1: The text says: "This exclusion could have underestimated the relationship between colonoscopy delay and risk of neoplasia. For example, older age was associated with higher odds of neoplasia in this study (OR 1.10; 95% CI, 1.02 to 1.19) and also could have made it more difficult to obtain a colon evaluation." However, isn't it possible that the exclusion may actually overestimate the risk of neoplasia as discussed earlier in the paragraph? If about 50% of those who are FOBT positive don't get colonoscopy within a year or so, but some of them with neoplasia develop anemia or bleeding or weight loss and get scoped, while those without neoplasia don't get scoped and are excluded, then the delay of a year would artificially overestimate the risk. I think that this section needs revising to make it more clear that you cannot predict the direction of the association.	Agree. Changed to: "If the reasons the excluded patients didn't have a colonoscopy within 18 months were proxies for other factors that modify the risk of neoplasia, then the exclusions could have either over- or underestimated the relationship between colonoscopy delay and risk of neoplasia For example, older age was associated with higher odds of neoplasia in this study (OR 1.10; 95% CI, 1.02 to 1.19) and also could have made it more difficult to obtain a colon evaluation. On the other hand, the risk of neoplasia could have been overestimated if the excluded patients actually did not have neoplasia and, likewise, didn't get a colonoscopy because they hadn't yet developed any symptoms or other risk factors that would raise concern about CRC."

REVIEWER COMMENT	RESPONSE
6) Page 8, Conclusion: The following statement should be changed such that the words "can reduce the" are replaced by "is associated with a lower": "There is low-strength evidence from a retrospective observational study that shorter follow-up evaluations of positive screening FOBT's can reduce the risk of neoplasia." If this finding is going to be put into one of the 3 bullet conclusions, I fear it will receive a great deal of attention from readers with limited medical knowledge. There is a tremendous risk of bias here due to the high proportion that doesn't get scoped. We know that people with symptoms have a fairly high chance of getting scoped, so it is quite possible that those with delays who ultimately get scoped are more likely to be symptomatic (and have more neoplasia) than those who don't get scoped. This point is discussed in the limitations, but I think it merits brief mention in the conclusion bullet to avoid inappropriate emphasis.	Agree. Changed conclusion statements entirely to emphasize the findings regarding the critical outcomes of mortality and CRC stage, rather than neoplasia. We agree that the relevance of neoplasia to the critical outcomes of survival and CRC stage is unclear and for that reason it was not originally listed as an included outcome. To better emphasize this, we added this statement to the Inclusion Criteria: "Prior to conducting the review, we did not list neoplasia as an included outcome because experts did not think it was sufficiently correlated with the critical outcomes. " We also revised our conclusion statement about neoplasia as follows: "We also examined evidence concerning colonoscopy delay and neoplasia, but as discussed in the results, the evidence about it is sparse, has multiple methodological limitations, and it is not clear that it is relevant to the critical outcomes of survival and invasive cancer. For advanced neoplasia, a composite outcome made up of significant polyps and invasive cancer, the positive association with longer time to colonoscopy over 18 months was not statistically significant (OR, 1.07; 95% CI, 0.98 to 1.18)."
I am not sure I agree with the approach to the question. The question asked is related to delay in colonoscopy after a positive FOBT and CRC outcomes. There are no studies which are adequate to address this question, because no study has any significant number of CRC outcomes. Looking at adenoma outcome is really not relevant to the question. It is simply not a good enough surrogate to address this particular question. I would suggest using decision models which have been developed to look at natural history of CRC and ask about how much delay would result in stage shift. For example, if you have a patient with Stage 1 CRC, over what time period might we expect a stage shift to Stage 2, which would impact the patient outcome. I believe CISNET might be able to address this question – and it is this question which is at the heart of the issue raised by VHA.	Agree. We added the following statements to emphasize the limitations of the surrogate and composite outcomes of neoplasia; (1) Added this statement to the Inclusion Criteria: "Prior to conducting the review, we did not list neoplasia as an included outcome because experts did not think it was sufficiently correlated with the critical outcomes. " (2) We also revised our conclusion statement about neoplasia as follows: "We also examined evidence concerning colonoscopy delay and neoplasia, but as discussed in the results, the evidence about it is sparse, has multiple methodological limitations, and it is not clear that it is relevant to the critical outcomes of survival and invasive cancer. For advanced neoplasia, a composite outcome made up of significant polyps and invasive cancer, the positive association with longer time to colonoscopy over 18 months was not statistically significant (OR, 1.07; 95% CI, 0.98 to 1.18)." We also agree with the Reviewer's point about no study having a significant enough number of CRC outcomes to address the question about CRC outcomes. Accordingly, we added this statement to the Results: "As there were only 26 Veterans with advanced adenoma (advanced adenomas and invasive cancer), this study is likely inadequately powered to definitely determine whether any relationship exists between colonoscopy delays and CRC outcomes." We agree with the suggestion of using natural CRC history models to address this question and have described such an approach in the Future Research section.

REVIEWER COMMENT	RESPONSE
Pg 1 last paragraph Empiric VHA studies of reasons for delayed colonoscopy have found inconsistent results. Citation 13 is referenced. I believe that this statement is somewhat misleading. Reference 13 refers to delays in diagnosis of CRC and not specifically delays in colonoscopy. In fact, the diagnosis is made through histology in this study. This study does not measure delay in colonoscopy ,specifically.	Agree. Removed the misleading sentence and changed paragraph as follows: "Recent qualitative data suggest that VHA providers attribute long delays in scheduling follow-up colonoscopies to ambiguity regarding referral guidelines, patient disengagement and nonadherence, and endoscopic resource limitations.[12] Analysis of quantitative data from that same study of 104 patients from a single VAMC, found that the most common reason for colonoscopy delay was delayed future colonoscopy appointment date given by the gastroenterology service and found no statistically significant differences were found in demographics or medical or mental health comorbidities in patients with and without delays.[12] Although not a specific measure of colonoscopy delay, another study of 468 patients from 15 Veterans Affairs Medical Center (VAMCs) found that being older, having comorbidities and residing in the Atlantic region were associated with a longer time to diagnosis."[13]
Under future research, 1st sentence. A large prospective study.. There is a large prospective study underway in VA to test two alternative colorectal cancer screening methods, FIT vs. Colonoscopy. Those with +FIT will undergo colonoscopy. There will be variation in time to colonoscopy in those who are FIT positive. The study will follow subjects for 10 years. The outcome is CRC mortality. This study will provide an opportunity to examine the effect of variation in time to colonoscopy on CRC mortality in those who are Fit positive. I think that this may be worth mentioning (CSP 577, Dominitz, Robertson, study chairs)	Agree. Added the following: "A large, prospective observational study that focused on the time course of colonoscopies that were specifically ordered as a direct result of a positive screening FOBT could guide decisions about the appropriate timing of colonoscopy, but would take many years to complete. For example, there may be an opportunity to examine the effect of variation in time to colonoscopy on CRC mortality in those who are FIT-positive based on data from the ongoing 10-year randomized controlled trial of Colonoscopy Versus Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM) sponsored by the VHA.(NCT01239082, CSP 577, Study Chairs Jason A. Dominitz, MD, MHS and Douglas Robertson, MD, MPH)."