Surveillance Colonoscopy in Older Stage I Colon Cancer Patients and the Association With Colon Cancer-Specific Mortality

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OBJECTIVES: **Guideline-issuing groups differ regarding the recommendation that patients with stage I colon cancer receive surveillance colonoscopy after cancer-directed surgery. This observational comparative effectiveness study was conducted to evaluate the association between surveillance colonoscopy and colon cancer-specific mortality in early stage patients.**

METHODS: **This was a retrospective cohort study of the Surveillance, Epidemiology, and End Results database combined with Medicare claims. Surveillance colonoscopy was assessed as a time-varying exposure up to 5 years after cancer-directed surgery with the following groups: no colonoscopy, one colonoscopy, and ≥ 2 colonoscopies. Inverse probability of treatment weighting was used to balance covariates. The time-dependent Cox regression model was used to obtain inverse probability of treatment weighting-adjusted hazard ratios (HRs), with 95% confidence intervals (CIs) for 5- and 10-year colon cancer, other cancer, and noncancer causes of death.**

RESULTS: **There were 8,783 colon cancer cases available for analysis. Overall, compared with patients who received one colonoscopy, the no colonoscopy group experienced an increased rate of 10-year colon cancer-specific mortality (HR = 1.63; 95% CI 1.31–2.04) and noncancer death (HR = 1.36; 95% CI 1.25–1.49). Receipt of ≥ 2 colonoscopies was associated with a decreased rate of 10-year colon cancer-specific death (HR = 0.60; 95% CI 0.45–0.79), other cancer death (HR = 0.68; 95% CI 0.53–0.88), and noncancer death (HR = 0.69; 95% CI 0.62–0.76). Five-year cause-specific HRs were similar to 10-year estimates.**

DISCUSSION: **These results support efforts to ensure that stage I patients undergo surveillance colonoscopy after cancer-directed surgery to facilitate early detection of new and recurrent neoplastic lesions.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B390, http://links.lww.com/AJG/B391, http://links.lww.com/AJG/B392

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INTRODUCTION

In the United States, the plurality of newly diagnosed patients with colon cancer is diagnosed with local disease (39%). These patients undergo curative surgery as treatment with most having a very favorable prognosis; 5-year relative survival is 90% (1). The primary goal of cancer surveillance testing in patients with colon cancer is to detect tumor recurrence or new neoplastic lesions at an earlier point than symptom-based detection (2,3). The premise of this strategy is that earlier detection in asymptomatic patients will decrease disease- and treatment-related morbidity and increase the likelihood of curative treatment for the recurrent or metachronous tumor, leading to a better prognosis (2,4,5). According to the US Multi-Society Task Force on Colorectal Cancer and several other guideline-issuing groups, surveillance testing in patients with stage I colon cancer consists of colonoscopy approximately 1 year after surgical resection and every 3–5 years thereafter (6–8). However, the American Society of Clinical Oncology, which endorsed the Practice Guideline of Cancer Care Ontario, does not recommend surveillance colonoscopy in stage I patients, citing a lack of evidence to support this practice (9,10). Inconsistency in guidelines and lack of evidence to inform recommendations lead to variation in clinical practice and, potentially, disparities in outcomes (11).

Considering the disagreement in guideline recommendations, the substantial proportion of patients with colon cancer who do not

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receive surveillance colonoscopy (12–14) and the lack of evidence regarding the effectiveness of colonoscopic surveillance testing in patients with stage I colon cancer, we conducted an observational comparative effectiveness research (CER) study to provide new evidence on this issue and inform discussions between physicians and their patients. To achieve this objective, we used the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results database combined with Medicare claims (SEER-Medicare) to evaluate whether the receipt of surveillance colonoscopy in older adult patients with colon cancer is associated with a better 5- and 10-year colon cancer-specific survival in stage I patients.

METHODS

The study protocol for our larger study has been described, although some differences will be noted (15). The study population consisted of patients with colon cancer who were diagnosed between 2002 and 2009 and included in the NCI's SEER-Medicare database. These years were included so that patients had the potential for at least 5 years of follow-up after surgery. Vital status and cause of death information was available up to the study's termination date, December 31, 2015. The flow diagram depicting inclusion/exclusion criteria is shown in Figure 1. This study was approved by the NCI and the Institutional Review Board of the University of Central Florida.

Ascertainment of study data

The SEER-Medicare data files used to conduct this study have been described (15). Relevant diagnostic and procedure codes used in this study are depicted in the supplemental content (see Table, Supplemental Digital Content 1, http://links.lww.com/AJG/B390, relevant codes). The cause of death was based on International Classification of Diseases, tenth edition, codes and recorded as death due to colon cancer, other cancer, and noncancer causes. Cases with only colon cancer diagnosis but with causes of death attributed to other cancers were recoded as colon cancer deaths. In addition, patients (n = 7) with more than one cancer diagnosis but with unspecified cancer (C80) as cause of death were recoded as colon cancer deaths. Finally, patients (n = 3) with cancer-related deaths not coded as colon cancer or other diagnosed cancers were recoded as colon cancer deaths. Medicare files to assess the receipt of surveillance testing were available up to December 31, 2014.

Surveillance colonoscopy classification

The timing of surveillance colonoscopy within 5 years of cancer-directed surgery was assessed for all patients. The timing of first colonoscopy was defined as the date of the first colonoscopy-related claim ≥ 3 months after cancer-directed surgery. Second surveillance colonoscopy was defined as the date of a colonoscopy-related claim ≥ 365 days after the first colonoscopy. This resulted in 3 surveillance categories: no colonoscopy, one colonoscopy, and ≥ 2 colonoscopies.

Inverse probability of treatment weighting

Generalized boosted models were used to obtain propensity scores according the 3 categories of surveillance colonoscopy (16). Propensity scores were obtained by adjusting models for age, race, sex, marital status, year of diagnosis, state buy-in coverage, census-tract poverty level, urban-rural designation, SEER region (17), tumor grade, tumor location (proximal/distal), and the individual comorbid conditions that comprise the Charlson comorbidity index (18). This procedure produces inverse probability of treatment weighting (IPTW) that balances covariates between surveillance groups.

Statistical analysis

Demographic and clinical variables were compared across the 3 surveillance categories. Pearson χ^2 was applied to detect differences in categorical variables. The median follow-up time between the groups was calculated by the reverse Kaplan-Meier method.

After obtaining IPTW and applying weights to the dataset, balance between potential confounding factors was assessed by the absolute standardized mean difference for each group compared with the study population mean (16). Differences ≥ 0.10 were considered as evidence of imbalance (19). For point estimates obtained in the regression models described below, the estimand is the average treatment effect.

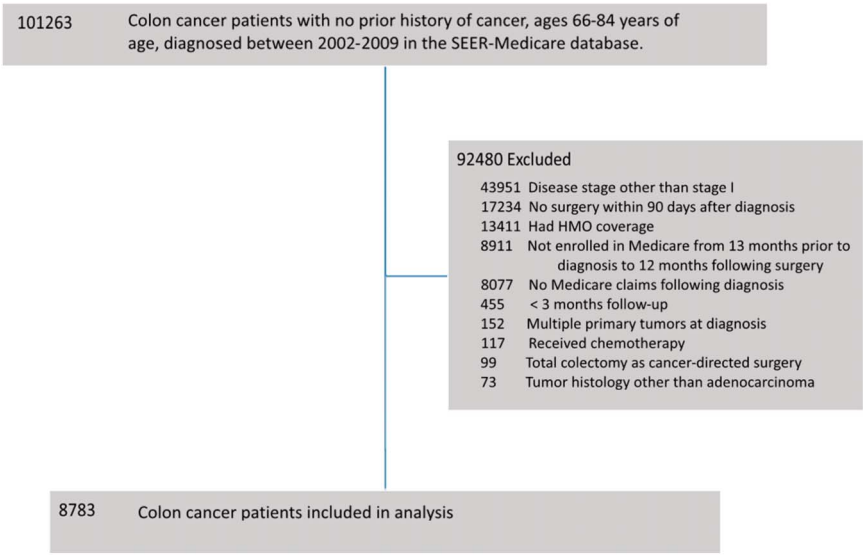

Figure 1. Inclusion and exclusion criteria.

The timing of first and second surveillance colonoscopy represents time-varying exposures with assessment extending into the follow-up period. Considering surveillance categories as fixed values at the start of follow-up based on the receipt of future surveillance colonoscopy testing introduces the potential for immortal time bias (20–23). To account for the time-varying nature of surveillance colonoscopy, study data were expanded using the counting process such that patients had one record corresponding to each follow-up period in which the time-varying exposure (surveillance colonoscopy) was constant (22,24). The time-dependent Cox regression model was used to obtain IPTW-adjusted estimates of a 5- and 10-year overall survival, and the cumulative incidence of colon cancer-specific death with 95% confidence intervals (CIs). The Cox models were also used to obtain cause-specific hazard ratios (HRs), with 95% CIs for the association between surveillance colonoscopy and 5- and 10-year colon cancer-specific, other cancer, and noncancer survival. As recommended, we report cause-specific HRs between surveillance colonoscopy and our primary outcome of colon cancer-specific survival and the competing outcomes of other cancer and noncancer mortality (25,26).

Post hoc/sensitivity analyses

To rule out the possibility that colonoscopies were performed for diagnostic rather than surveillance purposes, we performed a sensitivity analysis to evaluate the effect of first colonoscopy when received within 15 months of cancer-directed surgery. This period includes the guideline-recommended timeline of colonoscopy performed 1 year after the receipt of cancer-directed surgery plus a 3 month grace period. For this analysis, patients were required to have a complete follow-up during the time of first colonoscopy assessment (≥15 months).

To gain better insight into the associations between the 3 surveillance colonoscopy categories (no colonoscopy, one colonoscopy, and ≥ 2 colonoscopies) and cause-specific survival, we also assessed the 10-year conditional survival. For this analysis, we limited the data to patients who had complete follow-up information during the period of first and second colonoscopy assessments (patients with ≥ 5 years of follow-up).

Finally, to isolate the effect of surveillance colonoscopy on colon cancer-specific survival, we analyzed the data at fixed levels of carcinoembryonic antigen (CEA) testing and computed tomography (CT) examination testing. For this analysis, we restricted the data to patients with ≥ 3 years of follow-up and categorized patients according to the number of CEA (≤1 or ≥ 2) and CT (0 or ≥ 1) surveillance tests received within 3 years of surgery. Because we restricted the data to patients with ≥ 3 years follow-up, we only report 10-year colon cancer-specific survival to have enough events for the survival analysis.

RESULTS

Demographic and clinical characteristics of the study population (n = 8,783) are shown in Table 1. Only sex, urban/rural status, and tumor grade were unassociated with surveillance colonoscopy status. IPTW achieved balance on all measured potential confounders (Table, Supplemental Digital Content 2, http://links.lww.com/AJG/B391, assessment of covariate balance).

IPTW-adjusted estimates of 5- and 10-year overall survival and the cumulative incidence of colon cancer-specific death according to the categories of surveillance colonoscopy are given in Table 2. Focusing on 10-year outcomes, overall survival ranged from 32.0% for the no colonoscopy group to 56.5% for the ≥ 2 colonoscopies group. Figure 2 illustrates the 10-year overall survival curves according to surveillance colonoscopy status. The no colonoscopy group also had a higher 10-year cumulative incidence of colon cancer-specific death (8.1%) compared with the one colonoscopy group (5.8%) and the ≥ 2 colonoscopies group (4.3%). Figure 3 displays the 10-year cumulative incidence functions of colon cancer-specific mortality for each surveillance category.

IPTW-adjusted HRs for the 5-year and 10-year cause-specific mortality are provided in Table 3. For 10-year mortality, compared with colon cancer patients who received one surveillance colonoscopy, patients who failed to receive a surveillance colonoscopy had 63% increased rate of colon cancer-specific mortality (HR = 1.63; 95% CI 1.31–2.04) and a 36% increased rate of noncancer mortality (HR = 1.36; 95% CI 1.25–1.49). Patients who received ≥ 2 colonoscopies experienced a 40% decreased rate of colon cancer-specific death (HR = 0.60; 95% CI 0.45–0.79), a 32% decreased rate of other cancer death (HR = 0.68; 95% CI 0.53–0.88), and a 31% decreased rate of noncancer death (HR = 0.69; 95% CI 0.62–0.76). Similar results were obtained for the 5-year causes of death.

Post hoc/sensitivity analysis results

The sensitivity analysis focusing on the receipt of first surveillance colonoscopy is available online (Table, Supplemental Digital Content 3, http://links.lww.com/AJG/B392, first colonoscopy and 5-year colon cancer survival). The HRs comparing the one colonoscopy group to the no colonoscopy group are of higher magnitude than those reported in Table 3.

The results for the 10-year survival, conditional on patients having at least 5 years of follow-up after surgery, are shown in Table 4. No colonoscopy was associated with an 89% increased rate of colon cancer-specific death (HR = 1.89; 95% CI 1.27–2.83) and a 33% increased rate of noncancer death (HR = 1.33; 95% CI 1.17–1.51). Patients who received ≥ 2 colonoscopies had a 32% decreased rate of both colon cancer-specific death (HR = 0.68; 95% CI, 0.45–1.02) and noncancer death (HR = 0.68; 95% CI, 0.61–0.77). Surveillance colonoscopy was unassociated with death because of other cancers.

IPTW-adjusted HRs for 10-year colon cancer-specific mortality at fixed levels of CEA and CT testing are provided in Table 5. Focusing on CEA testing, less testing (≤1 CEA test) conferred a 2.2-fold increased rate of death (HR = 2.15; 95% CI 1.46–3.18) for the no colonoscopy group (HR = 2.15; 95% CI 1.46–3.18), whereas more testing (≥2 CEA tests) was associated with a 68% increased rate of death (HR = 1.68; 95% CI, 1.11–2.54). Receiving ≥ 2 colonoscopies did not convey a survival benefit for those who received less CEA testing but was associated with a 47% decreased rate of death (HR = 0.53; 95% CI, 0.36–0.80) for those who received ≥ 2 CEA tests.

Shifting to the effect of colonoscopy at fixed levels of CT examination testing, patients who failed to receive a colonoscopy had a higher rate of colon cancer-specific death that was of larger magnitude with no CT examination testing (HR = 2.35; 95% CI 1.52–3.62) than for patients who received ≥ 2 CT examinations (HR = 1.54; 95% CI 0.69–1.94). Patients who received ≥ 2 colonoscopies did not experience a survival benefit with no CT examinations but did see a 40% decreased rate (HR = 0.60; 95% CI 0.42–0.87) of colon cancer-specific death with one or more CT examinations.

Table 1. Demographic and clinical characteristics of patients with stage I colon cancer overall and according to the receipt of surveillance colonoscopy after cancer-directed surgery (n = 8,783)

Characteristic	All patients		No Colonoscopy		One Colonoscopy		≥ 2 Colonoscopies		*P*
	n	%	n	%	n	%	n	%	
Study population	8,783	100.0	2,594	29.5	2,565	29.2	3,624	41.3	
Median follow-up time									<0.001
95% CI, (yr)	10.3	10.2–10.4	10.8	10.5–11.3	10.1	9.9–10.3	10.3	10.2–10.4	
5-yr vital status									<0.001
Alive	6,611	75.3	1,410	54.4	1818	70.9	3,383	93.4	
Deceased	2,172	24.7	1,184	45.6	747	29.1	241	6.6	
5-yr cause of death									<0.001
Colon cancer	343	15.8	196	16.6	111	14.9	36	14.9	
Other cancer	236	10.9	91	7.7	108	14.5	37	15.4	
Noncancer	1,593	73.3	897	75.8	528	70.7	168	69.7	
10-yr vital status									<0.001
Alive	4,489	51.1	702	27.1	1,157	45.1	2,630	72.6	
Deceased	4,294	48.9	1892	72.9	1,408	54.9	994	27.4	
10-yr cause of death									<0.001
Colon cancer	503	11.7	255	13.5	158	11.2	90	9.0	
Other cancer	413	9.6	136	7.2	158	11.2	119	12.0	
Other	3,378	78.7	1,501	79.3	1,092	77.6	785	79.0	
Age at diagnosis									<0.001
66–74 yr	3,854	43.9	868	33.5	984	38.4	2002	55.2	
75–79 yr	2,627	29.9	779	30.0	814	31.7	1,034	28.5	
80–84 yr	2,302	26.2	947	36.5	767	29.9	588	16.2	
Race									<0.001
White	7,538	85.8	2,163	83.4	2,192	85.5	3,183	87.8	
Black	686	7.8	272	10.5	201	7.8	213	5.9	
Asian	261	3.0	68	2.6	88	3.4	105	2.9	
Other/unknown	195	2.2	63	2.4	49	1.9	83	2.3	
Hispanic	103	1.2	28	1.1	35	1.4	40	1.1	
Sex									0.209
Female	4,791	54.6	1,378	53.1	1,408	54.9	2005	55.3	
Male	3,992	45.4	1,216	46.9	1,157	45.1	1,619	44.7	
Marital status									<0.001
Married or partner	4,984	56.7	1,270	49.0	1,408	54.9	2,306	63.6	
Separated/divorced	567	6.5	207	8.0	144	5.6	216	6.0	
Single	633	7.2	221	8.5	188	7.3	224	6.2	
Widowed	2,289	26.1	785	30.3	746	29.1	758	20.9	
Unknown	310	3.5	111	4.3	79	3.1	120	3.3	
Year of diagnosis									0.010
2002–2003	2,527	28.8	698	26.9	719	28.0	1,110	30.6	
2004–2006	3,230	36.8	953	36.7	966	37.7	1,311	36.2	
2007–2009	3,026	34.4	943	36.4	880	34.3	1,203	33.2	

Table 1. (*continued*)

Characteristic	All patients		No Colonoscopy		One Colonoscopy		≥ 2 Colonoscopies		*P*
	n	%	n	%	n	%	n	%	
State buy-in coverage									<0.001
No	6,938	79.0	1876	72.3	1999	77.9	3,063	84.5	
Yes	1845	21.0	718	27.7	566	22.1	561	15.5	
Census tract poverty level									<0.001
Low	2,406	27.4	635	24.5	663	25.9	1,108	30.6	
Lower-middle	2,448	27.9	716	27.6	673	26.2	1,059	29.2	
Upper-middle	2,504	28.5	759	29.3	800	31.2	945	26.1	
High/unknown	1,425	16.2	484	18.7	429	16.7	512	14.1	
Geographic residency									0.394
Urban	7,738	88.1	2,310	89.0	2,258	88.0	3,170	87.5	
Less urban	847	9.6	227	8.8	248	9.7	372	10.3	
Rural	198	2.3	57	2.2	59	2.3	82	2.3	
SEER region									0.004
West	3,288	37.5	1,031	39.8	939	36.6	1,318	36.4	
South	2,261	25.7	678	26.1	685	26.7	898	24.8	
Northeast	1873	21.3	510	19.7	522	20.4	841	23.2	
Midwest	1,249	14.2	341	13.2	382	14.9	526	14.5	
Pacific	112	1.3	34	1.3	37	1.4	41	1.1	
Tumor grade									0.488
Low grade	7,365	83.9	2,191	84.5	2,129	83.0	3,045	84.0	
High grade	730	8.3	217	8.4	219	8.5	294	8.1	
Unknown	688	7.8	186	7.2	217	8.5	285	7.9	
Tumor site									0.041
Proximal colon	5,532	63.0	1,585	61.1	1,619	63.1	2,328	64.2	
Distal colon	3,251	37.0	1,009	38.9	946	36.9	1,296	35.8	
Comorbidity									<0.001
0	4,101	46.7	999	38.5	1,120	43.7	1982	54.7	
1	2,218	25.2	623	24.0	660	25.7	935	25.8	
2–3	1772	20.2	651	25.1	568	22.1	553	15.3	
4 +	692	7.9	321	12.4	217	8.5	154	4.2	

CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results

DISCUSSION

This is the first study to evaluate and demonstrate the colon cancer-specific survival benefit associated with surveillance colonoscopy in patients with stage I colon cancer. As has been reported in the US national cancer statistics (1), in this study, patients with stage I colon cancer had a low risk of colon cancer-related mortality. Despite the good prognosis of these patients, we found that failing to receive surveillance colonoscopy increased the hazard rate of colon cancer-specific death by 53% (5-year), 63% (10-year), and 89% (10-year conditional survival) compared with patients who received one surveillance colonoscopy. The detrimental effect of no colonoscopy was higher for those without additional surveillance testing (CEA/CT). In addition, the receipt of ≥ 2 colonoscopies was associated with a 45% (5-year), 40% (10-year), and 32% (10-year conditional survival) decreased rate of colon cancer-specific death. The additional survival benefit for patients who received ≥ 2 colonoscopies occurred within the context of greater frequency of CEA/CT examination testing.

Reporting cause-specific HRs provides insight into reported associations and characteristics of the study population according to the exposure of interest. For all time periods, the no colonoscopy group had an increased rate of noncancer causes of death and the ≥ 2 colonoscopies group had a decreased rate. Because the receipt of colonoscopy would have no impact on noncancer-related causes of death, colonoscopy status could be a marker for encounters with the healthcare system and management of comorbid conditions. For example, in addition to cancer-related care, patients in the no colonoscopy group may have had fewer encounters with the healthcare system in general, leading to poorer control of comorbid conditions and an increased rate of noncancer causes of death. Likewise, patients in the ≥ 2 colonoscopies group may have had more contact with healthcare providers, resulting in better management of comorbidities and a decreased rate of

Table 2. IPTW-adjusted 5- and 10-yr estimates of overall survival and cumulative incidence of colon cancer-specific mortality

	Overall survival		Cumulative incidence, colon cancer death	
Surveillance colonoscopy	Estimate	95% CI	Estimate	95% CI
5-yr outcomes				
Colonoscopy categorization				
No colonoscopy	69.0%	67.5%–70.6%	5.1%	3.7%–7.1%
One colonoscopy	76.0%	74.7%–77.4%	3.6%	2.3%–5.5%
≥ 2 colonoscopies	83.0%	81.8%–84.3%	2.7%	1.5%–5.1%
10-yr outcomes				
Colonoscopy categorization				
No colonoscopy	32.0%	29.8%–34.3%	8.1%	5.8%–11.1%
One colonoscopy	43.0%	41.0%–45.2%	5.8%	3.8%–8.8%
≥ 2 colonoscopies	56.5%	54.4%–58.6%	4.3%	2.2%–8.5%

CI, confidence interval; IPTW, inverse probability of treatment weighting.

noncancer death. Thus, although our method of IPTW balanced measured covariates, including comorbid conditions, between groups, prognostic differences in noncancer death still occurred which could be explained by longitudinal management of comorbid conditions before and after cancer diagnosis. In contrast to randomized controlled trials (RCTs), observational CER studies reflect the healthcare that patients actually receive in real-world clinical settings. This includes not only the exposure of interest but also, in the case of this study, the totality of health-seeking behavior that may have a bearing on competing causes of death.

Regarding the sensitivity analysis for the effect of first colonoscopy received within 15 months of cancer-directed surgery, the HRs comparing the one colonoscopy group with the no colonoscopy group are of higher magnitude than those reported in Table 3 for 2 reasons. First, the beneficial effect of those who went on to have ≥ 2 colonoscopies was combined with those who only received one colonoscopy. Second, patients who received later diagnostic colonoscopies (either first or subsequent) within 5 years of cancer-directed surgery were included in the surveillance colonoscopy groups in Table 3 but not in the one colonoscopy group for the sensitivity analysis because assessment ended at 15 months after surgery. If these diagnostic colonoscopies were associated with a higher risk of colon cancer-specific mortality, the survival benefit associated with surveillance colonoscopy would be biased toward the null value. For these reasons, HRs for the sensitivity analysis show a greater detrimental effect of failing to receive the recommended first colonoscopy within 15 months of cancer-directed surgery.

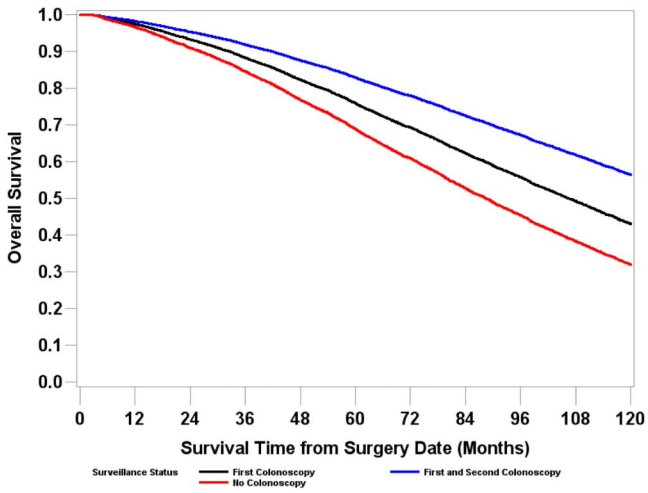

Figure 2. A 10-year overall survival by surveillance colonoscopy status.

Further explanation is needed to explain the association between greater frequencies of surveillance colonoscopy with death due to other cancers. For those who received ≥ 2 colonoscopies, there was a decreased rate of 5- and 10-year other cancer death. In addition to the scenario of greater health-seeking behavior described above, which could be associated with earlier detection of additional cancers, this could also reflect a treatment selection bias. For example, if a patient who was initially diagnosed with colon cancer was subsequently diagnosed with one or more cancers that posed a greater risk to mortality, undergoing a second colonoscopy might not be considered a high value procedure. Thus, patients who were deemed to be at higher risk for death due to other cancer diagnoses might not have been selected to undergo a second surveillance colonoscopy. This hypothesis is supported by focusing on the results for a 10-year conditional survival. For patients who lived at least 5 years after cancer surgery, there was no association between surveillance colonoscopy and other cancer mortality. By performing the analysis of 10-year conditional survival, we effectively removed the impact of a second cancer influencing the likelihood of receiving a second colonoscopy within 5 years of surgery and obtained the expected result of no association between surveillance colonoscopy and death due to other cancers.

The association between surveillance colonoscopy and survival in patients with colon cancer has been examined in previous retrospective cohort studies. Rulyak et al. (14) examined the association between surveillance colonoscopy and overall mortality in patients with stage 0-III colorectal cancer enrolled in a health maintenance organization. They demonstrated that surveillance colonoscopy was associated with a 42% decreased risk of death during follow-up. By reanalyzing our study data using the same categorization as these investigators (data not shown), we obtained similar results for a 5-year colon cancer-specific survival (≥1 colonoscopy vs none; HR, 0.57).

An older SEER-Medicare study by Ramsey et al. (13) used a matched case-control design to examine the relationship between

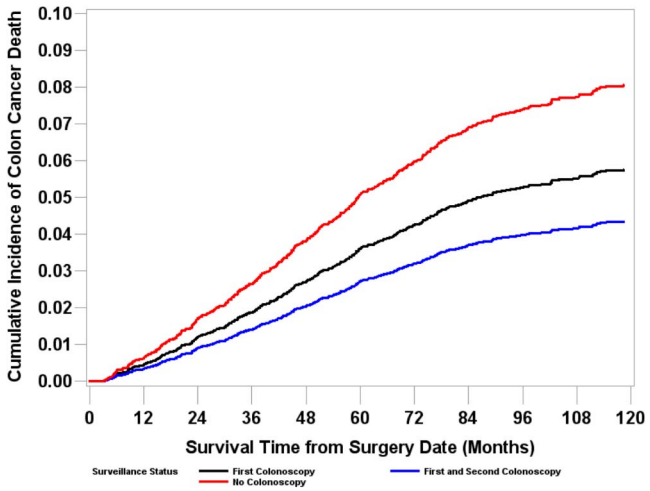

Figure 3. A10-year cumulative incidence of colon cancer-specific death by surveillance colonoscopy status.

surveillance endoscopy and colorectal cancer-specific mortality. They reported that surveillance colonoscopy was not associated with cancer-specific survival. In addition to the study design, characteristics of their study which may explain the differing results are as follows: (i) the inclusion of stage II/III patients who are also recommended to receive additional surveillance testing (6,27) and (ii) the time period of the study cohort (diagnosed 1986–1996) after which the treatment of primary and recurrent colon cancer improved (28–33).

Some investigators have reported that CEA testing is the most effective for detecting colon cancer recurrence (2,34,35), particularly for hepatic metastases (36). Although both CEA and CT examination testing are recommended for patients with stage II/III colon cancer, no guideline-issuing groups recommend these surveillance tests in stage I patients (6–10). In our study, we found that greater frequency of surveillance colonoscopy was associated with a higher likelihood of CEA (≥2 tests: ≥ 2 colonoscopies, 52.2%, one colonoscopy, 39.8%, and no colonoscopy, 25.1%) and CT (≥1 examination: ≥ 2 colonoscopies, 57.7%, one colonoscopy, 55.8%, and no colonoscopy, 44.7%) surveillance examinations within 3 years of surgery. Although we did not evaluate CEA and CT surveillance testing as additional time-varying exposures, we did perform a *post hoc* analysis to isolate the effect of colonoscopy by keeping CEA and CT status fixed. For both CEA and CT surveillance tests, we found that the increased risk of colon cancer-specific death for the no colonoscopy group was mitigated by additional surveillance testing. By contrast, there appeared to be a synergistic effect of greater surveillance testing conferring an additional survival benefit for patients in the ≥ 2 colonoscopies group compared with patients in the one colonoscopy group. Thus, the overall results in Table 3 reflect the greater likelihood of additional testing in patients with ≥ 2 colonoscopies and the additional survival benefit associated with such testing.

Our results should be interpreted within the context of study limitations. The main limitation concerns the assessment of surveillance colonoscopy and colon cancer-specific death through an observational CER study design rather than a RCT. However, conducting a trial in a cohort of patients with stage I colon cancer with ~90% 5-year relative survival would require enrolling a large number of patients with years of follow-up. The costs associated with a trial of this size may be prohibitive. In addition, given the consensus of most guideline-issuing groups on this topic, randomizing patients to receive no surveillance colonoscopy testing would likely be deemed ethically unacceptable. Observational CER studies,

Table 3. IPTW-adjusted hazard ratios for the association between surveillance colonoscopy and 5- and 10-year colon cancer-specific, other cancer, and noncancer mortality

	Colon cancer (events = 343)[a]		Other cancer (events = 236)[a]		Noncancer (events = 1,593)[a]	
Surveillance colonoscopy	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
5-yr mortality						
Colonoscopy categorization						
No colonoscopy	1.53	1.17–1.99	0.97	0.72–1.32	1.40	1.24–1.58
One colonoscopy	Ref		Ref		Ref	
≥ 2 colonoscopies	0.55	0.37–0.82	0.56	0.38–0.83	0.69	0.57–0.84
	Colon cancer (events = 503)[a]		**Other cancer (events = 413)[a]**		**Noncancer (events = 3,378)[a]**	
Surveillance colonoscopy	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
10-yr mortality						
Colonoscopy categorization						
No colonoscopy	1.63	1.31–2.04	1.02	0.79–1.30	1.36	1.25–1.49
One colonoscopy	Ref		Ref		Ref	
≥ 2 colonoscopies	0.60	0.45–0.79	0.68	0.53–0.88	0.69	0.62–0.76

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; Ref, reference group.
[a]The number of unweighted deaths.

Table 4. IPTW-adjusted hazard ratios for the association between surveillance colonoscopy and 10-year conditional[a] colon cancer-specific, other cancer, and noncancer mortality

	Colon cancer (events = 160)[b]		Other cancer (events = 177)[b]		Noncancer (events = 1785)[b]	
Surveillance colonoscopy	HR	95% CI	HR	95% CI	HR	95% CI
10-yr conditional mortality[a]						
Colonoscopy categorization						
No colonoscopy	1.89	1.27–2.83	1.12	0.73–1.70	1.33	1.17–1.51
One colonoscopy	Ref		Ref		Ref	
≥ 2 colonoscopies	0.68	0.45–1.02	0.80	0.55–1.15	0.68	0.61–0.77

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; Ref, reference group.
[a]Conditional on having ≥ 5 yr of post-surgery follow-up.
[b]The number of unweighted deaths.

although not without their own limitations, can provide valuable evidence when RCT designs are problematic and unlikely to be carried out (37). However, because of the potential for bias, relative to RCTs, more careful interpretation of results in observational CER is required, as is the caveat to avoid overstating the importance of findings (37–39). We have followed the recommendation of methodologists by reporting all cause-specific HRs, being transparent in defining our *a priori* outcomes of interest, and providing greater insight into our results by performing *post hoc* and sensitivity analyses (25,26,40).

There are additional limitations. This study relied on claims data which have been shown to have high accuracy for the detection of surveillance tests (41). However, we either did not have information or had incomplete data on CEA blood levels, polyp/adenoma history, and family history of cancer. Healthcare utilization frequency was inferred from surveillance testing frequency but not directly adjusted for when calculating IPTW. Furthermore, we attempted to distinguish between colon cancer-specific mortality and death due to other cancers. We relied on International Classification of Diseases, tenth edition, causes of death to make this distinction, and there could have been misclassification—some "other cancer" deaths may have been due to colon cancer. Last, information on tumor recurrence is not available in the SEER-Medicare database. Thus, it was not possible to differentiate true surveillance testing in asymptomatic patients from diagnostic testing in patients presenting with symptoms. The sensitivity analysis was conducted to address this limitation, demonstrating an over 2-fold increased risk of colon cancer-specific death for those who failed to receive their first surveillance colonoscopy within 15 months of cancer-directed surgery. Finally, our results apply to an older colon cancer population and the results may not generalize to younger patients. Considering these shortcomings, future studies in distinct patient populations which address these limitations are needed to confirm the findings of this study.

The controversy surrounding the use of surveillance testing in patients treated for colon cancer has been ongoing for several decades (42–44). The current study is the first to provide evidence demonstrating the benefit of surveillance colonoscopy for improving colon cancer-specific survival in patients with stage I disease. Although most stage I patients have a good prognosis after being treated surgically, patients who received surveillance colonoscopy in this study had significantly improved colon cancer-specific survival compared with those without such testing. While acknowledging the limitations in this observational CER study, we believe that the results presented warrant efforts to ensure that stage I patients undergo surveillance colonoscopy after cancer-directed surgery to facilitate early detection of new and recurrent neoplastic lesions.

Table 5. IPTW-adjusted HRs for the association between surveillance colonoscopy and 10-year colon cancer-specific mortality at fixed levels of CEA and CT exam testing

	≤ 1 CEA test (events = 164)[a]		≥ 2 CEA tests (events = 149)[a]		0 CT exams (events = 129)[a]		≥ 1 CT exams (events = 184)[a]	
Surveillance colonoscopy	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Colonoscopy categorization								
No colonoscopy	2.15	1.46–3.18	1.68	1.11–2.54	2.35	1.52–3.62	1.54	1.07–2.23
One colonoscopy	Ref		Ref		Ref		Ref	
≥ 2 colonoscopies	0.84	0.53–1.32	0.53	0.36–0.80	0.78	0.47–1.32	0.60	0.42–0.87

CEA, carcinoembryonic antigen; CI, confidence interval; CT, computed tomography; HR, hazard ratio; IPTW, inverse probability of treatment weighting; Ref, reference group.
[a]The number of unweighted deaths.

CONFLICTS OF INTEREST

Guarantor of the article: Robert B. Hines, PhD.

Specific author contributions: R.B.H.: conceptualization, funding acquisition, methodology, formal analysis, and writing. M.J.H.J.: data curation, formal analysis, and writing. A.V.S.: methodology and writing. P.V.: conceptualization and writing. E.L.: methodology and writing. S.P.T.: data curation and writing. S.Z.: methodology, formal analysis, and writing.

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Study Highlights

WHAT IS KNOWN

- ✓ Patients with stage I colon cancer have a good prognosis after surgery.
- ✓ The cancer-specific survival benefit of surveillance colonoscopy has not been demonstrated in these patients.

WHAT IS NEW HERE

- ✓ Receipt of surveillance colonoscopy was associated with better colon cancer-specific survival.
- ✓ The poorer colon cancer-specific survival associated with failing to receive a surveillance colonoscopy was mitigated if patients received additional CEA or CT examination testing.
- ✓ The beneficial effect of ≥ 2 colonoscopies occurred within the context of greater frequency of CEA/CT examination testing.

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