# Staging Chest CT in Patients With Early-Stage Colon Cancer: Analysis of Impact on Survival Using Inverse Probability Weighting and Causal Diagram

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**BACKGROUND.** Staging chest CT has been shown to have negligible diagnostic yield for detecting lung metastases in patients with early-stage colon cancer. Nonetheless, staging chest CT may have potential survival benefits, including opportunistic screening of comorbidity and provision of a baseline examination for future comparisons. Evidence is lacking regarding the impact of staging chest CT on survival in patients with early-stage colon cancer.

**OBJECTIVE.** The purpose of this study was to determine whether the performance of staging chest CT affects survival in patients with early-stage colon cancer.

**METHODS.** This retrospective study included patients with early-stage colon cancer (defined as clinical stage 0 or I on staging abdominal CT) at a single tertiary hospital between January 2009 and December 2015. Patients were divided into two groups according to the presence of a staging chest CT examination. To ensure comparability between the two groups, inverse probability weighting was applied to adjust for the confounders derived from a causal diagram. The between-group differences in adjusted restricted mean survival time at 5 years were measured for overall survival, relapse-free survival, and thoracic metastasis–free survival. Sensitivity analyses were performed.

**RESULTS.** A total of 991 patients (618 men and 373 women; median age, 64 years [IQR, 55–71 years]) were included: 606 patients (61.2%) had staging chest CT. For overall survival, the difference between groups in restricted mean survival time at 5 years was not significant (0.4 months [95% CI, −0.8 to 2.1 months]). The differences between groups in restricted mean survival at 5 years were also not significant for relapse-free survival (0.4 months [95% CI, −1.1 to 2.3 months]) and for thoracic metastasis–free survival (0.6 months [95% CI, −0.8 to 2.4 months]). Similar results were observed in sensitivity analyses that tested 3- and 10-year RMST differences, excluded patients who underwent FDG PET/CT during staging workup, and added treatment decision (surgery vs no surgery) to the causal diagram.

**CONCLUSION.** The use of staging chest CT did not affect survival in patients with early-stage colon cancer.

**CLINICAL IMPACT.** Staging chest CT may be omitted from the staging workup for patients with colon cancer of clinical stage 0 or I.

The benefit of staging chest CT in patients with early-stage colon cancer is controversial. Skepticism regarding its use primarily reflects the extremely low incidence of pulmonary metastasis in early-stage colon cancer [1–5]. For example, Hogan et al. [2] and Yongue et al. [3] asserted that staging chest CT may not be warranted for patients with low-risk colon cancer. In addition, Kim et al. [1] asserted that staging chest CT may only benefit patients with colon cancer who have hepatic or lymph node metastasis on staging abdominal CT.

If staging chest CT is not beneficial, then routinely performing staging chest CT for all patients with colon cancer would increase costs, examination time, and radiation exposure without impacting clinical decision-making. In addition, indeterminate pulmonary nodules

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are commonly detected and may lead to patient anxiety and unnecessary follow-up examinations [6, 7]. In a study investigating the efficacy of staging chest CT in patients with clinical stage 0 or I colon cancer, the false-referral rate (an indirect measure of a potentially detrimental effect) was 5.7% (27/474), and the diagnostic yield was negligible (0% [0/474]) [4].

Despite these observations, the results of prior studies do not indicate that chest CT should be omitted from staging workup for all patients with early-stage colon cancer. Staging chest CT may serve as a baseline examination and aid in the early diagnosis of thoracic metastasis on postoperative chest CT examinations. Furthermore, chest CT may serve as an opportunistic screening tool for other thoracic cancers or serious comorbidities. Indeed, important ancillary findings other than metastasis (e.g., lung cancer or pulmonary thromboembolism) were found on staging chest CT in 3.0% of patients with clinical stage 0 or I disease in the previous study [4].

To our knowledge, no prior study has evaluated the impact of staging chest CT on long-term clinical outcomes in patients with early-stage colon cancer; such insight would determine the necessity of chest CT as a staging workup. The present study aimed to determine whether the performance of staging chest CT affects survival in patients with early-stage colon cancer.

## Highlights

### Key Finding

- *In this study of 991 patients with early-stage colon cancer (clinical stage 0 or I on staging abdominal CT), overall survival, relapse-free survival, and thoracic metastasis–free survival did not differ between patients with and without staging chest CT (between-group differences in restricted mean survival time at 5 years: 0.4, 0.4, and 0.6 months, respectively).*

### Importance

- *In patients with colon cancer of clinical stage 0 or I, staging chest CT did not affect survival and may be omitted from staging workup.*

## Methods

The institutional review board approved this retrospective observational study and waived the requirement for written informed consent. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [8] and Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) [9] guidelines.

### *Patients*

The study was conducted at a single tertiary hospital. We searched the electronic hospital information system database to identify patients with newly diagnosed colon adenocarcinoma during the period from January 1, 2009, to December 31, 2015. Patients were then excluded for the following reasons: they did not undergo staging abdominal CT, they did not have early-stage disease (defined as clinical stage 0 or I on staging abdominal CT), or they had synchronous rectal cancer located within 15 cm of the anal verge [10]. Staging abdominal CT was defined as abdominal CT performed from 3 months before the date of pathologic diagnosis until the initiation of any definitive cancer treatment or until the decision was made to pursue watchful waiting [11]. A total of 473 patients in the study were included in an earlier study that investigated the diagnostic yield and false-referral rate of staging chest CT for patients with colon cancer [4].

### *Determination of Clinical Stage*

The clinical stage of colon cancer was extracted from patients' clinical abdominal CT reports. These reports used a standardized structured reporting form for recording stage based on the AJCC TNM staging system [12, 13]. The structured reporting form used at the institution for recording colon cancer stage has been previously described [4]. The form underwent revisions during the study period, including adoption of updates to the TNM staging system. However, these changes did not affect the present analysis. Because clinical stage was extracted from structured clinical reports generated as part of routine care, the interpreting radiologists were not blinded to endoscopic findings, if available. However, endoscopic ultrasound was not routinely performed as part of the staging workup of colon cancer at the institution during the study period.

### *Exposure, Including Chest CT Protocol*

Patients were stratified into two groups—those with staging chest CT and those without staging chest CT—according to

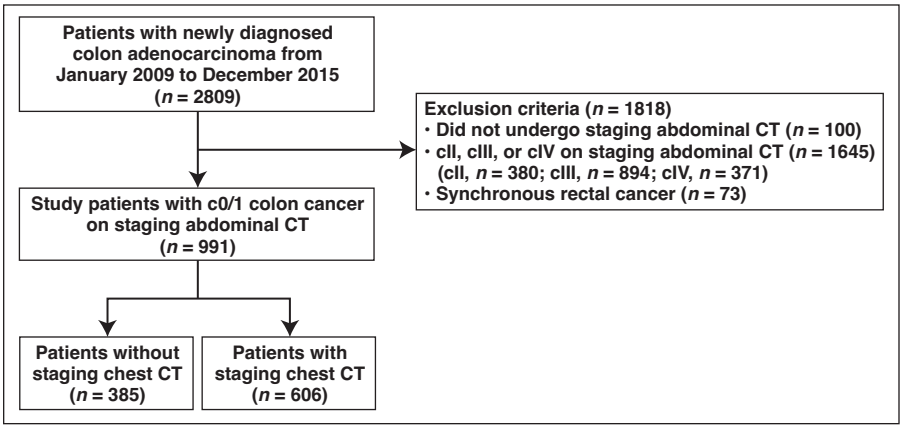


**Fig. 1**—Flow diagram. c0/I = clinical stage 0 or I, cII = clinical stage II, cIII = clinical stage III, cIV = clinical stage IV.

whether or not they underwent staging chest CT. Staging chest CT was defined as chest CT performed from 3 months before the date of pathologic diagnosis until the initiation of primary treatment or until the decision was made to pursue watchful waiting [11]. No institutional guidelines regarding the need for staging chest CT were in place during the study period. Thus, the decision of whether to order staging chest CT was made at the discretion of the patient's treating surgeon or other physician.

During the study period, chest CT was performed at the institution using 16-, 64-, and 256-MDCT scanners (Mx8000, Brilliance,

**TABLE 1: Variables Included in Causal Diagram**

| Variable | Category | Definition |
|---|---|---|
| Time to death | Primary outcome | The interval from the date that staging abdominal CT was performed to the date of death from any cause |
| Staging chest CT [11] | Exposure | Performed before initiation of any definitive cancer treatment (the group with staging chest CT and the group without staging chest CT) |
| Age | Demographic factor | At study entry |
| Sex | Demographic factor | Biologic sex (male and female) |
| Smoking status | Demographic factor | At the time of diagnosis, smoking status was assessed by asking patients to self-report their status (never smoker, former smoker, smoker, and missing) |
| Charlson comorbidity index [17] | Demographic factor | Based on the Charlson comorbidity index score, the severity of comorbidity was categorized into four categories, with a score of 0 denoting no; 1–2, mild; 3–4, moderate; and ≥ 5, severe |
| Family history | Demographic factor | Family history of colorectal polyps, colorectal cancer, and colorectal metastases in first-degree relatives (yes, no, and missing)<br>Family history of any cancer except colon cancer in first-degree relatives (yes, no, and missing) |
| Histologic grade via endoscopic procedure [18] | Tumor factor | Determined using the specimen obtained from endoscopic procedure; data were grouped into four categories (well differentiated, moderately differentiated, poorly differentiated, and missing) |
| Endoscopic appearance [19, 20] | Tumor factor | Superficial: polypoid, endoscopically removed, or endoscopic removal was attempted<br>Advanced: large size (> 3 cm), infiltrative, central depression, or encircling lesion with luminal narrowing or obstruction |
| Histologic grade [18][a] | Tumor factor | Determined using the surgical specimens. For patients who did not undergo surgery, histologic grade was determined using the specimen obtained from endoscopic procedure<br>The data were grouped into four categories (well differentiated, moderately differentiated, poorly differentiated, and missing) |
| Tumor location [18] | Tumor factor | Classified into three categories (right side [a tumor located 82 cm above the anal verge at endoscopy], left side [a tumor located between 15 and 82 cm from the anal verge at endoscopy], and missing) |
| Tumor size [18] | Tumor factor | The largest diameter (in centimeters) of the primary tumor measured on the surgical specimens; if patients did not undergo operation, the largest diameter was measured on the endoscopic specimens |
| Primary tumor invasion [18][a] | Tumor factor | The depth of tumor invasion in the primary cancer (pathologic T stage) |
| Regional lymph node [18][a] | Tumor factor | Number of positive regional lymph nodes (pathologic N stage) |
| Distant metastasis [18][a] | Tumor factor | Presence or absence of distant metastases (pathologic M stage) |
| Clinical T category [18][b] | Tumor factor | Clinical T stage from contrast-enhanced abdominal CT, as per the AJCC staging system; only patients with colon cancer of clinical category T0 or Tis, T1, or T2 were included |
| Clinical N category [18][b] | Tumor factor | Clinical N stage from contrast-enhanced abdominal CT, as per the AJCC staging system; only patients with colon cancer of clinical category N0 were included |
| Clinical M category [18][b] | Tumor factor | Clinical M stage from contrast-enhanced abdominal CT, as per the AJCC staging system; only patients with colon cancer of clinical category M0 were included |
| Diagnosis of colon cancer[b] | Tumor factor | Only patients with colon adenocarcinoma newly diagnosed from January 1, 2009, to December 31, 2015, at a single tertiary hospital were included |
| Year at diagnosis | Other possible risk factor | Divided into two categories (2009–2012 and 2013–2015) |
| Referral | Other possible risk factor | Whether or not the patient was referred from another hospital for suspected or diagnosed colorectal cancer |
| Periodic health examination[a] | Other possible risk factor | Whether or not the patient periodically underwent a periodic health examination |

Note—For a causal diagram, variables that were assumed to be common cause of both the exposure and the outcome and those that might be common causes of any two variables (all confounders) were included.
[a]Unmeasured covariates.
[b]Already stratified (i.e., adjusted) covariates.

and iCT, respectively [all manufactured by Philips Healthcare]). For chest CT examinations performed using IV contrast material, the contrast material was administered via the antecubital vein at a dose of 2 mL per kilogram of body weight and at an injection rate of 3 mL/s. Contrast-enhanced images were obtained 50 seconds after the injection of contrast material was initiated. Axial images of the chest were reconstructed at a section thickness of 3 mm with 2-mm intervals. Axial images reconstructed at a section thickness of 1 or 2 mm were also available for radiologist review.

### Follow-Up Management

Patients who underwent surgical resection for colon cancer generally underwent annual follow-up CT examinations of the chest and abdomen, although the timing of the follow-up examination may have differed on the basis of the ordering practitioner and the pathologic stage of colon cancer. Patients who did not undergo surgical resection for colon cancer may have undergone follow-up abdominal CT examinations at the discretion of the treating clinician, with the timing varying depending on the nature of the alternate treatment; however, they typically did not undergo routine follow-up chest CT examinations. If lung cancer was incidentally detected by staging chest CT, then further patient management was determined according to institutional and national lung cancer guidelines.

### Survival Outcome

The primary outcome was overall survival (OS). OS was defined as the interval from the date of staging abdominal CT to the date of death from any cause. Date of death was obtained from Statistics Korea [14]. Patients without death records were administratively censored on December 31, 2019.

Secondary outcomes were relapse-free survival (RFS) [15] and thoracic metastasis–free survival (TMFS) [16]. RFS was defined as the interval from the date of staging abdominal CT to the date of either death from any cause or colon cancer tumor relapse (i.e., locoregional recurrence or distant metastases), whichever occurred first. For RFS, patients alive without evidence of any tumor relapse were censored at the time of their last visit to the institution. TMFS was defined as the interval from the date of staging abdominal CT to the date of either death from any cause or the development of thoracic metastasis, whichever occurred first. For TMFS, patients who were alive and had no evidence of any thoracic metastasis were censored at the time of their last visit to the institution.

### Covariates

We first identified potential confounders, which were established or suspected to be associated with both the use of staging chest CT and the survival outcome, through a review of the literature and domain knowledge, regardless of the availability

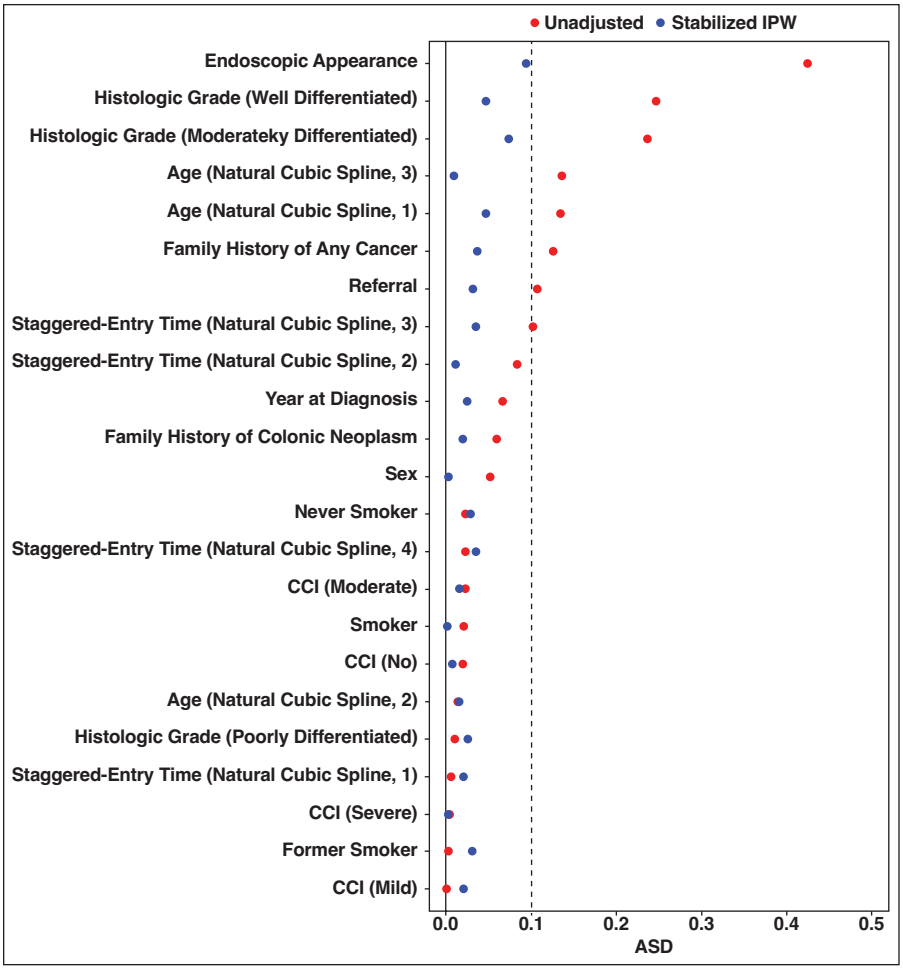


**Fig. 2**—Love plot shows balance of baseline characteristics between groups. Histologic grade was determined via endoscopic procedure. For some characteristics, natural cubic splines were applied to reduce possibility of model misspecification. Family history of any cancer was defined as history of any cancer (except colorectal cancer) in first-degree relatives. Family history of colonic neoplasm applied to first-degree relatives. Vertical dashed line indicates absolute standardized difference (ASD) of 0.1. IPW = inverse probability weight, CCI = Charlson comorbidity index.

**TABLE 2: Patient Characteristics Before and After Inverse Probability Weighting**

| Variable | Before Inverse Probability Weighting | | | After Inverse Probability Weighting[a,b,c] | | |
|---|---|---|---|---|---|---|
| | Group With Staging Chest CT | Group Without Staging Chest CT | ASD | Group With Staging Chest CT | Group Without Staging Chest CT | ASD |
| Total patients | 606 (100) | 385 (100) | | 606 (100) | 337 (100) | |
| Age at study entry (y), median (IQR) | 64 (56–72) | 62 (54–70) | 0.23 | 64 (55–70) | 62 (56–70) | 0.05 |
| Sex | | | | | | |
| Male | 366 (60.4) | 252 (65.5) | 0.05 | 375 (62.0) | 210 (62.2) | < 0.01 |
| Female | 240 (39.6) | 133 (34.5) | 0.05 | 231 (38.0) | 127 (37.8) | < 0.01 |
| Smoking status | | | | | | |
| Never smoker | 328 (54.1) | 165 (42.9) | 0.11 | 346 (57.1) | 202 (60.0) | 0.03 |
| Former smoker | 174 (28.7) | 91 (23.6) | 0.05 | 178 (29.3) | 89 (26.3) | 0.03 |
| Smoker | 84 (13.9) | 46 (11.9) | 0.02 | 82 (13.6) | 46 (13.7) | < 0.01 |
| Missing | 20 (3.3) | 83 (21.6) | 0.18 | — | — | — |
| Year at diagnosis | | | | | | |
| 2009–2012 | 237 (39.1) | 176 (45.7) | 0.07 | 248 (40.9) | 146 (43.3) | 0.02 |
| 2013–2015 | 369 (60.9) | 209 (54.3) | 0.07 | 358 (59.1) | 191 (56.7) | 0.02 |
| Referral from another hospital | | | | | | |
| Yes | 441 (72.8) | 239 (62.1) | 0.11 | 418 (68.9) | 221 (65.8) | 0.03 |
| No | 165 (27.2) | 146 (37.9) | 0.11 | 188 (31.1) | 115 (34.2) | 0.03 |
| Charlson comorbidity index | | | | | | |
| No | 388 (64.0) | 254 (66.0) | 0.02 | 391 (64.5) | 215 (63.8) | 0.01 |
| Mild | 172 (28.4) | 109 (28.3) | < 0.01 | 172 (28.4) | 102 (30.4) | 0.02 |
| Moderate | 34 (5.6) | 13 (3.4) | 0.02 | 29 (4.8) | 11 (3.2) | 0.02 |
| Severe | 12 (2.0) | 9 (2.3) | < 0.01 | 14 (2.3) | 9 (2.6) | < 0.01 |
| Staggered-entry time (d), median (IQR) | 1384.5 (788.3–2044.5) | 1292.0 (745.0–1938.0) | 0.13 | 1361.0 (774.7–2007.0) | 1314.0 (808.1–1968.3) | 0.02 |
| Family history of colonic neoplasm | | | | | | |
| Yes | 86 (14.2) | 32 (8.3) | 0.06 | 71 (11.7) | 33 (9.8) | 0.02 |
| No | 497 (82.0) | 268 (69.6) | 0.12 | 535 (88.3) | 304 (90.2) | 0.02 |
| Missing | 23 (3.8) | 85 (22.1) | 0.18 | — | — | — |
| Family history of any cancer | | | | | | |
| Yes | 185 (30.5) | 69 (17.9) | 0.13 | 158 (26.0) | 75 (22.4) | 0.04 |
| No | 398 (65.7) | 231 (60.0) | 0.06 | 448 (74.0) | 261 (77.6) | 0.04 |
| Missing | 23 (3.8) | 85 (22.1) | 0.18 | — | — | — |
| Endoscopic appearance | | | | | | |
| Superficial | 322 (53.1) | 368 (95.6) | 0.42 | 422 (69.6) | 266 (79.0) | 0.09 |
| Advanced | 284 (46.9) | 17 (4.4) | 0.42 | 184 (30.4) | 71 (21.0) | 0.09 |
| Histologic grade via endoscopic procedure | | | | | | |
| Well differentiated | 222 (36.6) | 233 (60.5) | 0.24 | 305 (50.3) | 185 (55.0) | 0.05 |
| Moderately differentiated | 335 (55.3) | 129 (33.5) | 0.22 | 288 (47.6) | 136 (40.3) | 0.07 |
| Poorly differentiated | 7 (1.2) | 2 (0.5) | 0.01 | 13 (2.2) | 16 (4.7) | 0.02 |
| Missing | 42 (6.9) | 21 (5.5) | 0.02 | — | — | — |

Note—Except where otherwise indicated, data are number with percentage in parentheses. ASD = absolute standardized difference.

[a]Adjusted for age at study entry, sex, smoking status, year at diagnosis, referral from another hospital, Charlson comorbidity index, staggered-entry time, family history of colonic neoplasm, family history of any cancer, endoscopic appearance, and histologic grade via endoscopic procedure.

[b]Results were obtained from multiple imputation by chained equations for missing values, which are denoted by a dash (—).

[c]Because of rounding after using inverse probability weighting, total sum of categories may not be equal to total number of patients for some variables. Also, percentages may not be equal to number of patients in each category divided by total number of patients.

of these variables [11, 17–20] (Table 1). We then drew a causal diagram using a graphic tool (DAGitty, version 3.0) [21], including the following variables: time to death (outcome), use of staging chest CT (exposure), potential confounders, preset patient characteristics (i.e., already adjusted covariates, such as the diagnosis of early-stage colon cancer), and possible common causes between variables (Fig. S1 in the online supplement). The causal diagram is recognized as a useful tool for understanding the potential interplay among variables and identifying sources of bias [22]. The presence of a causal relationship between variables was determined by consensus among the three authors (S.L., a biostatistician with 2 years of experience; Kyung H. Lee, a chest radiologist with 10 years of posttraining experience; and J.H.P., an abdominal radiologist with 11 years of posttraining experience). From the causal diagram, we identified the minimally sufficient adjustment set of covariates that required adjustment [23]. The minimally sufficient adjustment set of covariates included age at study entry, sex, smoking status, year at diagnosis, referral from another hospital, Charlson comorbidity index, family history of colonic neoplasm, family history of any cancer, endoscopic appearance, and histologic grade via endoscopic procedure. To account for differences in follow-up duration, the staggered-entry time, which was defined as the interval between the start date of the study (January 1, 2009) and the date of each patient's entry into the study, was also added into the minimally sufficient adjustment set of covariates [24]. Multiple imputation by chained equations was used for missing values [25].

### *Statistical Analysis*

Data were analyzed from March 2020 to December 2021. To enhance between-group comparability, inverse probability weighting was applied to the model using covariates in the minimally sufficient adjustment set of covariates. The balance of covariate distributions between the two groups was evaluated via the absolute standardized difference (ASD). An ASD lower than 0.10 was considered acceptable [26].

For the main analysis, we measured the between-group difference in the restricted mean survival time (RMST), with the RMST difference calculated as RMST for the group with staging chest CT RMST for the group without staging chest CT. RMST, defined as the area under the survival curve up to a specific time point, is recognized as a useful alternative to the HR [27–30]. Unlike relative effect measures such as an HR, RMST is an absolute effect measure, is intuitively interpretable, and is robust regardless of whether the proportional hazards assumption is violated. RMST at the prespecified time point (5 years) was estimated using the adjusted survival curve from a pooled logistic regression model. We also determined an HR, which is commonly used in medical research, using a Cox proportional hazards model.

Sensitivity analyses were also performed. First, we measured 3- and 10-year RMST differences for OS. Second, we performed an analysis of only complete cases by excluding 188 patients for whom information was missing. Third, we performed sensitivity analysis by excluding 140 patients who underwent FDG PET/CT during staging workup, since the FDG PET/CT may have substituted for staging chest

**TABLE 3: Results of Main Analysis of 5-Year RMSTs in Groups With and Without Staging Chest CT**

| Survival Outcome | Before Inverse Probability Weighting | | | After Inverse Probability Weighting[a] | | |
|---|---|---|---|---|---|---|
| | Group With Staging Chest CT | Group Without Staging Chest CT | Difference (95% CI)[b] | Group With Staging Chest CT | Group Without Staging Chest CT | Difference (95% CI)[b] |
| OS | 57.5 | 58.3 | −0.8 (−1.6 to −0.0) | 57.6 | 57.2 | 0.4 (−0.8 to 2.1) |
| RFS | 56.5 | 57.6 | −1.1 (−2.2 to −0.1) | 56.9 | 56.5 | 0.4 (−1.1 to 2.3) |
| TMFS | 57.2 | 57.9 | −0.8 (−1.8 to 0.1) | 57.4 | 56.7 | 0.6 (−0.8 to 2.4) |

Note—Except where otherwise indicated, data are restricted mean survival time (RMST) expressed as number of months. Because of rounding, the point estimate of RMST difference may not be equal to the value calculated by subtracting RMST for each group presented. OS = overall survival, RFS = relapse-free survival, TMFS = thoracic metastasis–free survival.

[a]Adjusted for age at study entry, sex, smoking status, year at diagnosis, referral from another hospital, Charlson comorbidity index, staggered-entry time, family history of colonic neoplasm, family history of any cancer, endoscopic appearance, and histologic grade via endoscopic procedure.

[b]The exposure effect is presented as a between-group difference in RMST (i.e., RMST for the group with staging chest CT minus RMST for the group without staging chest CT). Negative values indicate an increased risk after staging chest CT was used.

**TABLE 4: HRs for Overall Survival (OS), Relapse-Free Survival (RFS), and Thoracic Metastasis–Free Survival (TMFS)**

| Survival Outcome | Before Inverse Probability Weighting | | After Inverse Probability Weighting[a] | |
|---|---|---|---|---|
| | HR (95% CI) | *p*[b] | HR (95% CI) | *p*[b] |
| OS | 1.45 (0.98–2.19) | .06 | 0.85 (0.58–1.26) | .41 |
| RFS | 1.46 (1.00–2.17) | .05 | 0.88 (0.61–1.29) | .52 |
| TMFS | 1.38 (0.94–2.07) | .11 | 0.81 (0.55–1.20) | .29 |

[a]Adjusted for age at study entry, sex, smoking status, year at diagnosis, referral from another hospital, Charlson comorbidity index, staggered-entry time, family history of colonic neoplasm, family history of any cancer, endoscopic appearance, and histologic grade via endoscopic procedure.

[b]Calculated using a likelihood ratio test comparing models with and without exposure (i.e., staging chest CT).

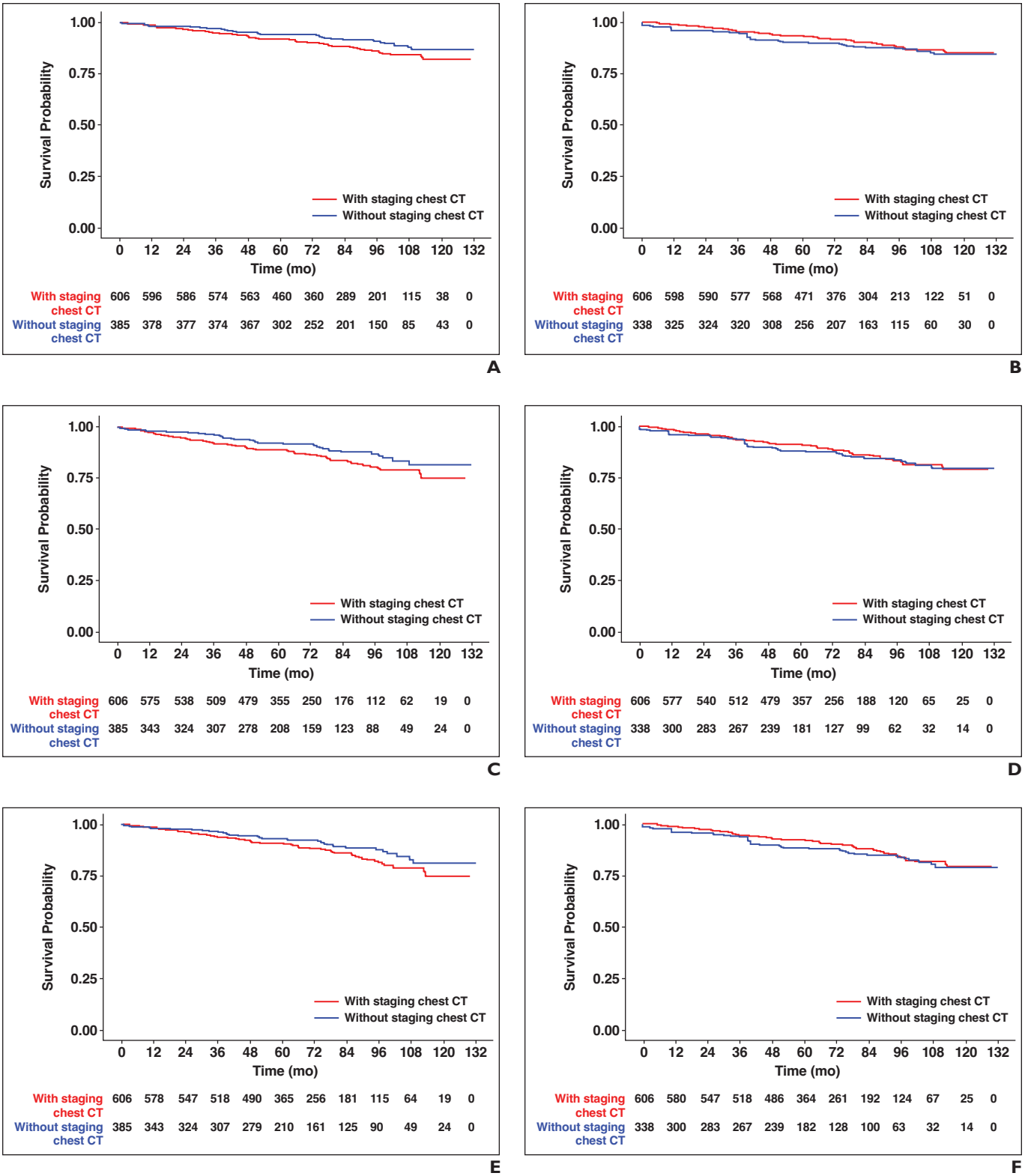


**Fig. 3**—Survival curves.
**A** and **B,** Unadjusted (**A**) and adjusted (**B**) survival curves for overall survival.
**C** and **D,** Unadjusted (**C**) and adjusted (**D**) survival curves for relapse-free survival.
**E** and **F,** Unadjusted (**E**) and adjusted (**F**) survival curves for thoracic metastasis–free survival.

CT. Fourth, we added the treatment decision (surgery vs no surgery) to the causal diagram as an additional confounder. Since data were collected retrospectively, whether the patient underwent surgery was used as a surrogate of the treatment decision. Fifth, the exposure group included only those chest CT examinations initially ordered for the purpose of colon cancer staging. Chest CT examinations initially ordered for the purpose of colon cancer staging were identified by review of the examination's stated indication and the ordering practitioner's specialty. Subgroup analyses were conducted by testing effect modification with an interaction term. Potential effect modifiers assumed to be associated with survival outcomes were considered.

The 95% CIs for the differences in RMST and for HR were calculated using the nonparametric bootstrap method. A two-sided *p* value less than .05 indicated statistical significance. In addition, a power analysis was performed to evaluate whether the number of patients was sufficient to detect a statistically significant result. All analyses were performed using R (version 4.1.0). The details of the statistical methods and their rationales are further described in the Supplemental Methods (available in the online supplement).

## Results

### *Patients*

The initial search identified 2809 patients who had newly diagnosed colon adenocarcinoma during the study period. Of these patients, 100 were excluded because they did not undergo staging abdominal CT; 1645 were excluded because they had clinical stage II, III, or IV disease on staging abdominal CT; and 73 were excluded because they had synchronous rectal cancer. These exclusions resulted

**TABLE 5: Results of Sensitivity Analyses for RMST**

| Survival Outcome | Before Inverse Probability Weighting | | | After Inverse Probability Weighting[a] | | |
|---|---|---|---|---|---|---|
| | Group With Staging Chest CT | Group Without Staging Chest CT | Difference (95% CI)[b] | Group With Staging Chest CT | Group Without Staging Chest CT | Difference (95% CI)[b] |
| Variation in truncation time point | | | | | | |
| 3-Year OS | 35.0 | 35.3 | −0.3 (−0.6 to −0.0) | 35.0 | 34.9 | 0.2 (−0.3 to 0.8) |
| 10-Year OS | 109.5 | 112.6 | −3.1 (−6.3 to −0.1) | 110.9 | 109.3 | 1.5 (−3.1 to 6.7) |
| Excluded patients | | | | | | |
| Those with missing information[c] | | | | | | |
| OS | 57.4 | 57.8 | −0.4 (−1.3 to 0.6) | 57.4 | 57.1 | 0.3 (−0.9 to 3.8) |
| RFS | 56.4 | 57.1 | −0.7 (−1.9 to 0.6) | 56.7 | 56.4 | 0.2 (−1.3 to 3.9) |
| TMFS | 57.1 | 57.5 | −0.4 (−1.5 to 0.7) | 57.2 | 56.7 | 0.5 (−1.0 to 4.1) |
| Those who underwent FDG PET/CT during staging workup | | | | | | |
| OS | 57.9 | 58.8 | −0.8 (−1.6 to −0.1) | 58.1 | 57.6 | 0.5 (−0.8 to 2.4) |
| RFS | 57.2 | 58.2 | −1.0 (−2.0 to −0.0) | 57.6 | 57.0 | 0.6 (−1.0 to 2.6) |
| TMFS | 57.6 | 58.5 | −0.8 (−1.7 to 0.0) | 57.9 | 57.2 | 0.7 (−0.7 to 2.7) |
| Treatment decision considered a confounder in causal diagram[d] | | | | | | |
| OS | 57.5 | 58.3 | −0.8 (−1.6 to −0.0) | 57.6 | 57.6 | −0.1 (−1.6 to 1.0) |
| RFS | 56.5 | 57.6 | −1.1 (−2.2 to −0.1) | 56.7 | 57.2 | −0.5 (−2.3 to 0.9) |
| TMFS | 57.2 | 57.9 | −0.8 (−1.8 to 0.1) | 57.2 | 57.4 | −0.2 (−1.8 to 1.1) |
| Patients regrouped[e] | | | | | | |
| OS | 57.6 | 58.1 | −0.4 (−1.2 to 0.4) | 57.7 | 56.9 | 0.8 (−0.5 to 2.0) |
| RFS | 56.7 | 57.3 | −0.7 (−1.7 to 0.4) | 57.0 | 56.1 | 0.9 (−0.7 to 2.2) |
| TMFS | 57.3 | 57.7 | −0.5 (−1.4 to 0.5) | 57.4 | 56.4 | 1.0 (−0.5 to 2.3) |

Note—Data are restricted mean survival time (RMST), expressed in months. Unless otherwise indicated, all data represent 5-year RMSTs. Because of rounding, the point estimate of RMST difference may not be equal to the value calculated by subtracting RMST for each group presented. OS = overall survival, RFS = relapse-free survival, TMFS = thoracic metastasis–free survival.

[a]Adjusted for age at study entry, sex, smoking status, year at diagnosis, referral from another hospital, Charlson comorbidity index, staggered-entry time, family history of colonic neoplasm, family history of any cancer, endoscopic appearance, and histologic grade via endoscopic procedure.

[b]The exposure effect is presented as a between-group difference in RMST (i.e., RMST for the group with staging chest CT minus RMST for the group without staging chest CT). Negative values indicate an increased risk after staging chest CT was used.

[c]Complete cases only.

[d]Surgery versus no surgery.

[e]Patients were regrouped on the basis of whether chest CT examinations were initially ordered for staging purposes.

in a final sample of 991 patients with early-stage colon adenocarcinoma included in the main analysis. Figure 1 shows the flow of patient selection. The 991 patients comprised 618 men (62.4%) and 373 women (37.6%). The median patient age was 64 years (IQR, 55–71 years). Among the included patients, values were missing for smoking status ($n$ = 103), family history of colonic neoplasm ($n$ = 108), family history of any cancer ($n$ = 108), and histologic grade via endoscopic procedure ($n$ = 63). One patient had undergone endoscopic ultrasound during the staging workup of colon cancer.

### Groups

The group with staging chest CT examinations included 606 patients (61.2%), and the group without staging chest CT examinations included 385 patients (38.8%). The baseline characteristics of the patients in each group, both before and after inverse probability weighting, are summarized in Table 2. Before inverse probability weighting, extreme between-group imbalances were present for some covariates, particularly for endoscopic appearance (ASD = 0.42). After inverse probability weighting, the baseline covariates were well balanced between the two groups (all ASDs < 0.10) (Table 2 and Fig. 2).

Of the 606 patients in the group that had staging chest CT examinations, 577 (95.2%) underwent chest CT at the study institution, and 29 (4.8%) underwent chest CT at an outside hospital before they were referred to the institution. Of these same 606 patients, 562 (92.7%) underwent contrast-enhanced chest CT, and 44 (7.3%) underwent unenhanced chest CT. A total of 394 (65.0%) underwent chest CT and abdominal CT on the same day, and 212 (35.0%) underwent chest CT and abdominal CT on different days. Among all patients who had staging chest CT examinations, the median interval between abdominal CT and chest CT was 0 days (IQR, 0–1 days) and the median interval between pathologic diagnosis and staging chest CT was 5 days (IQR, 1–13 days).

The median initial CEA level was 1.6 ng/mL (IQR, 1.0–2.6 ng/mL) in the group with staging chest CT examinations and 1.5 ng/mL (IQR, 1.0–2.2 ng/mL) in the group without staging chest CT examinations. The CEA level showed no between-group imbalance (ASD = 0.16).

Of the 606 patients in the group with staging chest CT examinations, 503 (83.0%) underwent surgery; 60 (9.9%), polypectomy; 41 (6.8%), endoscopic mucosal resection; zero (0.0%), endoscopic submucosal dissection; and two (0.3%), no treatment. Of the 385 patients in the group without staging chest CT examinations, 40 (10.4%) underwent surgery; 250 (64.9%), polypectomy; 90 (23.4%), endoscopic mucosal resection; two (0.5%), endoscopic submucosal dissection; and three (0.8%), no treatment.

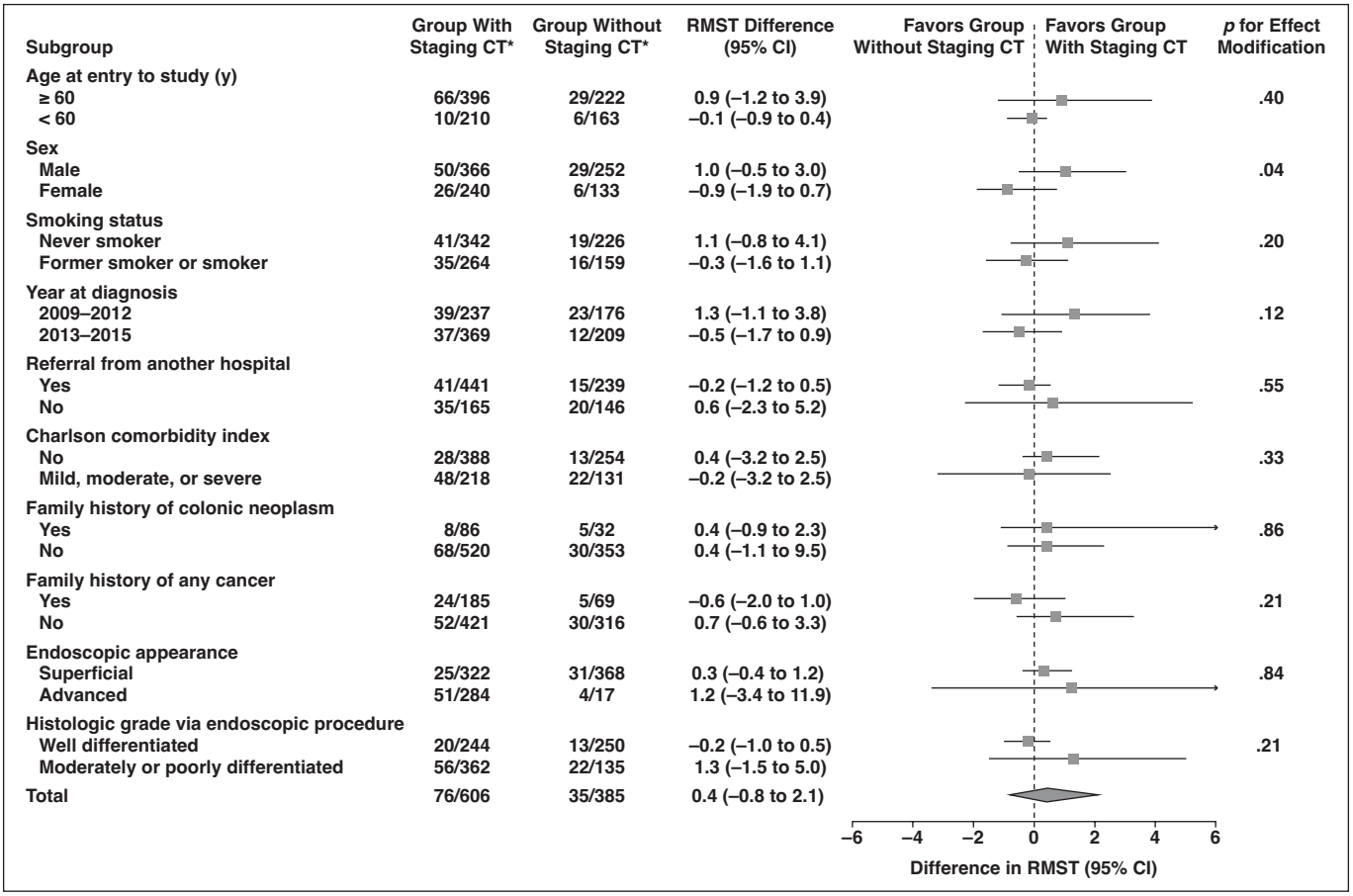


**Fig. 4**—Forest plot shows subgroup analyses for overall survival. Estimates of restricted mean survival time (RMST) and RMST difference were expressed as time in months. Dashed line indicates RMST difference of 0, squares represent point estimate of RMST difference, and error bars represent 95% CIs. Diamond indicates point estimate of RMST difference for total patients (center) and its 95% CI (ends). Asterisk denotes that data are expressed as number of events/number of patients.

### *Main Analysis: Effect of Staging Chest CT on Patient Survival*

For the main analysis, the results of unadjusted RMST difference and unadjusted HR are summarized in Tables 3 and 4, respectively. The median follow-up for OS, RFS, and TMFS was 6.9 years (IQR, 5.1–8.7 years), 5.4 years (IQR, 4.0–7.5 years), and 5.4 years (IQR, 4.1–7.6 years), respectively.

For the primary outcome of OS, there were 111 events (76 for the group with staging chest CT vs 35 for the group without staging chest CT). The unadjusted and adjusted survival curves are shown in Figure 3. The difference in adjusted 5-year RMST was 0.4 months (95% CI, −0.8 to 2.1 months), which was not statistically significant. Staging chest CT did not show prognostic benefits for OS (adjusted HR, 0.85; 95% CI, 0.58–1.26).

For the secondary outcome of RFS, there were 123 events (86 for the group with staging chest CT vs 37 for the group without staging chest CT). The difference in adjusted 5-year RMST was 0.4 months (95% CI, −1.1 to 2.3 months), which was not statistically significant. The adjusted HR was 0.88 (95% CI, 0.61–1.29), which also was not statistically significant.

For the secondary outcome of TMFS, there were 115 events (79 for the group with staging chest CT vs 36 for the group without staging chest CT). The difference in adjusted 5-year RMST was 0.6 months (95% CI, −0.8 to 2.4 months), which was not statistically significant. The adjusted HR was 0.81 (95% CI, 0.55–1.20), which also was not statistically significant.

### *Sensitivity Analyses*

The results of the sensitivity analyses were similar to those of the main analysis and are presented in Table 5. The 3- and 10-year RMST differences for OS were not significant. In the sensitivity analysis of complete cases only, the difference in 5-year RMST for OS was 0.3 months (95% CI, −0.9 to 3.8 months). In the sensitivity analysis that excluded patients who underwent FDG PET/CT during staging workup, the difference in 5-year RMST for OS was not significant (0.5 months [95% CI, −0.8 to 2.4 months]). When treatment decision (surgery vs no surgery) was added to the causal diagram as an additional confounder, the difference in 5-year RMST for OS was not significant (−0.1 months [95% CI, −1.6 to 1.0 months]). After the exposure group was redefined to include only patients in whom chest CT was initially ordered for staging purposes, there were 557 patients in the group with staging chest CT and 434 patients in the group without staging chest CT. The difference in 5-year RMST for OS was not significant (0.8 months [95% CI, −0.5 to 2.0 months]).

### *Subgroup Analyses*

No significant heterogeneity was observed across the subgroups (for effect modification, $p > .05$), except for subgroups by sex. A statistically significant effect modification was observed between male and female patients for OS (for effect modification, $p = .04$). The differences in 5-year RMST were not significant for all subgroups (Fig. 4).

## Discussion

To investigate the survival benefit of staging chest CT in early-stage colon cancer (i.e., clinical stage 0 or I disease), we compared survival outcomes between patients who did and did not undergo staging chest CT. We found no significant differences in OS (difference in 5-year RMST, 0.4 months [95% CI, −0.8 to 2.1 months]) or in RFS and TMFS (difference in 5-year RMST, 0.4 [95% CI, −1.1 to 2.3] and 0.6 [95% CI, −0.8 to 2.4], respectively). Likewise, for OS, RFS, and TMFS, the HRs did not show any significant differences between the two groups. Moreover, the results of multiple sensitivity analyses were analogous to those of the main analysis.

To our knowledge, this is the first study to investigate the impact of staging chest CT on long-term outcomes in patients with early-stage colon cancer. Multiple studies have reported limited clinical value of staging chest CT for detecting thoracic metastasis in patients with colon cancer, particularly those with early-stage disease [1–5]. Chest CT is recommended as part of the staging workup for many other abdominal tumors, including hepatocellular carcinoma, cholangiocarcinoma, gastric cancer, small-bowel cancer, and pancreatic cancer. Similar to the situation for colon cancer, these recommendations have been determined empirically on the basis of expert opinions without strong supporting evidence, and they are currently being challenged by studies showing a low yield of chest CT in the detection of pulmonary metastasis [31–34]. However, studies evaluating only short-term outcomes might not be sufficient to preclude recommendations for chest CT in staging workup. The negligible survival differences with narrow CIs in the current study provide strong evidence that staging chest CT does not affect survival in patients with early-stage colon cancer. The potential sources of survival benefit from staging chest CT, whether from opportunistic screening of comorbidity or from provision of a baseline examination for future comparisons, did not translate into actual differences in survival between patients who did and did not undergo staging chest CT. These results were consistent in terms of OS, RFS, and TMFS.

Because of its superior sensitivity when compared with chest radiography [35], chest CT is a best-supported diagnostic modality for detecting lung metastasis, according to the American College of Radiology Appropriateness Criteria, the American Society of Colon and Rectal Surgeons clinical practice guidelines, and the European Society for Medical Oncology practice guidelines for localized colon cancer [35–37]. However, it is unclear whether staging chest CT should be performed for all patients with colorectal cancer and for which subgroups staging chest CT may be omitted, since no guidelines other than the NCCN guidelines detail specific indications for staging chest CT in patients with colon cancer. The NCCN guidelines recommend staging chest CT for all patients who present with colon cancer appropriate for resection; staging chest CT can be omitted only in patients who do not undergo surgery after complete endoscopic removal of pedunculated or sessile polyp [38]. In addition to use of the NCCN guidelines, we propose step-by-step CT staging for patients with endoscopically low-stage cancer. We recommend performing staging abdominal CT first, in case endoscopic findings are indicative of early-stage cancer. Then, patients selectively undergo chest CT only if their clinical stage on abdominal CT is stage II or higher.

We applied multiple methods to ensure the robustness of the determination of whether staging chest CT affects survival. First, we used a causal diagram to identify covariates that needed to be controlled to minimize confounding bias [22]. Potential confounders were thoroughly reviewed, regardless of their availability, and the presence of causal relationships was carefully determined [39, 40]. Second, we used inverse probability weighting to enhance the comparability of patients who did and did undergo staging

chest CT. Third, we used both RMST and HR to show absence of between-group differences in terms of both relative and absolute effect measures [27–30]. Fourth, we conducted several sensitivity analyses to provide additional assurance of the findings.

The present study had limitations. First, as a retrospective study, whether to perform staging chest CT was a decision that was made at the discretion of the treating practitioner. We speculate that the treating practitioner determined the necessity of staging chest CT primarily on the basis of the endoscopic appearance of the tumor (superficial vs advanced). This appearance was included as one of the covariates. Nonetheless, multiple factors may have played a role in determining the necessity of chest CT, and the specific reason resulting in the decision to obtain chest CT could not be confidently determined for each patient. In addition, despite the measures taken to ensure robustness, the results were not completely free from the bias of unmeasured confounding. Second, generalizability was limited because this study was performed in a single tertiary institution; findings could be different in other patient populations. Third, to reflect real-world clinical practice, clinical stage was extracted from official CT reports, which reported clinical stage in a structured format. Accordingly, we did not measure the interobserver variability in the determination of clinical stage. Fourth, we did not measure intermediate-term outcomes, such as unnecessary follow-up examinations, due to false referrals. Fifth, we have no definitive explanation for the effect modification by sex in the subgroup analysis, which possibly was caused by chance. Sixth, the distribution of treatments differed between the two groups. Incorporation of treatment type into the minimally sufficient adjustment set of covariates would not have been warranted, as the minimally sufficient adjustment set of covariates should only incorporate variables measured before the time of exposure (i.e., staging chest CT). Finally, this exploratory study was not planned using a noninferiority design. To confirm noninferiority of not undergoing staging chest CT, a larger prospective study would be needed with a noninferiority margin set a priori. The present results may justify future studies seeking to identify subgroup of patients for whom staging chest CT provides true benefit.

In conclusion, the presence of staging chest CT did not affect survival in patients with early-stage colon cancer (i.e., clinical stage 0 or I). Thus, chest CT may be omitted from the staging workup in these patients.

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## Editorial Comment: Imaging of Early-Stage Colon Cancer—Is Chest CT Really Necessary?

Historically, imaging evaluation of patients with all stages of colon and rectal cancer included CT of the chest, abdomen, and pelvis [1]. However, recent publications, including the present *AJR* article, provide evidence that routine staging chest CT in the subset of patients with early clinical-stage colon cancer has negligible diagnostic yield, with a real potential for harm [2]. Indeed, despite guideline variation, common practice has shifted away from performing chest CT for this indication [3].

After the liver, the lung is the second most common organ of metastases in patients with colorectal cancer (CRC). However, CRC has venous drainage through the portal venous system and rarely spreads to the lung without prior development of liver metastasis. The major potential exception to this pattern involves distal rectal cancer, which may spread through the inferior hemorrhoidal vein to systemic circulation, bypassing the liver. Therefore, in most patients who present with early CRC, chest CT may be omitted unless abdominal CT shows hepatic involvement.

This change is important, since unneeded examinations expose the patient to increased risk from ionizing radiation and added expense for what is already an expensive workup. In addition, the incidental finding of lung nodules, most of which are benign, may require multiple follow-up CT studies or may prompt unnecessary biopsy with attendant potential complications, patient anxiety, pain, and expense. The shift away from routine chest CT in the staging of clinical stage 0 and I CRC is made more difficult by referrer utilization of static standing orders; automatic payment for and bundling of chest, abdomen, and pelvis CT by payers; and historical use patterns. It is expected that utilization of chest CT in the evaluation of early-stage CRC will further decrease as evidence of its lack of efficacy continues to mount.

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