Radiotherapy for Patients With Resected Tumor Deposit–Positive Colorectal Cancer

A Surveillance, Epidemiology, and End Results–Based Population Study

Laxmi B. Chavali, BDS, MPH; Adana A. M. Llanos, PhD; Jing-Ping Yun, MD, PhD; Stephanie M. Hill, MPH, CTR; Xiang-Lin Tan, MD, PhD; Lanjing Zhang, MD, MS

Context.—According to the American Joint Committee on Cancer’s Cancer Staging Manual, 7th edition, TNM classification, tumor deposit (TD)—positive colorectal cancers (CRCs) are classified as N1c. The effects of radiotherapy and the effects of the updated American Joint Committee on Cancer 7th edition TNM N1c classification for patients with TD-positive CRC are unclear.

Objective.—To investigate outcomes of radiotherapy in patients with resected TD-positive CRC.

Design.—Resected TD-positive CRCs diagnosed from 2010 to 2014 were identified in the Surveillance, Epidemiology, and End Results 18 database. Factors associated with overall survival (OS) and cancer-specific survival (CSS) were investigated using Kaplan-Meier and Cox proportional hazards models.

Results.—We included 2712 qualified CRC patients, who either underwent adjuvant radiotherapy (n = 187; 6.9%) or received no radiotherapy (n = 2525; 93.1%). Univariate Cox proportional models showed improved CSS among all CRC patients who underwent adjuvant radiotherapy (CSS hazard ratio, 0.73; 95% CI, 0.57–0.95) and among rectal cancer patients when separated by location (hazard ratio, 0.57; 95% CI, 0.40–0.83), although these associations were attenuated in multivariable-adjusted models. There was improved OS among rectal cancer patients (hazard ratio, 0.77; 95% CI, 0.59–0.99). In subgroup analyses, radiotherapy was not associated with OS or CSS in either metastatic or nonmetastatic CRC patients. Instead, N1c category (versus N0) was associated with worse OS than classifying TD positivity as N1c was associated with worse OS than classifying TD positivity as N0. The findings seem to challenge the benefits of radiotherapy and the new N1c classification of TD for TD-positive CRC patients.

Conclusions.—Radiotherapy did not independently improve OS among TD-positive CRC patients. In this study, classifying TD positivity as N1c was associated with worse OS than classifying TD positivity as N0. The findings seem to challenge the benefits of radiotherapy and the new N1c classification of TD for TD-positive CRC patients.

Accepted for publication September 8, 2017.
Published as an Early Online Release October 19, 2017.
From the Department of Epidemiology, Rutgers School of Public Health, Piscataway, New Jersey (Ms Chavali and Drs Llanos and Tan); the New Jersey State Cancer Registry (Ms Hill), Rutgers Cancer Institute of New Jersey (Drs Llanos, Tan, and Zhang), New Brunswick; the Department of Pathology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou, China (Dr Yun); the Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey (Dr Tan); the Department of Pathology, University Medical Center of Princeton, Plainsboro, New Jersey (Dr Zhang); the Department of Biological Sciences, Rutgers University, Newark, New Jersey (Dr Zhan); and the Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, New Jersey (Dr Zhang).

The authors have no relevant financial interest in the products or companies described in this article.

Corresponding author: Lanjing Zhang, MD, MS, Department of Pathology, University Medical Center of Princeton, 1 Plainsboro Rd, Plainsboro, NJ 08536 (email: lanjing.zhang@rutgers.edu or ljzhang@hotmail.com).
contour. This update of TD classification has allowed for more accurate prognostication and for refining treatment options for CRC patients.

Tumor deposit–positive CRCs have been proposed to be treated as stage III and have been shown to be strongly associated with worse DFS, compared with higher N stages. Radiotherapy (RT) has become part of the CRC treatment regimen, whereas 1 recent study showed that appropriate surgery without irradiation achieved excellent local control in N0 rectal cancers. Although various studies have evaluated the prognostic value of RT in N0 TD-positive primary tumors, it is still unclear whether RT is an appropriate option for these tumors. Previously, the 6-year and extended 12-year Dutch Total Mesorectal Excision trials found little evidence that RT lowered recurrence risk among rectal cancer patients, but the risk estimates were not stratified by TD status.

To our knowledge, the prognostic significance of RT in both N0 and N1c CRCs has been studied in small studies and mostly among rectal cancer cases. One study examined the effect of RT among 628 Korean patients with rectal cancer who underwent curative resection, showing that there was no significant difference in DFS or overall survival (OS) by TD status. A Japanese study showed that a short-term regimen of high-dose preoperative RT reduced the rates of local recurrence and improved survival among 551 patients with resectable rectal cancer. A recent analysis of Surveillance, Epidemiology, and End Results (SEER) data showed an incorrect classification of some TD-positive CRCs into the N0 category (rather than N1c). It is unclear whether misclassification of TD-positive CRC cases as N0 would lead to fewer patients receiving RT, which could potentially impact CRC survival rates. Therefore, we aimed to examine the prognostic factors among patients with surgically resected TD-positive N0 and N1c CRCs, including RT status and N status (N1c versus N0), because studies have shown local recurrence as a major problem in rectal cancer treatment.

Preoperative short-term RT has been shown to improve local control and survival in combination with conventional surgery. The Total Mesorectal Excision trial investigated the value of this regimen in combination with total mesorectal excision. Given the potential advantages of preoperative RT compared with postoperative RT and the finding that the addition of chemotherapy to RT improves survival, we conducted this comprehensive study to identify the potential, true effect of RT on the patients with surgically resected CRCs. Also, given that metastasis is a probable prognostic factor and RT has shown benefits among CRC patients with no metastasis, additional efforts were made to evaluate the potential hazards of RT according to distant metastasis status.

**MATERIALS AND METHODS**

**Data Source**

A population-based survival analysis was performed using the SEER-18 registries research database (November 2016 submission; 1973–2014). The SEER program currently covers approximately 30% of the US population across several disparate geographic regions. The Institutional Review Board of our institution approved this study.

**Patient Selection**

From the total 170,999 incident cases of CRC (colon, rectosigmoid junction, and rectum) diagnosed in years 2010 to 2014 with survival longer than 1 month, we examined a final sample of 2712 patients with TD-positive, N0 and N1c, surgically resected CRC who were receiving either adjuvant RT or no RT (Figure 1, highlighted in red boxes). Tumor location was identified by the International Classification of Diseases for Oncology, 3rd edition. All patients included in this study were 18 years or older at CRC diagnosis, with a mean age of 67 years (range, 23–99 years). The main inclusion criterion was CRC patients with N0 and N1c nodal category. Tumor deposit-negative patients, those whose tumors were not surgically resected, and those who were treated with preoperative RT were excluded. Data collected by SEER included information on patients’ characteristics, including age, sex, vital status, survival time in months, sequence of treatment, chemotherapy, and primary tumor information.

**Independent Variables**

Based on previous literature, RT, age, sex, tumor location, grade, AJCC T, N, and M categories, and chemotherapy were considered as study prognostic factors in this study. All variables used in the study were dichotomized. Radiotherapy was considered as the main exposure variable, with nodal category (N1c versus N0) as the secondary exposure variable. The original SEER variable indicating the method of RT performed (including external-beam radiation, radioactive implants, radioisotopes, or other radiation) as part of the first course of treatment was dichotomized. We also focused on patients with N1c CRC and patients with misclassified TD-positive N0 tumors. There were no missing values for RT or nodal status in our analytic data set. Additional prognostic factors dichotomously examined in this study were patient age (≤65 years, >65 years), sex (male, female), tumor location (colon, rectum), tumor grade (low, high), AJCC TNM T category (T1–T2, T3–T4), AJCC TNM M category (metastasis: Yes, No), and chemotherapy (Yes, No).

**Outcomes Assessment**

The primary outcomes of this study were OS, which has been described as the time (in months) from diagnosis to death due to CRC. The secondary outcome was cancer-specific survival (CSS), which has been described as the time (in months) from diagnosis to death due to cancer. The OS and CSS times were censored at the time of last follow-up for alive patients or at the time of death of the respective cause. According to SEER, the follow-up cutoff date for cases included in this analysis was December 31, 2014, and the CRC patients’ survival time in months from the time of diagnosis ranged from 2 to 59. There were no cases with missing survival time in the final study sample.

**Statistical Analysis**

All analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, North Carolina). The test was used to compare the distribution of patient demographic characteristics, and tumor- and treatment-related characteristics initially between patients with N0 and N1c CRC, and later between patients who underwent RT and those who did not. Kaplan-Meier survival curves were generated to compare differences in survival probabilities over time by RT status, and the log-rank test was used to determine whether Kaplan-Meier curves differed between the 2 groups. Univariate and multivariate Cox proportional hazards regression models were used to calculate the hazard ratios (HRs) and 95% CIs. The analysis was also repeated in different subgroups of patients to determine the consistency of findings across the sample. All statistical tests were 2-sided, and P ≤ .05 was considered statistically significant.

**Radiotherapy and Tumor Deposit–Positive CRC—Chavali et al**
RESULTS

Patient Characteristics

Baseline characteristics of the CRC patients included in the analysis by N status are shown in Table 1. Colorectal cancer patients with N0 and N1c statuses differed significantly by age ($P = .01$), histologic grade ($P = .02$), chemotherapy receipt ($P < .001$), and AJCC T category ($P = .02$). But they were not significant by RT status ($P = .66$).

Table 2 shows patients' baseline characteristics by RT status. Overall RT status significantly differed by age ($P < .001$), sex ($P = .03$), tumor location ($P < .001$), chemotherapy receipt ($P < .001$), and M categories ($P = .02$). There was no significant difference in RT status by AJCC 7 N0 and N1c categories ($P = .25$).

Identification of Prognostic Factors

Figures 2 and 3 show the OS and CSS univariate Kaplan-Meier analysis curves among patients who underwent adjuvant RT and those who did not, for combined colon and rectum tumor locations, and stratified by location. Overall, RT was not significantly associated with improved OS ($P = .07$) among all CRC patients or by tumor location.

Although the Kaplan-Meier survival curves tended to support the hypothesis that RT was a significant prognostic factor for CSS, a statistically significant association was
identified only for CSS among patients with rectal cancer (Figure 3, a and c). Rectal cancer patients who underwent adjuvant RT showed better survival probability than those who did not undergo RT (22% versus 18%; log-rank P = .002).

Similarly, in the univariate Cox proportional hazards models (Table 3), RT was identified as significantly associated with CSS only (CSS: HR, 0.77; 95% CI, 0.65–0.83). When stratified by tumor location, this protective effect was observed only among rectal cancer patients (CSS: HR, 0.73; 95% CI, 0.56–0.99; Table 4). Age, sex, histologic grade, AJCC 7 TNM N category, chemotherapy receipt, and metastasis were found to be independent, significant prognostic factors of CRC after adjusting for other prognostic factors. Unlike Cox proportional univariate analysis, patients with TD-positive N0M0 surgically resected CRC from categories T3 to T4 did not have significantly greater hazards of all-cause death and cancer-specific death compared with categories T1 to T2 after adjusting for other prognostic factors (results were not displayed in Table 4).

Subgroup analysis by distant metastases showed no significant difference in OS and CSS among surgically resected CRC patients treated with RT after adjustment by other prognostic factors (Tables 5 and 6). Radiotherapy was not found to be an independent prognostic factor among patients with no distant metastasis (OS: HR, 0.85; 95% CI, 0.69–1.04; CSS: HR, 1.05; 95% CI, 0.75–1.47), with no differences by tumor location (Table 6). Similar findings were observed among those with metastasis (OS: HR, 0.92; 95% CI, 0.53–1.60; CSS: HR, 1.15; 95% CI, 0.66–2.00; Table 6). Instead, age, histologic grade, AJCC TNM N category, and chemotherapy were identified as independent prognostic factors among CRC patients with distant metastases.

### Table 1. Assessment of the Baseline Characteristics Among Patients With Tumor Deposit–Positive N0 and N1c, Surgically Resected Colorectal Cancer That Was Diagnosed in the Years 2010 to 2014 (N = 3085)

| Characteristic | N0, No. (%) | N1c, No. (%) | P Value |
|---------------|-------------|--------------|---------|
| Sum           | 1381 (44.76) | 1704 (55.24) | .01     |
| Age           |             |              |         |
| <65 y         | 569 (41.20)  | 779 (45.72)  |         |
| ≥65 y         | 812 (58.80)  | 925 (54.28)  |         |
| Sex           |             |              | .12     |
| Male          | 696 (50.40)  | 907 (53.23)  |         |
| Female        | 685 (49.60)  | 797 (46.77)  |         |
| Tumor location|             |              | .77     |
| Colon         | 989 (71.61)  | 1212 (71.13) |         |
| Rectum        | 392 (28.39)  | 492 (28.87)  |         |
| Histologic grade|          |              | .02     |
| Low           | 1044 (75.60) | 1347 (79.05) |         |
| High          | 337 (24.40)  | 357 (20.95)  |         |
| AJCC TNM T category|     |              | .02     |
| T1–T2         | 168 (12.17)  | 163 (9.57)   |         |
| T3–T4         | 1213 (87.83) | 1541 (90.43) |         |
| AJCC TNM M category|     |              | .10     |
| Present       | 276 (19.99)  | 301 (17.66)  |         |
| Absent        | 1105 (80.01) | 1403 (82.34) |         |
| Radiotherapy  |             |              | .66     |
| Yes           | 246 (17.81)  | 314 (18.43)  |         |
| No            | 1135 (82.19) | 1390 (81.57) |         |
| Chemotherapy  |             |              |         |
| Yes           | 640 (46.34)  | 1067 (62.62) | <.001   |
| No            | 741 (53.66)  | 637 (37.38)  |         |

Abbreviation: AJCC, American Joint Committee on Cancer.

### Table 2. Assessment of the Baseline Characteristics Among Patients With Tumor Deposit–Positive N0 and N1c, Surgically Resected Colorectal Cancer Receiving Diagnosis in Years 2010 to 2014 by Adjuvant Radiotherapy Status (N = 2712)

| Characteristic | Received Radiotherapy, n = 187 | Did Not Receive Radiotherapy, n = 2525 | P Value |
|---------------|-------------------------------|--------------------------------------|---------|
| Age           |                               |                                      | <.001   |
| <65 y         | 111 (59.36)                  | 1006 (39.84)                         |         |
| ≥65 y         | 76 (40.65)                   | 1519 (60.16)                         |         |
| Sex           |                               |                                      | .03     |
| Male          | 109 (58.29)                  | 1268 (50.22)                         |         |
| Female        | 78 (41.71)                   | 1257 (49.78)                         |         |
| Tumor location|                               |                                      | <.001   |
| Colon         | 64 (34.22)                   | 2125 (84.16)                         |         |
| Rectum        | 123 (65.78)                  | 400 (15.84)                          |         |
| Histologic grade|                           |                                      | .16     |
| Low           | 153 (81.82)                  | 1953 (77.35)                         |         |
| High          | 34 (18.18)                   | 572 (22.65)                          |         |
| AJCC 7 TNM T category|                   |                                      | .52     |
| T1–T2         | 18 (9.63)                    | 282 (11.17)                          |         |
| T3–T4         | 169 (90.37)                  | 2243 (88.83)                         |         |
| AJCC 7 TNM N category|               |                                      | .25     |
| N0            | 76 (40.64)                   | 1135 (44.95)                         |         |
| N1c           | 111 (59.36)                  | 1390 (55.05)                         |         |
| AJCC 7 TNM M category|               |                                      | .02     |
| Present       | 25 (13.37)                   | 512 (20.28)                          |         |
| Absent        | 162 (86.63)                  | 2013 (79.72)                         |         |
| Chemotherapy  |                               |                                      | <.001   |
| Yes           | 171 (91.44)                  | 1172 (46.42)                         |         |
| No            | 16 (8.56)                    | 1353 (53.58)                         |         |

Abbreviation: AJCC 7, American Joint Committee on Cancer’s Cancer Staging Manual, 7th edition.
Similar results were seen with no distant metastases, along with sex, as independent predictors for survival.

**DISCUSSION**

This population-based study examined the factors associated with the OS and CSS of TD-positive surgically resected CRC in the patients with misclassified N0 or correctly classified N1c nodal category. In multivariate analysis, adjuvant RT was not found to be independently associated with survival rates (OS or CSS) among TD-positive CRC cases, but a survival benefit was observed among rectal cancer patients only. There were significant survival differences between the misclassified N0 and correctly classified N1c cases according to AJCC 7 TNM classification, with greater hazards of all-cause death among N1c compared with N0. These findings were similar to those of the study by Song et al, showing that there were no significant differences in OS by TD status. But, inconsistent with their study, we found that the category N1c does not have prognostic significance in patients with rectal cancer. Also, similar to the extended Total Mesorectal Excision trial, in which RT was found to be most useful for patients with certain tumor characteristics, we found that neither OS rates (56% versus 57%) nor distant failure rates (25% versus 28%) differed between treatment groups. This leads to the thought that RT is not a strong predictor of disease prognosis in our patient population, and instead other factors may play a role, such as chemotherapy receipt and distant metastases.

Our study is superior to previous studies by its inclusion of a relatively large, population-based group of US CRC patients. One study from the National Cancer Center of Korea calculated DFS and OS for examining the effect of chemoradiotherapy among 628 Korean patients only with rectal cancer who underwent curative resection, and found that there were no significant differences in DFS or OS by TD status. Another study calculated mortality and examined the clinical significance of RT in only 82 AJCC TNM T3 category rectal cancer patients, who underwent curative resection and received adjuvant RT. It found no improved disease-specific mortality rates in the RT group. Consistent with their findings, our study showed there was no significant reduction in adjusted cancer-specific mortality rates among rectal cancer patients who received RT. In fact, RT is given more commonly among rectal cancer patients than colon cancer patients, and there are variations in the type and sequence of surgery. Thus, the true effect of RT on survival rates may be influenced by the tumor location. To eliminate the confounding effect of tumor location, we examined the OS and CSS rates overall as well as among colon and rectal cancers separately. In contrast to previous studies, by addressing potential confounding by tumor location, this study might have eliminated the possible bias in the estimation of survival rates.

Unlike a previous study not adjusted for distant metastases, which identified a significant association between RT and DFS among 464 resected CRC patients, our study attempted to eliminate the confounding effect of metastases by adjusting for metastasis in the analysis of OS and CSS rates. We found that there was no significant difference in the OS and CSS HRs among all patients with TD-positive N0 and N1c CRC by metastasis status after adjustment for metastasis status.

**Figure 2.** Kaplan-Meier curves of the overall survival. (a) Overall survival among postoperative patients with tumor deposit-positive N0 and N1c colorectal cancer, and adjuvant radiotherapy status in both colon and rectum patients (with numbers at risk). (b) Overall survival among colon cancer patients. (c) Overall survival among rectum cancer patients.

**Figure 3.** Kaplan-Meier curves of the cancer-specific survival. (a) Cancer-specific survival among postoperative patients with tumor deposit-positive N0 and N1c colorectal cancer, and adjuvant radiotherapy status in both colon and rectum patients. (b) Cancer-specific survival among colon cancer patients. (c) Cancer-specific survival among rectum cancer patients.
Table 3. Unadjusted Hazard Ratios (HRs) of Prognostic Factors Associated With Overall Survival (OS) and Cancer-Specific Survival (CSS) Among Colorectal Cancer Patients Receiving Adjuvant Radiotherapy and Separated by Tumor Locations (Colon and Rectum; n = 2712)^{a}

| Characteristic               | All Patients | Colon Cancer Patients | Rectum Cancer Patients |
|------------------------------|--------------|-----------------------|------------------------|
|                              | OS           | CSS                   | OS                     | CSS                   | OS                      | CSS                     |
|                              | HR (95% CI)  | P Value               | HR (95% CI)            | P Value               | HR (95% CI)            | P Value               |
| Radiotherapy                 | .08          | .02                   | .99                    | .61                   | .35                    | .003                   |
| Yes                          | 0.86 (0.72, 1.02) | .005        | 1.00 (0.74, 1.36) | .005                  | 0.90 (0.71, 1.25) | .005                  |
| No                           | 1.00 (ref)   | 1.00 (ref)            | 1.00 (ref)             | 1.00 (ref)            | 1.00 (ref)             | 1.00 (ref)             |
| Age                          | .02          | <.001                 | .02                    | .02                   | .02                    | .01                    |
| ≥65 y                        | 0.89 (0.78, 0.98) | 1.00 (ref) | 0.87 (0.78, 0.96) | 1.00 (ref)            | 0.93 (0.76, 1.13) | 1.00 (ref)            |
| <65 y                        | 1.00 (ref)   | 1.00 (ref)            | 1.00 (ref)             | 1.00 (ref)            | 1.00 (ref)             | 1.00 (ref)             |
| Sex                          | .04          | .06                   | .02                    | .01                   | .63                    | .25                    |
| Male                         | 1.10 (1.01, 1.20) | 1.00 (ref) | 1.12 (1.02, 1.24) | 1.00 (ref)            | 1.05 (0.86, 1.28) | 1.00 (ref)            |
| Female                       | 1.00 (ref)   | 1.00 (ref)            | 1.16 (0.97, 1.28) | 1.00 (ref)            | 1.18 (0.89, 1.57) | 1.00 (ref)            |
| Tumor location               | .03          | .02                   | N/A                    | N/A                   | N/A                    | N/A                    |
| Rectum                       | 0.85 (0.76, 0.95) | 1.00 (ref) | N/A                   | N/A                   | N/A                    | N/A                    |
| Colon                        | 1.00 (ref)   | 1.00 (ref)            | 1.00 (ref)             | 1.00 (ref)            | 1.00 (ref)             | 1.00 (ref)             |
| Histologic grade             | .12          | <.001                 | .22                    | .001                  | .18                    | .02                    |
| High                         | 0.92 (0.82, 1.02) | 1.00 (ref) | 0.93 (0.82, 1.05) | 1.00 (ref)            | 0.84 (0.64, 1.09) | 1.00 (ref)            |
| Low                          | 1.00 (ref)   | 1.00 (ref)            | 1.31 (1.12, 1.52) | 1.00 (ref)            | 1.46 (1.06, 2.00) | 1.00 (ref)            |
| AJCC 7 TNM N category        | <.001        | .19                   | <.001                  | .40                   | .002                   | .24                    |
| N1c                          | 1.47 (1.34, 1.61) | 1.00 (ref) | 1.30 (1.35, 1.66) | 1.00 (ref)            | 1.39 (1.13, 1.70) | 1.00 (ref)            |
| N0                           | 1.00 (ref)   | 1.00 (ref)            | 0.91 (0.82, 1.08) | 1.00 (ref)            | 0.85 (0.64, 1.12) | 1.00 (ref)            |
| AJCC 7 TNM T category        | .07          | .004                  | .09                    | .01                   | .07                    | .19                    |
| T3–T4                        | 1.13 (0.99, 1.29) | 1.00 (ref) | 1.15 (0.98, 1.35) | 1.00 (ref)            | 1.03 (0.81, 1.33) | 1.00 (ref)            |
| T1–T2                        | 1.00 (ref)   | 1.00 (ref)            | 1.36 (1.07, 1.74) | 1.00 (ref)            | 1.29 (0.88, 1.90) | 1.00 (ref)            |
| AJCC 7 TNM M category        | .22          | <.001                 | .42                    | <.001                 | .29                    | <.001                 |
| Present                      | 1.08 (0.95, 1.25) | 1.00 (ref) | 1.60 (0.92, 1.23) | 1.00 (ref)            | 1.19 (0.86, 1.62) | 1.00 (ref)            |
| Absent                       | 1.00 (ref)   | 1.00 (ref)            | 2.76 (2.37, 3.21) | 1.00 (ref)            | 3.48 (2.56, 4.74) | 1.00 (ref)            |
| Chemotherapy                 | <.001        | <.001                 | <.001                  | <.001                 | <.001                  | <.001                 |
| Yes                          | 1.18 (1.08, 1.29) | 1.00 (ref) | 0.78 (0.68, 0.90) | 1.00 (ref)            | 0.61 (0.46, 0.80) | 1.00 (ref)            |
| No                           | 1.00 (ref)   | 1.00 (ref)            | 1.23 (1.00, 1.52) | 1.00 (ref)            | 0.55                    | .001                   |

Abbreviations: AJCC 7, American Joint Committee on Cancer's Cancer Staging Manual, 7th edition; N/A, cannot be calculated as separated by location; ref, reference.

^a HRs are adjusted by patient age, tumor location, tumor grade, circumferential resection margin status, and the AJCC categories of tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M).
### Table 4. Multivariate Adjusted Hazard Ratios (HRs) of Prognostic Factors Associated With Overall Survival (OS) and Cancer-Specific Survival (CSS) Among Colorectal Cancer Patients Receiving Adjuvant Radiotherapy and Separated by Tumor Locations (Colon and Rectum; n = 2712)*

| Characteristic | All Patients | Colon Cancer Patients | Rectum Cancer Patients |
|---------------|-------------|-----------------------|-----------------------|
|               | OS          | CSS                   | OS                    | CSS                   | OS                  | CSS                   |
|               | HR (95% CI) | P Value               | HR (95% CI)           | P Value               | HR (95% CI)         | P Value               |
| Radiotherapy  |             |                       |                       |                       |                     |                       |
| Yes           | 0.85 (0.71, 1.03) | 1.03 (0.78, 1.37) | 0.90 (0.66, 1.22) | 1.38 (0.92, 2.07) | 0.77 (0.59, 0.99) | 1.00 (ref)           |
| No            | 1.00 (ref)  | 1.00 (ref)            | 1.00 (ref)            | 1.00 (ref)            | 1.00 (ref)          | 1.00 (ref)            |
| AJCC 7 TNM N  |             |                       |                       |                       |                     |                       |
| category      | <.001       | .69                   | <.001                 | .46                   | .005                | .62                   |
| N1c           | 1.43 (1.31, 1.57) | 1.03 (0.90, 1.16) | 1.46 (1.31, 1.62) | 1.06 (0.91, 1.22) | 1.35 (1.09, 1.66) | 1.00 (ref)           |
| N0            | 1.00 (ref)  | 1.00 (ref)            | 1.00 (ref)            | 1.00 (ref)            | 1.00 (ref)          | 1.00 (ref)            |
| Chemotherapy  |             |                       |                       |                       |                     |                       |
| Yes           | 1.08 (0.98, 1.20) | 0.65 (0.56, 0.75) | 1.05 (0.94, 1.17) | 0.66 (0.56, 0.77) | 1.31 (1.01, 1.66) | 0.67 (0.48, 0.94) |
| No            | 1.00 (ref)  | 1.00 (ref)            | 1.00 (ref)            | 1.00 (ref)            | 1.00 (ref)          | 1.00 (ref)            |
| Tumor location|             |                       |                       |                       |                     |                       |
| Rectum        | 0.85 (0.75, 0.96) | 1.08 (0.91, 1.27) | N/A                  | N/A                  | N/A                 | N/A                  |
| Colon         | 1.00 (ref)  | 1.00 (ref)            |                       |                       |                     |                       |

Abbreviations: AJCC 7, American Joint Committee on Cancer’s Cancer Staging Manual, 7th edition; N/A, cannot be calculated as separated by location; ref, reference.

* Reported HRs and 95% CIs were due to main risk factor after adjusting for all other covariates. HRs are adjusted by patient age, tumor location, tumor grade, circumferential resection margin status, and the AJCC categories of tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M).

### Table 5. Multivariate Adjusted Hazard Ratios (HRs) of Prognostic Factors Associated With Overall Survival (OS) and Cancer-Specific Survival (CSS) Among Colorectal Cancer Patients Receiving Adjuvant Radiotherapy With Metastases and Separated by Tumor Locations (Colon and Rectum; n = 537)*

| Characteristic | All Patients (n = 537) | Colon Cancer Patients (n = 448) | Rectum Cancer Patients (n = 89) |
|---------------|-----------------------|---------------------------------|---------------------------------|
|               | OS                    | CSS                             | OS                              | CSS                          | OS                          | CSS                             |
|               | HR (95% CI)           | P Value                         | HR (95% CI)                     | P Value                      | HR (95% CI)                 | P Value                         |
| Radiotherapy  |                       |                                 |                                 |                               |                              |                                 |
| Yes           | 0.92 (0.53, 1.60)     | 1.15 (0.66, 2.00)               | 0.94 (0.48, 1.87)               | 1.43 (0.75, 2.73)            | 0.73 (0.25, 2.09)           | 1.00 (ref)                      |
| No            | 1.00 (ref)            | 1.00 (ref)                      | 1.00 (ref)                      | 1.00 (ref)                   | 1.00 (ref)                 | 1.00 (ref)                      |
| AJCC 7 TNM N  |                       |                                 |                                 |                               |                              |                                 |
| category      | <.001                 | .04                             | <.001                           | .04                           | .37                         | .76                             |
| N1c           | 1.68 (1.31, 2.17)     | 0.79 (0.63, 0.99)               | 1.74 (1.31, 2.10)               | 0.77 (0.60, 0.99)            | 1.35 (0.70, 2.62)           | 0.93 (0.54, 1.57)              |
| N0            | 1.00 (ref)            | 1.00 (ref)                      | 1.00 (ref)                      | 1.00 (ref)                   | 1.00 (ref)                 | 1.00 (ref)                      |
| Chemotherapy  |                       |                                 |                                 |                               |                              |                                 |
| Yes           | 1.68 (1.30, 2.17)     | 0.53 (0.41, 0.99)               | 1.29 (0.91, 1.83)               | 0.51 (0.39, 0.67)            | 1.36 (0.70, 2.63)           | 0.68 (0.37, 1.27)              |
| No            | 1.00 (ref)            | 1.00 (ref)                      | 1.00 (ref)                      | 1.00 (ref)                   | 1.00 (ref)                 | 1.00 (ref)                      |
| Tumor location|                       |                                 |                                 |                               |                              |                                 |
| Rectum        | .87                   | .43                             | N/A                             | N/A                          | N/A                        | N/A                             |
| Colon         | 0.97 (0.70, 1.36)     | 1.12 (0.84, 1.49)               | N/A                             | N/A                          | N/A                        | N/A                             |

Abbreviations: AJCC 7, American Joint Committee on Cancer’s Cancer Staging Manual, 7th edition; N/A, cannot be calculated as separated by location; ref, reference.

* Reported HRs and 95% CIs were due to main risk factor after adjusting for all other covariates. HRs are adjusted by patient age, tumor location, tumor grade, circumferential resection margin status, and the AJCC categories of tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M).
Table 6. Multivariate Adjusted Hazard Ratios (HRs) of Prognostic Factors Associated With Overall Survival (OS) and Cancer-Specific Survival (CSS) Among 2175 Radiotherapy and Tumor Deposit–Positive CRC Patients Receiving Adjuvant Radiotherapy Without Metastases and Separated by Tumor Locations (Colon and Rectum, n = 2175).

| Characteristic       | OS        | CSS       | OS        | CSS       | OS        | CSS       |
|----------------------|-----------|-----------|-----------|-----------|-----------|-----------|
|                      | HR (95% CI) | P Value | HR (95% CI) | P Value | HR (95% CI) | P Value |
| Radiotherapy         | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Yes                  | 0.85 (0.69, 1.04) | .12 | 1.05 (0.75, 1.47) | .08 | 0.98 (0.64, 1.52) | <.001 |
| No                   | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| AJCC 7 TNM N, stage   |           |           |           |           |           |           |
| Category             |           |           |           |           |           |           |
| N0                   | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| N1c                  | 1.40 (1.27, 1.53) | 1.00 (ref) | 1.55 (0.55, 1.34) | 1.00 (ref) | 1.19 (0.90, 1.42) | <.001 |
| N1d                  | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Chemotherapy         |           |           |           |           |           |           |
| Yes                  | 1.07 (0.95, 1.17) | .004 | 1.15 (0.93, 1.43) | .004 | 1.04 (0.93, 1.17) | .004 |
| No                   | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Tumor location       |           |           |           |           |           |           |
| Colon                | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Rectum               | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |

Abbreviations: AJCC 7, American Joint Committee on Cancer's Cancer Staging Manual, 7th edition. N/A, cannot be calculated as separated by location; ref, reference.

- Reported HRs and 95% CIs were due to main risk factor after adjusting for all other covariates. HRs are adjusted by patient age, tumor location, tumor grade, circumferential resection margin status, and the AJCC categories of tumor (T), nodal involvement (N), and the presence of metastases (M).

- This study had some strengths. This is the first study to compare baseline and prognostic characteristics of patients with N1c CRC, along with patients withmisclassified TD-positive N0 CRC, using SEER data. The prognostic significance of RT in TD-positive CRC patients, who were classified in either the N0 or the N1c category, has not been examined.

- Use of the SEER’s high-quality data with minimal or no selection bias is an additional strength. This study also appeared to have relatively long follow-up time to capture enough events, and hence had sufficient statistical power.
CONCLUSIONS

This study has shown that RT was not associated with better OS or CSS among all patients with surgically resected T3D-positive CRC, when adjusted for age, grade, localization, and AJCC TNM category. The better unadjusted CSS among rectal cancer patients and adjusted OS suggest other factors, like tumor location, might amplify the true effect of RT. This leads to the hypothesis that treatment by RT may not have a substantial impact on CRC survival or prognosis. Further investigation of survival outcomes (OS and CSS, along with DFS) are needed, particularly controlling for additional covariates, such as systemic diseases.

References

1. Cancer facts and figures 2016. American Cancer Society Web site. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf. Accessed August 29, 2017.
2. Key statistics for colorectal cancer. American Cancer Society Web site. https://www.cancer.org/content/dam/cancer-org/cancer-control/en/booklets-flyers/colorectal-cancer-fact-sheet.pdf. Accessed August 29, 2017.
3. Obrocea FL, Sajin M, Marincescu EC, Stoica D. Colorectal cancer and the 7th revision of the TNM staging system: review of changes and suggestions for uniform pathologic reporting. Rom J Morphol Embryol. 2011;52(2):317–544.
4. Chen VW, Hsieh MC, Charlton ME, et al. Analysis of stage and clinical/ prognostic factors for colon and rectal cancer from SEER registries: AJCC and collaborative stage data collection system. Cancer. 2014;120(suppl 23):3793–3806.
5. American Joint Committee on Cancer. Cancer Staging Manual, 5th ed. Philadelphia, PA: Lippincott Raven; 1997:84–86.
6. Resch A, Langner C. Lymph node staging in colorectal cancer: old controversies and recent advances. World J Gastroenterol. 2013;19(46):8515–8526.
7. Goldstein NS, Turner JR. Periculonic tumor deposits in patients with T3N+ disease: markers for reduced disease free survival and intra-abdominal metastases and their implications for TNM classification. Cancer. 2000;88(10):2228–2238.
8. Nagtegaal ID, Quirke P. Colorectal tumour deposits in the mesorectum and pericolic; a critical review. Histopathology. 2007;51(2):141–149.
9. Song JS, Chang HJ, Kim DY, et al. Is the N1c category of the new American Joint Committee on cancer staging system applicable to patients with rectal cancer who receive preoperative chemoradiotherapy? Cancer. 2011;117(17):3917–3924.
10. Song YX, Gao P, Wang ZN, et al. Can the tumor deposits be counted as metastatic lymph nodes in the UICC TNM staging system for colorectal cancer? PLoS One. 2012;7(3):e34087.
11. Nagayoshi K, Ueki T, Nishioka Y, et al. Tumor deposit is a poor prognostic indicator for patients who have stage II and III colorectal cancer with fewer than 4 lymph node metastases but not for those with 4 or more. Dis Colon Rectum. 2014;57(4):467–474.
12. Belt EJ, van Stijn MF, Bril H, et al. Lymph node negative colorectal cancers with isolated tumor deposits should be classified and treated as stage III. Ann Surg Oncol. 2010;17(12):3203–3211.
13. Glimeles B, Gronberg H, Jarhult J, Wallgren A, Cavallin-Stahl E. A systematic overview of radiation therapy effects in rectal cancer. Acta Oncol. 2003;42(5–6):476–492.
14. Lawes D, Rousse-PB. Advances in the management of rectal cancer. J R Soc Med. 2002;95(12):587–590.
15. Bonadeco FA, Vaccaro CA, Benati ML, Quintana GM, Garione YE, Teletana MT. Rectal cancer: local recurrence after surgery without radiotherapy. Dis Colon Rectum. 2001;44(3):374–379.
16. Yamano T, Semb S, Noda M, et al. Prognostic significance of classified extramural tumor deposits and extracapsular lymph node invasion in T3-D colorectal cancer: a retrospective single-center study. BMC Cancer. 2015;15:859.
17. Jin M, Roth R, Rock JB, Washington MK, Lehman A, Frankel WL. The impact of tumor deposits on colonic adenocarcinoma AJCC TNM staging and outcome. Am J Surg Pathol. 2015;39(1):109–115.
18. Cedermark B, Dahlberg M, Glimelius B, Pahlman L, Rutqvist LE, Wilking N. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336(14):980–987.
19. Cerezou L, Cirta JP, Areia L, et al. Current treatment of rectal cancer adapted to the individual patient. Rep Pract Oncol Radiother. 2013;18(6):353–362.
20. Allee PE, Tepper J, Gunderson LL, Munzenrider JE. Postoperative radiation therapy for incompletely resected colorectal carcinoma. Int J Radiat Oncol Biol Phys. 1989;17(6):1171–1176.
21. von Winterfeld M, Hoffmeister M, Ingold-Heppner B, et al. Frequency of therapy-related staging shifts in colorectal cancer through the introduction of pTN1c in the 7th TNM edition. Eur J Cancer. 2014;50(17):2958–2965.
22. Mayo E, Llanos AA, Yi X, Duan SZ, Zhang L. Prognostic value of tumor deposit and perineural invasion status in colorectal cancer patients: a SEER-based population study. Histopathology. 2016;69(2):230–238.
23. Sauer R, Becker H, Hoherberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731–1740.
24. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg. 2007;246(5):693–701.
25. Kariv Y, Kariv R, Hampl JP, Lavry IC. Postoperative radiotherapy for stage IIIa rectal cancer: is it justified? Dis Colon Rectum. 2008;51(10):1459–1466.
26. Gunderson LL. Past, present, and future of intraoperative irradiation for colorectal cancer. Int J Radiat Oncol Biol Phys. 1996;34(1):741–744.
27. Surveillance, Epidemiology, and End Results (SEER) Program Research Data. Bethesda, MD: National Cancer Institute; 2014. https://seer.cancer.gov/data/. Accessed August 29, 2017.
28. Jorgensen ML, Young JM, Dobkins TA, Solomon MJ. Does patient age affect receipt of adjuvant therapy for colorectal cancer in New South Wales, Australia? J Gastrointest Oncol. 2014;5(3):323–330.
29. Binh XQ, Lin Y, Li-Zhong Z, Dong-Wang M. Prognostic factors in the patients with T2N0M0 colorectal cancer. World J Surg Oncol. 2016;14(1):6.
30. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. 2011;12(6):575–582.
31. Resch A, Harbaum L, Pollheimer MJ, Kornprat P, Lindthauer RA, Langner C. Inclusion of cytological features in tumor grading improves prognostic stratification of patients with colorectal cancer. Int J Colorectal Dis. 2016;31(3):535–541.
32. Gunderson LL, Sargent DJ, Tepper J, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. J Clin Oncol. 2004;22(10):1785–1796.
33. Tsi AS, Fu YH, Ho MC, et al. Clinicopathological features and prognosis in resectable synchronous and metachronous colorectal liver metastasis. Ann Surg Oncol. 2007;14(2):786–794.
34. Fábian A, Bor R, Farkas K, et al. Rectal tumour staging with endorectal ultrasound: is there any difference between Western and Eastern European countries? Gastroenterol Res Pract. 2016;2016:861381.
35. Petersen SH, Harling H, Kirkeby LT, Wille-Jorgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev. 2012(3):CD004078.
36. Onaitis MW, Noone RB, Hartwig M, et al. Neoadjuvant chemotherapy for resectable rectal cancer: analysis of clinical outcomes from a 13-year institutional experience. Ann Surg. 2001;233(6):778–785.
37. Yabata E, Udagawa M, Okamoto H. Effect of tumor deposits on overall survival in colorectal cancer patients with regional lymph node metastases. J Rural Med. 2014;9(1):20–26.
38. Ueno H, Mochizuki H, Hashiguchi Y, et al. Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging. Am J Clin Pathol. 2007;127(2):287–294.
39. Hong TS, Ryan DP. Adjuvant chemotherapy for locally advanced rectal cancer: is it a given? J Clin Oncol. 2015;33(17):1878–1880.
40. O’Connell MJ, Martensson JA, Wieden HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med. 1994;331(8):502–507.