Patterns of Practice and Improvements in Survival Among Patients With Stage 2/3 Rectal Cancer Treated With Trimodality Therapy

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IMPORTANCE This study quantifies the trends in trimodality therapy use and its association with pathologic stage and overall survival of patients with rectal cancer at the population level.

OBJECTIVE To describe changes between 2006 and 2016 in the sequence and use of chemotherapy/radiation therapy (C/RT), multiagent (MA) chemotherapy, and total neoadjuvant therapy (TNT) for patients with stage 2/3 rectal cancer and identify associations with pathologic stage and survival over time.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort analysis included patient records from the National Cancer Database between 2006 and 2016. Of 110,372 patient records, 77,905 were excluded owing to not receiving trimodality therapy and other predefined exclusion criteria. The final analytic cohort comprised 32,467 patients records treated with trimodality therapy, with 24,297 considered in the survival analysis. Data analysis was performed between June 2020 and December 2021.

EXPOSURES Trimodality therapy was defined as including all of the following: definitive surgery; radiation therapy (RT), alone or in combination with chemotherapy; and neoadjuvant/adjuvant single-agent (SA) or multiagent (MA) chemotherapy independent of RT.

MAIN OUTCOMES AND MEASURES Using Cox multivariable survival analyses across demographics, surgery type, stage, year of diagnosis, and facility type, treatment groups were allocated as the following: group A: TNT (n = 8,883 [27%]); group B: preoperative C/RT plus postoperative SA chemotherapy (n = 59,67 [18%]); group C: preoperative C/RT plus postoperative MA chemotherapy (n = 12,926 [40%]); and group D: postoperative C/RT plus MA chemotherapy (n = 46,89 [14%]).

RESULTS The final analytic cohort comprised 32,467 patients (mean [SD] age at diagnosis, 57.6 [11.6] years; 12,549 [38.7%] women and 19,918 [61.3%] men). Comparing 2016 with 2006, treatment shifted to fewer patients receiving postoperative C/RT (group D) (28% vs 8%; P < .001), and more preoperative C/RT and postoperative MA chemotherapy (group C) (24% vs 45%; P < .001) being used. While clinical stage 2 and 3 distribution remained unchanged, pathologic downstaging was observed to stages 0, 1, 2, and 3: 0.60%, 10%, 31%, and 57% vs 2.8%, 22%, 29%, and 45%, from 2006 to 2015, respectively (P < .001). More recent year of diagnosis was associated with an adjusted hazard ratio of 0.77 (95% CI, 0.67-0.87) for mortality within 36 months after diagnosis (2015 vs 2006).

CONCLUSIONS AND RELEVANCE In this cohort study, the shift toward preoperative C/RT and lower pathologic stage was associated with improved overall survival in stage 2/3 rectal cancers.

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Colorectal cancer remains the second leading cause of US cancer mortality. Between 2000 and 2014, mortality decreased by 34% in individuals 50 years and older owing to improved treatment, changing risk factors, and increased screening. Unfortunately, the combined reporting of colon and rectal cancer and pathologic stage migration after preoperative therapy for rectal cancer limits the ability to define the critical components responsible for these improvements.

Trimodality therapy with chemotherapy/radiation therapy (C/RT), chemotherapy, and total mesorectal excision (TME) surgery remains standard care for patients with stage 2/3 rectal cancer. Current evidence establishes a superiority of preoperative C/RT over postoperative C/RT, as well as total neoadjuvant therapy (TNT) compared with postoperative chemotherapy, with postoperative multiagent (MA) chemotherapy showing inconsistent benefit. Understanding how this evidence has affected practice patterns in different treatment settings is critical to designing clinically relevant trials in the future.

The National Cancer Database (NCDB) includes approximately 70% of all newly diagnosed cancers from more than 1500 Commission on Cancer–accredited hospitals. Revision of NCDB data fields in 2006 allowed us to investigate changes in the sequence and use of C/RT, MA chemotherapy, and TNT for patients with stage 2/3 rectal cancer between 2006 and 2016 and their associations with pathologic stage and overall survival over time.

### Methods

Study exemption was obtained from the Benaroya Research Institute Institutional Review Board because data were deidentified and kept by the NCDB registry. The study included patients with stage 2/3 rectal adenocarcinomas. Excluded were those with squamous histology, distant metastatic disease, unknown tumor stage, or prior malignant neoplasm. Hospital type was defined by total oncologic volume and teaching status. Definitive surgery comprised sphincter sparing (or no) TME surgery, or local tumor excision.

Of 110,372 patients with rectal cancer, 32,467 received trimodality therapy with definitive surgery; RT alone or with C/RT; and neoadjuvant/adjuvant-intent single-agent (SA) or MA chemotherapy independent of RT (eFigure 1 in the Supplement).

Group A (8883 [27%]) received TNT, preoperative C/RT, and MA chemotherapy only. Group B (5967 [18%]) received preoperative C/RT plus postoperative SA chemotherapy. Group C (12,928 [40%]) received preoperative C/RT and postoperative MA chemotherapy. Group D (4689 [14%]) received postoperative C/RT and MA chemotherapy.

Survival analyses used Kaplan-Meier estimates, Cox univariable, and multivariable hazard ratios (HRs) adjusted for perioperative therapy, sex, race, year of diagnosis, stage, facility type, and age at diagnosis. Survival outcomes were only available for 24,297 patients diagnosed from 2006 to 2015, with a median (IQR) follow-up of 48.1 (26.9-76.3) months.

### Results

The final analytic cohort comprised 32,467 patients (mean [SD] age at diagnosis, 57.6 [11.6] years; 12,549 [38.7%] women and 19,918 [61.3%] men). Cohorts were numerically similar in age, race, and sex, while clinical stage 2 and 3 distribution was 40% and 60%, respectively, across the groups. Pathologic stage differed significantly, with group D having 75% stage 3 cancers compared with 48% in the total cohort (P < .001). The sphincter-sparing TME surgery rate was 67% in groups A, B, and C and 75% in group D (P < .001). Academic/research programs used significantly less postoperative C/RT (group D) than other facility types (eTable in the Supplement).

A dramatic reduction in postoperative C/RT plus MA chemotherapy (group D) between 2006 (28%) and 2016 (8%) (P < .001) was accompanied by an increase in preoperative chemotherapy and postoperative MA chemotherapy (group C) (24% to 45%, respectively). Use of preoperative C/RT and postoperative SA chemotherapy increased (14% to 25%; P < .001), while use of TNT decreased (34% to 23%; P < .001) (analyses and P values based on chi-square tests) (Figure 1).

With the exception of group D, overall pathologic stage 0, 1, 2, 3 progressively downstreamed (Figure 2) from 1%, 10%, 31%, and 57% in 2006 to 3%, 22%, 29%, and 45% in 2016 (P < .001). All predictors (treatment group, year of diagnosis, clinical stage)
in the ordinal logistic regression model with pathologic stage as the outcome were highly significant by likelihood ratio χ² tests (P < .001; supporting data illustrated in Figure 2).

Survival analyses are provided in the Table. Both men and Black patients experienced worse survival than women (adjusted HR, 1.21; 95% CI, 1.15-1.28) and White patients (adjusted HR, 1.41; 95% CI, 1.29-1.55), respectively. Clinical stage 3 disease and non–sphincter-sparing surgery were associated with inferior survival, as was treatment in community cancer programs (HR, 1.22; 95% CI, 1.11-1.35; P < .001). More recent
diagnosis (5-year increments) was associated with improved survival (adjusted HR, 0.86; 95% CI, 0.80-0.93; \( P < .001 \)) with the cumulative effect of a diagnosis in 2015 vs 2006 improving the HR to 0.77 (95% CI, 0.67-0.87) (Table; and eFigure 2 in the Supplement, respectively).

Exploratory Kaplan-Meier survival analysis by treatment group demonstrated significant differences in survival (\( P < .001 \); supporting data illustrated in eFigure 3 in the Supplement), with the most favorable outcomes seen in group C and the poorest in group D, representing the largest (45%) and smallest (8%) treatment groups by 2016, respectively, and contributed to the survival improvements during the period of the study.

### Discussion

Our investigation of a population-based cohort of patients with stage 2/3 rectal cancer between 2006 and 2016 revealed (1) a shift from postoperative to preoperative RT, (2) no increase in TNT, (3) migration to lower pathologic stage, and (4) time-dependent improvements in overall survival.

Use of postoperative C/RT gradually declined, reinforcing that preoperative C/RT improves locoregional control and decreases toxic effects.2,4 In our study, 90.5% had received preoperative C/RT by 2015, when this became an important Commission on Cancer rectal cancer quality-of-care benchmark.10 Comparing 2015 with 2006, the mortality risk declined (HR, 0.77; 95% CI, 0.67-0.87), suggesting the association of survival with preoperative C/RT in the clinical setting and mirroring survival gains reported in a meta-analysis of prospective trials of the addition of preoperative RT to surgery.11

The superiority of TNT compared with a strategy of preoperative C/RT and postoperative MA chemotherapy was confirmed only in 2020.5,6 In contrast, comparatively low survival was seen in patients receiving TNT in the current study (eFigure 3 in the Supplement), possibly reflecting the practice to limit TNT to high-risk patients, including low or close circumferential margin tumors. These variables were not prospectively collected in the NCDB data fields, and without this, no conclusions can be made about the relative effectiveness of TNT. Estimates of TNT use may have been overestimated in this study because NCDB criteria do not distinguish MA

### Table. Summary of Multivariable Models of Overall Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cox PH (n = 23 819)</th>
<th>P value</th>
<th>Time-stratified Coxb 0-36 mo After Dx (n = 23 819)</th>
<th>P value</th>
<th>&gt;36 mo After Dx (n = 15 122)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Dxc</td>
<td>1.41 (1.35-1.47)</td>
<td>&lt;.001</td>
<td>1.41 (1.35-1.47)</td>
<td>&lt;.001</td>
<td>1.41 (1.35-1.47)</td>
<td>&lt;.001</td>
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<td></td>
</tr>
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<td>NA</td>
<td>1 [Reference]</td>
<td>NA</td>
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<tr>
<td>Male</td>
<td>1.21 (1.14-1.28)</td>
<td>&lt;.001</td>
<td>1.21 (1.15-1.28)</td>
<td>&lt;.001</td>
<td>1.21 (1.15-1.28)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>Black</td>
<td>1.42 (1.29-1.56)</td>
<td>&lt;.001</td>
<td>1.41 (1.29-1.55)</td>
<td>&lt;.001</td>
<td>1.41 (1.29-1.55)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Otherd</td>
<td>1.01 (0.88-1.15)</td>
<td>.94</td>
<td>1.01 (0.88-1.15)</td>
<td>.92</td>
<td>1.01 (0.88-1.15)</td>
<td>.92</td>
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<tr>
<td>Unknown</td>
<td>0.86 (0.59-1.26)</td>
<td>.43</td>
<td>0.87 (0.59-1.26)</td>
<td>.46</td>
<td>0.87 (0.59-1.26)</td>
<td>.46</td>
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<td>Overall stage</td>
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<td>Stage 2</td>
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<td>1 [Reference]</td>
<td>NA</td>
<td>1 [Reference]</td>
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<tr>
<td>Stage 3</td>
<td>1.19 (1.12-1.26)</td>
<td>&lt;.001</td>
<td>1.31 (1.20-1.42)</td>
<td>&lt;.001</td>
<td>1.09 (1.01-1.18)</td>
<td>.02</td>
</tr>
<tr>
<td>Surgery type</td>
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<td>TME with SP</td>
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<td>1 [Reference]</td>
<td>NA</td>
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<tr>
<td>TME without SP</td>
<td>1.37 (1.29-1.45)</td>
<td>&lt;.001</td>
<td>1.47 (1.36-1.60)</td>
<td>&lt;.001</td>
<td>1.28 (1.18-1.38)</td>
<td>&lt;.001</td>
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<tr>
<td>No. LN harvested</td>
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<td></td>
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<tr>
<td>≥12</td>
<td>0.97 (0.91-1.02)</td>
<td>.24</td>
<td>0.91 (0.84-0.99)</td>
<td>.03</td>
<td>1.01 (0.94-1.10)</td>
<td>.72</td>
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<td>Facility type</td>
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<td>Academic/research</td>
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<td>1 [Reference]</td>
<td>NA</td>
<td>1 [Reference]</td>
<td>NA</td>
</tr>
<tr>
<td>Community cancer</td>
<td>1.22 (1.10-1.35)</td>
<td>&lt;.001</td>
<td>1.22 (1.11-1.35)</td>
<td>&lt;.001</td>
<td>1.22 (1.11-1.35)</td>
<td>&lt;.001</td>
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<tr>
<td>Comprehensive community cancer</td>
<td>1.07 (1.01-1.15)</td>
<td>.03</td>
<td>1.08 (1.01-1.15)</td>
<td>.03</td>
<td>1.08 (1.01-1.15)</td>
<td>.03</td>
</tr>
<tr>
<td>Integrated network cancer</td>
<td>1.09 (1.00-1.19)</td>
<td>.05</td>
<td>1.09 (1.00-1.19)</td>
<td>.05</td>
<td>1.09 (1.00-1.19)</td>
<td>.05</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.11 (0.93-1.34)</td>
<td>.25</td>
<td>1.12 (0.93-1.34)</td>
<td>.24</td>
<td>1.12 (0.93-1.34)</td>
<td>.24</td>
</tr>
<tr>
<td>Year of Dxe</td>
<td>0.94 (0.88-0.99)</td>
<td>.03</td>
<td>0.86 (0.80-0.93)</td>
<td>&lt;.001</td>
<td>1.09 (0.99-1.21)</td>
<td>.08</td>
</tr>
</tbody>
</table>

Abbreviations: Cox PH, Cox proportional hazards; Dx, diagnosis; HR, hazard ratio; LN, lymph nodes; NA, not applicable; SP, sphincter preservation; TME, total mesorectal excision.

a The model titled “Cox PH” depicts Cox PH relative survival using all follow-ups available for the identified set of participants.

b The model titled “0-36 mo After Dx” focuses on the first time strata of a time-stratified Cox PH model that stratifies follow-up time into before and after 36 months from diagnosis.

c Modeled as restricted cubic spline. The hazard ratio represents IQR effect.

d “Other” includes Asian, Pacific Islander, and Native American.

* Hazard ratio per 5-year increase in diagnosis year.
chemotherapy used concurrently or independently of preoperative RT for patients receiving TNT (group A). The use of MA chemotherapy concurrent with RT was shown to be ineffective in randomized clinical trials,\(^12\) which may explain the apparent decrease in TNT use in 2010 seen in this study and stabilizing thereafter. Recent reports of improved distant disease-free survival with the use of TNT\(^5,6\) are expected to increase acceptance of this approach.

Downstaging of pathologic stage was observed with time in groups A, B, and C, likely associated with improved overall survival. Other treatment variables included increased rectal magnetic resonance imaging for staging,\(^13\) enhancing preoperative treatment, better drug delivery (including capecitabine instead of infusional fluorouracil with preoperative C/RT),\(^12\) and improved supportive care. Improvements in surgical TME technique that decreased perioperative morbidity and improved nodal harvest likely also contributed.\(^14\)

The greater use of postoperative C/RT (group D) in nonacademic/research centers possibly was associated with slightly inferior 5-year overall survival outcomes in community cancer centers. The recent significant increase in preoperative C/RT may mitigate this difference. Since 2015, preoperative RT has been an important Commission on Cancer quality metric\(^10\) and the American College of Surgeons National Accreditation Program for Rectal Cancer may further standardize therapy.

Limitations

The analysis is retrospective, designed to measure associations between patient variables, treatments, and outcomes.

Conclusions

In this cohort study, survival outcomes have improved in patients with stage 2/3 rectal cancer receiving trimodality therapy. This study provides an important benchmark of trimodality therapy and sets the context for trials to define optimal management of rectal cancer.

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Conflict of Interest Disclosures: Dr. Lin reported receiving personal fees from QED, Exelixis, Bayer, Daichi Sankyo, and Pfizer outside the submitted work. Dr. Simianu reported receiving grants from Robert and Helen Hitchman Charitable Trust—Special Project Grant Award Internal Foundation grant to support analyst work for this project during the conduct of the study; and receiving nonfinancial support from Intuitive Surgical for education/travel and C-SATS for serving as a consultant/expert reviewer outside the submitted work. No other disclosures were reported.

REFERENCES


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