Improvement of Survival With Response to Neoadjuvant Radiation Therapy for Rectal Cancer

Eric T. Castaldo, MD, MPH; Alexander A. Parikh, MD; C. Wright Pinson, MD, MBA; Irene D. Feurer, PhD; Nipun B. Merchant, MD

Objectives: To determine whether patients with a complete or near-complete response to neoadjuvant radiation therapy (XRT) have improved survival compared with those with less of a response and to compare survival between patients with disease downstaged after neoadjuvant XRT and patients with stage I disease undergoing resection alone.

Design, Setting, and Patients: Retrospective cohort of 10,971 patients (3,760 patients with neoadjuvant XRT; 7,211 with stage I disease with resection alone) from the Surveillance, Epidemiology, and End Results registry using data from January 1, 1994, through December 31, 2003.

Main Outcome Measures: Overall survival and disease-specific survival (DSS) of patients undergoing resection for nonmetastatic rectal adenocarcinoma receiving neoadjuvant XRT and patients with stage I disease undergoing surgical resection alone.

Results: The 5-year DSS and overall survival were 94% and 82%, respectively, for responders to neoadjuvant XRT, 78% and 60%, respectively, for nonresponders, and 97% and 79%, respectively, for patients with stage I disease undergoing resection alone. Responders had improved DSS (P < .001) and overall survival (P < .001) compared with nonresponders by Cox regression. Patients with stage I disease undergoing resection alone had improved DSS (P = .01) but not overall survival (P = .89) compared with XRT responders.

Conclusions: Patients with rectal adenocarcinoma downstaged after neoadjuvant XRT have improved survival compared with nonresponders. While DSS is excellent for responders to neoadjuvant XRT, it did not equal the DSS of patients with stage I disease undergoing resection alone.

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COLORECTAL CANCER IS THE third most common cancer and the third leading cause of cancer-related mortality in the United States, and rectal cancer composes about 30% of these cases. In particular, patients with T3 or node-positive rectal adenocarcinoma (stage II or III) are at high risk for local recurrence and distant metastasis.

See Invited Critique at end of article

The treatment of rectal cancer has evolved significantly during the past 25 years. In the 1980s, the National Surgical Adjuvant Breast and Bowel Protocol R01 trial and the Gastrointestinal Tumor Study Group Protocol 7175 trial demonstrated the benefit of adjuvant chemotherapy and radiation therapy (XRT) for local control and/or survival in patients with stage II and III rectal cancer.

The utility of neoadjuvant chemoradiation therapy has emerged as a promising treatment for rectal cancer. Prospective randomized trials have demonstrated improved local control and survival with neoadjuvant XRT compared with surgical resection alone for rectal cancer. Recently, the German Rectal Cancer Study Group showed that neoadjuvant chemoradiation therapy is less toxic, enhances sphincter preservation, and results in significant downstaging of rectal tumors compared with adjuvant chemoradiation therapy. This trial also demonstrated that neoadjuvant chemoradiation therapy improves local control of rectal cancer, but it did not show a survival benefit compared with patients who received adjuvant chemoradiation therapy. Additionally, a recent meta-analysis concluded that neoadjuvant XRT improved overall survival (OS) and disease-specific survival (DSS) as well as local recurrence compared with resection alone.
Other studies have shown similar benefits of neoadjuvant chemoradiation therapy, and complete response rates of 10% to 30% have been reported. It is becoming more evident that neoadjuvant XRT, with or without chemotherapy, is becoming the standard treatment approach for stage II and III rectal adenocarcinoma.

We and others have shown in single-institution studies that a clinically significant response to neoadjuvant therapy for rectal cancer improves outcomes in these patients. Other studies have also assessed the differences in survival based on morphologic patterns and response rates to neoadjuvant therapy, indicating improved survival for patients with strong clinical response.

To our knowledge, there has been no population-based study to date that has noted the effect of pathologic response to neoadjuvant XRT on survival. The primary aim of this study was to determine, in a large population-based database, whether patients with a good clinical response to neoadjuvant XRT for rectal adenocarcinoma have improved survival compared with patients who do not have a good response. The secondary aim was to then determine whether patients who have disease successfully downstaged to stage 0 or I by neoadjuvant XRT prior to surgical resection have survival similar to that in patients with stage I disease who undergo resection alone.

Data were extracted from the Surveillance, Epidemiology, and End Results (SEER) registry (SEER-17, 1973-2003 data set) of the National Cancer Institute (November 2005 edition) using SEER*Stat software version 6.2.4 (Surveillance Research Program, National Cancer Institute, Bethesda, Maryland). The SEER program collects and publishes cancer incidence and survival data from geographically defined, population-based cancer registries covering approximately 26% of the US population. The data contained in the SEER program are deidentified and publicly available. The populations captured in the data are considered representative of the United States as a whole.

The study population consisted of all patients with adenocarcinoma of the rectum who received neoadjuvant XRT and were diagnosed as having American Joint Committee on Cancer stage 0, I, II, or III on pathologic analysis after surgical resection from January 1, 1994, through December 31, 2003. Exclusion criteria consisted of the following: patients with a second primary malignant neoplasm, patients who received any form of radiation other than neoadjuvant external-beam XRT, patients who did not undergo operative resection, patients who underwent local excisions only, and patients with incomplete data. For the secondary analysis, all of the patients with complete data who were diagnosed with stage I disease and received surgical resection alone were extracted, excluding those who underwent local excisions only. Other collected information included age, race, sex, year of diagnosis, tumor histological findings, tumor grade, surgical procedure, mortal status, and cause of death. Follow-up time was calculated from the time of diagnosis until the last contact, the date of death, or the date used as a cutoff in the database.

Preoperative and preradiation clinical stages are not available in this database. Neoadjuvant XRT is recommended for patients with preoperatively diagnosed stage II or III rectal cancer. Therefore, patients were classified as responders to neoadjuvant XRT if their stage at pathologic evaluation after surgical resection was 0 or I, indicating a clinical downstaging of disease. If patients had stage II or III disease on pathologic analysis, they were considered nonresponders to neoadjuvant XRT. Although some downstaging of disease may have occurred in these patients, this was not considered to be a significant clinical response for comparison in this study.

Information on local or distant recurrence is not provided in this database, so disease-free survival cannot be determined. Patients who die of unrelated causes before disease recurrence are categorized as having experienced disease recurrence, and therefore, evaluation of disease-free survival is not possible. Statistical analysis for disease-free survival was accomplished via Kaplan-Meier methods and the log-rank test. Cox proportional hazard regression was used to model survival for patients with good clinical response to neoadjuvant XRT compared with nonresponders.
RESULTS

A total of 10,971 patients were included in the study (Table 1). There were 3,760 patients who received neoadjuvant XRT for rectal cancer; 21% (n = 792) were responders (pathologic stage 0 or I) and 79% (n = 2,968) were nonresponders (pathologic stage II or III) at the time of surgical resection. There were 7,211 patients with stage I disease who underwent surgical resection alone. The median follow-up time for the entire cohort was 31 months (range, 0-119 months). There were 9,084 patients alive at last follow-up. Death due to rectal cancer was reported in 493 patients (4%), and 1,394 deaths (13%) were due to other causes.

Figure 1A shows a Kaplan-Meier DSS curve comparing responders to neoadjuvant XRT against nonresponders. The 3- and 5-year DSSs for responders to neoadjuvant XRT were 97% and 94%, respectively. The 3- and 5-year DSSs for nonresponders were 86% and 78%, respectively. These differences were statistically significant (P < .001). The Cox regression model confirmed that responders had improved DSS compared with nonresponders (hazard ratio [HR] = 0.29; 95% confidence interval [CI], 0.19-0.43; P < .001). Cox regression also demonstrated worse DSS for patients aged 60 years or older (HR = 1.44; 95% CI, 1.10-1.88; P = .001), and patients with poor or anaplastic tumor grades (HR = 2.69; 95% CI, 1.54-4.71; P = .001). The results of Cox regression for DSS are summarized in Table 2.

The Kaplan-Meier OS curve for responders and nonresponders to XRT is seen in Figure 1B. The 3- and 5-year OSs for responders were 91% and 82%, respectively, and the 3- and 5-year OSs for nonresponders were 74% and 60%, respectively (P < .001). Cox regression confirmed that responders had improved OS compared with nonresponders (HR = 0.41; 95% CI, 0.32-0.51; P < .001). Worse OS was demonstrated for patients aged 60 years or older (HR = 1.79; 95% CI, 1.53-2.09; P < .001), African American patients (HR = 1.44; 95% CI, 1.10-1.88; P = .01), and patients with poor or anaplastic tumor grades (HR = 2.27; 95% CI, 1.56-3.30; P < .001). The results of the Cox regression model for OS are summarized in Table 2.

Table 2. Cox Regression of Disease-Specific and Overall Survivala

<table>
<thead>
<tr>
<th>Variableb</th>
<th>DSS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to neoadj XRT</td>
<td>0.29 (0.19-0.43)</td>
<td>0.41 (0.32-0.51)</td>
</tr>
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<td>Age ≥60 y</td>
<td>1.44 (1.15-1.90)</td>
<td>1.79 (1.53-2.09)</td>
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<td>Female</td>
<td>1.25 (1.00-1.56)</td>
<td>1.05 (0.89-1.22)</td>
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<td>Race</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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<tr>
<td>African American</td>
<td>1.83 (1.29-2.62)</td>
<td>1.44 (1.10-1.88)</td>
</tr>
<tr>
<td>Other</td>
<td>1.00 (1.69-2.46)</td>
<td>1.10 (0.86-1.41)</td>
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<tr>
<td>Tumor grade</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.36 (0.79-2.35)</td>
<td>1.34 (0.94-1.92)</td>
</tr>
<tr>
<td>Poor or anaplastic</td>
<td>2.69 (1.54-4.71)</td>
<td>2.27 (1.56-3.30)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival; XRT, radiation therapy.

a P < .001 for the DSS model and P < .001 for the OS model.

b The reference categories for race and tumor grade are white and well-differentiated grade, respectively.

The Kaplan-Meier OS curve for responders and nonresponders to XRT is seen in Figure 1B. The 3- and 5-year OSs for responders were 91% and 82%, respectively, and the 3- and 5-year OSs for nonresponders were 74% and 60%, respectively (P < .001). Cox regression confirmed that responders had improved OS compared with nonresponders (HR = 0.41; 95% CI, 0.32-0.51; P < .001). Worse OS was demonstrated for patients aged 60 years or older (HR = 1.79; 95% CI, 1.53-2.09; P < .001), African American patients (HR = 1.44; 95% CI, 1.10-1.88; P = .01), and patients with poor or anaplastic tumor grades (HR = 2.27; 95% CI, 1.56-3.30; P < .001). The results of the Cox regression model for OS are summarized in Table 2.

Figure 2A shows a Kaplan-Meier DSS curve comparing responders to neoadjuvant XRT with patients with stage I disease undergoing surgical resection alone. The 3- and 5-year DSSs of patients with stage I disease undergoing resection alone were 98% and 97%, respectively (responders had a 3-year DSS of 97% and a 5-year DSS of 94%). The DSS was significantly better for these patients compared with responders to neoadjuvant XRT (P = .01). Cox regression demonstrated worse DSS for responders to neoadjuvant XRT compared with patients with stage I disease undergoing resection alone (HR = 1.82; 95% CI, 1.19-2.77; P = .01). Cox regression showed worse DSS for patients aged 60 years or older (HR = 2.04; 95% CI, 1.42-2.93; P < .001). The results from the Cox regression model are summarized in Table 3.

A Kaplan-Meier OS curve comparing responders to neoadjuvant XRT with patients with stage I disease undergoing resection alone can be seen in Figure 2B. The 3- and 5-year OSs of patients with stage I disease undergoing resection alone were 88% and 79%, respectively (responders had a 3-year OS of 91% and a 5-year OS of 82%). This difference was statistically significant (P = .04). However, OS was not statistically significant via Cox regression (HR = 0.89; 95% CI, 0.71-1.12; P = .89). Cox regression (Table 3) demonstrated worse OS for patients aged 60 years or older (HR = 3.96; 95% CI, 1.19-12.22; P = .05) and for patients with moderately differentiated tumors (HR = 1.30; 95% CI, 1.08-1.53; P = .01) but improved OS for women (HR = 0.79; 95% CI, 0.71-0.88; P < .001).
Review of a large cohort of patients in this study demonstrates that patients who respond to neoadjuvant XRT for rectal adenocarcinoma and have disease downstaged to American Joint Committee on Cancer stage 0 or I had significantly improved survival compared with patients with disease that remains at stage II or III after neoadjuvant therapy.

This study from a large population database confirms findings in recent single-institution studies showing that complete or near-complete responders to neoadjuvant XRT have improved survival. García-Aguilar et al demonstrated a 93% 5-year OS in patients with a complete pathologic response to neoadjuvant chemoradiation therapy. Guillem et al also demonstrated that patients with a greater than 95% response rate to neoadjuvant therapy had a 93% 5-year OS and had significantly improved OS compared with patients with a less than 95% response rate. We have previously shown that patients with disease downstaged to stage 0 or I after neoadjuvant chemoradiation therapy had an 88% 5-year DSS at a median follow-up of 62 months, whereas patients with a complete pathologic response had a 100% 5-year OS and a 100% 5-year DSS.

The results of this study also show that patients with disease downstaged to stage 0 or I have an excellent long-term DSS (approximately 94% at 5 years). Despite the excellent outcomes in these patients, DSS in responders still remained significantly less than that in patients with stage I disease who do not require neoadjuvant XRT (5-year DSS of approximately 97%). This statistical significance is likely owing to the very large number of patients (n = 7211) in the group with stage I disease undergoing resection alone. When comparing the OS, however, the outcomes are similar in each group. This indicates that patients with stage II or III rectal cancer who have a complete or near-complete response to neoadjuvant XRT can achieve survival rates similar to that of patients who present with stage I disease.

Furthermore, as others have shown, responders to neoadjuvant XRT may undergo local excision and still achieve excellent long-term outcomes. Carrying this concept one step further, Habr-Gama et al have shown that patients who have a complete clinical response to neoadjuvant XRT may be observed without surgical resection and maintain excellent outcomes. In a cohort of 99 patients managed nonoperatively after a complete clinical response to neoadjuvant chemoradiation therapy sustained for at least 12 months, they demonstrated a 5-year OS of 93% and a disease-free survival of 89%. Of the 5% of these

### Figure 2. Kaplan-Meier curves. A, Kaplan-Meier curve demonstrating improved disease-specific survival (P = .01) for patients with stage I disease undergoing resection alone compared with patients who respond to neoadjuvant radiation therapy and have disease downstaged to stage 0 or I. The median survival was not reached for either group. B, Kaplan-Meier curve demonstrating similar overall survival in patients who are responders to neoadjuvant radiation therapy compared with patients with stage I rectal cancer undergoing resection alone. The curves were statistically significantly different (P = .04); however, the curves cross, giving the log-rank test low power to detect a true difference. The median survival was not reached for either group.

### Table 3. Cox Regression of Disease-Specific and Overall Survival of Responders to Neoadjuvant Radiation Therapy vs Patients With Stage I Disease Undergoing Resection Alone

<table>
<thead>
<tr>
<th>Variable</th>
<th>DSS (HR)</th>
<th>P Value</th>
<th>OS (HR)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder to neoadjuvant XRT</td>
<td>1.82 (1.19-2.77)</td>
<td>.01</td>
<td>0.89 (0.71-1.12)</td>
<td>.89</td>
</tr>
<tr>
<td>Age ≥60 y</td>
<td>2.04 (1.42-2.93)</td>
<td>&lt;.001</td>
<td>3.96 (3.30-4.76)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.79 (0.59-1.05)</td>
<td>.10</td>
<td>0.79 (0.71-0.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race</td>
<td>0.47</td>
<td></td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>African American</td>
<td>1.34 (0.74-2.41)</td>
<td>.33</td>
<td>1.24 (0.98-1.58)</td>
<td>.08</td>
</tr>
<tr>
<td>Other</td>
<td>0.84 (0.49-1.42)</td>
<td>.50</td>
<td>0.82 (0.67-1.01)</td>
<td>.06</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1.38 (0.85-2.25)</td>
<td>.20</td>
<td>1.30 (1.08-1.55)</td>
<td>.01</td>
</tr>
<tr>
<td>Poor or anaplastic</td>
<td>1.76 (0.96-3.23)</td>
<td>.07</td>
<td>1.08 (0.84-1.39)</td>
<td>.55</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival; XRT, radiation therapy.

a P < .001 for the DSS model and P < .001 for the OS model.

b The reference categories for race and tumor grade are white and well-differentiated grade, respectively.
patients who had an isolated local recurrence, all cases were able to be salvaged with surgical intervention. 24

Rates of pathologic downstaging of rectal cancer vary from 19% to 61%. 15,25 In this study, the rate of pathologic downstaging to stage 0 or I was 21% of patients who received neoadjuvant XRT. This finding is similar to a study by Shia et al 16 in which 19% of their patients without stage IV disease had their disease downstaged to stage 0 or I. This finding is also similar to several other studies in which complete pathologic response rates ranged from 13% to 18%. 13,14,20,25

Information on patients receiving preoperative or postoperative chemotherapy is not included in the SEER database; therefore, the effect of chemotherapy with XRT in the neoadjuvant setting or its overall effect on OS and DSS cannot be addressed. However, in the United States, standard neoadjuvant therapy generally includes fluorouracil-based chemotherapy with concomitant externalbeam XRT (4500-5040 cGy [the conversion of centigray to rad is 1:1]), followed by surgical resection 4 to 8 weeks later, and then followed by 4 to 6 cycles of additional adjuvant fluorouracil-based chemotherapy. Therefore, an assumption has to be made that patients who received XRT would have received chemotherapy also. However, standard neoadjuvant treatment for rectal cancer in Europe involves high-fraction, short-course XRT followed by surgical resection after a short interval (5-14 days) and no subsequent chemotherapy. This treatment regimen has been shown to improve survival compared with surgery alone. 3,26 Therefore, the role of chemotherapy in this analysis may not have a significant effect on outcomes in these patients. Although the use of adjuvant chemotherapy in this population is unknown, the similarity of outcomes of responders to neoadjuvant therapy (with stage 0 or I disease) and outcomes of patients with stage I disease undergoing resection alone, who do not require additional chemotherapy, calls into question the need for further adjuvant chemotherapy among those patients with a complete or near-complete pathologic response after neoadjuvant chemoradiation.

Preoperative staging of rectal cancer remains difficult. At best, transrectal ultrasonography shows 80% to 90% accuracy for T category and 70% to 75% for N category. 27-30 Preoperative staging information is unavailable in the SEER registry. Because neoadjuvant therapy is indicated in stage II and III rectal cancer, patients in the database who received neoadjuvant XRT were therefore assumed to have stage II or III disease at their initial diagnosis. Because it is difficult to assess minimal response rates (ie, stage III downstaged to stage II) even in a prospective fashion, responders to neoadjuvant XRT were considered only if the pathologic specimen was at stage 0 or I at the time of surgical resection. Patients with disease that remained at stage II or III on pathologic staging at the time of surgical resection after neoadjuvant XRT were assumed to have minimal or no response. Because some patients may have had neoadjuvant XRT and received only a local excision, only patients undergoing abdominoperineal resection or low anterior resection were included in this study.

Several studies have suggested that African American patients have higher mortality rates from colorectal cancer compared with white patients. We have previously shown significantly worse median survival for African American patients compared with white patients in both a university setting and a city hospital setting. 31 Our results confirm the increased risk of death due to rectal cancer for African American patients even when adjusting for response to radiation, age, sex, and tumor grade in our Cox regression model. There are several reasons that have been investigated to explain these differences. They include such factors as the following: access to care, socioeconomic status, difference in screening, more progressive disease at diagnosis, genetic differences, and therapeutic differences 32,33; however, these could not be addressed from the SEER database.

Other limitations of this study include the lack of information on the dose and/or completion of XRT. Inherent in database studies are the potential pitfalls of data quality. The SEER program is considered the standard for data quality around the world and is the authoritative source for cancer statistics in the United States. Furthermore, in an effort to be assured that the tumor staging data were accurate, a random sample of 1000 patients was validated. The primary tumor characteristics were obtained and converted into the TNM staging system, and these results were cross-referenced to the stage of disease as listed in the SEER program. There was a 100% correlation. Additionally, it should be noted that the median follow-up in this study is only 31 months. However, in a prospective study, neoadjuvant XRT previously demonstrated decreased local failure rates (2.4%) at 2 years. 7

We have shown in a large population database that patients with rectal cancer who have a complete or near-complete response to neoadjuvant XRT have improved DSS and OS compared with those with a minimal response. Furthermore, the survival of patients with an excellent response to neoadjuvant XRT is similar to that in patients with stage I rectal cancer undergoing resection alone.

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Author Contributions: Study concept and design: Castaldo, Parikh, Pinson, Feurer, and Merchant. Acquisition of data: Castaldo. Analysis and interpretation of data: Castaldo and Feurer. Drafting of the manuscript: Castaldo. Critical revision of the manuscript for important intellectual content: Parikh, Pinson, Feurer, and Merchant. Statistical analysis: Castaldo and Feurer. Administrative, technical, and material support: Parikh, Pinson, and Merchant. Study supervision: Parikh, Pinson, and Merchant.

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REFERENCES

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reoperative combined modality therapy (CMT) including radiation (50.40 Gy) and fluorouracil-based chemotherapy followed by radical resection is the preferred treatment paradigm for locally advanced (T3-T4 and/or N1-N2) rectal cancer in the United States.\textsuperscript{1} Castaldo et al report data from a large cohort of patients with rectal cancer from the SEER registry that corroborate the finding, previously noted in single- and multi-institution reports,\textsuperscript{2,3} that complete or near-complete pathologic responders to CMT have significantly improved OS and DSS compared with poor responders. Evidence further suggests that decreased distant failure in complete responders may be largely responsible for this phenomenon.\textsuperscript{2,3,4} Taken together, these studies strongly suggest that primary tumor response to CMT may be a reliable surrogate for systemic control and long-term outcome. One must avoid the temptation, however, to interpret these data as license to be less aggressive in treating complete or near-complete responders. For instance, Castaldo and colleagues suggest that postoperative chemotherapy may have been central to their excellent outcome. Likewise, limiting surgery to local excision or resection only. However, it is likely that most of the patients to patients presenting with stage I disease undergoing surgery only. However, it is likely that most of the patients with pre-CMT stage II and III disease in their study received 4 to 6 cycles of postoperative chemotherapy. Given the increased likelihood of harboring occult micrometastatic disease in these high-risk patients, postoperative chemotherapy may have been central to their excellent outcome. Likewise, limiting surgery to local excision or avoiding surgery entirely in complete responders, analogous to anal squamous cell carcinoma, is appealing and