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Mortality Risk After Preoperative Versus Postoperative Chemotherapy and Radiotherapy in Lymph Node–Positive Rectal Cancer

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Abstract

Introduction—Persistent lymph node positive disease after preoperative radiotherapy for rectal cancer is associated with adverse outcomes. We quantified mortality risks of persistent pathologic lymph nodes in lymph node positive rectal cancer patients treated with preoperative versus postoperative chemoradiation.

Methods—This was a retrospective population-based analysis of 2,038 patients with stage III rectal cancer diagnosed 1994–2005 with follow-up through 2007 using data from the California Cancer Registry. Survival estimates were generated using the Kaplan Meier method. Multivariate cancer-specific and overall mortality analyses were performed using Cox proportional-hazard ratios with adjustment for age, gender, race/ethnicity, tumor grade, T stage, N stage, socioeconomic status, and time period (1994–7, 1998–2001, 2002–5).

Results—Overall survival was higher among lymph node positive patients receiving postoperative chemoradiation compared to lymph node positive patients receiving preoperative chemoradiation (median overall survival= 87 versus 62 months, $P=0.0002$). In adjusted analyses, patients with persistent lymph node positive disease after preoperative chemoradiation treatment had increased overall (HR =1.69, 95% CI, 1.42–2.01) and CRC-specific (HR=1.78, 95% CI, 1.44–2.19) mortality risk compared to lymph node positive disease after postoperative chemoradiation treatment.

Conclusions—Stage III rectal cancer patients with persistent pathologic lymph nodes after preoperative chemoradiation represent a high-risk group, with higher mortality than those treated with postoperative chemoradiation.

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Keywords

Chemoradiation; Lymph Nodes; Mortality; Rectal Cancer

Introduction

Mortality rates have continued to decrease for colorectal cancer (CRC) over the past few decades, as a result of screening, early detection, and treatment advances.¹ Rectal cancer is a unique subset of CRC comprising approximately one-third of CRC cases in the U.S. Modern therapy for rectal cancer is complex, involving a multidisciplinary and highly coordinated approach to care. Key advances in rectal cancer treatment include optimizing the surgical technique (total mesorectal excision, TME, is now standard of care), delivery and timing of radiation therapy, the addition of chemotherapy as a radiation sensitizer (i.e., concurrent chemoradiation), and the optimization of adjuvant chemotherapy regimens – (often derived from results of adjuvant colon cancer clinical trials).

In the 1990's, adjuvant chemoradiation became the standard of care for locally advanced rectal cancer. The NIH consensus statement from 1990 states “the best current adjuvant therapy for rectal cancer involves postoperative treatment with both chemotherapy and radiotherapy. However, the absolute necessity for radiotherapy for survival benefit is by no means convincingly demonstrated at this time, and we must await the completion of current trials for clarification of this issue”.²

The shift to the routine use of preoperative chemoradiation was gradual, supported by a number of published articles including a seminal paper in 2001.³ In that study, among locally advanced rectal cancer patients who received preoperative concurrent chemoradiation, tumor down-staging was observed in 62% of the cases, which predicted improvement in overall survival. After a median follow up of 36 months, the analysis demonstrated that any response to chemoradiation significantly impacted outcome, and the patients who responded to 5-fluorouracil (5FU) during preoperative chemoradiation would also predictably respond to 5FU-based adjuvant chemotherapy. In 2004, the use of preoperative concurrent chemoradiation was reported to improve local control with reduced toxicity compared to postoperative chemoradiation, but a survival benefit was not observed.⁴

Today, the use of preoperative concurrent chemoradiation is the mainstay treatment for locally advanced rectal cancer. Recently, Chang et al demonstrated that the pathologic lymph node status (ypN) after preoperative radiotherapy is a marker of prognosis.⁵ Patients who are ypN+ were noted to have an increased mortality risk.⁵ However, the study was limited by a lack of information on chemotherapy use – which could be a confounder for the reported observations. Here, we set out to determine if ypN+ is an adverse prognosis compared to ypN- using the California Cancer Registry (CCR) in rectal cancer patients who received therapy with chemotherapy and radiation (chemoradiation).

Material & Methods

Study Population

Data was obtained from the CCR, California's statewide population-based cancer surveillance system and also part of the NCI SEER program. California requires all cancer cases treated in California to be reported to the CCR since 1988.⁶ Cause of death according to International Classification of Disease criteria at the time of death, and the last date of follow up, either the date of death or the last date of contact, are reported to the CCR.⁷ In

1998, the CCR developed standardized data collection and quality control procedures.^{8,9} Case reporting with follow-up has a completion rate greater than 95% for most tumors.¹⁰

The study only included patients with pathologically confirmed stage III rectal cancer following radical surgical resection who also received chemotherapy and radiation during their treatment course; all other stages/patients were excluded. 2,038 rectal cancer cases were identified from 1994 to 2005 with follow up until 2007. Age, sex, ethnicity/race, socioeconomic status, histology and histologic grade, TNM stage classification were recorded as done previously.¹¹ Analysis was based on preoperative and postoperative chemoradiation groups. T and N classification are defined as according to American Joint Committee on Cancer (AJCC) rectal cancer staging.¹² N1 involved metastasis in 1 to 3 regional lymph nodes and N2 metastases in 4 or more regional lymph nodes.

Statistical Analysis

Cases were stratified into preoperative and postoperative chemoradiation groups. The demographic characteristics, including age, sex, ethnicity/race, SES quintile, histology, histology grade, tumor stage (T stage), and lymph node involvement were analyzed with the χ^2 Test or Fisher Exact Probability Test for categorical variables or nonparametric one-way ANOVA for numeric variables, by preoperative and postoperative chemoradiation status. Survival curves were generated using the Kaplan Meier Method and comparisons made by Log-Rank tests. Multivariable Cox proportional hazards regression analyses were performed to estimate CRC-specific mortality and overall mortality for preoperative and postoperative chemoradiation groups with adjustment for age, sex, ethnicity/race, SES, histology, tumor grade, T stage, N stage, and time period of diagnosis (1994–7, 1998–2001, 2002–5). Statistical Analysis System 9.2 statistical software (SAS Institute, Cary, NC) was used for all statistical analysis in the study.

Ethical Considerations

The study utilized existing data from the CCR database with no subject intervention for analysis, and no identifiers were linked to subjects. The University of California at Irvine Institutional Review Board approved this study under the category “exempt status” (Institutional Review Board no.2010–7853).

Results

Demographic Characteristics

The patients' demographic and clinical characteristics are listed in Table 1. A total of 2,038 cases with radical surgical resection for stage III rectal cancer were identified, as shown in Fig. 1. 32% of cases received preoperative chemoradiation, and 67.9% of cases received postoperative chemoradiation. In the preoperative chemoradiation group, the median age was 59 years, which was younger than the postoperative chemoradiation group (median age = 63 years). The majority of patients in both preoperative and postoperative chemoradiation groups were Caucasian (60.3% and 67.3% respectively). African American patients represented the fewest number of patients by race/ethnicity in both groups (5.2% and 5.3%). Socioeconomic group was categorized into 5 quintiles (with 1st quintile the lowest). There were fewer cases in the 1st quintile of socioeconomic status compared with the other 4 quintiles. For histologic types, adenocarcinoma represented 84% of cases, followed by mucinous adenocarcinoma, then adenocarcinoma-NOS other. The most common histologic grade was moderately differentiated: 70%, followed by poorly differentiated: 25%, well differentiated: 4.3% and undifferentiated: 0.7%.

T and N Classification according to Chemoradiation Sequence

Only stage III rectal cancer cases were included in this study. T classification was categorized to 4 groups, based on AJCC criteria shown on Table 2. In both preoperative and postoperative chemoradiation groups, 70% of cases were identified as T3. 17% of cases are staged as T2, while T1 and T4 group had only 3% and 10 % of cases, respectively.

Regional lymph node involvement was also based on AJCC criteria. As shown in Table 2, in both the preoperative and postoperative chemoradiation groups, N1 (included metastasis in 1 to 3 regional lymph nodes) was observed in 49% of total cases, and N2 (involved metastasis in 4 or more lymph node) was observed in 30% of total cases, while node-positive but unspecified number of lymph nodes represented 21.2% of the cases.

Overall and CRC-Specific Mortality

The cause of mortality was as follows for the adjuvant therapy group: 31% due to CRC, 2.75% due to coronary artery disease, 5.64% due to other causes; 53% were alive at the end of follow-up, and 5.7% had missing data. For the neoadjuvant therapy group, 22% of cases died from CRC, 0.9% due to coronary artery disease, 4.8% due to other causes; 63% were still alive at the end of follow-up, and 7.6% had missing data. As seen in Fig. 2, the 5-year overall survival rate in the preoperative chemoradiation group was significantly lower than the postoperative chemoradiation group 50% vs. 60% ($P=0.0002$). The univariate HR for ypN+ (vs. pN+) was 1.34 (1.15–1.56), indicating a 34% increased risk of death from any cause in the ypN+ group. The 5-year CRC-specific survival rate in the preoperative chemoradiation group was 65% vs. 68% ($p=0.32$, NS) in the postoperative chemoradiation group. The univariate CRC-specific survival HR for ypN+ (vs. pN+) was 1.10 (0.91–1.33). As would be expected (and as shown in Table 1), patients diagnosed in the early time period (1994–1997) were more likely to receive adjuvant therapy while the group diagnosed in the later period (2002–2005) were more likely to receive neoadjuvant therapy. This resulted in higher rates of censored events in the later period, and relatively few CRC-specific events in the latter time period. Additional multivariate regression analyses revealed that time period of diagnosis was largely responsible for differences between the univariate and multivariate risk estimates. The latter time period (2002–2005) had only 68 events among 764 cases in the CRC-SS analysis, resulting in a HR for ypN+ (vs. pN+) of 1.16 (0.72–1.88) (NS). This was in contrast to the significant results for the earlier time periods: 1998–2001, 257 events among 717 cases, HR of 1.70 (1.31–2.19) for ypN+ (vs. pN+); 1994–1997, 264 events among 557 cases, HR of 1.97 (1.23–3.14).

In an adjusted analysis accounting for age, sex, race/ethnicity, SES, histology, tumor grade, T stage, N stage, and time period of diagnosis, the risk of CRC-specific mortality was 78% greater among patients with positive lymph node disease having received preoperative chemoradiation (i.e., ypN+) compared to lymph node positive disease among those having received postoperative chemoradiation (i.e., pN+) (HR=1.78, 95% CI, 1.44–2.19). Adjusted overall mortality analysis revealed similar results. The risk of overall mortality among patients with positive lymph node disease in the preoperative chemoradiation group (ypN+) was increased by 69% compared to lymph node positive rectal cancer patients in the postoperative chemoradiation group (pN+) (HR =1.69, 95% CI, 1.42–2.01). Information was available for 1313 of 2038 (64%) patients from 1999 onwards regarding whether treatment was rendered at a hospital certified as an American College of Surgeons (ACOS)-approved Cancer Program. In a subset regression analysis of these 1313 patients, treatment at an ACOS-approved program was associated with a 25% decreased risk of CRC-specific mortality, after adjustment for all variables tested in the full regression model (Non-ACOS hospital, HR=1.00, referent; ACOS hospital HR=0.75, 95% CI, 0.58–0.96). Even so, the

mortality estimates for patients in the preoperative ypN+ group vs. post-operative N+ group did not differ by more than 5–10% from estimates in the main models, as stated above.

Discussion

From our analysis of data from the California Cancer Registry, persistent stage III rectal cancer patients following preoperative chemoradiation have increased mortality risk compared to stage III patients treated with postoperative chemoradiation. In rectal cancer, patients with persistent pathologically involved lymph nodes after preoperative treatment represent a high-risk group of patients. It is critically important to distinguish the differences between the pre- and post- treatment groups to understand these observations. The postoperative group consists of all stage III patients that did not receive preoperative chemoradiation. The preoperative treatment group on the other hand is a subset of all patients that received preoperative chemoradiation therapy, and had pathologic lymph nodes at the time of surgical resection. Some of the originally-staged clinical stage III patients in the preoperative chemoradiation group (ie, including patients not accounted for in the present analysis) were undoubtedly down-staged and became a ypT3/T4N0M0 stage II, or stage I ypT1/T2N0M0, or stage 0 (ypTis/T0N0M0, i.e., those having a pathologic complete response after neoadjuvant therapy). So in actuality, in the present analysis we are comparing poor responders in the preoperative treatment group to all stage III patients in the postoperative group.

Another important difference between the two groups is that the preoperative chemoradiation treatment patients may be MMR deficient. MMR-deficient patients have limited benefit from 5FU based chemotherapy¹³. Although this subset of patients is typically small, it is an important fact to consider.

Our findings raise the question: how best to optimize treatment for lymph node positive rectal cancer? One option is to be more aggressive in the preoperative period by incorporating additional chemotherapy and perhaps targeted biological agents into the radiation therapy protocol. Such potent regimens most certainly will have increased side effects and possibly result in overtreatment of patients who may have responded with 5FU/ radiotherapy alone. This is especially true since some patients treated with preoperative chemoradiation will be overstaged and therefore over treated. Results from the German Rectal Cancer study showed a high number of stage 1 patients in the postoperative RT group who were felt to have stage 2–3 disease based on preoperative imaging.⁴

Additionally, the problem of inconclusive staging following chemoradiation is a major limiting factor. Unfortunately, there is no consensus and NCCN guidelines suggest either MRI or endoscopic ultrasound. In a review by Bipat et al¹⁴, endoscopic ultrasound of perirectal tissue invasion showed better diagnostic accuracy than that of CT and MR imaging. One problem is the endoscopic ultrasound is operator-dependent and not widely available. The use of MRI is growing and in an abstract published ahead of print by Al-Sukhni et al¹⁵ concluded that MRI has good accuracy for both circumferential resection margin and T staging and concluded that MRI should be considered for preoperative rectal cancer staging. Unfortunately in our study, we could not account for the type of preoperative imaging patients received.

There have been multiple recent trials investigating XELOX (Xeloda [capecitabine] + oxaliplatin) with radiotherapy in the preoperative setting.^{16–19} The NSABP R-04 trial has four arms with XRT – 5FU, 5FU + oxaliplatin, capecitabine, and capecitabine + oxaliplatin, and hopefully this trial will provide an answer to which regimen has better outcome when

combining treatment with radiation,¹⁹ especially relevant for patients known to have stage 3 disease.

There are numerous ongoing clinical trials incorporating more aggressive preoperative regimens. A few of the trials are employing chemotherapy combinations including oxaliplatin with 5FU,^{19, 20} and irinotecan with 5FU.²¹ Others are incorporating targeted biologics with chemotherapy such as: bevacizumab with 5FU,²² cetuximab with 5FU,²³ panitumumab with 5FU,²⁴ and one trial is investigating the addition of the anti-inflammatory cyclooxygenase-2 inhibitor celecoxib with 5FU.²⁵ However, the role of targeted biologic therapeutics in treatment of locally-advanced stage colorectal cancer has been called into question in light of recent data showing lack of efficacy in the adjuvant treatment of stage II and III colon cancer (NSABP C-08,²⁶ AVANT trial,²⁷ NCCTG-N0147).²⁸

The role of adjuvant chemotherapy in rectal cancer has been controversial. An earlier study by Bosset et al²⁹ concluded that for rectal cancer patients receiving preoperative radiotherapy, adding 5FU-based chemotherapy preoperatively or postoperatively has no significant effect on survival. This study suggests that the benefits of chemotherapy are limited to improving local control. Furthermore, in a subsequent analysis, it was demonstrated that only patients with good prognosis (ie, those who were downstaged to ypT0-2) benefit from adjuvant chemotherapy. The progression-free survival and overall survival curves diverged only after the poor prognosis patients (ypT3-4) had experienced treatment failure.³⁰ FOLFOX (XELOX) is now used as the standard of care for the ypT3/4 N1/2 patient,³¹⁻³³ but is this enough? In addition, should a non-5FU-based regimen be used if the patient did not respond to 5FU preoperatively? Newer agents and testing of MSI,³⁴ thymidylate synthase,³⁵ ERCC-1³⁶ and EGFR³⁷ may be implemented in future clinical trials to customize chemotherapy for the individual patient.

The timing of surgery after chemoradiation therapy is another key factor warranting consideration. Typically rectal cancer surgery is performed 6–8 weeks after chemoradiation is completed. A trial by Habr-Gama et al³⁸ demonstrated that addition of chemotherapy during the resting period after neoadjuvant chemoradiation for rectal cancer increased rates of complete tumor regression. In addition, preliminary analysis from a four arm phase II clinical trial³⁹, evaluating locally-advanced rectal cancer patients treated with neoadjuvant chemoradiation followed by additional chemotherapy and delay in surgery indicate a high pathologic complete response rate without additional complications. These preliminary results raise the question whether all patients should be treated with additional pre-operative chemotherapy beyond standard preoperative concurrent chemoradiation, and also raise questions about further extending the interval between chemoradiation and surgery.

The course of radiation therapy is also evolving. The Swedish Rectal Cancer Registry conducted a retrospective analysis on short course radiation therapy. The short course of radiation was administered post operatively and the data revealed beneficial effects on 5 year survival, especially in patients with low tumors, and revealed a decrease in local recurrent rates.⁴⁰ Short course radiation therapy is not routinely administered in the US, but is a treatment option that should be considered.

There are several important limitations to this study. The study is considered a retrospective study even though CCR prospectively collects the data. The change of surgical technique from 1994 to 2005 is evident by the increased use of TME (total mesorectal excision). Low anterior resection with TME improves the chance of a negative circumferential resection margin (CRM) compared to blunt dissection, however the CCR does not have patient-level information on surgical techniques employed, CRM status, or functional outcomes. The

CCR data set does not distinguish between different chemotherapy regimens, length of chemotherapy treatment, or radiation dose and duration. However, data from CCR provide information indicating which cases received chemotherapy or not, and whether radiation occurred before or after surgery. Since preoperative radiation by itself is not common, in this study it was assumed that all patients who received radiation therapy and chemotherapy treatment prior to surgery received concurrent (as opposed to sequential) chemoradiation. The same assumption was applied to postoperative radiation group as well; all patients in the postoperative radiation group who also received chemotherapy were presumed to have received concurrent chemoradiation with or without additional adjuvant chemotherapy. Due to these limitations, we were unable to get detailed information on postoperative chemotherapy alone. Despite these limitations, CCR data provides important clinical prognostic factors for mortality after rectal cancer diagnosis, allowing for multivariate regression analysis of a large number of rectal cancer patients in a geographically contiguous region.

Conclusion

Our study evaluated the overall mortality and CRC-specific mortality of rectal cancer patients who received preoperative chemoradiation. We found that stage III rectal cancer patients having received preoperative chemoradiation represent a high-risk group, as this group had worse prognosis compared with stage III patients receiving postoperative chemoradiation. Our findings support additional clinical studies on preoperative and postoperative regimens for this high-risk patient subset.

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Fig. 1. Case ascertainment from the California Cancer Registry, 1994–2005 (with follow-up through 2007).

No. At Risk							
Post op	1383	1104	715	461	293	141	95
Pre op	655	432	147	57	17	17	17

Fig. 2.
Overall survival for preoperative and postoperative chemoradiation treatment in lymph node positive rectal cancer cases.
----- Postoperative chemoradiation treatment (pN+)
_____ Preoperative chemoradiation treatment (ypN+)

Table 1

Demographic information for stage III (lymph-node positive) rectal cancer cases, 1994–2005, California Cancer Registry (only includes patients who received either preoperative or postoperative chemoradiation).

	Total n (%)	Preoperative Chemoradiation (%)	Postoperative Chemoradiation (%)	P-Value
No. of patients	2,038 (100)	655 (32.1)	1,383 (67.9)	
Sex				0.0083
Male	1,222 (60.0)	420 (64.1)	802 (58.0)	
Female	816 (40.0)	235 (35.9)	581 (42.0)	
Age ¹ (Median, Range)	61.0 (15 – 92)	59.0 (20 – 87)	63.0 (15 – 92)	< 0.0001 ²
Ethnicity/race				0.0065
White	1,325 (65.0)	395 (60.3)	930 (67.3)	
African American	107 (5.3)	34 (5.2)	73 (5.3)	
Asian	254 (12.5)	91 (13.9)	163 (11.8)	
Hispanic	343 (16.8)	134 (20.5)	209 (15.1)	
Other	9 (0.4)	1 (0.2)	8 (0.6)	
Socioeconomic status				0.4877
1 st quintile	280 (13.7)	85 (13.0)	195 (14.1)	
2 nd quintile	378 (18.6)	130 (19.9)	248 (17.9)	
3 rd quintile	425 (20.9)	124 (18.9)	301 (21.8)	
4 th quintile	476 (23.4)	156 (23.8)	320 (23.1)	
5 th quintile	479 (23.5)	160 (24.4)	319 (23.1)	
Histologic subtype				< 0.0001
Adenocarcinoma	1,711 (84.0)	506 (77.3)	1,205 (87.1)	
Mucinous adenocarcinoma	259 (12.7)	121 (18.5)	138 (10.0)	
Other	68 (3.3)	28 (4.3)	40 (2.9)	
Histologic grade ³				0.0297
Well differentiated	85 (4.3)	38 (6.3)	47 (3.4)	
Mod. differentiated	1,389 (70.4)	424 (70.0)	965 (70.6)	
Poorly differentiated	485 (24.6)	139 (22.9)	346 (25.3)	
Undifferentiated	14 (0.7)	5 (0.8)	9 (0.7)	
Time Period				<0.001
Group 1-1994–1997	557 (27.3)	31 (4.7)	526 (38.0)	
Group 2-1998–2001	717 (35.2)	201 (30.7)	516 (37.3)	
Group 3-2002–2005	764 (37.5)	423 (64.6)	341 (24.7)	

¹ Age at diagnosis

² Nonparametric one-way analysis

³Data missing from 65 patients

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Table 2

T and N classification according to chemoradiation sequence in stage III rectal cancer cases. T and N classification were based on AJCC criteria.

T Classification ^I	Total n (%)	Preoperative Chemoradiation (%)	Postoperative Chemoradiation (%)	P-Value
T1	50 (3.1)	4 (1.1)	46 (3.7)	0.0002
T2	266 (16.6)	44 (11.8)	222 (18.0)	
T3	1,128 (70.2)	274 (73.7)	854 (69.2)	
T4	162 (10.1)	50 (13.4)	112 (9.1)	
N Classification				
N1	1,004 (49.3)	257 (39.2)	747 (54.0)	<0.0001
N2	602 (29.5)	115 (17.6)	487 (35.2)	
N+	432 (21.2)	283 (43.2)	149 (10.8)	

^IData missing from 432 patients.