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NRG Oncology Radiation Therapy Oncology Group 0822: A phase II study of preoperative chemoradiotherapy utilizing intensity modulated radiation therapy (IMRT) in combination with capecitabine and oxaliplatin for patients with locally advanced rectal cancer

Theodore S. Hong, MD¹, Jennifer Moughan, MS², Michael C. Garofalo, MD³, Johanna Bendell, MD⁴, Adam C. Berger, MD⁵, Nicklas B.E. Oldenburg, MD⁶, Pramila Rani Anne, MD⁵, Francisco Perera, MD⁷, R. Jeffrey Lee, MD⁸, Salma K. Jabbour, MD⁹, Adam Nowlan, MD¹⁰, Albert DeNittis, MD¹¹, and Christopher Crane, MD¹²

¹Massachusetts General Hospital

²NRG Oncology Statistics and Data Management Center, Philadelphia, PA

³University of Maryland School of Medicine

⁴Sarah Cannon Research Institute

⁵Thomas Jefferson University Hospital

⁶North Main Radiation Oncology

⁷London Regional Cancer Program/Western Ontario

⁸Intermountain Medical Center

⁹Rutgers Cancer Institute of New Jersey

¹⁰Piedmont Hospital

¹¹Main Line CCOP

¹²University of Texas-MD Anderson Cancer Center

Abstract

Purpose—To evaluate the rate of gastrointestinal (GI) toxicity of neoadjuvant chemoradiation with capecitabine, oxaliplatin, and intensity modulated radiation therapy (IMRT) in cT3-4 rectal cancer.

Corresponding author: Theodore S. Hong, M.D., Department of Radiation Oncology, Massachusetts General Hospital, 100 Blossom Street, COX-3, Boston, MA 02114, Telephone: (617)-726-6050/Fax: (617)-726-3603, tshong1@mgh.harvard.edu.

Conflict of Interest- None

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Materials and Methods—Patients with localized, non-metastatic T3 or T4 rectal cancer < 12 cm from the anal verge were enrolled in a prospective, multi-institutional, single arm study of preoperative chemoradiation. Patients received 45 Gy with IMRT in 25 fractions, followed by a 3D-conformal boost of 5.4 Gy in 3 fractions with concurrent capecitabine/oxaliplatin (CAPOX). Surgery was performed in 4-8 weeks following completion of therapy. Patients were recommended to receive FOLFOX chemotherapy after surgery. The primary endpoint of the study was acute grade 2-5 GI toxicity. Seventy-one patients provided 80% probability to detect at least a 12% reduction in the specified GI toxicity with the treatment of CAPOX and IMRT, at a significance level of 0.10 (1-sided).

Results—79 patients were accrued, of whom 68 were evaluable. 61 patients (89.7%) had cT3 and 37 (54.4%) cN (+) disease. 42/68 patients received post-operative chemotherapy. 58 patients had target contours drawn per protocol, 5 patients with acceptable variation, and 5 patients with unacceptable variations. 35 patients (51.5%) developed grade 2 GI toxicity. 12 patients (17.6%) developed grade 3 or 4 diarrhea. pCR was achieved in 10 patients (14.7%). With a median follow-up of 3.98 years, the 4-year locoregional failure (LRF) rate was 7.4% (95% CI: 1.0% - 13.7%). 4-year OS and DFS were 82.9% (95% CI: 70.1% - 90.6%) and 60.6% (95% CI: 47.5% - 71.4%), respectively.

Conclusion—The use of IMRT in neoadjuvant chemoradiation for rectal cancer did not reduce the rate of gastrointestinal toxicity.

Introduction

Neoadjuvant chemoradiation is the standard of care for locally advanced (T3/4, or node (+)) rectal cancer. However, acute gastrointestinal (GI) toxicity, typically manifesting as diarrhea, is common, and may be exacerbated by additional agents including oxaliplatin.¹⁻³ Radiation Therapy Oncology Group (RTOG) 0247, a randomized phase II trial studying two treatment regimens, radiation with capecitabine/oxaliplatin (CAPOX) or capecitabine/irinotecan (CAPIRI), was suspended due to an unexpectedly high rate of non-hematologic grade 3/4 toxicity.⁴ The chemotherapy dosing was decreased in the CAPOX arm, but a 19% grade 3 preoperative GI toxicity remained upon final analysis even with the first 17 patients excluded from analysis. Intensity modulated radiation therapy (IMRT) affords the potential to decrease the acute toxicity of pelvic chemoradiation. In anal cancer, IMRT appears to decrease grade 3 or greater GI toxicity of chemoradiation.⁵ Retrospective series evaluating neoadjuvant chemoradiation in rectal cancer have suggested that IMRT reduces acute bowel toxicity.^{6,7} NRG Oncology RTOG 0822 was initiated to determine if the use of IMRT could similarly decrease the rate of GI toxicity with multi-agent neoadjuvant chemoradiation in rectal cancer.

Materials and Methods

Eligibility Criteria

Patients provided informed consent to this prospective study (NCT00613080) according to each center's Institutional Review Board's guidelines. Histologically confirmed adenocarcinoma of the rectum beginning within 12 cm from the anal verge as determined by sigmoidoscopy and colonoscopy was required, staged as clinical T3 or T4, N0-2 disease

based on transrectal ultrasound or pelvic MRI. Negative metastatic staging with a CT or MRI of the abdomen and pelvis, as well as chest CT or radiograph, or PET-CT (whole-body) was required. Patients had to have a Zubrod performance status of 0-2, adequate hematologic, renal and hepatic function, and potentially resectable disease.

Radiation Therapy

The radiation treatment plan consisted of two phases: 1) an inverse-planned IMRT phase to the rectum and the draining lymphatics at-risk to 45 Gy in 1.8 Gy/fraction and 2) a 3D-CRT boost to the gross disease plus a 2 cm margin including all of the presacral space to 5.4 Gy in 1.8 Gy/fraction. A minimum of 6 MV photons were required for treatment. Patients were allowed to be CT-simulated supine or prone in a belly board.

Pelvic clinical target volumes (CTV) for the initial phase were defined as outlined in the RTOG anorectal atlas.⁸ For T3 disease, the initial CTV included all gross disease, the internal iliac lymph nodes, and the entire presacral space. For T4 tumors, the external iliac lymph nodes were also included. The unified CTV included the rectal gross tumor volume (GTV) expanded 1.5 cm radial and 2.5 cm craniocaudally, nodal GTV expanded 1.5 cm symmetrically, internal iliac vessels expanded 1 cm symmetrically (externals included for T4), presacral space defined as the 8 mm of soft tissue anterior to the sacrum from mid-S1-S5, and the mesorectum/perirectal lymphatics.

The planning target volume (PTV) was defined as a 0.5 cm expansion of the unified CTV. Organs at risk (OARs) were also contoured. Specifically, the small bowel was defined as the peritoneal space ("shrink-wrapped" bag) containing the small bowel.

IMRT treatment plans were required to cover 98% of the PTV with 93% of the prescribed dose, with 10% receiving 105% and 5% receiving 115% of the prescribed dose. Small bowel dose was limited to $V_{35} < 180\text{cc}$, $V_{40} < 100\text{cc}$, and $V_{45} < 65\text{cc}$. Femoral head dose was limited to $V_{40} < 40\%$, $V_{45} < 25\%$, and a maximum dose of 50 Gy. Bladder dose was limited to $V_{40} < 40\%$, $V_{45} < 15\%$, and a maximum dose 50 Gy.

Real-time Quality Assurance

Real-time quality assurance was performed remotely by the study chair or the radiation oncology co-chair *prior* to initiation of treatment for the first 40 cases. The final cases enrolled were reviewed within 3 months after accrual was completed. Review included evaluation of CTV and PTV, OARs, and treatment plan dosimetry.

Chemotherapy

Chemotherapy was delivered concurrently during the pre-operative radiation therapy beginning on the first day of therapy. Capecitabine was administered orally at 825 mg/m^2 twice daily. Oxaliplatin was administered at 50 mg/m^2 IV weekly for 5 doses.

Patients were recommended to receive post-operative chemotherapy, to begin between 4-8 weeks after surgery. Post-operative chemotherapy consisted of 9 cycles of FOLFOX, given every 14 days. FOLFOX consisted of oxaliplatin 85 mg/m^2 IV delivered day 1 over 2 hours,

leucovorin 400 mg/m² delivered day 1 over 2 hours, 5-FU 400 mg/m² delivered day 1 IV push, followed by 5-FU 2400 mg/m² infusion beginning day 1 over 46 hours.

Surgery

Surgery was performed 4 to 8 weeks following completion of radiation therapy. Total mesorectal excision (TME) was strongly recommended. All cases were reviewed by the surgical co-chair.

Measurement of effect, toxicity, and follow-up evaluation

Patients were evaluated for adverse events weekly during preoperative chemoradiation, within 14 days prior to surgical resection, and prior to each cycle of postoperative chemotherapy. Patients were then evaluated every 3 months for 2 years, every 6 months for the next 3 years, and then annually.

Pathologic response was scored based on the resected specimen. Post-treatment T and N stage were reported, as well as margin status, and if a pathologic complete response (pCR) was achieved. Imaging was performed prior to surgery and then after treatment at the discretion of the treating physician.

Statistics

The primary endpoint of the study was to determine the rate of grade 2 preoperative treatment-related gastrointestinal (GI) adverse events (AEs) (per National Cancer Institute Common Terminology Criteria for AEs, version 3.0 [MedDRA version 9.0]). With 40% of these AEs from the conventional CAPOX arm in RTOG 0247, using a chi-squared test, a sample size of 71 patients provides 80% probability to detect at least a 12% reduction in these AEs with the treatment of CAPOX and IMRT, at a significance level of 0.10 (1-sided). Adjusting for patients determined to be ineligible or who do not start protocol treatment (5%), a total sample size of 75 patients was required.

There were two planned interim looks for each of two secondary endpoints, AEs and abdominoperineal resections (APRs), after 24 and 48 patients were entered and evaluable (eligible patients who began protocol treatment), using Fleming's method.⁹ Unacceptable AEs were grade 3 and 4 non-hematologic AEs related to treatment (excluding nausea/vomiting and alopecia) occurring preoperatively (90 days from the start of concurrent treatment for non-surgical patients). The study chairs prospectively determined rates of 40% (90% power) and 50% (95% power) as unacceptable for the defined AEs and APRs, respectively, with an overall significance level of 0.05 for each. If there were 11/16 patients with AEs and/or 14/21 patients with APRs among the first 24/48 patients, then the study would have exceeded the limit for the protocol-specified treatment-related AEs and/or APR rate and accrual would be stopped, if applicable, otherwise accrual would continue to the full sample size. At the final analysis, 22 patients with AEs and/or 29 patients with APRs would result in a conclusion of excessive AEs and/or APRs.

The protocol-defined efficacy endpoints were overall survival (OS), disease-free survival (DFS), local failure (LF), regional failure (RF), local-regional failure (LRF), and distant

failure (DF). These were defined as: OS failure - death due to any cause; LF - (1) any recurrence or surgery to the primary site after a complete response (CR) reported at surgery or reported after the end of protocol treatment; or (2) persistence, absence of CR after protocol treatment was completed and patient lived at least 90 days from the end of treatment; RF - (1) any recurrence after a nodal CR reported at surgery or reported after the end of protocol treatment; or (2) persistence, absence of nodal CR after protocol treatment was completed and patient lived at least 90 days from the end of treatment; DF - the appearance of peritoneal seeding or distant metastases. All efficacy endpoints were measured from study entry to date of first failure or last follow-up for censored patients. Persistent disease was considered a failure one day post study entry. Death was considered a competing risk for LRF, LF, RF, and DF. OS and DFS were estimated univariately with the Kaplan-Meier method¹⁰ and LRF, LF, RF, and DF were estimated by the cumulative incidence method.¹¹ Logistic regression was used to evaluate correlations between occurrence of AEs and dosimetric parameters. All analyses were performed using SAS/STAT® software.

Results

Seventy-nine patients were entered from 34 institutions from April 2008- November 2009. Eleven patients were deemed ineligible or received no protocol treatment (4 - disease extended into the anal canal; 1 - TRUS not performed; 1 - prior malignancy; 1 - lab dates outside protocol-defined window; and 4 - no protocol treatment), leaving 68 analyzable patients.

Pretreatment characteristics are listed in Table 1. Median age was 51 years, and 30 patients (44.1%) were female. Seven patients (10.3%) had cT4 and 61 (89.7%) had cT3 tumors. Thirty-one (45.6%), 33 (48.5%) and 4 (5.9%) patients had cN0, cN1, and cN2 disease, respectively.

Radiation plan review

Radiation therapy planning contour and dose review was completed in all 68 patients (100%). Fifty-eight patients (85%) had a target volume contouring score per protocol, and only 5 patients (7.4%) had an unacceptable variation (Table 2). Similarly, a high compliance was noted in dose-volume analysis, with only 1 unacceptable variation (1.5%) in tumor dose-volume analysis, and 3 unacceptable variations (4.4%) in OAR dose-volume analysis.

Treatment compliance

Only one patient did not complete chemoradiation (death during treatment due to myocardial infarction). All 67 patients who completed chemoradiation underwent surgery, of which 4 patients (6%) did not have documentation of total mesorectal excision (TME).

Abdominoperineal resections (APRs) were performed on 14/67 patients (20.9%). The APR rate never crossed the predefined boundary in the two interim evaluations or final analysis. Forty-two patients (63%) received postoperative chemotherapy, the most common reason of not receiving chemotherapy being patient refusal (n=10), followed by physician preference (n=4), and non-protocol specific AE (n=4).

Primary Endpoint

GI AEs reported as occurring preoperatively are listed in Table 3. Of 68 patients, there were 35 patients (51.5%) with a grade 2 GI AE reported. Although the protocol was designed for 71 evaluable patients, there is still a higher percentage of grade 2 GI AEs compared to the 40% from RTOG 0247 with fewer (68) evaluable patients. The one-sided chi-square p-value for testing a reduction in grade 2 GI AEs from 40% was 0.93. The percentage of grade 2 GI AEs in NRG Oncology RTOG 0822, therefore, was not statistically significantly lower than that seen in RTOG 0247. When specifically looking at diarrhea, there were 24 (35.3%) and 12 (17.6%) patients with grade 2 and grade 3, respectively.

Secondary Endpoints

The two interim protocol-specified evaluations for the secondary endpoint of AEs were performed in 2009 and 2010. Because the early stopping rules for AE boundaries were not crossed at either time, the study continued accrual. In the final analysis, there were 22 patients (32.4%) with a grade 3 non-hematologic AE, excluding nausea/vomiting and alopecia, reported as occurring preoperatively. Since there are 22 unacceptable AEs out of the 68 evaluable patients, it cannot be concluded that the true unacceptable AE rate is < 40%.

The summary of worst AE definitely, probably, or possibly related to treatment per patient for various time periods are listed in Supplement, Table S1. Thirty-three patients (48.5%) had a grade 3 AE reported as occurring preoperatively. Of the 67 patients who underwent surgery, a grade 3 non-hematologic AE occurring 30 days from the date of surgery was reported for 5 (7.5%) patients. Of the 42 patients who had postoperative chemotherapy, a grade 3 non-hematologic AE occurring 90 days from the end of postoperative chemotherapy was reported for 17 (40.5%) and any grade 3 AE reported for 31 (73.8%). Overall, 38 patients (56%) had a grade 3 non-hematologic AE reported and 53 (77.9%) had any grade 3 AE reported. The most common grade 3 non-GI, non-hematologic AE categories occurring from the start of concurrent treatment to the end of follow-up were pain (n=12), metabolic/laboratory (n=11), and neurologic (n=8).

Efficacy outcomes

Median follow-up is 3.98 years (min-max: 0.13-5.18). The 4-year LRF was 7.4% (95% confidence interval [CI]: 1.0% - 13.7%), with 5 total LRF. Four-year DF was 29.7% (95% CI: 18.7% - 40.8%). Four-year OS and DFS were 82.9% (95% CI: 70.1% - 90.6%) and 60.6% (95% CI: 47.5% - 71.4%), respectively (Figure 1a and 1b). DF was reported for 20 patients, with lung being the most common site (n=13), followed by liver (n=6). Nineteen patients (27.9%) had DF as their only failure; 4 patients (5.9%) had local and/or regional failure; and 1 patient had LRF and DF. pCR was achieved in 10 patients (14.7%). All 10 patients who had a pCR remained alive without disease recurrence at the time of analysis.

In evaluating failure patterns with treatment compliance, 4/58 patients with per protocol contours on RT planning review, 0/5 with acceptable variations, and 1/5 patients with unacceptable protocol contours had LRF. Thirty-one out of 42 patients (73.8%) who received postoperative chemotherapy had no failure (DF or LRF) while 11/25 patients

(44.0%) who did not receive postoperative chemotherapy had no failure. DF and LRF were 9/42 (21.4%) and 2/42 (4.8%), respectively, in patients receiving postoperative chemotherapy. In contrast, DF and LRF were 11/25 (44.0%) and 3/25 (12.0%) in patients who did not receive postoperative chemotherapy.

Correlation of GI toxicity with small bowel DVH parameters

Small bowel volume (cc) receiving 10 to 40 Gy at 5 Gy intervals were compared between patients who had < grade 2 vs. grade 2 GI toxicity and also between patients who had < grade 3 vs. grade 3 GI (Supplement, Table S2). No statistically significant difference was seen at any dose. Additionally, when evaluating the small volume receiving 10 to 40 Gy at 5 Gy intervals dichotomized based on the threshold volumes by Baglan and colleagues,¹² no statistically significant differences were seen for grade 2 (Supplement, Table S3) or grade 3 toxicity (Supplement, Table S4). Specifically, when V15 was dichotomized by 150 cc, as suggested by Baglan, or 120 cc as suggested in the update by Robertson and colleagues,¹³ there was still no association in rates of grade 3 GI toxicity (Table 4). Twelve out of 45 (26.7%) have grade 3 GI AEs for patients with V15 of 150 vs. 4/23 (17.4%) for patients with V15 of <150. Twelve out of 51 (23.5%) have grade 3 GI AEs for patients with V15 of 120 vs. 4/17 (23.5%) for patients with V15 of <120. Logistic regression was also performed with toxicity (outcome) and dose/volume (independent predictor) and showed no correlation (Supplement Table S5 - S6). Similar analyses for small bowel DVH parameters were performed restricted to grade 2 or 3 diarrhea and also showed no correlations (Supplement Tables S7-S10).

Late AEs

Late AEs, > 90 days from the end of postoperative chemotherapy, were evaluated. There was only one grade 3 late AE, peripheral sensory neuropathy. Details are shown in Supplement Tables S11-S12).

Discussion

Neoadjuvant chemoradiation for rectal cancer can be associated with acute GI toxicity, with grade 2-5 rates of ~ 30% with single agent chemotherapy.^{14,15} While oxaliplatin is unlikely to be further developed with neoadjuvant chemoradiation in rectal cancer given the increased toxicity and lack of clinical benefit seen phase III studies,¹⁻⁴ other studies showing encouraging activity with experimental regimens also are hampered by added GI toxicity.¹⁶ Therefore, efforts to decrease the contribution of radiation to acute GI toxicity continue to be important.

Retrospective^{6,7} and prospective studies¹² have demonstrated that IMRT can decrease the rate of acute GI toxicity. In spite of the low rate of unacceptable variations in radiation planning upon final review, the study failed to meet its primary endpoint, with a grade 2 GI toxicity rate of 51.5% occurring preoperatively, which substantially exceeded not just the target rate of 28%, but also the observed rate of 40% in RTOG 0247. Even when restricting the analysis to diarrhea, the current study, the grade 3 diarrhea rate of 17.6% does not

improve upon the ~15% rate grade 3 observed in the oxaliplatin arms in randomized trials (Table 5).

One possible reason for the inability of IMRT to reduce GI toxicity may be that insufficient dosimetric constraints were used for small bowel dose. While early studies have highlighted the role of the volume of small bowel receiving high dose radiation (> 45 Gy),^{17,18} more recent data suggests that the volume receiving 15 Gy may be more important whether using physician scoring^{12,13} or patient reported outcomes (PROs).¹⁹ While this study failed to show a difference in grade 3 toxicity based on V15, only 23 patients had a V15 <150 cc as suggested by Baglan¹² and only 17 patients had a V15 <120 cc as suggested by Robertson.¹³ With so few patients meeting this dosimetric constraint, a true evaluation of the importance of this threshold parameter is difficult as the sample sizes for the various comparisons provide $< 20\%$ power to detect the observed differences. Also, it is unlikely that the small bowel contouring strategy of peritoneal space, rather than loops of bowel, contributed to the negative results of this study²⁰ as a previous study demonstrated that either technique was predictive of DVH association with symptoms.

Physician-reported outcomes such as CTC scoring may be the wrong measure of patient's quality of life. In a rectal study evaluating PROs during chemoradiation, patients scored by physicians as having grade 2 GI toxicity had a wide range of patient reported diarrhea,²¹ highlighting that physician grading of toxicity lacks sufficient granularity to reflect actual differences in diarrhea. In future studies of toxicity reduction, PROs may be useful to further define toxicity differences with a given interventions.

The role of IMRT in rectal cancer remains undetermined. IMRT has been used as a method to dose paint or accelerate therapy with mixed results.²²⁻²⁴ Additionally, IMRT may be beneficial in situations where genitalia may be irradiated⁵ or when there is substantially more bowel at risk of being irradiated, such as patients with T4 tumors where external iliac coverage is needed, or patients who have had prior pelvic surgery (such as hysterectomy), or are being treated postoperatively.⁹ However, for a typical patient treated preoperatively for a T3 rectal cancer with 3D fields to the posterior pelvis with single agent chemotherapy, therapy is usually sufficiently well tolerated due to lack of small bowel in the field. Future evaluations should focus on identification of appropriate dosimetric constraints, use of PROs, and selection of patients most likely to benefit from IMRT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol*. 2011; 29:2773–80. [PubMed: 21606427]
2. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405 PRODIGE 2. *J Clin Oncol*. 2010; 28:1638–44. [PubMed: 20194850]
3. O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: Surgical end points from National Surgical Adjuvant Breast and Bowel Trial R-05. *J Clin Oncol*. 2014; 32:1927–34. [PubMed: 24799484]
4. Wong SJ, Winter K, Meropol NJ, et al. Radiation Therapy Oncology Group 0247: a randomized Phase II study of neoadjuvant capecitabine and irinotecan or capecitabine and oxaliplatin with concurrent radiotherapy for patients with locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys*. 2012; 82:1367–75. [PubMed: 21775070]
5. Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys*. 2013; 86:27–33. [PubMed: 23154075]
6. Samuelian JM, Callister MD, Ashman JB, et al. Reduced acute bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys*. 2012; 82:1981–1987. [PubMed: 21477938]
7. Parekh A, Truong MT, Pashtan I, et al. Acute gastrointestinal toxicity and tumor response with preoperative intensity modulated radiation therapy for rectal cancer. *Gastrointest Cancer Res*. 2013; 6:137–143. [PubMed: 24312687]
8. Myerson RJ, Garofalo MC, El Naqa I, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a Radiation Therapy Oncology Group consensus panel contouring atlas. *Int J Radiat Oncol Biol Phys*. 2009; 74:824–30. [PubMed: 19117696]
9. Fleming T. One-sample multiple testing procedure for phase II clinical trials. *Biometrics*. 1982; 38:143–151. [PubMed: 7082756]
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958; 53:457–481.
11. Kalbfleish, JD. The statistical analysis of failure time data. New York: John Wiley & Sons; 1980. p. 167-169.
12. Baglan KL, Frazier RC, Yan D, et al. The dose-volume relationship of acute small bowel toxicity from concurrent 5-FU-based chemotherapy and radiation for rectal cancer. *Int J Radiat Oncol Biol Phys*. 2002; 52:176–83. [PubMed: 11777636]
13. Robertson JM, Lockman D, Han D, Wallace M. The dose-volume relationship of small bowel irradiation and acute grade 3 diarrhea during chemoradiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys*. 2008; 70:413–418. [PubMed: 17904305]
14. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004; 351:1731–40. [PubMed: 15496622]
15. Bosset JF, Collete L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med*. 2006; 355:1114–23. [PubMed: 16971718]
16. Blaszkowsky LS, Ryan DP, Szymonifka J, et al. Phase I/II study of neoadjuvant bevacizumab, erlotinib, and 5-fluorouracil with concurrent external beam radiation therapy in locally advanced rectal cancer. *Ann Onc*. 2014; 25:121–126.
17. Gallagher MJ, Brereton HD, Rostock RA, et al. A prospective study of treatment techniques to minimize the volume of pelvic small bowel with reduction of acute and late effects associated with pelvic irradiation. *Int J Radiat Oncol Biol Phys*. 1986; 12:1565–1573. [PubMed: 3759581]
18. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. 1991; 21:109–122. [PubMed: 2032882]

19. Chen RC, Mamon HJ, Ancukiewicz M, et al. Dose-volume effects on patient-reported acute gastrointestinal symptoms during chemoradiation therapy for rectal cancer. *Int J Radiat Oncol Biol Phys.* 2012; 83:e513–e517. [PubMed: 22436781]
20. Banerjee R, Chakroborty S, Nygren I, et al. Small bowel dose parameters predicting acute toxicity in rectal cancer patients treated with neoadjuvant chemoradiation: An independent validation study comparing peritoneal space versus small bowel loop contouring techniques. *Int J Radiat Oncol Biol Phys.* 2013; 85:1225–1231. [PubMed: 23182394]
21. Chen RC, Mamon HJ, Chen Y, et al. Patient-reported acute gastrointestinal symptoms during concurrent chemoradiation treatment for rectal cancer. *Cancer.* 2010; 116:1379–86.
22. Freedman GM, Meropol NJ, Digurdson ER, et al. Phase I trial of preoperative hypofractionated intensity-modulated radiotherapy with incorporated boost and oral capecitabine in locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys.* 2007; 67:1389–1393. [PubMed: 17394942]
23. Zhu J, Gu W, Lian P, et al. A phase II trial of neoadjuvant IMRT-based chemoradiotherapy followed by one cycle of capecitabine for stage II/III rectal adenocarcinoma. *Radiat Oncol.* 2013; 8:130–136. [PubMed: 23718210]
24. Ballonoff A, Kavanagh B, McCarter M, et al. Preoperative capecitabine and accelerated intensity-modulated radiotherapy in locally advanced rectal cancer: A phase II trial. *Am J Clin Oncol.* 2008; 31:264–270. [PubMed: 18525306]

Summary

Neoadjuvant chemoradiation for rectal cancer can be associated with substantial gastrointestinal (GI) toxicity. Intensity modulated radiation therapy (IMRT) was prospectively evaluated in a cooperative group trial to assess whether GI toxicity grade 2 could be reduced to 40%. 68 patients were treated with IMRT to 45 Gy, followed by a conventional boost of 5.4 Gy with concurrent capecitabine and oxaliplatin. IMRT did not improve the rate of grade 2 GI toxicity.

Figure 1.
Survival outcomes. Overall survival (a) and Disease-free survival (b) are shown.

Table 1
Pretreatment Characteristics (n=68)

Age (years)	
Median	51
Min – Max	29 - 77
Q1 - Q3	46 - 61.5
Gender	
Male	38 (55.9%)
Female	30 (44.1%)
Race	
Asian	1 (1.5%)
Black or African American	5 (7.4%)
White	62 (91.2%)
Ethnicity	
Hispanic or Latino	9 (13.2%)
Not Hispanic or Latino	59 (86.8%)
Zubrod Performance Status	
0	56 (82.4%)
1	12 (17.6%)
Clinical T Stage (AJCC 6th Edition)	
T3	61 (89.7%)
T4	7 (10.3%)
Clinical N Stage (AJCC 6th Edition)	
N0	31 (45.6%)
N1	33 (48.5%)
N2	4 (5.9%)

Q1 = first quartile; Q3 = third quartile

Table 2
Radiation Therapy Planning Review (n=68)

Tumor volume contouring score	
Per protocol	58 (85.3%)
Acceptable variation	5 (7.4%)
Unacceptable variation	5 (7.4%)*
Organs at risk contouring score	
Per protocol	62 (91.2%)
Acceptable variation	6 (8.8%)
Unacceptable variation	0 (0.0%)
Tumor volume dose volume analysis score	
Per protocol	59 (86.8%)
Acceptable variation	8 (11.8%)
Unacceptable variation	1 (1.5%)
Organs at risk dose volume analysis score	
Per protocol	48 (70.6%)
Acceptable variation	17 (25.0%)
Unacceptable variation	3 (4.4%)

* All 5 patients had unacceptable variations in their CTV and PTV.

Table 3
(PRIMARY ENDPOINT) Number of Patients with a GI AE by Term and Grade Definitely, Probably, or Possibly Related to Protocol Treatment Occurring Preoperatively or, if no surgery, then 90 days from the Start of Concurrent Treatment (n=68)

Category	Grade				
	1	2	3	4	5
Term					
GASTROINTESTINAL [†]	21	19	15	1	0
Abdominal distension	3	2	0	0	0
Anal exam abnormal	1	0	0	0	0
Anorexia	8	5	1	0	0
Constipation	9	1	0	0	0
Dehydration	2	6	3	1	0
Diarrhea	23	12	11	1	0
Dyspepsia	3	0	1	0	0
Dysphagia	0	1	0	1	0
Endoscopy large bowel abnormal	0	0	1	0	0
Enteritis	0	1	1	0	0
Fecal incontinence	1	0	0	0	0
Flatulence	3	0	0	0	0
Gastrointestinal disorder	5	1	0	0	0
Hemorrhoids	1	0	0	0	0
Mucositis oral	3	0	0	1	0
Nausea	23	7	2	0	0
Proctitis	0	4	0	0	0
Taste alteration	6	1	0	0	0
Vomiting	8	3	3	0	0

Adverse events were graded with CTCAE version 3.0.

[†]This line represents the worst grade reported per patient across all the GI terms.

An individual patient can appear in multiple term rows for a given grade. For example, grade 1 for diarrhea, nausea, and proctitis and a grade 4 dehydration are all reported for the same patient and reflected in all of the corresponding term rows, but only shows up once in the category row for their worst grade, grade 4.

Table 4
Volume of Small Bowel receiving 15 Gy by 3 GI Toxicity

	Grade < 3 GI Toxicity (n=52)	Grade 3 GI Toxicity (n=16)	Total (n=68)
Volume of the small bowel that got at least 15 Gy			
< 120	13 (76.5%)	4 (23.5%)	17 (100.0%)
120	39 (76.5%)	12 (23.5%)	51 (100.0%)
Total (p-value* = 1.00)	52 (76.5%)	16 (23.5%)	68 (100.0%)
Volume of the small bowel that got at least 15 Gy			
< 150	19 (82.6%)	4 (17.4%)	23 (100.0%)
150	33 (73.3%)	12 (26.7%)	45 (100.0%)
Total (p-value* = 0.55)	52 (76.5%)	16 (23.5%)	68 (100.0%)

* Two-sided p-value from the Fisher's Exact Test

Table 5
Grade 3 Diarrhea in Oxaliplatin Chemoradiation Arms from Phase III Studies

Study	n	Other chemotherapy agents in trial	Number of patients with grade 3 diarrhea (%)
STAR-01 (1)	353	5-FU	54 (15%)
ACCORD 12/0405 PRODIGE 2 (2)	291	Capecitabine	36 (12.6%)
NSABP R-04 (3)	644	5-FU or Capecitabine	106 (16.5%)
NRG Oncology RTOG 0822	68	Capecitabine	12 (17.6%)