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ABSTRACT


PURPOSE The standard of care for locally advanced rectal cancer in North America is neoadjuvant pelvic chemoradiation with fluorouracil (5FUCRT). Neoadjuvant chemotherapy with fluorouracil and oxaliplatin (FOLFOX) is an alternative that may spare patients the morbidity of radiation. Understanding the relative patient experiences with these options is necessary to inform treatment decisions.

METHODS PROSPECT was a multicenter, unblinded, noninferiority, randomized trial of neoadjuvant FOLFOX versus 5FUCRT, which enrolled adults with rectal cancer clinically staged as T2N+, cT3N-, or cT3N+ who were candidates for sphincter-sparing surgery. Neoadjuvant FOLFOX was given in six cycles over 12 weeks, followed by surgery. Neoadjuvant 5FUCRT was delivered in 28 fractions over 5.5 weeks, followed by surgery. Adjuvant chemotherapy was suggested but not mandated in both groups. Enrolled patients were asked to provide patient-reported outcomes (PROs) at baseline, during neoadjuvant treatment, and at 12 months after surgery. PROs included 14 symptoms from the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Additional PRO instruments measured bowel, bladder, sexual function, and health-related quality of life (HRQL).

RESULTS From June 2012 to December 2018, 1,194 patients were randomly assigned, 1,128 initiated treatment, and 940 contributed PRO-CTCAE data (493 FOLFOX; 447 5FUCRT). During neoadjuvant treatment, patients reported significantly lower rates of diarrhea and better overall bowel function with FOLFOX while anxiety, appetite loss, constipation, depression, dysphagia, dyspnea, edema, fatigue, mucositis, nausea, neuropathy, and vomiting were lower with 5FUCRT (all multiplicity adjusted $P < .05$). At 12 months after surgery, patients randomly assigned to FOLFOX reported significantly lower rates of fatigue and neuropathy and better sexual function versus 5FUCRT (all multiplicity adjusted $P < .05$). Neither bladder function nor HRQL differed between groups at any time point.

CONCLUSION For patients with locally advanced rectal cancer choosing between neoadjuvant FOLFOX and 5FUCRT, the distinctive PRO profiles inform treatment selection and shared decision making.

ACCOMPANYING CONTENT

 Listen to the podcast by Drs Basch and Schrag at <https://sites.libsyn.com/58526/JCO>

 Appendix

 Data Supplement

 Protocol

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INTRODUCTION

The benefits of cancer therapies often come at the expense of adverse events, causing symptoms that impair functioning and quality of life.¹⁻³ A goal of cancer clinical research and care delivery is to optimize the benefit-to-risk ratio of therapies and to inform patients and clinicians about

short-term and long-term symptomatic adverse events so they can make informed decisions.⁴

Guidance from international regulatory authorities and professional consensus statements has emphasized the importance of incorporating the patient experience in the assessment of cancer treatment tolerability, through the systematic evaluation

CONTEXT

Key Objective

In the neoadjuvant treatment of locally advanced rectal cancer, do patient-reported outcomes differ between chemotherapy with fluorouracil and oxaliplatin (FOLFOX) versus pelvic chemoradiation with fluorouracil (5FUCRT)?

Knowledge Generated

During neoadjuvant treatment, patients receiving FOLFOX experienced less diarrhea and better bowel function, whereas those receiving 5FUCRT had less anxiety, appetite loss, constipation, depression, dysphagia, dyspnea, edema, fatigue, mucositis, nausea, neuropathy, and vomiting. In contrast, at 6, 12, and 18 months after treatment, patients receiving FOLFOX had less fatigue and neuropathy and better sexual function, compared with 5FUCRT. Overall quality of life remained similar between treatment groups during and after treatment.

Relevance (A.H. Ko)

As treatment paradigms evolve for locally advanced rectal cancer, the quality of life and toxicity data from this large PROSPECT trial—as reported directly by patients—can help inform decision-making and counseling patients in deciding between neoadjuvant FOLFOX or fluorouracil-based chemoradiation.*

*Relevance section written by JCO Associate Editor Andrew H. Ko, MD, FASCO.

of patient-reported outcomes (PROs).⁵⁻⁹ To enable patient self-reporting of symptomatic adverse events in cancer trials, the National Cancer Institute (NCI) developed the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).¹⁰ When there are treatment options with similar clinical benefits, a comparative understanding of adverse event profiles, including time course and severity levels, may particularly inform individual treatment choices.

Since 1990, management for patients with locally advanced rectal cancer has included pelvic chemoradiation with fluorouracil (5FUCRT) administered in 28 fractions over 5.5 weeks to reduce the risk of pelvic recurrence, an outcome with high morbidity,¹¹ with neoadjuvant 5FUCRT demonstrating better local control and tolerability than adjuvant 5FUCRT.¹² Yet, 5FUCRT is associated with both short-term and long-term AEs, particularly impaired bowel and sexual function.^{13,14}

The PROSPECT (N1048) randomized trial was designed to investigate whether neoadjuvant chemotherapy with fluorouracil and oxaliplatin (FOLFOX), with chemoradiation reserved only for the subset of patients intolerant of chemotherapy or whose tumors do not respond well to chemotherapy (<20% radiographic response), is noninferior to 5FUCRT for patients with clinical stage cT2N+, cT3N-, and cT3N+ tumors. As described by Schrag et al¹⁵ in a manuscript reporting the primary clinical efficacy outcomes of the PROSPECT trial, neoadjuvant FOLFOX was found to be noninferior to neoadjuvant 5FUCRT for the primary end point of disease-free survival, and there were no significant differences between treatment groups for secondary efficacy outcomes including overall survival, local recurrence, complete resection rate, and pathologic complete response. To understand the comparative patient

experiences with treatments in the PROSPECT trial, we evaluated PRO-CTCAE and measures of health-related quality of life (HRQL) between those assigned to neoadjuvant FOLFOX versus neoadjuvant 5FUCRT before sphincter-sparing surgery.

METHODS

Trial Design and Patients

PROSPECT (North Central Cancer Treatment Group [now part of the Alliance for Clinical Trials in Oncology] N1048; ClinicalTrials.gov identifier: [NCT01515787](https://clinicaltrials.gov/ct2/show/study/NCT01515787)) was a multicenter, unblinded, randomized controlled noninferiority trial comparing neoadjuvant FOLFOX with selective use of pelvic chemoradiation (intervention) to neoadjuvant 5FUCRT (control) conducted in the United States, Canada, and Switzerland. Eligible patients were adults with previously untreated locally advanced rectal cancer, clinically staged as cT2N+, cT3N-, or cT3N+ on the basis of the American Joint Committee on Cancer seventh edition of the tumor node metastasis staging system. In addition, to be eligible, the patient's surgeon had to determine that neoadjuvant 5FUCRT followed by sphincter-sparing surgery was the indicated standard treatment. Random assignment was 1:1 using dynamic allocation with stratification by Eastern Cooperative Oncology Group performance status score (0-1 v 2). The trial Protocol (online only) was approved by the NCI central institutional review board and/or institutional review board at each participating institution. All patients provided written informed consent before enrolling.

Patients in the 5FUCRT group received neoadjuvant pelvic chemoradiation in 28 daily fractions accompanied by

sensitizing chemotherapy with either fluorouracil or capecitabine over a 6-week period, followed by surgery. Patients in the FOLFOX group received six cycles of FOLFOX without radiation every 2 weeks over a 12-week period, followed by pelvic imaging and rectal endoscopy. If the primary tumor decreased in size by $\geq 20\%$ compared with baseline, surgery was performed. Otherwise, patients received neoadjuvant 5FUCRT. Patients unable to complete at least five cycles of FOLFOX were also prescribed neoadjuvant 5FUCRT. In both groups, adjuvant treatment was also suggested but not mandated. Specifically, for the 5FUCRT group, eight cycles of adjuvant FOLFOX or capecitabine with oxaliplatin (CAPOX) were suggested, and for the FOLFOX group, an additional six cycles of FOLFOX or CAPOX were suggested.

End Points

PROSPECT was designed as a noninferiority trial, with the primary end point of disease-free survival. Prespecified secondary end points included overall survival, surgical and pathologic outcomes, and PROs, the focus of this manuscript. Prespecified PRO end points included the PRO-CTCAE and additional PRO measures of bowel, bladder, and sexual function, as well as overall HRQL, with the purpose to characterize the patient experience between treatment groups.

The PRO-CTCAE is a validated library of patient-reported items that measure 78 distinct symptomatic adverse events.^{10,16} For each adverse event, up to three individual attribute items assess frequency, severity, and interference with usual or daily activities over the past 7 days. Scores for each attribute can be reported individually or can be combined into a single composite score ranging from 0–3 for each symptom via an established algorithm.¹⁷ Higher individual or composite scores indicate worse magnitude for a given symptom. PRO-CTCAE items salient in a given clinical trial are selected and assembled into a survey on the basis of previous evidence and/or mechanism of action.^{18,19} In the PROSPECT trial, the investigators selected 14 PRO-CTCAE symptoms on the basis of evidence from previous clinical trials and patient representative input. The selected symptoms were anxiety, appetite loss, constipation, depression, diarrhea, dysphagia, dyspnea, edema, fatigue, mucositis, nausea, neuropathy, pain, and vomiting.^{2,13}

All patients in PROSPECT enrolled in the United States or Canada who spoke English or Spanish were asked to complete PRO-CTCAE self-report items at baseline, weekly during neoadjuvant treatment for up to 12 weeks, and then at 6, 12, and 18 months after surgery (patients enrolled to PROSPECT in Switzerland were not included in PRO collection because language translations and technology access were not feasible in Switzerland at the time of trial initiation).²⁰ As described previously, patients could complete these items remotely between visits either by web, smart device, or automated telephone system.^{20,21} Each patient received an electronic message by email or telephone weekly

at a time of their preference to remind them to complete the survey. After 24 and 48 hours, additional reminder messages were sent to noncompleters, and after 72 hours, a central coordinator contacted patients who still had not completed the survey to collect responses. The primary PRO-CTCAE analyses were prespecified as the time points encompassing neoadjuvant treatment and 12 months after surgery, with additional supporting time points at 6 and 18 months.

Additional PROs were assessed via the Memorial Sloan Kettering Bowel Function Instrument²²; one question about bladder function each from the Prostate Health-Related QOL questionnaire²³ and the International Prostate Symptom Score (IPSS)²⁴; the International Index of Erectile Function (male patients only)²⁵; the Female Sexual Function Index (female patients only)²⁶; and the EuroQoL EQ-5D-5L for overall HRQL.^{27,28} These additional instruments were offered to approximately the first 500 patients enrolled in the United States or Canada via paper booklet at baseline, the end of neoadjuvant treatment (approximately 1–2 weeks before surgery), and at 12 and 24 months after surgery.

Statistics

Details of the trial design, random assignment, and statistical power are described in the Protocol and statistical analysis plan.

For each PRO-CTCAE symptomatic adverse event, a composite score was computed.¹⁷ The proportion of patients with each PRO-CTCAE composite score level for each of the 14 symptoms was tabulated at baseline. During neoadjuvant therapy, the maximum composite score, adjusting for baseline symptoms, was tabulated per patient.^{29,30} At 12 months after surgery, PRO-CTCAE scores per patient were cross-sectionally tabulated and adjusted for baseline. Maximum neoadjuvant and cross-sectional 12-month composite scores were primarily dichotomized as 0 versus ≥ 1 (absent v present) and supplemented with dichotomization at ≤ 2 versus 3 and were compared between groups using Chi squared tests. To account for multiplicity, Hochberg's step-up procedure³¹ was applied across 28 comparisons (14 PRO-CTCAE symptoms assessed at two time points). All patients who initiated protocol treatment as randomly assigned (per-protocol population) and who completed baseline and at least one postbaseline PRO-CTCAE were included in analyses. Previous analyses were reported on completion rates (92.0% patient completion rate for PRO-CTCAE surveys) and reasons for nonresponse.²⁰ In this analysis, patient nonresponse was assumed to be missing at random.

For the additional supporting time points at 6 and 18 months after surgery, similar supplemental analyses were conducted. The 6-month time point encompassed the period of optional administration of adjuvant chemotherapy and therefore was conducted both including and excluding patients still receiving active chemotherapy at that time point. Supplemental analyses also considered

individual PRO-CTCAE attribute item scores representing frequency, severity, and interference.

For the additional PRO end points, a linear combination of parameters from a general linear mixed model was used to estimate and compare mean changes from baseline between groups at each time point. Each model included all available data from all time points from all patients who initiated protocol treatment as randomly assigned and who completed baseline and at least one postbaseline assessment. Fixed effects included treatment group, time point, and treatment group by time point interaction. Repeated observations by patient were modeled using compound symmetric correlation structure over time. For the comparisons of bowel (MSKCC Bowel Function Instrument Aggregate Global Score), bladder (bladder emptying question from the IPSS), sexual function (International Index of Erectile Function Total Score for males and Female Sexual Function Index Total Score for females), and overall HRQL (EQ-5D-5L Index) at 12 months, $P < .01$ was considered statistically significant using a Bonferroni adjustment. Similar to PRO-CTCAE analysis, patient nonresponse was assumed to be missing at random. General linear models produce unbiased estimates under this missing data assumption.

Statistical testing was two-sided and carried out in SAS v9.4 (SAS Institute Inc, Cary, NC) or R v4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) on the study database frozen on December 15, 2022. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Management Center. Data quality was ensured by review of data by the Alliance Statistics and Data Management Center and by the study chairperson following Alliance policies.

RESULTS

Participants

From June 2012 to December 2018, 1,194 patients were randomly assigned, 1,128 initiated protocol-assigned treatment, and 940 completed baseline and at least one postbaseline PRO-CTCAE assessment (493 assigned to FOLFOX; 447 to 5FUCRT; Fig 1). The median age was 57 (range, 19–86) years, with 124 of 940 (13.2%) younger than 45 years, 322 of 940 (34.3%) female, 814 of 940 (86.6%) White, and 370 of 940 (39.4%) with high school education or less (Table 1). Baseline clinical and demographic characteristics were similar among those completing PRO-CTCAE and the additional PRO measures of HRQL with the overall per-protocol trial population (Appendix Table A1, online only). Baseline symptoms were frequent and similar between treatment groups, with more than half of patients reporting fatigue and diarrhea and approximately one quarter reporting appetite loss, constipation, depression, dyspnea, nausea, neuropathy, and pain at enrollment (Appendix Fig A2, online only).

Treatments Received

In the FOLFOX group, during neoadjuvant treatment, 555 of 585 (94.9%) patients received at least five cycles of FOLFOX, and 53 of 585 (9.1%) went on to receive neoadjuvant chemoradiation. In the 5FUCRT group, 515 of 543 (95.0%) received the full planned dose of 50.4 Gy radiation. In the FOLFOX group, 535 of 585 (91.4%) and in the 5FUCRT 510 of 543 (93.9%) completed surgery. In the FOLFOX group, 438 of 585 (74.8%) received adjuvant chemotherapy, of which 352 of 438 (80.4%) was FOLFOX with a median of six cycles (range, 1–12), whereas in the 5FUCRT group, 423 of 543 (77.9%) received adjuvant chemotherapy, of which 281 of 423 (66.4%) was FOLFOX with a median of eight cycles (range, 1–12). In the FOLFOX group, 1.4% (8 of 585) received postoperative radiation.

PROs

During neoadjuvant treatment, patients in the FOLFOX group reported significantly lower rates of diarrhea while rates of anxiety, appetite loss, constipation, depression, dysphagia, dyspnea, edema, fatigue, mucositis, nausea, neuropathy, and vomiting were significantly lower with 5FUCRT (all multiplicity adjusted $P < .05$; Fig 2; Appendix Table A2, online only). Severe (composite score 3) symptoms during neoadjuvant treatment with FOLFOX reported by at least 15% of patients included appetite loss (107 of 492, 21.7%), constipation (132 of 493, 26.8%), fatigue (205 of 492, 41.7%), nausea (102 of 490, 20.8%), neuropathy (94 of 492, 19.1%), and pain (109 of 493, 22.1%) and with 5FUCRT included diarrhea (88 of 447, 19.7%), fatigue (87 of 446, 19.5%), and pain (81 of 446, 18.2%; Appendix Table A3, online only).

At 12 months after surgery, symptom rates were significantly lower with FOLFOX for fatigue and neuropathy (both multiplicity adjusted $P < .05$; Fig 2; Appendix Fig A1, online only). At this time point, there were no symptoms reported as severe (composite score 3) by at least 15% of patients in either group (Appendix Table A3). Differences between groups were similar 6 months after surgery (Appendix Table A4, online only), at which time 186 of 655 (28.4%) patients who completed PRO-CTCAE assessments were still receiving chemotherapy (33 of 348 [9.5%] FOLFOX; 153 of 307 [49.8%] 5FUCRT). Differences between groups were also similar at 18 months after surgery in a post hoc analysis (Appendix Fig A1; Appendix Table A5, online only).

Additional PROs elicited from 373 patients (200 FOLFOX; 173 5FUCRT) demonstrated significantly better preoperative bowel function with FOLFOX compared with 5FUCRT and better sexual function for both males and females 12 months after surgery (raw $P < .01$ and multiplicity adjusted $P < .05$ at 12 months; Fig 3; Appendix Fig A3, online only; Data Supplement [Table], online only). No significant differences in bladder function or overall HRQL were detected at any time point after adjustment for multiple comparisons.

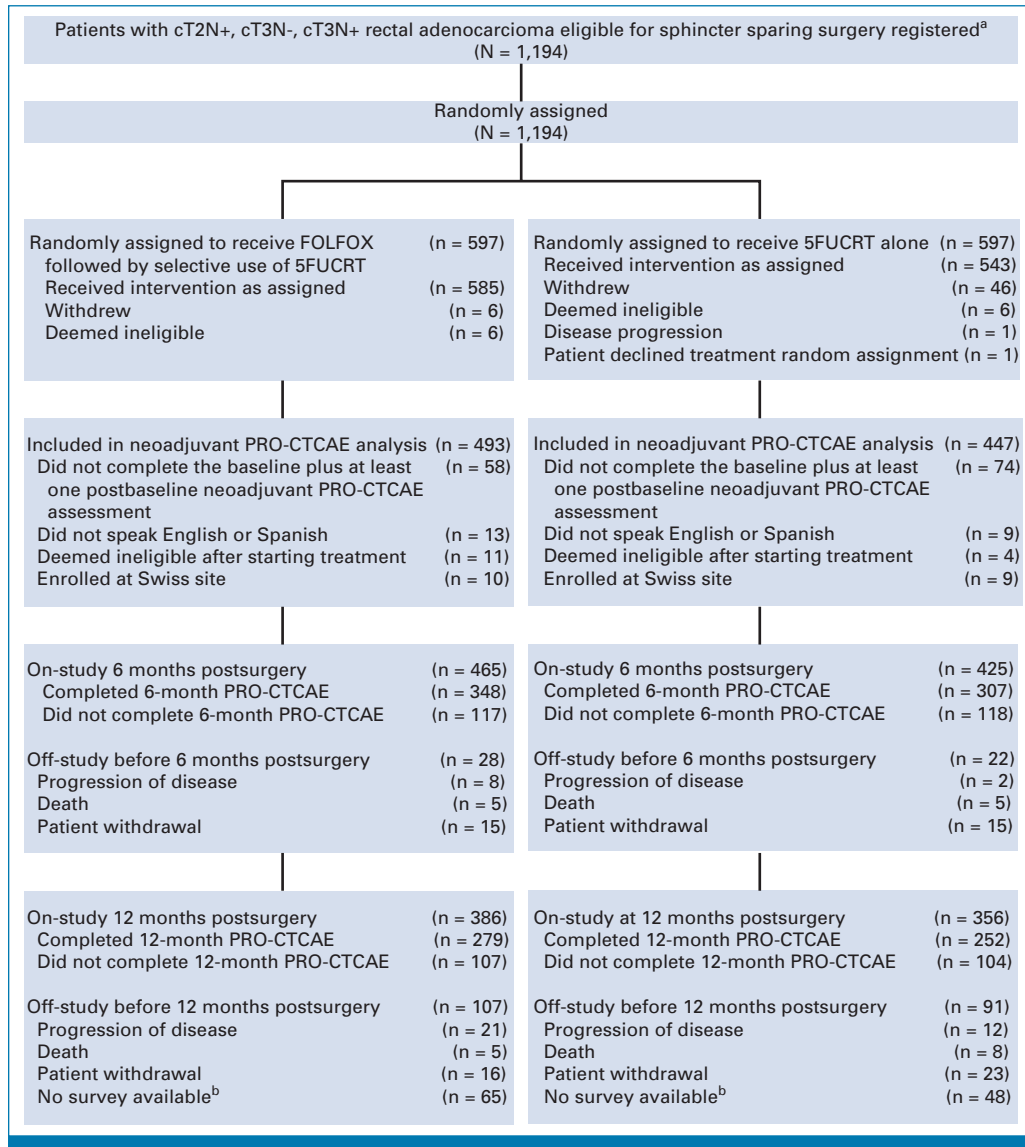


FIG 1. CONSORT diagram, patient enrollment and outcomes. ^aSites were not required to provide screening logs during recruitment; therefore, the number of patients assessed for eligibility is not available. ^bData at 12-month postsurgery time point is missing in these patients because the software system for electronic PRO-CTCAE data collection was discontinued in September 2019. 5FUCRT, chemoradiation with fluorouracil; c, clinical; FOLFOX, fluorouracil and oxaliplatin; N, node; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; T, tumor.

In an evaluation of patient-reported severity, frequency, and activity interference of each symptom, in the FOLFOX group, 15% or more patients reported high (score ≥ 3) severity for appetite loss, constipation, fatigue, mucositis, neuropathy, and pain; high frequency for anxiety, diarrhea, nausea, and pain; and high interference due to fatigue, mucositis, neuropathy, and pain during neoadjuvant treatment (Appendix Fig A2). In the 5FUCRT group, 15% or more patients reported high severity for fatigue and pain; high frequency for diarrhea and pain; and high interference due to fatigue and pain during neoadjuvant treatment. At 12 months, the only high-level symptom attribute reported by at least 15% of patients was high diarrhea frequency in the 5FUCRT group.

DISCUSSION

In a randomized clinical trial in patients with locally advanced rectal cancer, compared with the current standard of neoadjuvant 5FUCRT, patients receiving neoadjuvant FOLFOX followed by selected use of chemoradiation experienced significantly lower rates of diarrhea and better overall bowel function but higher rates of anxiety, appetite loss, constipation, depression, dysphagia, dyspnea, edema, fatigue, mucositis, nausea, neuropathy, and vomiting. Once treatment was complete (12 months after surgery), most acute treatment-related symptomatic adverse events had resolved in both groups, although significantly higher rates

TABLE 1. Characteristics of the Participants

Characteristic	FOLFOX (N = 493)	5FUCRT (N = 447)
Age, years		
Median (range)	57 (19-86)	58 (25-84)
Sex, No. (%)		
Male	315 (63.9)	303 (67.8)
Female	178 (36.1)	144 (32.2)
Race, No. (%)		
White	423 (85.8)	391 (87.5)
Black or African American	28 (5.7)	12 (2.7)
Asian	16 (3.2)	10 (2.2)
American Indian or Alaskan Native	2 (0.4)	9 (2.0)
Native Hawaiian or Pacific Islander	3 (0.6)	0 (0.0)
Not reported or unknown	21 (4.3)	25 (5.6)
Ethnicity, No. (%)		
Hispanic or Latino	41 (8.3)	37 (8.3)
Not Hispanic or Latino	436 (88.4)	395 (88.4)
Not reported or unknown	16 (3.2)	15 (3.4)
ECOG performance status, No. (%)		
0-1	490 (99.4)	444 (99.3)
2	3 (0.6)	3 (0.7)
Highest education level, No. (%)		
Less than high school	21 (4.3)	25 (5.6)
High school graduate or equivalent	171 (34.7)	153 (34.2)
Some college	104 (21.1)	83 (18.6)
College graduate or more	181 (36.7)	177 (39.6)
Not reported	16 (3.2)	9 (2.0)
Country of residence, No. (%)		
The United States	449 (91.1)	406 (90.8)
Canada	44 (8.9)	41 (9.2)
Clinical stage, No. (%)		
cT2N+	52 (10.6)	32 (7.2)
cT3N-	202 (41.0)	164 (36.7)
cT3N+	239 (48.5)	251 (56.2)

NOTE. Patients included in this analysis were enrolled in the PROSPECT trial, initiated protocol-assigned treatment, and completed baseline and at least one postbaseline patient-reported outcomes assessment.

Abbreviations: 5FUCRT, chemoradiation with fluorouracil; c, clinical; ECOG, Eastern Cooperative Oncology Group; FOLFOX, fluorouracil and oxaliplatin; N, node; T, tumor.

of fatigue, neuropathy, and sexual dysfunction persisted among patients assigned to receive 5FUCRT. These findings were similar at 18 months. Despite these differences in symptoms and functioning between groups, overall HRQL did not significantly differ between groups at any time point.

Given the noninferiority between FOLFOX and 5FUCRT for disease-free survival and the similarity of other efficacy end points as described by Schrag et al,¹⁵ these findings can inform decision making by patients and their clinicians. For those concerned about acute impairments in bowel function during presurgical treatment, or fatigue and sexual

function a year or more after surgery, FOLFOX may be preferable. For side effects beyond bowel function, 5FUCRT treatment resulted in fewer presurgical side effects and may remain preferable for some patients. Notably, the neoadjuvant treatment period for patients assigned to FOLFOX was nearly twice as long as 5FUCRT, which may explain the greater number of symptoms reported by this group.

Neuropathy has been highlighted previously as a concerning symptom associated with oxaliplatin in the FOLFOX regimen.³² In the PROSPECT trial, more patients initially experienced neuropathy during neoadjuvant chemotherapy with FOLFOX than with 5FUCRT, but this pattern reversed after treatment was completed, with more patients subsequently experiencing neuropathy at 12 and at 18 months in the 5FUCRT group. Given that most patients who receive neoadjuvant FOLFOX are subsequently administered fewer cycles of adjuvant oxaliplatin-based chemotherapy compared with those who receive neoadjuvant 5FUCRT (median of six v eight adjuvant cycles),¹⁵ the 12 and 18 month findings may be related to the timing and intensity of chemotherapy proximate to that time point or could reflect an enduring toxicity imbalance in a small number of patients favoring neoadjuvant FOLFOX.

Although no significant differences were seen between groups for overall HRQL, the instrument used in this trial, the EuroQoL EQ-5D-5L, only elicits information about mobility, self-care, daily activities, anxiety/depression, and pain toward the tabulation of its overall score^{27,28} and as such may have been insensitive to detecting the impact of the differential symptom burden observed between groups in this trial. Therefore, this metric may not reflect nuances of the overall patient experience with these treatments. Nonetheless, the EQ-5D-5L is a widely used instrument in clinical research, and the findings provide reassurance that there were not significant differences in functional impairment between treatment groups.

This trial demonstrates the value of PROs to characterize how patients feel and function, especially in a non-inferiority trial. Few previous rectal cancer trials have included longitudinal PROs.^{33,34} Although PROs have been cited as a key component of understanding cancer treatment tolerability⁷ and are encouraged by international regulatory authorities,^{5,6,9} most drug development programs still do not adequately incorporate PRO end points.³⁵ Patient-reported adverse events, such as measured in this trial with the PRO-CTCAE, can particularly illustrate the impact of treatments on patients.^{9,10,16} As the landscape for treatments in this disease evolves in the future, it will be informative to employ rigorous evaluation of PROs to understand the patient experience. As reported previously,²⁰ PRO-CTCAE completion rates were high in this trial (>90%) because of rigorous data collection including multiple modes for PRO completion by patients and telephone backup calls to noncompleters.

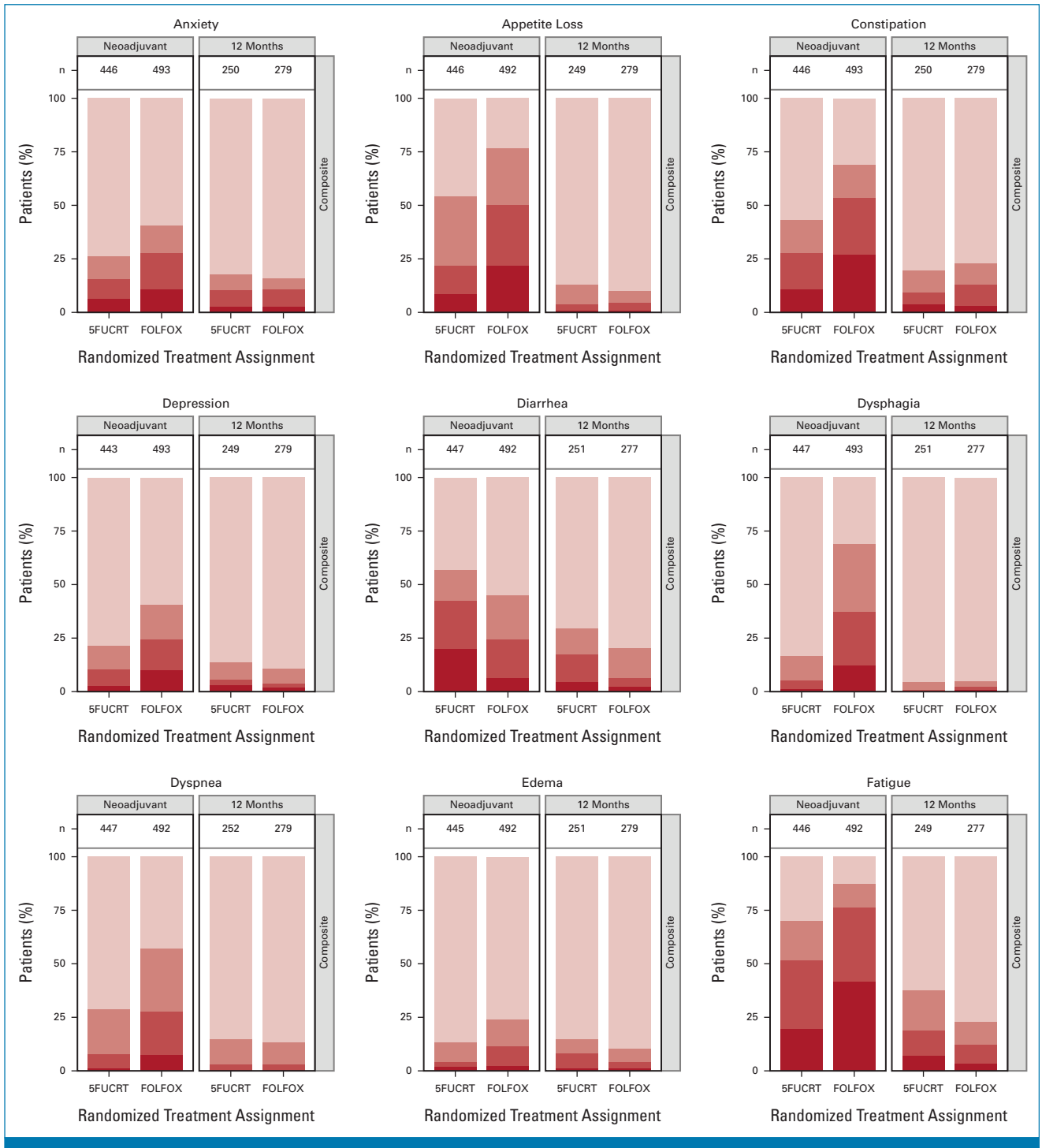


FIG 2. PRO-CTCAE composite score distributions for each symptom during the neoadjuvant treatment period and 12 months after surgery, adjusted for baseline symptoms. Higher scores (represented by darker colors) are worse. The lightest color shading represents a score of zero. Column labels (n) show the number of subjects with an observed score. 5FUCRT, chemoradiation with fluorouracil; FOLFOX, fluorouracil and oxaliplatin; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events. (continued on following page)

In fact, this trial is a landmark for the NCI’s PRO-CTCAE. Although now used widely in oncology drug development, to our knowledge, PROSPECT was the first large trial into which the PRO-CTCAE was embedded. The US Food and Drug Administration and other international regulatory authorities now encourage assessment of

patient-reported symptomatic adverse events in cancer drug development.^{9,10}

Since the PROSPECT trial was conceived and began recruitment in 2012, a variety of other strategies for management of rectal cancer have emerged. For example, total

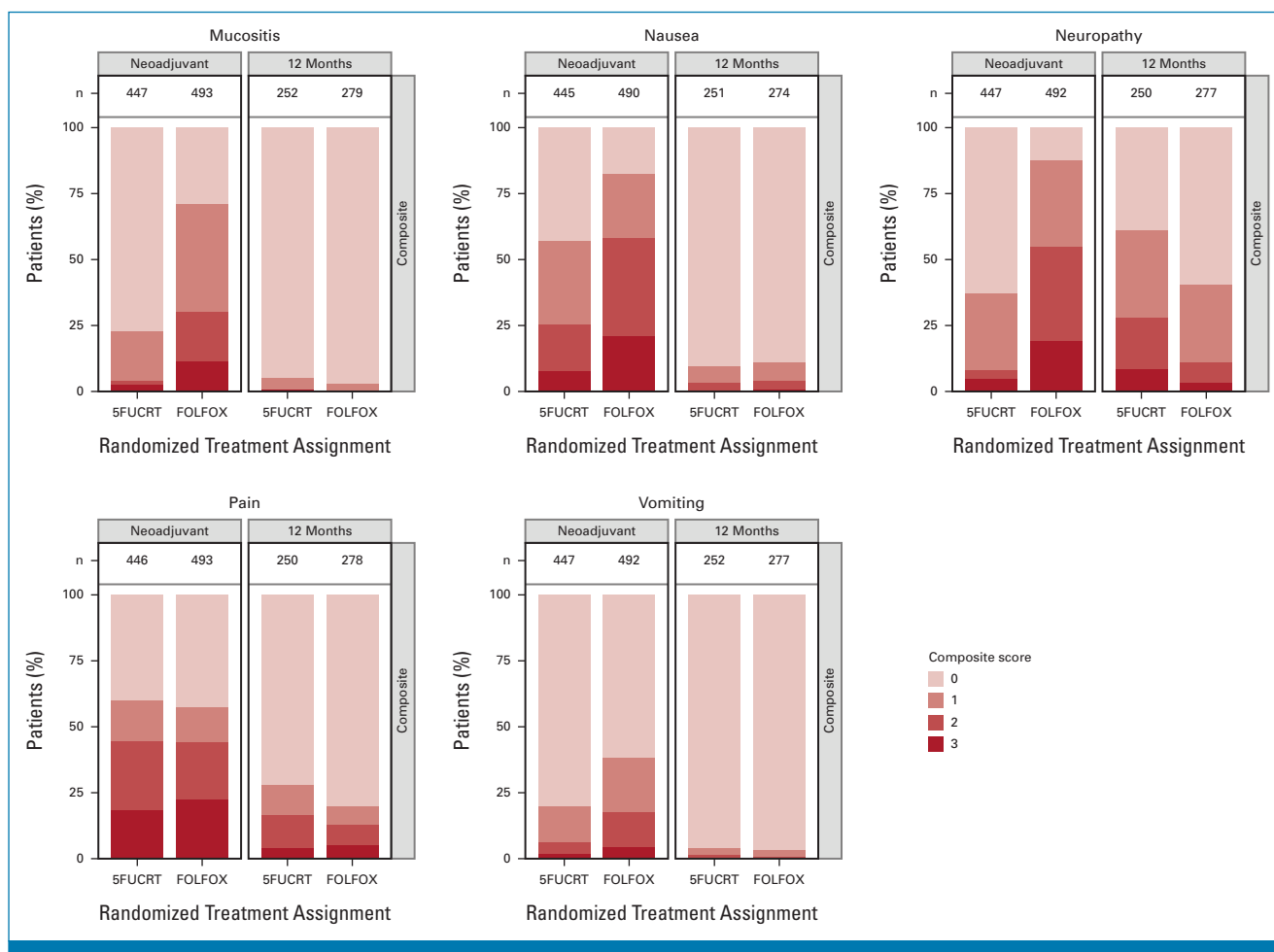


FIG 2. (Continued).

neoadjuvant therapy with 5FUCRT and chemotherapy followed by nonoperative management has potential to spare some patients the morbidity of surgery although this is offset by the need for close surveillance and high rates of recurrence in others.³⁶ Other approaches include immunotherapy alone as a curative strategy for the subset of patients with mismatch repair-deficient rectal cancer.³⁷ It is plausible that these approaches further decrease adverse symptoms and improve HRQL but there are not yet prospective trials comparing these strategies to 5FUCRT. A previous trial compared neoadjuvant short course radiation followed by chemotherapy to neoadjuvant 5FUCRT followed by adjuvant chemotherapy in a higher risk population of patients with rectal cancer than those recruited to PROSPECT and found that long-term quality of life outcomes were similar.³⁴

This study has several limitations. When the trial was designed, clinicians were concerned that omission of radiation could compromise clinical outcomes, and therefore, patients with high-risk features such as T4 tumors or distal tumors requiring an abdominoperineal resection were excluded. Accordingly, these findings pertain to patients with

moderate risk locally advanced tumors who were candidates for sphincter-sparing surgery at presentation. A prespecified set of symptoms was assessed, and there may have been other salient symptoms in this population, although there was a free-text option for patients to write in additional symptoms, which was previously examined in a pooled analysis.³⁸ Although sexual function was assessed, reproductive outcomes were not analyzed, which may be important to patients of child-bearing age. Other domains such as patient preference (eg, time on treatment, convenience of treatment) also were not included. Not all enrolled patients were included in the PRO collection, although most provided data for PRO-CTCAE (940 of 1,128 [83.3%]) and a smaller prespecified subset for HRQL (373 of 604 [61.8%]). Baseline characteristics were similar between those completing PROs in these two subgroups and the overall per-protocol trial population. Nonetheless, there may have been informative missing data because of patients who dropped out or did not complete PROs, although PRO completion rates were generally high in this trial.²⁰ The overall trial population was predominantly White and based in the United States and Canada and therefore does not reflect the diversity of

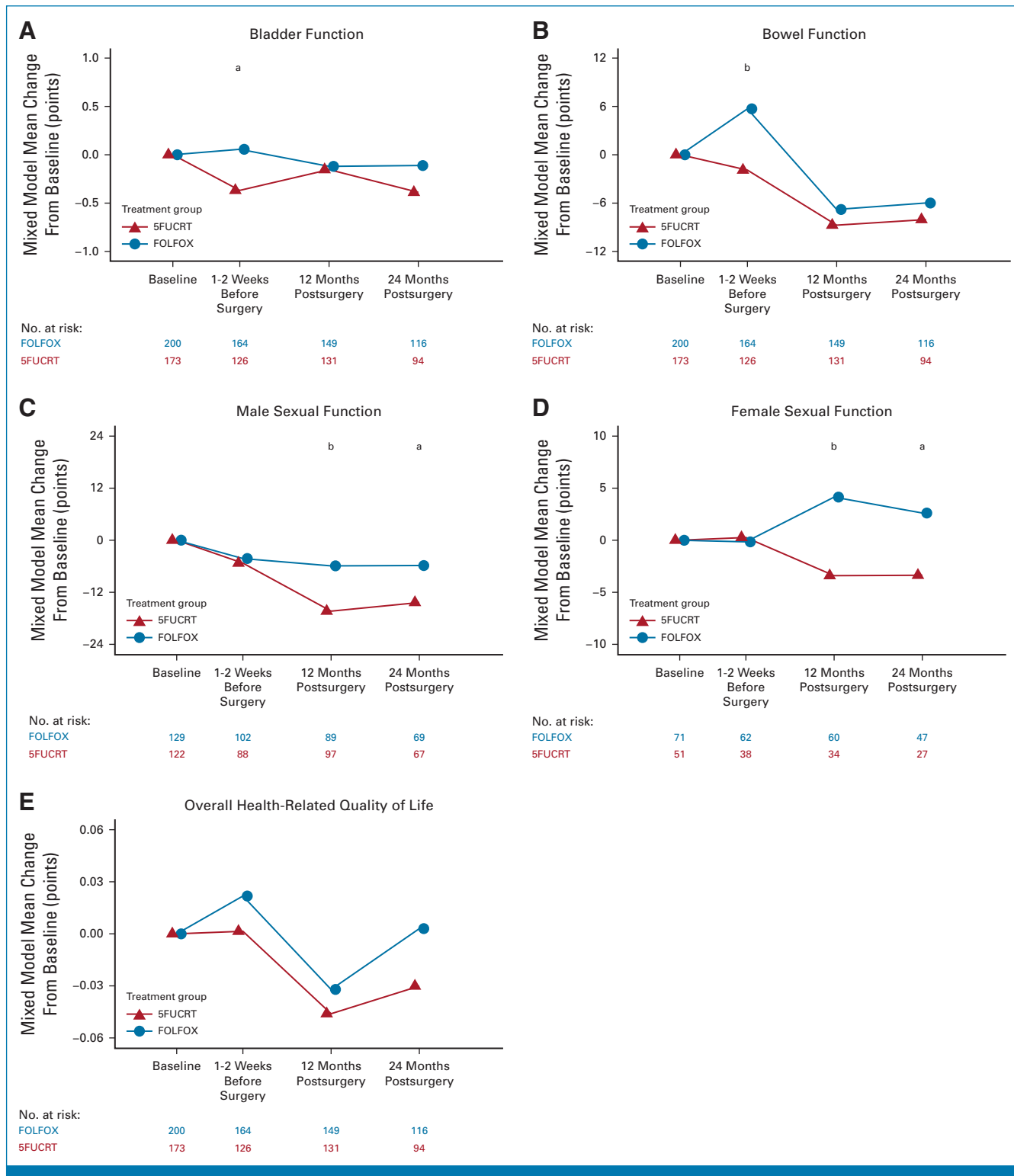


FIG 3. Mean changes from baseline between groups during neoadjuvant treatment (1-2 weeks before surgery) and at 12 and 24 months after surgery for (A) bladder function (bladder emptying question from the International Prostate Symptom Score, administered both to males and females); (B) bowel function (Memorial Sloan Kettering Bowel Function Instrument Aggregate Global Score); (C) male sexual function (International Index of Erectile Function Total Score, administered to males only); (D) female sexual function (Female Sexual Function Index Total Score, administered to females only); and (E) overall health-related quality of life (EuroQoL EQ-5D-5L Index). Positive values represent improvement compared with baseline for all scales. Means were estimated using a general linear mixed model for each scale. Between-group differences with raw $P < .05$ are demarcated with ^a and $P < .01$ with ^b. The results for all domain subscales are shown in the Data Supplement. ^aBetween-group difference raw $P < .05$. ^bBetween-group difference raw $P < .01$ (12 months only: multiplicity-adjusted $P < .05$). 5FUCRT, chemotherapy with fluorouracil; FOLFOX, fluorouracil and oxaliplatin.

patients facing treatment decisions for locally advanced rectal cancer. Future studies should focus on populations that have been underrepresented in clinical trials.

In conclusion, during neoadjuvant treatment, patients treated with FOLFOX experienced less diarrhea and better bowel function than those treated with 5FUCRT but had a higher burden of other symptoms including fatigue, anxiety, nausea, and neuropathy. After a year or more

following surgery, patients assigned to FOLFOX reported significantly lower rates of fatigue and neuropathy and better sexual function compared with those assigned to 5FUCRT. By this time, rates of severe symptoms were low in both groups and there were no discernible differences in overall HRQL. For patients with locally advanced rectal cancer choosing between neoadjuvant chemotherapy and chemoradiation, the distinctive PRO profiles inform treatment selection and shared decision making.

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APPENDIX

TABLE A1. Patient Characteristics by Cohort, Comparing Those in the Group Providing Baseline and At Least One Postbaseline PRO-CTCAE Report During Neoadjuvant Therapy, Those in the Subgroup Reporting Additional Patient-Reported Outcomes (HRQL cohort), and Those in the Overall Trial Population for the Analysis of Clinical End Points

Characteristic	PRO-CTCAE Cohort (n = 940)	HRQL Cohort (n = 373)	Overall Trial Cohort (N = 1,128)
Age, years, median (range)	57 (19-86)	56 (19-81)	57 (19-91)
Female sex, No. (%)	322 (34.3)	122 (32.7)	389 (34.5)
Race, No. (%)			
American Indian or Alaskan Native	11 (1.2)	2 (0.5)	13 (1.2)
Asian	26 (2.8)	9 (2.4)	51 (4.5)
Black or African American	40 (4.3)	16 (4.3)	50 (4.4)
Native Hawaiian or Pacific Islander	3 (0.3)	1 (0.3)	3 (0.3)
White	814 (86.6)	334 (89.5)	959 (85.0)
Not reported or unknown	46 (4.9)	11 (0.3)	52 (4.6)
Hispanic or Latino ethnicity, No. (%)	78 (8.3)	16 (4.3)	96 (8.5)
ECOG performance status 0-1, No. (%)	934 (99.4)	373 (100)	1,122 (99.5)
Highest education level, No. (%)			
Less than high school	46 (4.9)	12 (3.2)	58 (5.1)
High school or equivalent	324 (34.5)	130 (34.9)	415 (36.8)
Some college	187 (19.9)	74 (19.8)	221 (19.6)
College graduate or more	358 (38.1)	149 (39.9)	405 (35.9)
Not reported	25 (2.7)	8 (2.1)	29 (2.6)
Country of residence, No. (%)			
The United States	855 (91.0)	343 (92.0)	1,013 (89.8)
Canada	85 (9.0)	30 (8.0)	96 (8.5)
Switzerland	—	—	19 (1.7)
Stage, No. (%)			
cT2N+	84 (8.9)	35 (9.4)	101 (9.0)
cT3N–	366 (38.9)	136 (36.5)	430 (38.1)
cT3N+	490 (52.1)	202 (54.2)	596 (52.8)
Not reported or unknown	—	—	1 (0.09)
History of cardiovascular disease, No. (%)	171 (18.2)	59 (15.8)	204 (18.1)
History of diabetes, No. (%)	136 (14.5)	49 (13.1)	164 (14.5)

Abbreviations: c, clinical; ECOG, Eastern Cooperative Oncology Group; HRQL, health-related quality of life; N, node; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; T, tumor.

TABLE A2. Proportion of Patients in Each Group Experiencing Any PRO-CTCAE Symptomatic Adverse Event (composite score >0) During Neoadjuvant Treatment and at 12 Months After Surgery, Adjusted for Baseline Symptoms

PRO-CTCAE	Neoadjuvant Treatment				12 Months After Surgery			
	FOLFOX	5FUCRT	Raw <i>P</i>	Multiplicity-Adjusted <i>P</i>	FOLFOX	5FUCRT	Raw <i>P</i>	Multiplicity-Adjusted <i>P</i>
Anxiety	200/493 (41%)	117/446 (26%)	<.001	<.001	44/279 (16%)	44/250 (18%)	.57	.86
Appetite loss	376/492 (76%)	241/446 (54%)	<.001	<.001	28/279 (10%)	32/249 (13%)	.31	.86
Constipation	339/493 (69%)	192/446 (43%)	<.001	<.001	64/279 (23%)	49/250 (20%)	.35	.86
Depression	199/493 (40%)	94/443 (21%)	<.001	<.001	30/279 (11%)	34/249 (14%)	.31	.86
Diarrhea	220/492 (45%)	253/447 (57%)	<.001	.004	56/277 (20%)	74/251 (29%)	.01	.18
Dysphagia	340/493 (69%)	74/447 (17%)	<.001	<.001	13/277 (5%)	11/251 (4%)	.86	.86
Dyspnea	281/492 (57%)	128/447 (29%)	<.001	<.001	37/279 (13%)	37/252 (15%)	.64	.86
Edema	117/492 (24%)	58/445 (13%)	<.001	<.001	29/279 (10%)	37/251 (15%)	.13	.86
Fatigue	429/492 (87%)	312/446 (70%)	<.001	<.001	63/277 (23%)	93/249 (37%)	<.001	.004
Mucositis	349/493 (71%)	102/447 (23%)	<.001	<.001	8/279 (3%)	13/252 (5%)	.18	.86
Nausea	404/490 (82%)	253/445 (57%)	<.001	<.001	30/274 (11%)	24/251 (10%)	.60	.86
Neuropathy	431/492 (88%)	166/447 (37%)	<.001	<.001	112/277 (40%)	152/250 (61%)	<.001	<.001
Pain	283/493 (57%)	267/446 (60%)	.44	.86	55/278 (20%)	70/250 (28%)	.03	.32
Vomiting	187/492 (38%)	88/447 (20%)	<.001	<.001	9/277 (3%)	10/252 (4%)	.66	.86

NOTE. Raw *P* values are shown, as well as multiplicity-adjusted *P* values using Hochberg's step-up procedure applied across 28 comparisons (14 PRO-CTCAE symptoms assessed at two time points).

Abbreviations: 5FUCRT, chemoradiation with fluorouracil; FOLFOX, fluorouracil and oxaliplatin; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

TABLE A3. Proportion of Patients in Each Group Experiencing a PRO-CTCAE Severe Adverse Event (composite score 3) During Neoadjuvant Treatment and at 12 Months After Surgery, Adjusted for Baseline Symptoms

PRO-CTCAE	Neoadjuvant Treatment		Raw <i>P</i>	12 Months After Surgery		Raw <i>P</i>
	FOLFOX	5FUCRT		FOLFOX	5FUCRT	
Anxiety	53/493 (11%)	28/446 (6%)	.01	7/279 (3%)	6/250 (2%)	.94
Appetite loss	107/492 (22%)	38/446 (9%)	<.001	2/279 (1%)	2/249 (1%)	.91
Constipation	132/493 (27%)	47/446 (11%)	<.001	8/279 (3%)	9/250 (4%)	.63
Depression	49/493 (10%)	12/443 (3%)	<.001	5/279 (2%)	7/249 (3%)	.43
Diarrhea	30/492 (6%)	88/447 (20%)	<.001	6/277 (2%)	11/251 (4%)	.15
Dysphagia	59/493 (12%)	5/447 (1%)	<.001	2/277 (1%)	0/251 (0%)	.18
Dyspnea	36/492 (7%)	4/447 (1%)	<.001	1/279 (0%)	1/252 (0%)	.94
Edema	11/492 (2%)	8/445 (2%)	.63	3/279 (1%)	3/251 (1%)	.90
Fatigue	205/492 (42%)	87/446 (20%)	<.001	9/277 (3%)	17/249 (7%)	.06
Mucositis	55/493 (11%)	11/447 (2%)	<.001	0/279 (0%)	1/252 (0%)	.29
Nausea	102/490 (21%)	33/445 (7%)	<.001	2/274 (1%)	0/251 (0%)	.18
Neuropathy	94/492 (19%)	21/447 (5%)	<.001	9/277 (3%)	21/250 (8%)	.01
Pain	109/493 (22%)	81/446 (18%)	.13	14/278 (5%)	10/250 (4%)	.57
Vomiting	20/492 (4%)	7/447 (2%)	.02	1/277 (0%)	0/252 (0%)	.34

Abbreviations: 5FUCRT, chemoradiation with fluorouracil; FOLFOX, fluorouracil and oxaliplatin; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

TABLE A4. Proportion of Patients in Each Group Experiencing Any PRO-CTCAE Symptomatic Adverse Event (composite score >0) at 6 Months After Surgery, Adjusted for Baseline Symptoms, Both With and Without Patients Still Receiving Active Adjuvant Chemotherapy at That Time Point Included in the Analysis

PRO-CTCAE	6 Months After Surgery (all patients)		Raw <i>P</i>	6 Months After Surgery (only patients off chemotherapy)		Raw <i>P</i>
	FOLFOX	5FUCRT		FOLFOX	5FUCRT	
Anxiety	48/344 (14%)	52/303 (17%)	.26	42/311 (14%)	24/154 (16%)	.55
Appetite loss	65/341 (19%)	107/304 (35%)	<.001	54/309 (17%)	43/154 (28%)	.009
Constipation	51/345 (15%)	50/305 (16%)	.57	48/312 (15%)	19/154 (12%)	.38
Depression	47/343 (14%)	46/300 (15%)	.56	39/310 (13%)	21/152 (14%)	.71
Diarrhea	83/345 (24%)	89/306 (29%)	.15	73/312 (23%)	44/154 (29%)	.23
Dysphagia	30/344 (9%)	60/305 (20%)	<.001	23/311 (7%)	19/154 (12%)	.08
Dyspnea	62/343 (18%)	90/303 (30%)	<.001	55/310 (18%)	40/153 (26%)	.04
Edema	34/343 (10%)	36/302 (12%)	.41	29/310 (9%)	17/153 (11%)	.55
Fatigue	129/342 (38%)	175/306 (57%)	<.001	112/309 (36%)	78/154 (51%)	.003
Mucositis	46/345 (13%)	72/306 (24%)	<.001	38/312 (12%)	22/154 (14%)	.52
Nausea	56/342 (16%)	110/304 (36%)	<.001	42/309 (14%)	42/154 (27%)	<.001
Neuropathy	217/347 (63%)	204/306 (67%)	.27	194/314 (62%)	84/154 (55%)	.13
Pain	88/343 (26%)	90/305 (30%)	.27	76/310 (25%)	46/154 (30%)	.22
Vomiting	19/342 (6%)	32/305 (10%)	.02	17/309 (6%)	13/154 (8%)	.23

Abbreviations: 5FUCRT, chemoradiation with fluorouracil; FOLFOX, fluorouracil and oxaliplatin; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

TABLE A5. Proportion of Patients in Each Group Experiencing PRO-CTCAE Symptomatic Adverse Events at 18 Months After Surgery, Adjusted for Baseline Symptoms

PRO-CTCAE	Any Symptomatic Adverse Event (composite score >0)			Any Severe Adverse Event (composite score 3)		
	FOLFOX	5FUCRT	Raw <i>P</i>	FOLFOX	5FUCRT	Raw <i>P</i>
Anxiety	30/236 (13%)	34/203 (17%)	.23	5/236 (2%)	8/203 (4%)	.26
Appetite loss	17/237 (7%)	31/205 (15%)	.007	0/237 (0%)	0/205 (0%)	—
Constipation	61/238 (26%)	52/204 (25%)	.97	4/238 (2%)	8/204 (4%)	.15
Depression	24/238 (10%)	21/198 (11%)	.86	3/238 (1%)	1/198 (1%)	.41
Diarrhea	50/237 (21%)	62/205 (30%)	.03	6/237 (3%)	8/205 (4%)	.41
Dysphagia	8/238 (3%)	10/204 (5%)	.41	0/238 (0%)	0/204 (0%)	—
Dyspnea	25/237 (11%)	27/203 (13%)	.37	1/237 (0%)	1/203 (0%)	.91
Edema	25/238 (11%)	36/203 (18%)	.03	1/238 (0%)	3/203 (1%)	.24
Fatigue	55/235 (23%)	68/204 (33%)	.02	13/235 (6%)	7/204 (3%)	.29
Mucositis	10/238 (4%)	10/205 (5%)	.73	0/238 (0%)	1/205 (0%)	.28
Nausea	32/233 (14%)	23/205 (11%)	.43	0/233 (0%)	0/205 (0%)	—
Neuropathy	97/237 (41%)	114/205 (56%)	.002	8/237 (3%)	10/205 (5%)	.43
Pain	45/237 (19%)	48/205 (23%)	.25	10/237 (4%)	10/205 (5%)	.74
Vomiting	9/237 (4%)	6/205 (3%)	.61	0/237 (0%)	0/205 (0%)	—

Abbreviations: 5FUCRT, chemoradiation with fluorouracil; FOLFOX, fluorouracil and oxaliplatin; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

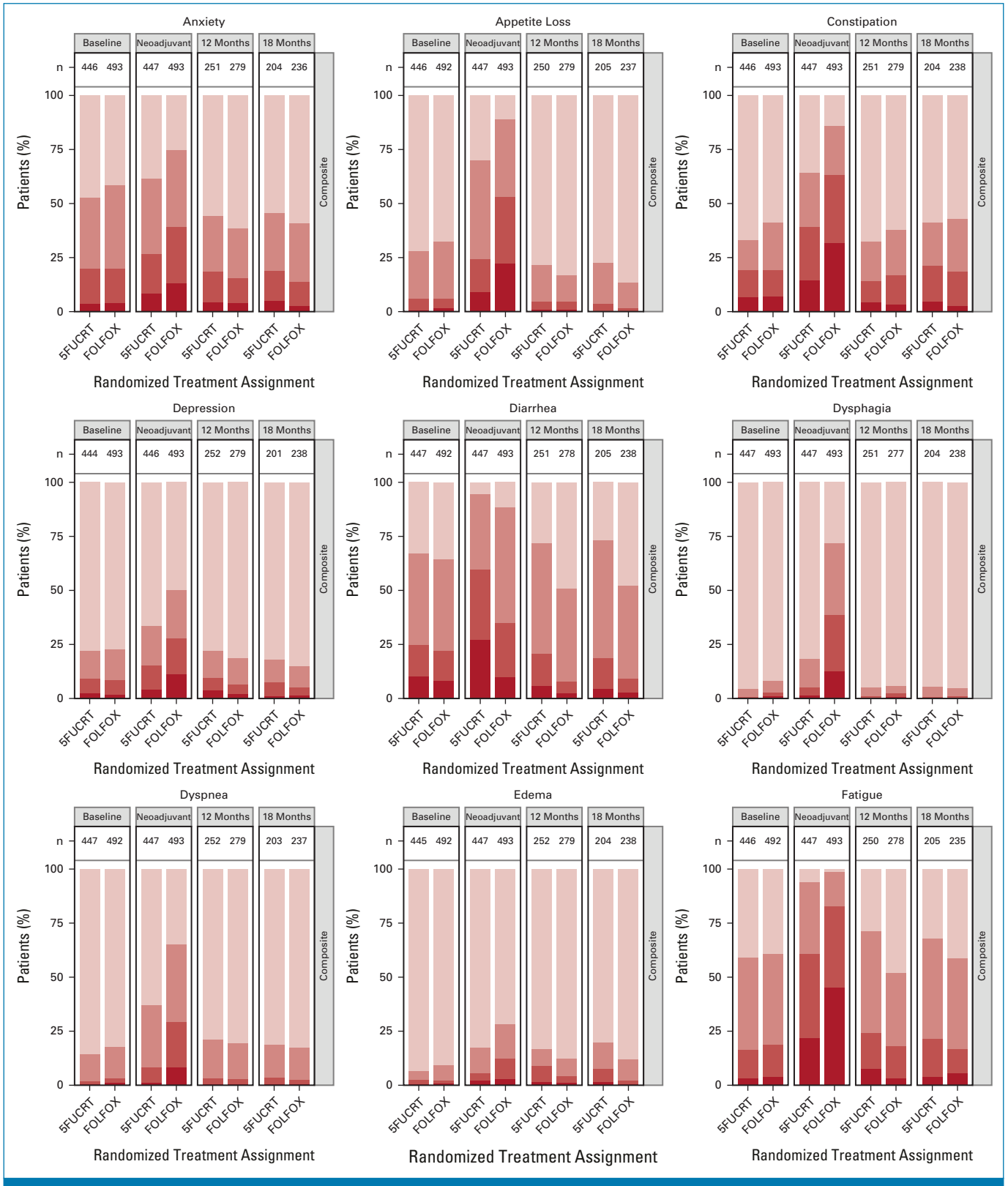


FIG A1. PRO-CTCAE composite score distributions at baseline, during neoadjuvant treatment (unadjusted for baseline scores), and 12 and 18 months after surgery (unadjusted for baseline scores). Higher scores indicate worse magnitude of a given symptom. Column labels (n) show the number of patients with an observed score. 5FU/CRT, chemoradiation with fluorouracil; FOLFOX, fluorouracil and oxalipatin; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events. (continued on following page)

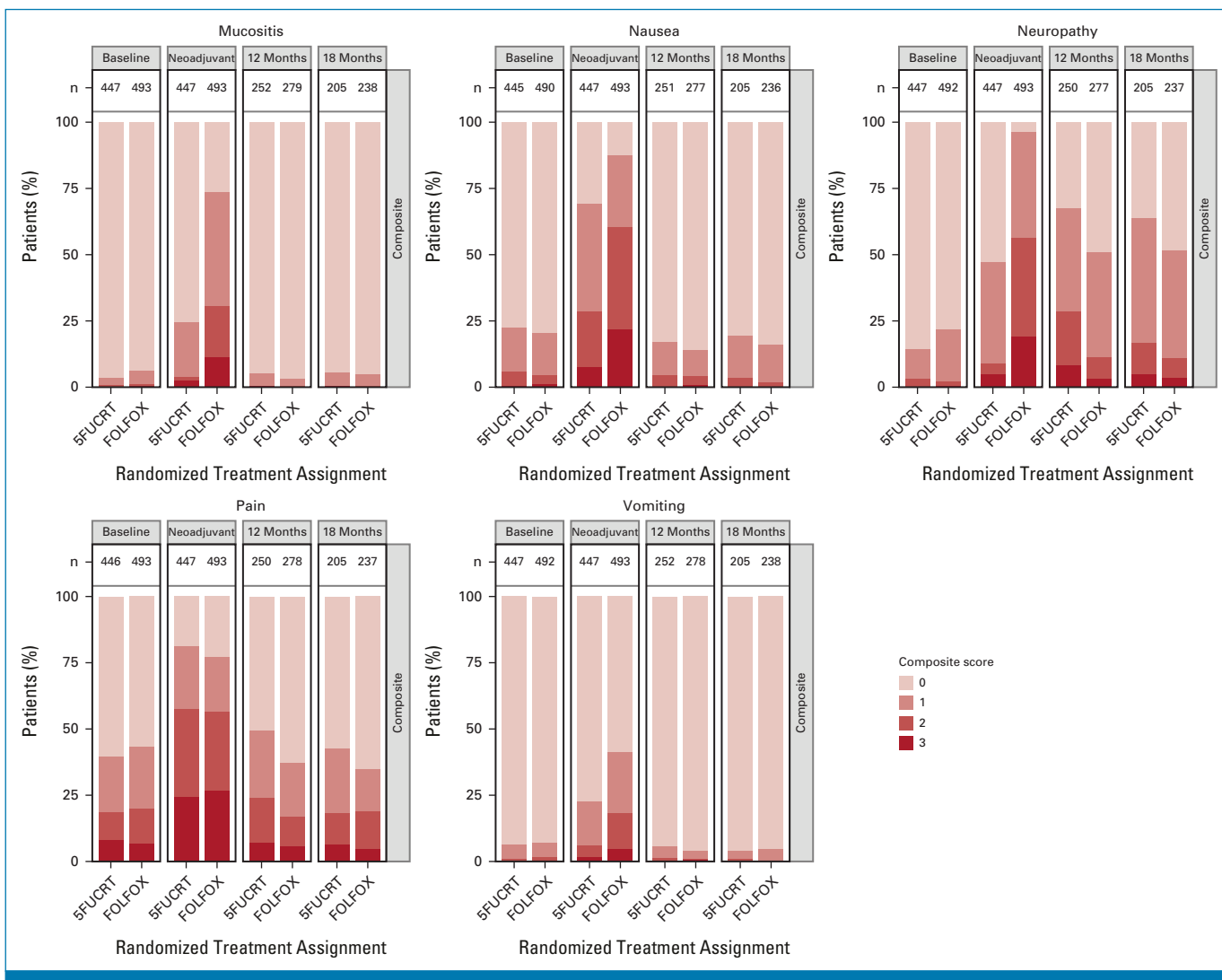


FIG A1. (Continued).

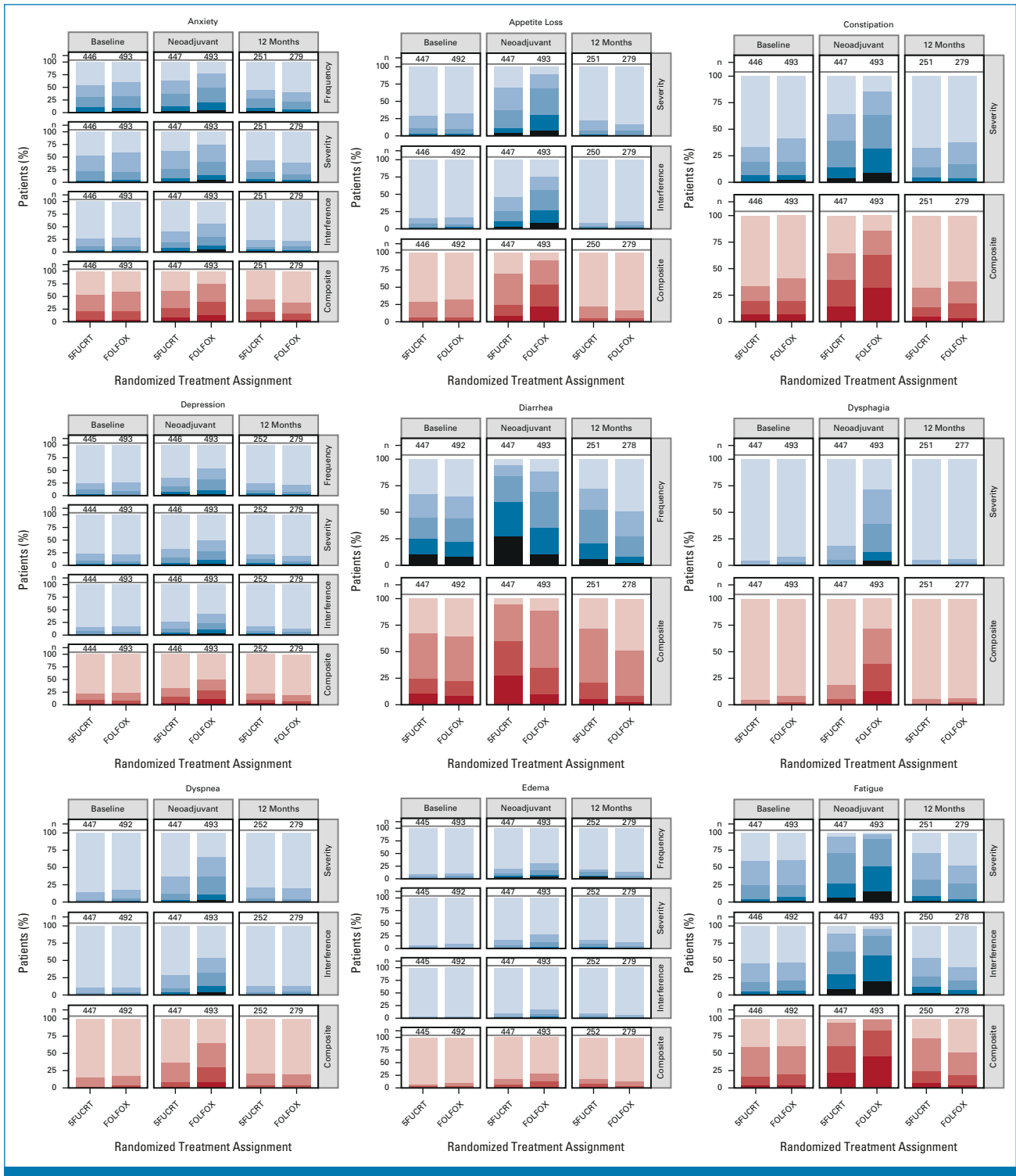


FIG A2. PRO-CTCAE individual attribute item score distributions for symptoms at baseline, during neoadjuvant treatment (unadjusted for baseline symptoms), and 12 months after surgery (unadjusted for baseline symptoms). Higher scores indicate worse magnitude of a given symptom. Column labels (n) show the number of patients with an observed score. 5FU/RT, chemoradiation with fluorouracil; FOLFOX, fluorouracil and oxaliplatin; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (continued on following page)

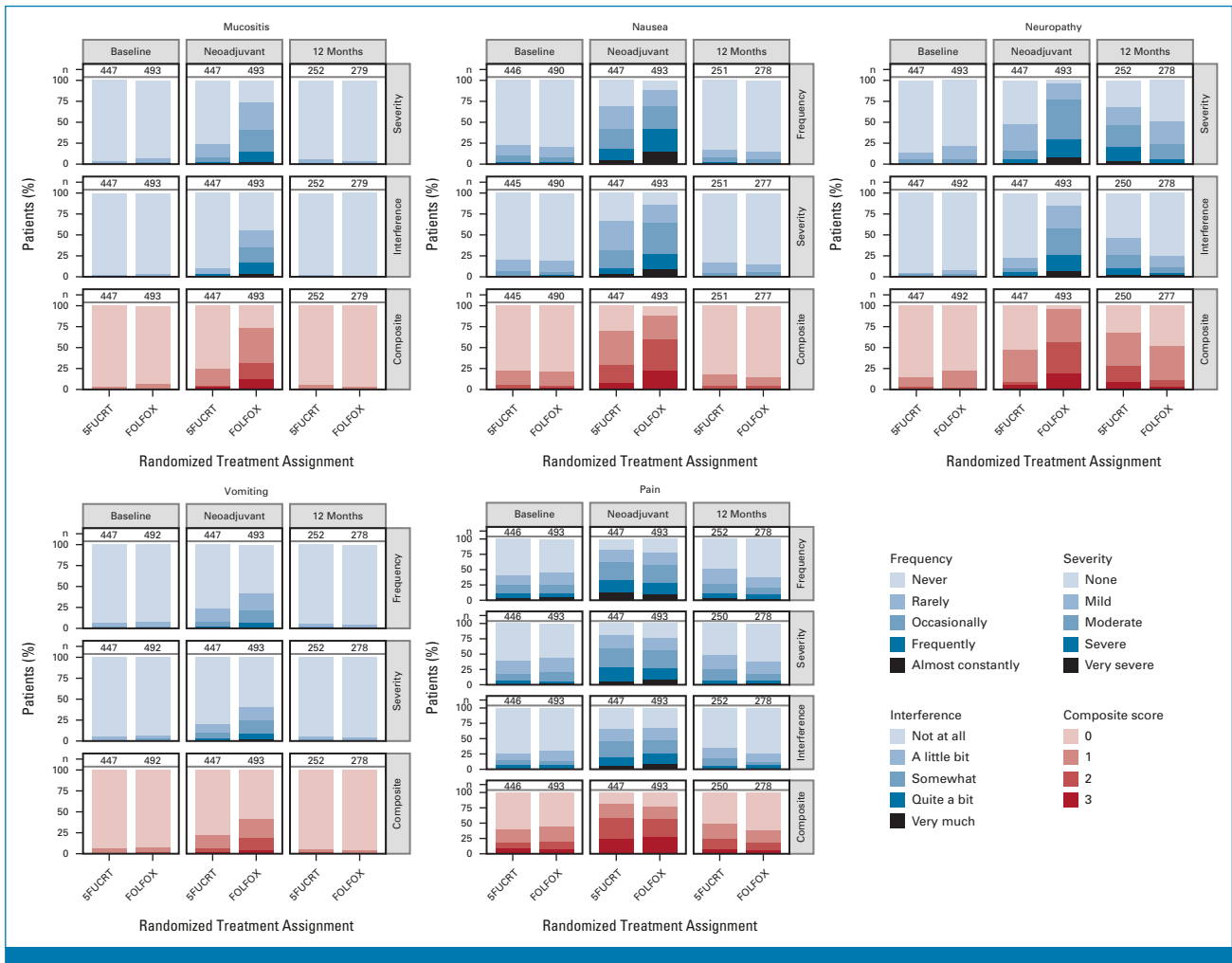


FIG A2. (Continued).

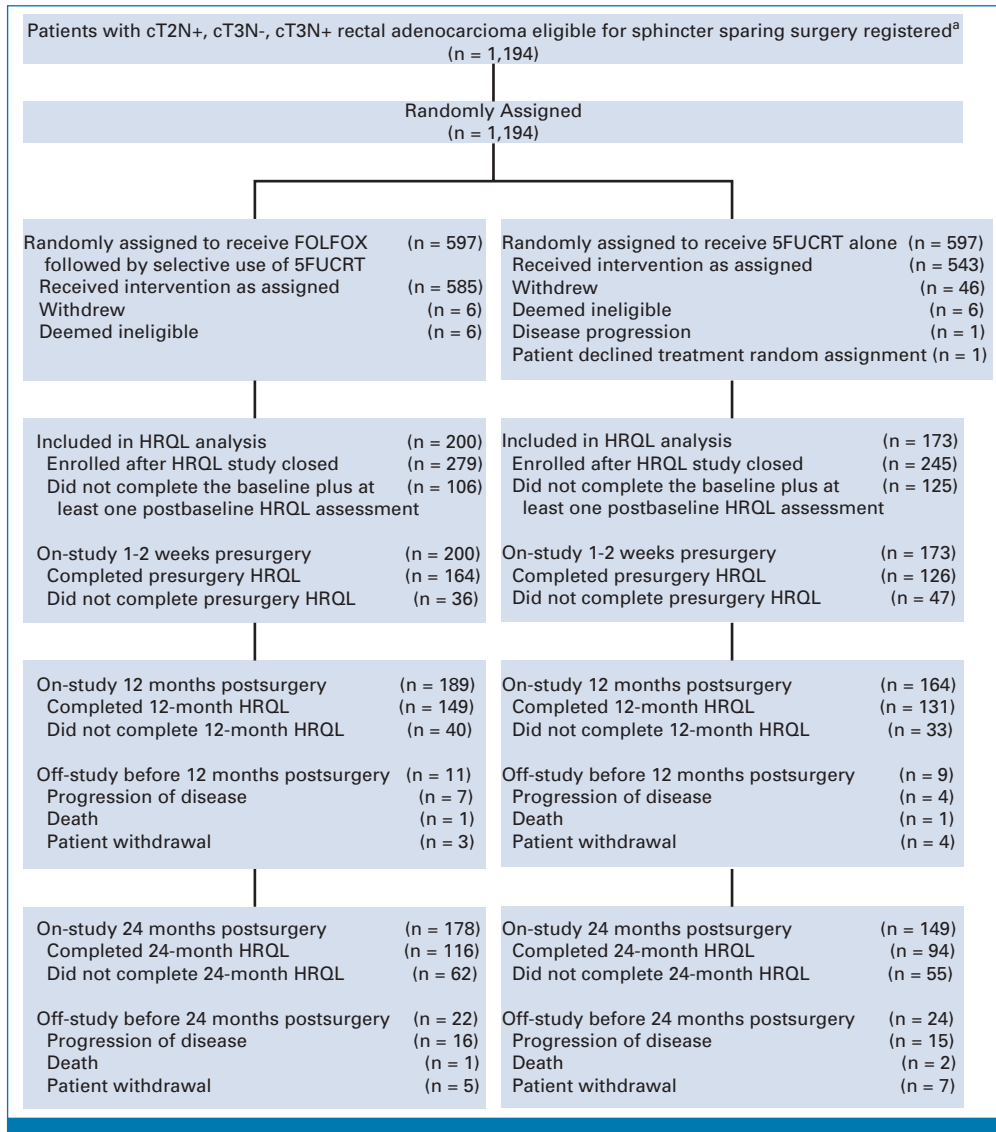


FIG A3. CONSORT diagram for HRQL measures evaluating bowel, bladder, sexual function, and overall HRQL. ^aSites were not required to provide screening logs during recruitment; therefore, the number of patients assessed for eligibility is not available. c, clinical; HRQL, health-related quality of life; N, node; T, tumor.