Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2017 April 01; 97(5): 924–930. doi:10.1016/j.ijrobp.2016.12.015.

Single Nucleotide Polymorphism TGF β 1 R25P Correlates with Acute Toxicity during Neoadjuvant Chemoradiotherapy in Rectal Cancer Patients

J. Joshua Smith, MD, PhD^{#,*}, Isaac Wasserman, MPH^{*,†}, Sarah A. Milgrom, MD[‡], Oliver S. Chow, MD^{*}, Chin-Tung Chen, MS^{*}, Sujata Patil, PhD[§], Karyn A. Goodman, MD[‡], and Julio Garcia-Aguilar, MD, PhD^{*}

^{*}Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York

[‡]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

[§]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York

[†]Icahn School of Medicine at Mount Sinai, New York, New York

[#] These authors contributed equally to this work.

Abstract

Purpose—To validate the finding of an association between single nucleotide polymorphisms (SNPs) and toxicity during chemoradiotherapy (CRT) in rectal cancer patients, in an independent population.

Methods and Materials—The cohort consisted of 165 patients who received CRT for rectal cancer from 2006 to 2012. Prospectively recorded toxicity information, graded according to the Common Terminology Criteria for Adverse Events version 3.0, was retrieved from the medical record. Additionally, a subset of 52 patients recorded their gastrointestinal symptoms weekly during CRT, using the 7-item Bowel Problems Scale. Deoxyribonucleic acid was extracted from normal tissue in the proctectomy specimens and screened for 3 SNPs: *XRCC1* R399Q, *XPB* K751Q, and *TGF β 1* R25P. Univariable and multivariable logistic regression models were constructed.

Results—The median radiation dose was 50.4 Gy, and all patients received concurrent chemotherapy. Toxicities measured by the Common Terminology Criteria for Adverse Events were closely associated with patient-reported outcomes for the patients who completed the 7-item Bowel Problems Scale. Grade 3 toxicity occurred during CRT in 14 patients (8%). All 14 patients had either *XRCC1* R399Q or *TGF β 1* R25P polymorphisms. The *TGF β 1* R25P polymorphism was significantly associated with grade 3 toxicity (odds ratio [OR] 3.47, $P=.04$) and, in patients who completed the Bowel Problems Scale, with grade 4 toxicity (OR 5.61, $P=.02$). The latter finding

Reprint requests to: Julio Garcia-Aguilar, MD, PhD, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065. Tel: (212) 639-5117; garciaaj@mskcc.org.

Conflict of interest: none.

persisted in a multivariable logistic regression model controlling for ethnicity, age, and gender (adjusted OR 1.83, $P=.02$).

Conclusions—We have validated the correlation between the *TGFβ1* R25P SNP and acute toxicity during CRT in an independent cohort using both clinician- and patient-reported toxicity. The information from our study could be used as a basis to formulate a prospective trial testing the utility of this SNP as a biomarker of acute toxicity during neoadjuvant treatment in locally advanced rectal cancer.

Introduction

Neoadjuvant chemoradiotherapy (CRT) is a standard component of multimodality care in locally advanced rectal cancer. The benefits of CRT include possible increased rates of sphincter preservation and improved locoregional disease control (1, 2). Additionally, patients who achieve a pathologic complete response to neoadjuvant CRT experience fewer distant recurrences and improved overall survival (3, 4). However, CRT is associated with acute and late morbidity, which may have a significant impact on patients' quality of life (5). Furthermore, acute toxicity—typically gastrointestinal side effects—may cause interruption or truncation of neoadjuvant therapy, limiting its full efficacy. Therefore, the ability to identify those patients who are likely to develop significant toxicity has clinical importance.

Numerous studies have reported correlations between germline genetic variation, reported as single nucleotide polymorphisms (SNPs), and normal tissue complication risk (6). Our group and others have investigated the association of SNPs with acute CRT-induced toxicity in rectal cancer patients in an attempt to identify factors that diminish the full efficacy of neoadjuvant treatment and adversely affect patient quality of life (7, 8). Previously, our group screened 132 rectal cancer patients for 22 SNPs in 17 genes. Of the 22 SNPs, 2 were correlated with toxicity during CRT that was grade 3 ($P<.05$), according to the Common Terminology Criteria for Adverse Events (CTCAE). These 2 SNPs were an arginine-to-glutamine substitution at codon 399 (Q399R) in *XRCC1* and a lysine-to-glutamine substitution at codon 751 (K751Q) in *XPD* (7). Additionally, another group of researchers screened 163 rectal cancer patients for 9 SNPs in *TGFβ1*. Of the 9 SNPs, 1 was associated with CTCAE grade 2 toxicity (8). This SNP, an arginine-to-proline substitution at codon 25 (R25P), was not included in the 22 SNPs in our previous work. In the present study we sought to validate the association of these 3 SNPs (*XRCC1* R399Q, *XPD* K751Q, and *TGFβ1* R25P) with acute toxicity during CRT in an independent cohort of 165 rectal cancer patients.

Methods and Materials

Patients

Patients who received long-course neoadjuvant CRT for rectal cancer at a single institution between October 2006 and September 2012 were identified ($n = 323$). Appropriate institutional review board approval and consent was obtained. Of these 323 patients, patients were excluded if they did not have tissue available for analysis, or they had not provided written consent stating that their tissue may be used for scientific investigation ($n = 120$).

Additionally, they were ineligible if their CRT was administered in the adjuvant ($n = 15$) or recurrent ($n = 17$) setting. Last, they were excluded if they did not have toxicity information recorded prospectively during the course of CRT ($n = 5$) or did not receive concurrent chemotherapy ($n = 1$). Ultimately, 165 patients were eligible.

Treatment

The recommended treatment consisted of long-course pelvic external beam radiation therapy (RT) with concurrent infusional 5-fluorouracil (5-FU; 225 mg/m², 5 days per week) or capecitabine (825 mg/m², twice daily, 5 days per week). The use of 5-FU versus capecitabine was decided by the treating medical oncologist, who considered multiple factors, including patient reliability.

Radiation therapy was provided with a conventional 3-field technique or with intensity modulated RT (IMRT), according to institutional practice. The decision of whether to use a 3-field approach or IMRT was made by the treating radiation oncologist, taking into account patient anatomy and body habitus. Beginning in 2007, IMRT planning was used for patients with low-lying rectal tumors, or those with a history of prior pelvic surgery resulting in a larger volume of small bowel in the pelvis. By 2011 the majority of patients were treated using IMRT to minimize dose to the normal tissues. The 3-field approach used posterior— anterior and opposed lateral fields to treat the whole pelvis to 45 Gy, followed by a 5.4-Gy boost to the rectal tumor, to give a total dose of 50.4 Gy at 1.8 Gy per fraction. With IMRT the pelvis was treated to 45 Gy at 1.8 Gy per fraction and the rectal tumor to 50 Gy at 2 Gy per fraction, using an integrated boost. Contouring was performed according to the Radiation Therapy Oncology Group consensus guidelines (9). Patients were treated in the prone position. An Aquaplast mold was used for immobilization. Some patients were also treated with a full bladder, to minimize the amount of small bowel in the field.

Toxicity assessment

During CRT each patient met with the treating physician at least once per week. Symptoms were assessed and graded according to the CTCAE version 3.0. Grades for the following symptoms were documented on a standardized form: fatigue, dermatitis, mucositis, nausea, vomiting, diarrhea, proctitis, and cystitis. This prospectively recorded toxicity information was retrieved from the electronic medical record for each patient in the cohort. Clinically significant toxicity was defined as any adverse event (AE) that occurred during CRT and was grade 3. This cut-off value was used to distinguish patients who experienced clinically significant CRT-related toxicity (requiring treatment with opioids) from those who experienced milder side effects.

For a subset of our validation cohort, patient-reported outcomes (PROs) were available, and we used these data to further substantiate the clinical relevance of the CTCAE grade 3 endpoint. Weekly during CRT, these patients completed the 7-item Bowel Problems Scale, a questionnaire originally designed to assess bowel symptoms in prostate cancer patients and later applied to rectal cancer patients (10-12). This questionnaire asks patients to score the frequency of diarrhea, bowel urgency, rectal tenderness or pain, hematochezia, abdominal cramping or pain, mucus passage from the rectum, and tenesmus. Patients assigned a score

to each symptom ranging from 0 (“not at all”) to 5 (“very frequently”). Patients who reported grade 4 or 5 toxicity at any point during their treatment (except if initially reported at baseline) were considered as having experienced 4+ patient-reported toxicity. Of the 165 patients in the validation cohort, 52 completed the PRO instrument. Those who did not complete the PRO instrument were mostly treated before September 2009. Before this time, the PRO instrument had not been implemented for routine use. We then compared clinician- and patient-reported gastrointestinal toxicity in this subset of patients to ensure that AEs, as graded by the clinician, were a meaningful endpoint from the patient’s perspective. In this subgroup, significant patient-reported toxicity was defined as 4 for at least one of the 7 symptoms on the Bowel Problems Scale.

Polymorphism screening

Formalin-fixed, paraffin-embedded normal tissue from the proximal margin of the proctectomy specimen was obtained for each patient. This tissue was likely outside the irradiated volume. Deoxyribonucleic acid was extracted using the QIAamp DNA FFPE Tissue Kit (Qiagen, Valencia, CA), according to the manufacturer’s instructions. The DNA was of good quality, as assessed by spectrophotometry. The SNPs *XRCC1* R399Q (rs25487), *XPD* K751Q (rs13181), and *TGFβ1* R25P (rs1800471), identified in previous studies (7, 8), were assessed using iPLEX SNP Genotyping with the MassArray platform (Sequenom, San Diego, CA).

Statistical analysis

Univariate analysis using Fisher’s exact test was performed to assess for an association between patient and treatment-related characteristics, the aforementioned SNPs of interest, and CTCAE grade 3 toxicity. Additionally, a multivariable logistic regression model was constructed to assess the association between variables with $P < .25$ in univariate analysis and patient-reported toxicity of grade 4. All analyses were performed using SAS v9.3 (SAS Institute, Cary, NC).

Results

Patient, disease, and treatment characteristics

Characteristics of the 165-patient cohort are summarized in Table 1. The median age at the time of CRT was 55 years. One hundred and two patients (62%) were male, and 135 (82%) were Caucasian. The majority of patients had stage III disease (81%). Patients were treated to a median dose of 50.4 Gy. Seventy-four patients (45%) were treated with IMRT and 91 (55%) with a 3-field technique. One hundred one patients received 5-FU, and 64 received capecitabine.

Toxicity information

In total, 14 of 165 patients (8%) developed at least 1 CTCAE grade 3 AE during CRT (Fig. 1). Twelve patients (7%) experienced grade 3 gastrointestinal toxicity, 2 patients (1%) experienced grade 3 genitourinary morbidity, and 1 patient (0.6%) experienced a grade 3 infectious complication. Included in these numbers is 1 patient who experienced grade 3 gastrointestinal and genitourinary morbidity. There were no grade 4 or 5 AEs.

Those who self-identified as being of either Asian or Black ethnicity had a significantly higher association with grade 3 toxicities ($P = .05$).

In the subset of 52 patients who completed the 7-item Bowel Problem Scale, 20 (38%) experienced “frequent” or “very frequent” (score 4 or 5) patient-reported gastrointestinal toxicity during CRT (12). All but 1 of these patients scored more than 1 symptom with a 4 or 5. These consisted of diarrhea ($n = 17$), bowel urgency ($n = 18$), rectal tenderness or pain ($n = 20$), hematochezia ($n = 7$), abdominal cramping or pain ($n = 19$), mucus passage from the rectum ($n = 11$), and tenesmus ($n = 12$). Every patient who had a CTCAE grade 3 AE during CRT and who filled out a PRO assessment reported “very frequent” gastrointestinal toxicity. Furthermore, of 42 patients who required opiate analgesics for proctitis symptoms, 12 of the 13 who completed PRO assessments reported scores of 4 or 5. Patient-reported significant gastrointestinal toxicity correlated with clinician-reported grade 3 gastrointestinal toxicity ($P < .05$), confirming that clinician-reported AEs according to the CTCAE scale were a clinically relevant endpoint in this cohort.

Association of SNPs with toxicity

The previously reported association of toxicity with the SNPs of interest was based on an autosomal dominant mode of inheritance, comparing patients with 1 or 2 minor alleles with those with none (7, 8). Therefore, our analysis was performed in the same fashion.

On univariate analysis, patients with at least 1 minor allele of *TGFβ1* R25P were more likely to experience grade 3 toxicity during CRT ($P = .05$), as shown in Table 2. There was a trend showing that patients with at least 1 minor allele of *XRCC1* R399Q experienced grade 3 toxicity during CRT (odds ratio [OR] 4.25, $P = .06$), but this did not reach statistical significance. Every patient with grade 3 toxicity had either *XRCC1* R399Q ($n = 12$) or *TGFβ1* R25P ($n = 5$) minor alleles. On the other hand, no significant association was identified between *XPB* K751Q and CRT-related morbidity. Thus, the association of *TGFβ1* R25P polymorphism with toxicity during CRT has been validated in this independent cohort.

There was also a trend showing that patients with at least 1 minor allele of *XRCC1* R399Q reported higher toxicity on average ($P = .09$). Although *XPB* K751Q was not found to be significant in the univariate analysis for toxicity, we did note an association with patient-reported outcome (Table 3). This finding was not further investigated because it did not persist in multivariable modeling. In contrast, patients with at least 1 minor allele of *TGFβ1* R25P had a statistically significant association with patient-reported toxicity of 4 on the Bowel Problems Scale (Table 3; both $P < .05$). Notably, even after controlling for ethnicity, age, and gender, *TGFβ1* R25P was associated with increased odds of patient-reported toxicity (OR 1.84, $P = .02$) (Table 4).

Association of SNPs with tumor response

An association has been reported between acute toxicity and rectal tumor regression in response to CRT (13). Therefore, we assessed for a correlation between each SNP and pathologic response rates. Interestingly, no significant correlation was identified.

Discussion

In this study we have validated the correlation of the *TGFβ1* R25P polymorphism with acute toxicity, as reported by both clinicians and patients, during neoadjuvant CRT in rectal cancer patients. Previous work by our group and others established an association between acute toxicity and *XRCC1* R399Q, *XPB* K751Q, and *TGFβ1* R25P (7, 8). When first published, these results were of interest; however, validation was critical, because these studies assessed multiple SNPs, leading to a high probability of false-positive associations. We have now validated the association in an independent cohort of 165 patients, demonstrating the robustness of the initial findings. In univariate analysis, patients with at least 1 minor allele of *TGFβ1* R25P experienced significantly higher rates of CTCAE grade 3 toxicity during the course of CRT. This finding was further confirmed in univariable and multivariable analyses using patient-reported toxicity of 4 on the Bowel Problems Scale. This confirmation in a completely independent cohort using both a clinician- and patient-reported toxicity scale supports the prior association and demonstrates the potential clinical utility of this polymorphism.

The severity of radiation toxicity varies widely, even when controlling for patient, disease, and treatment variables (14-16). In one study, more than 70% of individual variation remained unexplained after considering these factors (16), suggesting that genetic differences may be a major determinant. The ability to predict which patients are likely to develop severe radiation-induced toxicity would allow the clinician to tailor treatment recommendations to the individual. Although the 8% toxicity found in our study is within the range reported by some series (eg, Sauer et al [2] [12%] and Samuelian et al [17] [10%]), it is considerably lower than the 18% reported in our previous study (7). These findings may be explained by homogeneity in the present study population with a consistent treatment strategy, whereas prior studies have been multi-centric with a more heterogeneous spectrum of applied treatment strategies.

Studies of various cancer types indicate that patients may report a greater prevalence of cancer- and treatment-related symptoms than do clinicians (18-22). For example, it has been shown that clinicians tend to underreport proctitis during CRT for rectal cancer, compared with patients (10). Grading of subjective symptoms, such as proctitis, by the individual patient should be considered an essential standard. A subset of our cohort self-reported their gastrointestinal symptoms weekly during CRT, using the 7-item Bowel Problems Scale (10). We used this information to confirm not only that toxicity, as assessed by the clinician, was a meaningful endpoint from the patients' perspective, but also that the SNPs were associated with this outcome. The most common AE in our cohort was gastrointestinal toxicity. In the 31% of our cohort that completed the Bowel Problems Scale, clinician- and patient-reported significant gastrointestinal toxicities were correlated, confirming that this endpoint was clinically meaningful. To the best of our knowledge, this is the first identified association between an SNP and patient-reported toxicity during CRT. The availability of patient-reported symptom assessments is an important strength of our study.

Multiple theoretical mechanisms exist by which SNPs may influence treatment-related toxicity. For example, they may influence toxicity by affecting radiation-induced

inflammation. TGF β 1 is a cytokine that regulates various cellular functions, such as proliferation, differentiation, and angiogenesis (23). It has been implicated in post-RT injury. Genetic variants have been put forth as predictive markers for presurgical CRT in locally advanced rectal cancer, and some focus has been on those correlated with TGF β 1 (8). For example, sustained overexpression of TGF β 1 has been identified in various irradiated tissues (eg, lung, skin, intestine), and high expression levels have been associated with greater toxicity (24-26). The minor allele of *TGF β 1* R25P has been associated not only with acute morbidity in rectal cancer patients but also with late erectile dysfunction after RT for prostate cancer (27). This SNP is located in a region of the protein involved in its transport across the membrane of the endoplasmic reticulum. Further, the rectum may not be a special case in regard to this SNP because codon 25 has been implicated in breast tissues after RT (28), and a separate *TGF β 1*-related SNP (C-509T) has been correlated with severe esophagitis in patients with lung cancer treated with radiation. Clinical studies suggest that the SNP at codon 25 may influence TGF β 1 expression (29), providing a mechanism by which it could affect radiation toxicity. The identification of individuals who are predisposed to severe radiation toxicity due to TGF β 1 overexpression may lead to the development of novel therapeutic interventions. As an example, neutralizing antibodies and small-molecule inhibitors of TGF β 1 reduce radiation-induced lung injury in mice and rats (30, 31). An intervention that targets this pathway may be clinically useful in appropriately selected patients. The validation of the association between *TGF β 1* R25P polymorphism and CRT-associated toxicity in this independent cohort lends further support for investigation of this SNP in prospective trials as a predictor of radiation-induced toxicity.

XRCC1 acts as a scaffold for enzymes that catalyze DNA repair. The SNP *XRCC1* R399Q causes conformational changes in the BRCT1 domain of the protein, which interacts with multiple DNA repair enzymes, including BRCA1 (which may influence DNA repair efficiency). The conformational changes result in loss of secondary structural features, such as α -helices, which are necessary for protein—protein interactions (32). Thus, it may be hypothesized that this SNP could affect the coordination by XRCC1 of DNA repair in normal tissues, predisposing individuals to radiation toxicity. The *XRCC1* R399Q SNP identified from the initial study did not demonstrate statistical significance in this independent validation cohort ($P = .06$). This could suggest a trend toward clinical relevance; however, it could also mean that our initial discovery was a false positive. XRCC1 may still prove to be clinically relevant to toxicity but may not have reached statistical significance given the relatively small number of grade 3 events in this particular cohort. Interestingly, although the minor allele was associated with an increased risk of toxicity in rectal cancer patients in our initial study and that of Duldulao et al (7), it has been associated with a decreased risk of late fibrosis in breast cancer and head and neck cancer patients and late pneumonitis in lung cancer patients (33-35). These findings suggest that the *XRCC1* R399Q variant may have complex temporal or tissue-specific effects on the radiation response.

In this validation study, the association between *XPDK751Q* and acute toxicity (7) was observed in patient-reported data but not in CTCAE data. Again, it is possible that the prior discovery was a false-positive finding. The discrepant findings of the 2 studies could be attributed to differences in the patient populations, neoadjuvant therapy, grading of toxicity, or inadequate patient numbers to provide sufficient power needed to detect true differences.

Given the relative rarity with which grade 3 toxicity occurs, one limitation of this study is achieving adequate power to construct a multivariate model predicting acute toxicity. Attempts were made to expand the analysis to a less strict outcome of interest (2+ toxicity); however, the increase in power was outweighed by a loss of statistical significance. For example, after controlling for ethnicity, *TGFβ1* R25P was associated with 3.107 higher odds of 3+ toxicity ($P = .06$). Similarly, after controlling for ethnicity and age, the OR for *TGFβ1* R25P was 2.819 ($P = .10$). Nevertheless, we believe that despite the relatively rare number of events, our study validates not only previous studies, but also—more importantly—the correlation between patient-reported outcomes and various SNPs.

This work is subject to the limitations inherent in retrospective research. However, every effort was made to select a homogeneously treated patient population with accurate toxicity information. Therefore, only patients who were treated at a single institution and had prospectively recorded toxicity data were eligible. Further validation of these findings in prospective studies with adequate sample size is necessary to prove the clinical utility of the SNPs we and others have identified in preliminary studies. Future, prospective studies can also gather information about the dose-volume response of the area receiving radiation; a dose-volume parameter will be especially useful in crafting a predictive model.

The identification of genetic markers that predict normal tissue radiosensitivity is highly desirable. Predictors of treatment-related morbidity could contribute to therapeutic decision making. For example, clinicians may be less likely to recommend CRT for patients predicted to experience severe side effects. If they require CRT, these patients may derive particular benefit from new technologies that minimize integral dose. On the other hand, patients who are not predicted to experience severe toxicity may benefit from dose-escalated CRT to improve the likelihood of a pathologic complete response. Furthermore, insight into the mechanisms by which individuals experience radiation toxicity may lead to the development of targeted therapeutic interventions. Additional study is warranted to identify markers of normal tissue radiosensitivity. Robust predictors of toxicity may be used to guide treatment recommendations and maximize the therapeutic ratio of CRT. The information from our study could be used as a basis to formulate a prospective trial testing the utility of the SNP as a biomarker of acute toxicity during neoadjuvant treatment in locally advanced rectal cancer.

Acknowledgments

This work was supported in part by National Institutes of Health grants P30 CA008748 and R25 CA020449. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Additional support was provided by the Joel J. Roslyn Faculty Award, a limited-project grant from the American Society of Colon and Rectal Surgeons, and a grant from The Society of Memorial Sloan Kettering.

References

1. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: Increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg*. 2007; 246:693–701. [PubMed: 17968156]
2. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004; 351:1731–1740. [PubMed: 15496622]

3. de Campos-Lobato LF, Stocchi L, da Luz Moreira A, et al. Pathologic complete response after neoadjuvant treatment for rectal cancer decreases distant recurrence and could eradicate local recurrence. *Ann Surg Oncol*. 2011; 18:1590–1598. [PubMed: 21207164]
4. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: A pooled analysis of individual patient data. *Lancet Oncol*. 2010; 11:835–844. [PubMed: 20692872]
5. Ooi BS, Tjandra JJ, Green MD. Morbidities of adjuvant chemotherapy and radiotherapy for resectable rectal cancer: An overview. *Dis Colon Rectum*. 1999; 42:403–418. [PubMed: 10223765]
6. Barnett GC, West CM, Dunning AM, et al. Normal tissue reactions to radiotherapy: Towards tailoring treatment dose by genotype. *Nat Rev Cancer*. 2009; 9:134–142. [PubMed: 19148183]
7. Duldulao MP, Lee W, Nelson RA, et al. Gene polymorphisms predict toxicity to neoadjuvant therapy in patients with rectal cancer. *Cancer*. 2013; 119:1106–1112. [PubMed: 23096768]
8. Schirmer MA, Mergler CP, Rave-Frank M, et al. Acute toxicity of radiochemotherapy in rectal cancer patients: A risk particularly for carriers of the TGFB1 Pro25 variant. *Int J Radiat Oncol Biol Phys*. 2012; 83:149–157. [PubMed: 22000747]
9. 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; 74:824–830. [PubMed: 19117696]
10. Flores LT, Bennett AV, Law EB, et al. Patient-reported outcomes vs. clinician symptom reporting during chemoradiation for rectal cancer. *Gastrointest Cancer Res*. 2012; 5:119–124. [PubMed: 23077685]
11. Chen RC, Mamon HJ, Chen YH, et al. Patient-reported acute gastrointestinal symptoms during concurrent chemoradiation treatment for rectal cancer. *Cancer*. 2010; 116:1879–1886. [PubMed: 20166212]
12. Clark JA, Talcott JA. Symptom indexes to assess outcomes of treatment for early prostate cancer. *Med Care*. 2001; 39:1118–1130. [PubMed: 11567174]
13. Wolff HA, Gaedcke J, Jung K, et al. High-grade acute organ toxicity during preoperative radiochemotherapy as positive predictor for complete histopathologic tumor regression in multimodal treatment of locally advanced rectal cancer. *Strahlenther Onkol*. 2010; 186:30–35. [PubMed: 20082185]
14. Turesson I. Individual variation and dose dependency in the progression rate of skin telangiectasia. *Int J Radiat Oncol Biol Phys*. 1990; 19:1569–1574. [PubMed: 2262383]
15. Bentzen SM, Overgaard J. Patient-to-patient variability in the expression of radiation-induced normal tissue injury. *Semin Radiat Oncol*. 1994; 4:68–80. [PubMed: 10717093]
16. Turesson I, Nyman J, Holmberg E, et al. Prognostic factors for acute and late skin reactions in radiotherapy patients. *Int J Radiat Oncol Biol Phys*. 1996; 36:1065–1075. [PubMed: 8985028]
17. Samuelian JM, Callister MD, Ashman JB, et al. Reduced bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys*. 2012; 82:1981–1987. [PubMed: 21477938]
18. Basch E, Iasonos A, McDonough T, et al. Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: Results of a questionnaire-based study. *Lancet Oncol*. 2006; 7:903–909. [PubMed: 17081915]
19. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: Relationships with clinical outcomes. *J Natl Cancer Inst*. 2009; 101:1624–1632. [PubMed: 19920223]
20. Fromme EK, Eilers KM, Mori M, et al. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. *J Clin Oncol*. 2004; 22:3485–3490. [PubMed: 15337796]
21. Butler L, Bacon M, Carey M, et al. Determining the relationship between toxicity and quality of life in an ovarian cancer chemotherapy clinical trial. *J Clin Oncol*. 2004; 22:2461–2468. [PubMed: 15197209]
22. Stephens RJ, Hopwood P, Girling DJ, et al. Randomized trials with quality of life endpoints: Are doctors' ratings of patients' physical symptoms interchangeable with patients' self-ratings? *Qual Life Res*. 1997; 6:225–236. [PubMed: 9226980]

23. Pickup M, Novitskiy S, Moses HL. The roles of TGFbeta in the tumour microenvironment. *Nat Rev Cancer*. 2013; 13:788–799. [PubMed: 24132110]
24. Zhao L, Wang L, Ji W, et al. Elevation of plasma TGF-beta1 during radiation therapy predicts radiation-induced lung toxicity in patients with non-small-cell lung cancer: A combined analysis from Beijing and Michigan. *Int J Radiat Oncol Biol Phys*. 2009; 74:1385–1390. [PubMed: 19231104]
25. Randall K, Coggle JE. Long-term expression of transforming growth factor TGF beta 1 in mouse skin after localized beta-irradiation. *Int J Radiat Biol*. 1996; 70:351–360. [PubMed: 8800206]
26. Wang J, Zheng H, Sung CC, et al. Cellular sources of transforming growth factor-beta isoforms in early and chronic radiation enteropathy. *Am J Pathol*. 1998; 153:1531–1540. [PubMed: 9811345]
27. Peters CA, Stock RG, Cesaretti JA, et al. TGFB1 single nucleotide polymorphisms are associated with adverse quality of life in prostate cancer patients treated with radiotherapy. *Int J Radiat Oncol Biol Phys*. 2008; 70:752–759. [PubMed: 17689884]
28. Andreassen CN, Alsner J, Overgaard M, et al. Risk of radiation-induced subcutaneous fibrosis in relation to single nucleotide polymorphisms in TGFB1, SOD2, XRCC1, XRCC3, APEX and ATM—dash—a study based on DNA from formalin fixed paraffin embedded tissue samples. *Int J Radiat Biol*. 2006; 82:577–586. [PubMed: 16966185]
29. Guo Z, Binswanger U, Knoflach A. Role of codon 10 and codon 25 polymorphisms on TGF-beta 1 gene expression and protein synthesis in stable renal allograft recipients. *Transplant Proc*. 2002; 34:2904–2906. [PubMed: 12431652]
30. Anscher MS, Thrasher B, Rabbani Z, et al. Antitransforming growth factor-beta antibody 1D11 ameliorates normal tissue damage caused by high-dose radiation. *Int J Radiat Oncol Biol Phys*. 2006; 65:876–881. [PubMed: 16751069]
31. Flechsig P, Dadrich M, Bickelhaupt S, et al. LY2109761 attenuates radiation-induced pulmonary murine fibrosis via reversal of TGF-beta and BMP-associated proinflammatory and proangiogenic signals. *Clin Cancer Res*. 2012; 18:3616–3627. [PubMed: 22547771]
32. Monaco R, Rosal R, Dolan MA, et al. Conformational effects of a common codon 399 polymorphism on the BRCT1 domain of the XRCC1 protein. *Protein J*. 2007; 26:541–546. [PubMed: 17899335]
33. Andreassen CN, Alsner J, Overgaard M, et al. Prediction of normal tissue radiosensitivity from polymorphisms in candidate genes. *Radiother Oncol*. 2003; 69:127–135. [PubMed: 14643949]
34. Alsbeih G, Al-Harbi N, Al-Hadyan K, et al. Association between normal tissue complications after radiotherapy and polymorphic variations in TGFB1 and XRCC1 genes. *Radiat Res*. 2010; 173:505–511. [PubMed: 20334523]
35. Kelsey CR, Jackson IL, Langdon S, et al. Analysis of single nucleotide polymorphisms and radiation sensitivity of the lung assessed with an objective radiologic endpoint. *Clin Lung Cancer*. 2013; 14:267–274. [PubMed: 23313170]

Summary

Our group and others have identified an association between single nucleotide polymorphisms and acute toxicity in patients receiving neoadjuvant chemoradiotherapy for rectal cancer. The present study validated these correlations in an independent cohort of 165 patients.

Fig. 1.
Types of grade 3 Common Terminology Criteria for Adverse Events toxicity in the patient cohort. One patient reported both gastrointestinal and genitourinary grade 3 toxicity.

Table 1

Patient, disease, treatment, and toxicity information

Characteristic	Overall (n = 165)	No grade 3 toxicity (n = 151)	Grade 3 toxicity (n = 14)	<i>P</i> *
Age (y), median (range)	55 years (24-89)	55 (24-89)	49 (38-71)	.098
Gender				
Male	102 (62)	91 (60)	11 (79)	.253
Female	63 (38)	60 (39)	3 (21)	
Self-reported ethnicity				
Caucasian	135 (82)	128 (85)	7 (50)	.006
Black	13 (8)	10 (7)	3 (21)	
Asian	17 (10)	13 (9)	4 (29)	
Clinical stage				
I	10 (6)	10 (7)	0 (0)	.517
II	21 (13)	18 (12)	3 (21)	
III	134 (81)	123 (81)	11 (79)	
RT dose (Gy), median (range)	50.4 (37.8-56)	50.4 (37.8-56)	50.4 (50-50.4)	.574
RT technique				
IMRT	74 (45)	69 (45)	5 (36)	.581
3-Field	91 (55)	82 (54)	9 (64)	

Abbreviations: IMRT = intensity modulated radiation therapy; RT = radiation therapy.

Values are number (percentage) unless otherwise noted.

* Fisher's exact test.

Table 2

Univariable analysis for association with grade 3 toxicity

SNP	Genotype	Grade 3 toxicity, n (%)	OR	(95% CI)	P
<i>XRCC1</i> R399Q	G/G	2/64 (3)	1.00	-	-
	G/A or A/A	12/101 (12)	4.25	(0.92-19.64)	.064
<i>XPD</i> K751Q	T/T	7/67 (10)	1.00	-	-
	T/G or G/G	7/98 (7)	0.67	(0.22-2.01)	.475
<i>TGFβ1</i> R25P	G/G	9/139 (6)	1.00	-	-
	G/C or C/C	5/26 (19)	3.47	(1.06-11.35)	.04

Abbreviations: CI = confidence interval; OR = odds ratio.

Univariable logistic regression with CTCAE grade 3 toxicity as outcome.

Table 3

Univariable analysis for association with grade 4 patient-reported toxicity

SNP	Genotype	Grade 3 toxicity, n (%)	OR	(95% CI)	P
<i>XRCC1</i> R399Q	G/G	7/26 (24)	1.00	-	-
	G/A or A/A	13/26 (50)	2.71	(0.85-8.65)	.09
<i>XPD</i> K751Q	T/T	14/26(54)	1.00	-	-
	T/G or G/G	6/26 (23)	0.26	(0.08-0.85)	.03
<i>TGFβ1</i> R25P	G/G	12/40 (30)	1.00	-	-
	G/C or C/C	8/12 (67)	4.67	(1.18-18.50)	.03

Abbreviations as in Table 2.

Univariable logistic regression with Bowel Problems Scale grade 4 toxicity as outcome.

Table 4

Multivariable analysis for association with grade 4 patient-reported toxicity

Variable	β	OR	P
<i>TGFβ1</i> R25P	1.83	6.28	.02
Ethnicity	0.99	2.69	.009
Age	0.003	1.00	.91
Male gender	-1.24	0.29	.09

Abbreviation as in Table 2.

Multivariable logistic regression controlling for ethnicity, age, and gender, with Bowel Problems Scale grade 4 toxicity as outcome.