Preoperative radiation (PRT) significantly reduces local recurrences (LR) in rectal cancer. Identifying patients at risk for LR allows for refinement in patient selection for PRT. We previously demonstrated a PIK3CA mutation prevalence of 7.9% in rectal cancer and a strong association with increased risk of LR in nonirradiated stage I to III rectal cancer patients (5-year risks, 27.8% vs 9.4%; \( P = 0.006 \)) from the total mesorectal excision (TME) trial (1), in which resectable rectal cancer patients were randomized for TME surgery only or short-term PRT (5 Gy) followed by surgery (2). We have now performed further analysis in the irradiated patients to investigate whether PIK3CA mutant patients benefit from PRT in preventing LR.

The 5-year LR risks were 11.3% (74/675) and 5.2% (32/626) for nonirradiated and irradiated stage I to III patients, respectively, for an HR of 2.32 (95% CI: 1.53–3.52, \( P < 0.001; \) ref. 3). PIK3CA mutation in exons 9 and 20 was analyzed on 30 tumor samples out of all 32 patients who developed an LR in the irradiated arm. We previously found 20.8% (5/24) PIK3CA mutations in the nonirradiated LR patients (1), whereas we now identified 6.7% (2/30) mutations in the irradiated LR patients. The interaction odds ratio (OR) of 0.3 (95% CI: 0.05–1.56) revealed that the relative benefit from PRT versus non-PRT with regard to LR was 3 times greater among carriers (PIK3CA mutation) compared with noncarriers. Although the difference is not statistically significant, it suggests that PIK3CA mutant patients seem to benefit from PRT in preventing LR.

The OR between genotype and treatment among LR patients is an unbiased and efficient estimate of the interaction OR if the outcome is rare and treatment and genotype are independent (4, 5). Both assumptions are fulfilled in this randomized trial, and genotyping the 643 LR-negative patients in the irradiated arm is therefore not necessary for the assessment of the interaction. However, main effect HRs as well as absolute survival cannot be estimated in the case-only design, and our analysis is still lacking power due to the low LR rate and low mutation frequency. In fact, 1,006 to 1,328 stage I to III patients would be required in each arm to increase the power to an 80% to 90% level.

Given that the TME trial is 1 of the largest rectal cancer trials, our observation suggests and provides some evidence that PIK3CA mutations may not only be a prognostic factor, as previously shown by us and others (1), but may also be predictive with regard to PRT benefit. If this is confirmed in further studies, it would mean that selection of patients for PRT could be based on biopsy proven mutant cancers and could thereby largely reduce unnecessary radiotherapy morbidity in the low-risk rectal cancer patients.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Acknowledgments
We thank Marie-Louise F. van Velthuysen and Eliane C.M. Zeestraten for their continued contribution to the TME trial translational research and Michael Hauptmann for his valuable suggestions in statistics. We thank Izabela Mikolajewska-Hanclich and the Sequencing Core Facility in the Netherlands Cancer Institute for DNA mutation analysis.

Grant Support
This work was supported by Dutch Cancer Society grant NKI 2007-3945.

Received 05/27/2010; revised 07/26/2010; accepted 08/20/2010; published online 12/15/2010.

References
Do Rectal Cancer Patients with \textit{PIK3CA} Mutations Benefit from Preoperative Radiotherapy with Regard to Local Recurrences?

Youji He, Laura J. Van't Veer, Marta Lopez-Yurda, et al.