Nonoperative management (watch and wait) is an emerging novel strategy for organ preservation in patients with rectal cancer. Nonoperative management for rectal cancer can be renamed as “surveillance with selective delayed surgery,” in which patients who achieved a clinical complete response after neoadjuvant therapy do not immediately receive surgery but undergo surveillance with an option to convert to delayed surgery when residual cancer cells develop an evident local regrowth. With improved complete response rates in total neoadjuvant therapy (TNT), physicians have more opportunities to counsel patients and decide whether to proceed with or postpone surgery. Conventional static clinical calculators or staging systems to estimate risk of recurrence are not applicable in nonoperative management in which pathologic parameters are not available and patients are expected to migrate from a nonoperative to operative management for salvage surgery. The work by Weiser et al in JAMA Network Open developed a novel clinical calculator in rectal cancer treated with TNT that incorporated a principle of conditional survival to provide dynamic estimates of recurrence by timeline and by treatment type (upfront surgery or nonoperative management with/without delayed surgery). The study has high originality in incorporating a concept of time lapse in a model to allow dynamic migration of treatment strategy from nonoperative management to delayed surgery. The created calculator provides objective conditional survival estimates of operative vs nonoperative management at any time during follow-up.

This retrospective observational study was conducted in a single comprehensive cancer center, and the authors have been taking a global leadership role in developing TNT and nonoperative management for rectal cancer. The study cohort was well qualified with a long follow-up period under an established clinical protocol of nonoperative management including the neoadjuvant regimens, diagnostic criteria of complete response, decision to proceed with nonoperative management, and a surveillance program. Another strength of the study was that all patients underwent total neoadjuvant therapy (induction systemic FOLFOX/CAPOX followed by chemoradiotherapy), a modern neoadjuvant approach with a higher response rate compared to conventional chemoradiotherapy alone. Adding to successful development of a novel dynamic model for estimating a recurrence risk in nonoperative and operative management of rectal cancer, the study provided a couple of important findings.

First, recurrence-free survival was similar regardless of the interval from TNT to salvage surgery in patients who developed local regrowth after nonoperative management. The findings appear to support oncologic safety of delayed surgery after nonoperative management without increasing a risk of distant metastasis under an appropriate surveillance protocol. However, it should be noted that the study was conducted by a multidisciplinary team with expertise in nonoperative management and under a meticulous surveillance protocol to identify and salvage a local regrowth. The study cohort underwent proctoscopy and magnetic resonance imaging (MRI) every 3 to 6 months for the first 2 years and every 6 to 12 months for the next 3 years in addition to annual computed tomography scans. It should be noted that nonoperative management without an appropriate surveillance protocol might result in poorer oncologic outcomes.

Second, migration to delayed surgery after nonoperative management due to regrowth occurred mostly (40 of 54 patients) within the first 12 months after completion of TNT. According to a study from the International Watch and Wait Database, the probability of remaining free from local
regrowth for additional 2 years if a patient had a sustained clinical complete response for 1 year was 88.1% and for 3 years was 97.3%. These data seem to support the need for intensive surveillance at least during the first 12 months.

Third, a conditional recurrence-free survival of the nonoperative management cohort at 12 months from completion of TNT approached more closely to the true complete responders who had undergone surgery and had a pathologic complete response than the nonoperative management cohort at 3 months from completion of TNT. Consistent with this, accuracy of the model improved over time from 3 months to 12 months after TNT. In the International Watch and Wait Database study, patients with sustained clinical complete response without distant metastasis for 1 year had a low risk of further developing distant metastasis, with 93.8% conditional distant metastasis-free survival. In light of these findings, 12 months after TNT seems to be a reasonable time point to reevaluate a risk of recurrence in nonoperative management.

What can we expect after this study? With an increased number of patients undergoing nonoperative management, subsequent busy surveillance with a scope is an emerging issue in the clinics for physicians and patients. Improved model performance over time in this study highlights the importance of reassessing oncologic risk and reformulating a surveillance plan at 12 months after TNT once patients and physicians can foresee the future more clearly. Can we deescalate surveillance with a longer interval for a low-risk group? A prospective study is needed to investigate safety of less intensive surveillance using a dynamic clinical calculator at 12 months after TNT.

Patients who achieve complete response after neoadjuvant therapy have favorable prognosis, and event number of recurrence is limited in a single-center study. The clinical calculator presented in this study needs external validation in a larger multicenter cohort. Particularly, given diverse TNT regimens used in modern practice with short-course radiotherapy or triplet systemic chemotherapy, validation and revision of the calculator would be needed in the cohorts treated with different TNT regimens. This study provides a strong message that clinical calculators need continued improvement and updating to fit current clinical practice. Decision-making in modern multidisciplinary treatment for rectal cancer needs comprehensive assessment of various risk factors such as molecular profiling (eg, microsatellite status, KRAS status), radiologic malignant features on MRI (eg, extramural venous invasion, circumferential resection margin, lateral pelvic lymph node) and posttreatment circulating tumor DNA. Further efforts are encouraged to evolve a prediction model.

ARTICLE INFORMATION
Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2022 Konishi T. JAMA Network Open.
Corresponding Author: Tsuyoshi Konishi, MD, PhD, Associate Professor, Division of Surgery, Department of Colon and Rectal Surgery, The University of Texas MD Anderson Cancer Center, 1400 Pressler St, Unit 1484, Houston, TX 77030 (tkonishi@mdanderson.org).
Author Affiliation: Division of Surgery, Department of Colon and Rectal Surgery, The University of Texas MD Anderson Cancer Center, Houston.
Conflict of Interest Disclosures: None reported.
REFERENCES


