JNCI J Natl Cancer Inst (2020) 112(8): djaa005

doi: 10.1093/jnci/djaa005
First published online January 13, 2020
Editorial

EDITORIAL

Nonoperative Management of Rectal Cancer Shows Cost-Effectiveness, but Can Comparative Effectiveness Be Established?

Paul B. Romesser , MD, PhD,[1] Grace Smith, MD, PhD, MPH,[2] Christopher H. Crane, MD[1,*]

[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA and [2]MD Anderson Cancer Center, Department of Radiation Oncology, Houston, TX, USA

*Correspondence to: Christopher H. Crane, MD, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, USA (e-mail: cranec1@mskcc.org).

Locally advanced rectal cancer (LARC) treatment traditionally includes preoperative chemoradiation, radical surgery, and postoperative chemotherapy (1). Although highly effective, this standard leads to substantial rates of long-term morbidity, including permanent colostomy, low anterior resection syndrome, urinary dysfunction, and sexual dysfunction (1–3). Patients with mid- and low rectal cancers who achieve a clinical complete response (cCR) present a dilemma to the thoughtful surgeon because the preoperative discussion must include the very real possibility that the specimen would not contain cancer. Patients' refusal of radical surgery and surgeons' desire to balance oncologic outcomes with quality of life (QOL) have led investigators to embark on organ preservation strategies in complete responders. Although the nonoperative management (NOM, also known as watch-and-wait) strategy has been increasingly accepted, radical surgery is still considered the standard, and randomized evidence determining the comparative effectiveness of NOM remains to be established. In this issue of the Journal, Miller and colleagues evaluate other important considerations of effectiveness, specifically the cost-effectiveness and quality-adjusted survival of NOM (4).

The NOM strategy was initially introduced by Habr-Gamma and colleagues in 2004 (5). Patients with LARC who achieved a substantial clinical response to chemoradiation were offered NOM if they were agreeable to stringent monthly clinical reassessments (5). The 5-year overall survival and disease-free survival of the 72 patients who underwent NOM were 100% and 92%, respectively (5). Importantly, all of the patients with regrowth of the primary tumor were successfully salvaged with mesorectal excision. Although initially controversial, this pioneering work provided proof of principle that the majority of patients who achieve a cCR to preoperative chemoradiation can be managed without radical surgery. Multiple groups have subsequently reported 70–80% durable local disease control in LARC complete responders on NOM, and close surveillance has led to timely salvage surgery with no clear oncologic disadvantage (6–13).

Miller and colleagues developed a decision-analytic Markov model to evaluate cost-effectiveness of this strategy compared with standard radical surgery (4). Importantly, with respect to clinical interpretation and application, this analysis includes only patients who have achieved cCR to neoadjuvant therapy. NOM was found to have incremental cost savings of $28 500 and $32 100 and incremental benefit in quality-adjusted-life years of 0.527 and 0.601 compared with low anterior resection and abdominoperineal resection, respectively. The main cost differences were predominantly driven by the upfront cost of surgery, which was absent or deferred in patients managed with NOM and statistically significantly offset the added cost of enhanced screening. Results were presented from a US payer perspective and validate similar findings demonstrating cost-effectiveness of NOM from a UK payer perspective (14). The model by Miller and colleagues (4) further suggests quality-adjusted survival benefit from NOM, based on population-based QOL and health utility data. This finding highlights the need for ongoing studies of NOM to detail patient-reported QOL measures that encompass pain, symptoms, body image, and sexual function, data that will ultimately be needed to inform individual treatment decision making about NOM for clinically eligible patients. In the setting of unavoidably increasing limits on health-care resources, the authors' finding of the incremental cost savings of NOM after cCR also suggests that developing therapeutic strategies to optimize and expand cCR rates could substantially affect not only individual patient outcomes but also public health.

There is considerable interest in expanding the pool of eligible patients for organ preservation by increasing the cCR. One strategy that appears to be successful is giving the adjuvant chemotherapy component of treatment before surgery, either before chemoradiation (induction) or after completion of chemoradiation (consolidation). This strategy has become known

Received: December 23, 2019; **Accepted:** January 7, 2020

as total neoadjuvant therapy (TNT). The TIMING trial (NCT00335816) showed that delivering increasing number of cycles (zero, two, four, or six cycles) of consolidative FOLFOX in sequential cohorts of patients with LARC increased the pathologic complete response (pCR) rate to 25%, 30%, and 38%, respectively, compared with 18% for chemoradiation alone, suggesting that giving all of the chemotherapy upfront while increasing the time to surgery increases the pCR (15). A recent meta-analysis of 10 comparative studies demonstrated that TNT increased the likelihood of a pCR by 39% (16). An ongoing, randomized phase II trial of TNT compares sequencing 5-Fluorouracil, Leucovorin, and Oxaliplatin before or after chemoradiation, in which patients with LARC who achieve a cCR are offered NOM (NCT02008656) (17). A similar trial has recently been reported with planned surgery showing a slight increase in pCR with consolidation (18). Efforts also continue in earnest to develop selective radiosensitizers that may improve pCR. NRG-GI002 is an ongoing phase II study evaluating sequential experimental arms integrating radiosensitizers into a TNT platform in patients with high-risk LARC. (NCT02921256). Although TNT strategies have resulted in higher response rates, approximately two-thirds of patients with LARC still require radical surgery (19). As efforts continue, better regimens will likely emerge that will improve complete response rates, which will change the proportion of patients eligible for NOM and ultimately increase the acceptance of the NOM approach. Although the results from Miller et al. will not likely persuade nonbelievers, they do provide an important contribution to our understanding of the advantages of a NOM strategy (4).

Although the concept of organ preservation for patients with LARC is appealing, prospective randomized cooperative group studies are needed to confirm the oncologic noninferiority of NOM and the applicability of NOM to routine community oncological practice. In Brazil, Cecconello and colleagues are conducting a randomized phase II trial comparing the 3-year disease-free survival of NOM and radical surgery in LARC patients who achieve a cCR after preoperative chemoradiation (NCT02052921) (20). Although this is an important first step, widespread adoption of NOM will likely be limited and the use of NOM will likely remain controversial until randomized phase III data demonstrate noninferiority and improved patient reported outcomes. The feasibility of randomizing patients to radical surgery vs organ preservation will likely be challenging in the United States because of patient preferences either for or against radical surgery. Nevertheless, outcomes data from prospective randomized trials are critical to provide the knowledge needed to harmonize the insights gained from a cost-effectiveness model of NOM with real-world clinical practice.

Notes

P. B. Romesser is a consultant for EMD Serono for work on radiation sensitizers. The other authors have no disclosures.

References

1. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351(17):1731–1740.
2. Marijnen CA. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol*. 2002;20(3):817–825.
3. Peeters KCMJ, van de Velde CJH, Leer JWH, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients–a Dutch colorectal cancer group study. *J Clin Oncol*. 2005;23(25):6199–6206.
4. Miller JA, Wang H, Chang DT, Pollom EL. Cost-effectiveness and quality-adjusted survival of watch-and-wait after complete response to chemoradiotherapy for rectal cancer. *J Natl Cancer Inst*. 2020. pii: djaa003. doi: 10.1093/jnci/djaa003. [Epub ahead of print]
5. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg*. 2004;240(4):711–717; discussion 717–718.
6. Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. *JAMA Oncol*. 2019;5(4):e185896.
7. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet*. 2018;391(10139):2537–2545.
8. Lim L, Chao M, Shapiro J, et al. Long-term outcomes of patients with localized rectal cancer treated with chemoradiation or radiotherapy alone because of medical inoperability or patient refusal. *Dis Colon Rectum*. 2007;50(12):2032–2039.
9. Maas M, Beets-Tan RGH, Lambregts DMJ, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol*. 2011;29(35):4633–4640.
10. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2017;2(7):501–513.
11. Appelt AL, Pløen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. *Lancet Oncol*. 2015;16(8):919–927.
12. Hupkens BJP, Martens MH, Stoot JH, et al. Quality of life in rectal cancer patients after chemoradiation: watch-and-wait policy versus standard resection-a matched-controlled study. *Dis Colon Rectum*. 2017;60(10):1032–1040.
13. Habr-Gama A, Lynn PB, Jorge JMN, et al. Impact of organ-preserving strategies on anorectal function in patients with distal rectal cancer following neoadjuvant chemoradiation. *Dis Colon Rectum*. 2016;59(4):264–269.
14. Rao C, Sun Myint A, Athanasiou T, et al. Avoiding radical surgery in elderly patients with rectal cancer is cost-effective. *Dis Colon Rectum*. 2017;60(1):30–42.
15. Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. *Lancet Oncol*. 2015;16(8):957–966.
16. Petrelli F, Trevisan F, Cabiddu M, et al. Total neoadjuvant therapy in rectal cancer: a systematic review and meta-analysis of treatment outcomes. *Ann Surg*. 2019;271(3):440–448.
17. Smith JJ, et al. Organ preservation in rectal adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management. *BMC Cancer*. 2015;15:767.
18. Fokas E, Allgäuer M, Polat B, et al. Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12. *J Clin Oncol*. 2019;37(34):3212–3222.
19. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. *JAMA Oncol*. 2018;4(6):e180071.
20. Nahas SC, Rizkallah Nahas CS, Sparapan Marques CF, et al. Pathologic complete response in rectal cancer: can we detect it? Lessons learned from a proposed randomized trial of watch-and-wait treatment of rectal cancer. *Dis Colon Rectum*. 2016;59(4):255–263.