Extended Intervals after Neoadjuvant Therapy in Locally Advanced Rectal Cancer: The Key to Improved Tumor Response and Potential Organ Preservation

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BACKGROUND: Many rectal cancer patients experience tumor downstaging and some are found to achieve a pathologic complete response (pCR) after neoadjuvant chemoradiotherapy (nCRT). Previous data suggest that there is an association between the time interval from nCRT completion to surgery and tumor response rates, including pCR. However, these studies have been primarily from single institutions with small sample sizes. The aim of this study was to examine the relationship between a longer interval after nCRT and pCR in a nationally representative cohort of rectal cancer patients.

STUDY DESIGN: Clinical stage II to III rectal cancer patients undergoing nCRT with a documented surgical resection were selected from the 2006 to 2011 National Cancer Data Base. Multivariable logistic regression analysis was used to assess the association between the nCRT–surgery interval time (<6 weeks, 6 to 8 weeks, >8 weeks) and the odds of pCR. The relationship between nCRT–surgery interval, surgical morbidity, and tumor downstaging was also examined.

RESULTS: Overall, 17,255 patients met the inclusion criteria. An nCRT–surgery interval time >8 weeks was associated with higher odds of pCR (odds ratio [OR] 1.12, 95% CI 1.01 to 1.25) and tumor downstaging (OR 1.11, 95% CI 1.02 to 1.25). The longer time delay was also associated with lower odds of 30-day readmission (OR 0.82, 95% CI 0.70 to 0.92).

CONCLUSIONS: An nCRT–surgery interval time >8 weeks results in increased odds of pCR, with no evidence of associated increased surgical complications compared with an interval of 6 to 8 weeks. These data support implementation of a lengthened interval after nCRT to optimize the chances of pCR and perhaps add to the possibility of ultimate organ preservation (nonoperative management). (J Am Coll Surg 2015;221:430–440. © 2015 by the American College of Surgeons)

Colorectal cancer is the third most frequently diagnosed malignancy in the US, with approximately 40,000 new cases of rectal cancer annually.[1] Multimodal therapy, which consists of chemoradiation followed by surgery in the form of a total mesorectal excision, has become the standard of care for locally advanced rectal cancer (stage II and stage

Disclosure Information: Nothing to disclose.

Disclosures outside the scope of this work: Dr Wexner is a consultant for CareFusion, Edwards LifeSciences, GI View, Incontinence Devices Inc, Johnson & Johnson Medical, Karl Storz Endoscopy-America, Lexington Medical, LifeBond, Mederi Therapeutics, Medtronic, Novadaq, Precision Therapeutics, and Renew Medical. Dr Wexner holds patents and receives royalties from Covidien, Karl Storz Endoscopy-America, novoGI, and Unique Surgical Innovations. Dr Wexner has stock and stock options for Asana Medical, LifeBond, CRH Medical, EZ Surgical, Neatstitch, and novoGI. All other authors have nothing to disclose.

Received February 18, 2015; Revised April 6, 2015; Accepted April 9, 2015.

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http://dx.doi.org/10.1016/j.jamcollsurg.2015.04.010
ISSN 1072-7515/15

Abbreviations and Acronyms
NCDB = National Cancer Data Base
nCRT = neoadjuvant chemoradiotherapy
OR = odds ratio
pCR = pathologic complete response

III disease). Neoadjuvant chemoradiotherapy (nCRT) has been shown to significantly reduce the local recurrence rate and has been associated with an increase in the overall survival rate.[2] Despite this, a large percentage of patients in the US still undergo a total proctectomy (abdominoperineal resection) with permanent end colostomy. In contrast, few patients undergo rectal-preserving treatments, such as local excision, or achieve complete tumor disappearance and thereby avoid any surgery whatsoever.[3,4]

The traditional North American paradigm for delivery of neoadjuvant therapy in rectal cancer consists of 45 to 50.4 Gray (Gy) delivered in 25 to 28 fractions, with sensitizing continuous fluorouracil infusion or capecitabine administered throughout the radiation course. Patients then undergo surgical resection approximately 6 to 8 weeks after finishing nCRT.[5,6] This recommendation is based primarily on the Lyon R90-01 trial, which found improved clinical tumor response and pathologic downstaging in patients undergoing surgery 6 to 8 weeks after radiation therapy compared with those with a 2-week interval.[7] As a result of neoadjuvant therapy, many patients experience significant tumor downstaging, and some are found to have a pathologic complete response (pCR) on histologic examination of the resected specimen.[8,9] There is a growing body of data that suggests that pCR is significantly associated with a reduction in both local and systemic recurrence and superior overall survival compared with that in patients with partial or no response.[10] Although pCR may potentially be a marker for favorable tumor biology, it is still imperative in clinical practice to attempt to maximize our chances of attaining pCR. This is especially true if a nonoperative or observational approach is to be considered.

So there is great clinical interest in identifying factors that may increase tumor regression and enhance the pCR rate. This has prompted some researchers to examine the relationship between the length of time between nCRT completion and surgery (nCRT–surgery interval) and subsequent tumor response. These studies suggested a potential association between a longer nCRT–surgery interval and an increased rate of pCR.[11] However, this work has been primarily from single institutions with small sample sizes (between 33 and 397 patients). Consequently, these studies lack sufficient power to adjust for the confounding impact of different radiotherapy dosages and variations in time to surgery after neoadjuvant therapy. The aim of this study was to examine the relationship between an increased nCRT–surgery interval compared with the current standard of care and pCR in a large, nationally representative cohort of rectal cancer patients who underwent neoadjuvant therapy before definitive surgical resection.

METHODS

Study population

Data for this study were retrieved retrospectively from the National Cancer Data Base (NCDB). This hospital-based cancer registry is sponsored by a joint program between the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The database collects information on all types of cancer from more than 1,500 hospitals with Commission-accredited cancer programs in the United States and Puerto Rico. Available information includes patient demographics, treatment regiments, tumor histology, and oncologic staging, as well as other patient characteristics.[12] Participating NCDB institutions report information based in the Facility Oncology Data Standards manual.[13]

A total of 321,768 rectal cancer cases were identified in the NCDB Participant User File report. The analysis was limited to cases of adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma diagnosed between 2006 and 2011. The sample was further restricted to patients with clinical stage II and III rectal cancer who underwent chemoradiotherapy before surgery and who had a documented surgical resection. Patients with incomplete information about time from diagnosis to surgery and radiation as well as pathologic T and N status were excluded, for a total sample size of 17,255. Figure 1 shows this inclusion process.

Measurement of neoadjuvant chemoradiotherapy–surgery interval time

The database does not contain an explicit variable for nCRT–surgery interval time, but does contain information on number of days between the date of initial diagnosis and the date of the most definitive surgical procedure (A), number of days between the date of diagnosis and the date of radiation therapy initiation at any facility (B), and number of days of radiation therapy treatment (C). The nCRT–surgery interval time was calculated using the following formula: nCRT–surgery interval time = A − B − C. A priori, the nCRT–surgery interval time was categorized as <6 weeks, 6 to 8 weeks, and >8 weeks, based on current clinical practice of a 6- to