Optimal Timing to Surgery after Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer

Zhifei Sun, MD, Mohamed A Adam, MD, Jina Kim, MD, Mithun Shenoi, MD, John Migaly, MD, FACS, Christopher R Mantyh, MD, FACS

BACKGROUND: Neoadjuvant chemoradiotherapy (nCRT) has demonstrated proven benefit in tumor regression and improved long-term local control for patients with locally advanced rectal cancer. However, precise analysis of the optimal waiting time that maximizes oncologic benefits of nCRT has not been established.

STUDY DESIGN: The 2006–2012 National Cancer Data Base was queried for patients with stage II and III rectal adenocarcinoma who underwent nCRT followed by surgical resection. Time to surgery was defined as the difference between last date of radiotherapy and date of surgery. Primary study endpoints included resection margin positivity and pathologic downstaging. Multivariable regression modeling with restricted cubic splines was used to evaluate the adjusted association between time to surgery and our study endpoints, and to establish an optimal time threshold for surgery.

RESULTS: A total of 11,760 patients were included. Median time to surgery was 53 days (interquartile range [IQR] 43 to 63 days). After adjusting for patient demographic, clinical, tumor, and treatment characteristics, our model determined an inflection point at 56 days after end of radiotherapy associated with the highest likelihood of complete resection and pathologic downstaging. With adjustment, the risk of margin positivity was increased in those who underwent surgery after 56 days from end of radiotherapy (odds ratio [OR] 1.40, 95% CI 1.21 to 1.61, $p < 0.001$). The likelihood of downstaging was increasing up to 56 days after radiotherapy (≥56 days vs <56 days, OR 1.2, 95% CI 1.02 to 1.23, $p = 0.01$).

CONCLUSIONS: This study objectively determined the optimal time for surgery after completion of nCRT for rectal cancer based on completeness of resection and tumor downstaging. Eight weeks appears to be the critical threshold for optimal tumor response. (J Am Coll Surg 2016;222:367–374.

In conjunction with the use of total mesorectal excision, combined modality treatment has dramatically reduced local recurrence and improved long-term survival for rectal cancer patients.[1] Before the advent of adjunctive therapies in the 1970s, conventional surgery without mesorectal clearance was associated with recurrence rates of greater than 50%.[2] After 4 decades of step-wise improvements in multimodality therapies, the 2004 German randomized trial established the effectiveness of preoperative administration of fluorouracil-based chemoradiotherapy, with improved local recurrence rates to 7%.[3] From these efforts, the current standard of care for patients with locally advanced rectal cancer in the United States includes use of neoadjuvant chemoradiotherapy and surgery, followed by adjuvant chemotherapy.[4]

Although established recommendations are highly specific regarding each component of the multimodality treatment of cancer, they offer little guidance in aspects of coordinated care, such as the appropriate waiting time to therapies, which have been shown to affect colorectal oncologic outcomes.[5] Specifically in rectal cancer, a correlative relationship between time to surgery and local tumor response has been well observed.[6-12] Francois and colleagues[13] demonstrated that a longer interval between neoadjuvant radiation and surgery was associated with

Disclosure Information: Nothing to disclose.

Presented at the 127th Southern Surgical Association meeting, Hot Springs, VA, December 2015.

Received November 27, 2015; Accepted December 10, 2015.

From the Department of Surgery, Duke University, Durham, NC.

Correspondence address: Zhifei Sun, MD, Duke University Medical Center, Box 3443, Durham, NC 27710. email: zhifei.sun@duke.edu

http://dx.doi.org/10.1016/j.jamcollsurg.2015.12.017

ISSN 1072-7515/15

Abbreviations and Acronyms

IQR = interquartile range
NCDB = National Cancer Data Base
nCRT = neoadjuvant chemoradiotherapy
OR = odds ratio
RCS = restricted cubic splines

improved tumor clinical response and pathologic downstaging. However, a precise duration after radiotherapy that maximizes tumor-killing effects without allowing regrowth for rectal cancer has remained unclear. Although other studies have evaluated this question, conclusions drawn from these studies have been largely based on analysis of predefined time intervals. Therefore, we sought to examine the association between time of neoadjuvant chemoradiotherapy to surgery and oncologic outcomes using a generalizable national-level dataset, with the hypothesis that an optimal timing may be established.

METHODS

Study design

We queried the National Cancer Data Base (NCDB), which collects information on approximately 70% of newly diagnosed cancer cases in the United States and Puerto Rico from more than 1,500 cancer centers. The 2006 to 2012 Participant Use File for rectal tumors was used for this analysis.

Adults who underwent surgical resection after combined preoperative chemotherapy and radiotherapy for pathologic stage II and III rectal adenocarcinoma were included, using the corresponding International Classification of Disease for Oncology, 3rd edition codes. Time to surgery was defined as being from the end of preoperative radiotherapy to the date of surgery. Patients with more than 1 primary malignancy or missing timing data were excluded. Finally, in order to control for the influence of outliers, cases within the top and bottom 2.5% of time to surgery were excluded, resulting in the final distribution, as shown in Figure 1. The Duke University Institutional Review Board reviewed and granted exempt status for this retrospective study.

Outcomes

The primary outcomes of this study were margin positivity (either distal or circumferential) and pathologic downstaging (either by T- or N-stage), with the aim to determine a threshold of time to surgery at which the risk of margin positivity was minimized while maximizing the benefit of tumor pathologic downstaging. Secondary outcomes included postoperative unplanned readmission within 30 days from hospital discharge, 30-day mortality, and overall survival. Local recurrence could not be examined due to limitations of the dataset.

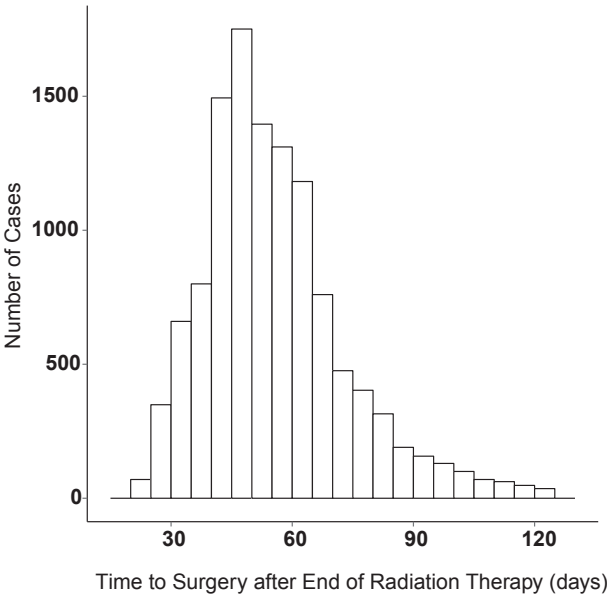

Figure 1. Histogram of time to surgery after end of preoperative radiotherapy among patients with stage II and III rectal cancers. Interval width for each bar is 5 days. Range for time to surgery is 23 to 124 days.

Statistical analysis

In order to model the relationship between time to surgery and our primary outcomes of interest, we developed multivariable logistic regression models incorporating restricted cubic splines (RCS) functions. The RCS is a piecewise, polynomial function that can flexibly examine the association between a predictor and an outcome without assuming any relationship a priori.[14] Using RCS permitted a more precise method to model the complex relationship between time to surgery and our endpoints, while adjusting for age, sex, race, insurance status, Charlson/Deyo comorbidity index, treatment hospital type (academic, comprehensive community, and community), radiation dose, pathologic stage, and extent of surgery. Furthermore, graphic visualization of the model output can objectively determine the existence of a threshold for the optimal time to surgery. Three knots at the 5th, 50th, and 90th percentiles were determined to be appropriate for the RCS model based on the lowest Akaike Information Criterion, as previously described.[15]

The model-derived threshold was then used to dichotomize the initial study cohort into short- and long-interval groups, defined as patients who underwent surgery before and after the threshold, respectively.